Coagulation During and After Orthotopic Transplantation of the Human Liver

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In earlier reports from this institution changes in hemostasis were described in five patients treated with orthotopic homotransplantation of the liver. There was an intraoperative bleeding diathesis at the same time as fibrinolysis and hypofibrinogenemia developed. In four of the cases, the hemorrhage was eventually controlled after the administration of epsilon aminocaproic acid (EACA), fibrinogen, and fresh blood. Subsequently, three of the four survivors formed thrombi at or near femoral venotomy sites which had been used for the insertion of external bypass catheters; in all three, the eventual result was multiple pulmonary embolization.

Appreciation of the seriousness of these problems prompted a number of investigations to be performed in dogs and pigs to more fully characterize the clotting abnormalities of liver transplantation and to learn if a succeeding period of hypercoagulability was an inherent part of the picture. It has been established from these studies that hepatic homotransplantation can cause fibrinolysis, thrombocytopenia, and depression of various clotting factors; that the extent of these changes are prognostic inasmuch as they are proportional to the magnitude of liver injury; and that the depression of clotting is not necessarily succeeded by hypercoagulability if thrombogenic agents are not administered.

The present report, based on experience with ten more recent cases of clinical orthotopic transplantation, will show that the same conclusions apply in man.

Methods

The diseased recipient livers were removed and replaced with orthotopic homografts; splenectomy was concomitantly carried out in all but two cases. External bypasses, to decompress the occluded splanchic and inferior vena caval beds during the anhepatic phase, were not used. The ten patients were 13 months to 43 years old. In the first two cases, organs were used that had sustained a severe ischemic injury as judged by high postoperative rises in the recipient serum transaminases, poor hepatic function from the outset including rapidly progressive jaundice, and death of the patients seven days and ten days later from combined hepatic and renal failure.

The next eight patients benefited from more discriminating donor selection and from the application of an effective technique for interim preservation of the homografts. The liver injury was mild to moderate by the above criteria, and all patients had satisfactory early homograft function. Five patients with jaundice cleared their hyperbilirubinemia. In the three others, normal postoperative bilirubin levels remained unchanged, at least until the onset of rejection. All these eight recipients survived for at least one month, and four are still alive after one to ten months with liver function that ranges from good to excellent. The details of these cases including the regimen of immunosuppression have been reported elsewhere.

In seven of the ten patients coagulation was studied several times during operation and, in all, the blood was examined at regular intervals thereafter. The battery of examinations and the techniques of analyses were the same as in a recent study of the same problem in dogs; the details of methodology will not be repeated here. The tests could be divided as follows on the basis of what they measure:

A. Clotting Factors Known or Thought to be Produced by the Liver.
   These included factors I (fibrinogen), II (prothrombin), V (accelerator globulin), VII (proconvertin), IX (Christmas), and X (Stuart). Except for fibrinogen which was quantitated in mg/100 cc, the results were expressed in percent of normal. In a few instances, the less specific Quick prothrombin time was obtained.

B. Extrahepatic Elements of Clotting.—Factor VIII (antithemophilic globulin) and platelets were measured.

C. Indicators of Fibrinolysis.—The presence of plasmin (fibrinolysin) was

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assayed directly with the heated fibrin plate method. Indirect evidence of fibrinolysis was sought with several methods. The latter involved tests to detect or to measure or both plasminogen (which is low with fibrinolysis), plasminogen activators (determined with the unheated fibrin plate method or with euglobulin lysis times), and the products of partial fibrinogen degradation (fibrinogen split products, FSP).

D. Antithrombin Activity.—This was assayed by determining the thrombin time; in some samples with prolonged thrombin time the level of plasma heparin was measured.

Results

Severe Liver Injury.—These two patients were first studied in the postoperative period, at which time profound coagulation abnormalities were present. In a 13-month-old child, whose original diagnosis was biliary atresia, the liver-produced factors II, V, IX, and X were all less than 15% of normal; fibrinogen was never higher than 125 mg/100 cc (Fig 1). The Quick prothrombin time and the thrombin time were both extremely prolonged. In contrast, factor VIII was supernormal for the entire ten postoperative days (Fig 1). There was a progressive thrombocytopenia despite daily platelet infusions. Euglobulin lysis times (ELT) were prolonged. Hemorrhage was not troublesome until gastrointestinal bleeding became continuous during the last two days of life.

A 28-year-old man with a hepatoma had similar but widely fluctuating changes. Bleeding was, however, a far more significant problem. During the operation and the seven postoperative days he received 33 liters of blood and 3.5 liters of fibrinogen solution.

Moderate or Mild Liver Injury.—Early: All the seven recipients in which intraoperative studies were obtained had similar changes which varied only in degree from case to case. None received thrombogenic agents. The courses of the two patients with the most and least profound changes respectively are shown in Fig 2 and 3. The factors synthesized by the liver, which began to fall during the hepatectomy, decreased further during the anhepatic phase and reached a nadir shortly after the homograft was revascularized. Factors V and IX were usually the most severely affected; factors II, VII, and X next; and fibrinogen the least. The alterations in factor VIII, which is not produced in hepatic tissue, varied from profound depression (Fig 2) in some cases to a moderate decrease in others (Fig 3). The platelets were transiently depressed in five of the seven patients.

Following the anhepatic phase all patients had a marked activation of the fibrinolytic system as shown by

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Fig 1.—Measures of coagulation and fibrinolysis in a 13-month-old child who never had satisfactory function of his orthotopic liver homograft. Note that factor VIII remained supernormal while all the liver-based coagulation factors were severely depressed. Euglobulin lysis time (ELT) was infinite.

Fig 2.—Intraoperative and early postoperative coagulation changes in a 16-month-old child with life sustaining but impaired immediate homograft function. All coagulation factors studied were depressed below 50% of normal. These gradually returned toward normal. FSP, Fibrinogen split products (see text).
the occurrence of lysis on heated plates, decreases in plasminogen levels, and shortening of the ELT. Concomitantly fibrinogen split products appeared in the serum.

Prolongation of the thrombin time occurred after revascularization of the homograft in all cases. In the patient with the most profound changes in hemostasis measurable amounts of plasma heparin (47 μg/ml) occurred at this time. Three other patients studied had no detectable heparin in their plasma in spite of prolonged thrombin times.

Two hours after revascularization of the homografts, a restitution of the clotting factors toward normal had generally begun. By this time, the studies of fibrinolysis also showed improvement (Fig 2 to 4). During the ensuing week the majority of hemostatic parameters returned to essentially normal levels. Exceptions were the platelets and plasminogen levels which usually remained subnormal for several weeks. There was little or no evidence of delayed hypercoagulability.

Abnormal intraoperative bleeding was encountered only in the patient with the most profound alterations in hemostasis (Fig 2). The hemorrhagic state in this case was, however, transient.

Late: The later postoperative course was studied in the eight best cases. The clotting values were closely correlated to the quality of homograft function as measured by standard liver function tests. The patient with the longest survival (ten months) had good liver function and essentially normal coagulation and fibrinolysis throughout. Two patients who died of progressive liver failure 4½ and 6 months after transplantation had slowly declining levels of the clotting factors synthesized by the liver as well as decreases in plasminogen (Fig 4). During this course, factor VIII remained unaffected.

Comment

Several mechanisms apparently account for the sudden decrease in clotting factors during orthotopic liver transplantation. The most important are probably consumption.

Fig 3.—Changes in a 14-month-old child with satisfactory immediate liver function. All coagulation factors studied were transiently but only minimally depressed. FSP, Fibrinogen split products.

Fig 4.—Postoperative changes in a 20½-month-old patient. Early homograft function was satisfactory but progressive liver failure due to chronic rejection subsequently developed. During the late course, factor VIII remained supernormal while the liver-based II and V and plasminogen ultimately declined.
of the coagulation factors due to intravascular coagulation, and counterregulatory fibrinolysis. Temporary cessation of hepatic synthesis is presumably a contributory factor. The precise mechanism of these changes has been discussed elsewhere. In only one case could prolongation in thrombin time be related to the occurrence of plasma hepamin as suggested by Stremple; the trace quantities could have been due to the heparin solutions used to perfuse and flush the grafts. In the others, the antithrombin activity was attributable to the occurrence of fibrinogen split products.

In a recent laboratory study, it was shown that the severity of the hemostatic breakdown after orthotopic liver transplantation in dogs was related to the quality of the homografts. The conclusion was the same in the human cases herein reported. The two patients who received livers badly damaged by ischemia developed profound and persistent abnormalities in clotting while the recipients of well-preserved homografts had only minor or moderate changes which were reversible. None of the latter patients required administration of clot promoting or antifibrinolytic agents. Moderate bleeding such as experienced in one of these patients should not necessarily be regarded with alarm nor treated pharmacologically since spontaneous improvement can be expected. The avoidance of pharmacologic manipulation of hemostasis and omission of an external decompressing bypass in the venous system undoubtedly helped prevent postoperative thromboembolism such as that seen in earlier cases. If treatment should become necessary for a hemorrhagic diathesis, it should be guided by frequent measures of clotting parameters.

Although most of the clotting factors analyzed in this study are known to be synthesized in hepatic tissue, the origin of factor VIII (antihemophilic globulin) remains obscure. In several of the patients, who had also had splenectomy, factor VIII remained normal or supernormal as the other factors declined concomitant with acute or chronic hepatic failure; in one such case, the recipient was essentially anhepatic (Fig 1). It thus appears that neither the spleen nor functional liver tissue are essential for the maintenance of adequate levels of antihemophilic globulin.

References


Summary

Orthotopic liver homotransplantation in humans was accompanied by acute depression in multiple coagulation factors, thrombocytopenia, and pathologic fibrinolysis. Two patients with poor homograft function had severe and persistent changes; eight subsequent recipients with satisfactory immediate liver function developed only minor or moderate derangements which were reversible and did not require therapy with thrombogenic agents. Later in the course coagulation was normal except with the advent of chronic hepatic failure when depression occurred of the coagulation factors synthesized by the liver.

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