691

12 Intraoperative Coagulation Changes in Liver Transplantation

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INTRODUCTION

Liver transplantation is being used to treat (correct?) end-stage liver disease caused by a wide variety of congenital or acquired disorders. Improved methods for procurement and preservation of donor livers, innovative surgical techniques, and reasonably satisfactory immunosuppression have made liver transplants feasible for many with severely damaged liver parenchyma, vasculature, or bile ducts. One of the major difficulties has been the excessive use of blood transfusion, which reflects the loss of blood during the operation. This chapter deals with some of the many parameters of coagulation and the changes found during the surgical procedure.

MATERIALS AND METHODS

Patient Material

In an 18-month period (12/03/82 to 5/28/84), intraoperative coagulation studies were carried out on 67 adult individuals undergoing their first liver transplants. The coagulation tests were performed at the request of the anesthesiologists or surgeons for patient care purposes and were not considered research, although the Coagulation Laboratory did allow a special, reduced price for each series of tests. The tests performed employed previously published methods (1–3) and included prothrombin time (PT), activated partial thromboplastin time (APTT), fibrin split products (FSP), euglobulin lysis time (ELT), and assays of coagulation factors I, II, V, VII, VIII, IX, X, XI, and XII. Frequently, but not always, platelet counts, thrombin times, and assays of plasminogen, antiplasmin (4), and F VIIIR:Ag were done.

The 67 first liver transplants investigated represented all of the adult liver transplant procedures done during this period, with the exception of a few that were performed when our on-call technician was unavailable.

Each study consisted of 12 or more samples that did not always follow a consistent time pattern. Usually, there was an initial sample, one taken just as the liver was isolated from the circulation, and another 5 min after circulation was established in the new liver. Stage I (explantation of the diseased liver) begins with the skin incision, stage II (anhepatic) with removal of the patient's liver from the circulation, and stage III (implantation of the new liver) with restoration of circulation to the implant.

Patient Categorization

Table 12.1 shows the diagnostic categories. PNC includes chronic active hepatitis (CAH) following hepatitis B or nonA, nonB and lupoid hepatitis. (Alcoholic cirrhotics are very rarely suitable for transplant therapy.) Most of the CA group suffered from hepatoma, but one each had cholangiocarcinoma and angiocarcinoma. The MISC group included two with α-1-antitrypsin deficiency and three with Wilson's disease. The FUL group included

TABLE 12.1. Diagnostic Categories of 67 Patients Receiving Their First Liver Transplants (December 3, 1982 to May 28, 1984)

Diagnosis	*No*	*M*	*F*	*Age Range*
PNC—postnecrotic cirrhosis	18	11	7	19–53
PBC—primary biliary cirrhosis	18	0	18	39–54
SC—primary sclerosing cholangitis	9	6	3	23–46
MISC—miscellaneous	9	5	4	16–41
CA—neoplasia/malignancy	8	2	6	21–35
FUL—fulminant hepatitis	5	5	0	25–57
Total	67	29	38	19–54

one due to gold toxicity, one following exposure to methylethylketone and vinyl paint, and the remainder following viral infections.

RESULTS

Figures 12.1 through 12.4 illustrate the findings in a single patient (10378). She was a 35-year-old white woman with the diagnosis of angiosarcoma of the liver. Intraoperative blood use was high. During the 14-h procedure she received 148 units of red blood cells (RBCs), 128 units of fresh frozen plasma (FFP), 52 units of platelets, and 30 bags of cryoprecipitate. Figure 12.1 shows the levels of factors II, V, VII, and X during the operation. In this patient, these factors were low initially owing to parenchymal liver disease. In the first hour she received 400 ml FFP, which resulted in a moderate increase in factor levels. During the anhepatic period the factors fell, but all except F V rose to preoperative levels by the end of surgery.

Figure 12.2 shows a similar pattern occurring in factors I, IX, XI, and XII. All of these factors were in the normal range preoperatively. All fell during the anhepatic period and recovered by the end of surgery. There was no evidence to suggest activation of factor XII, which might be important to the fibrinolytic activation shown in Figure 12.3.

Figure 12.3 shows the euglobulin lysis time (ELT) and the F VIII:C and F VIIIR:Ag. The ELT revealed rapid lysis (15 min) early in stage II that continued throughout this period and into early

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y 28, 1984)

F	*Age Range*
7	19–53
18	39–54
3	23–46
4	16–41
6	21–35
0	25–57
38	19–54

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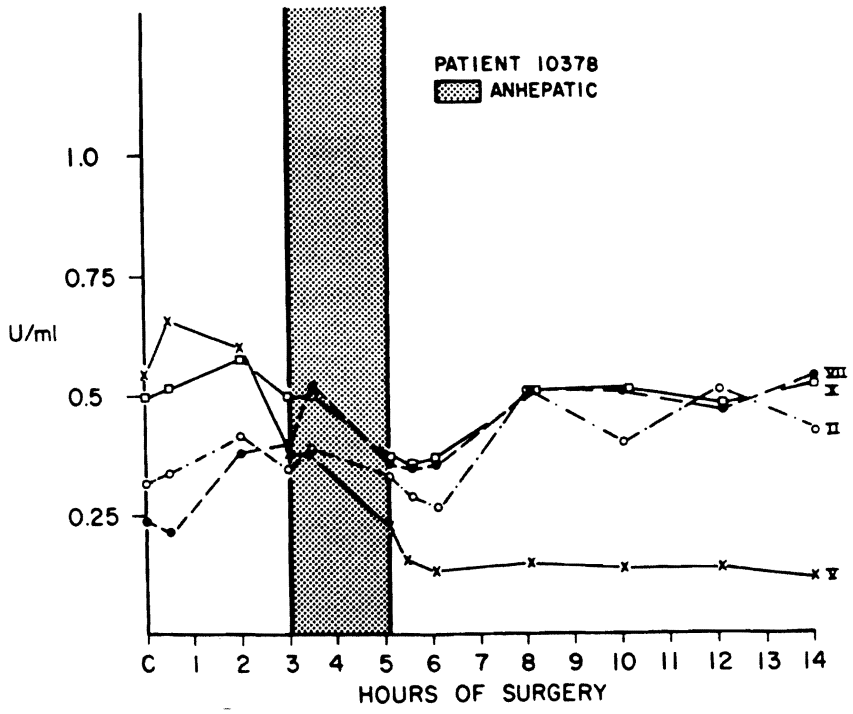


FIGURE 12.1. Intraoperative findings in coagulation factors II, V, VII and X.

stage III. Factor VIII:C fell from its high initial level of 1.45 U/ml to 0.18 U/ml at the end of the bypass, when circulation through the new liver was established. There was a lag of about 1 h before VIII:C started to rise again. The extent of the fall in F VIII:C level and the fact that it was greater than that observed for some of the other clotting factors suggests that some active process was happening and that this did not simply reflect lack of production and irregular replacement therapy.

In addition, factor VIIIR:Ag fell more slowly and to a lesser extent than VIII:C. This discrepancy in the falls of F VIII:C and VIIIR:Ag further enhances the argument for destruction of F VIII:C. The mechanism involved could be due to plasmin or to thrombin. In this patient, the latter explanation seems unlikely because there was no significant indication of disseminated intravascular coagulation (DIC) such as fibrin monomer or increased split products.

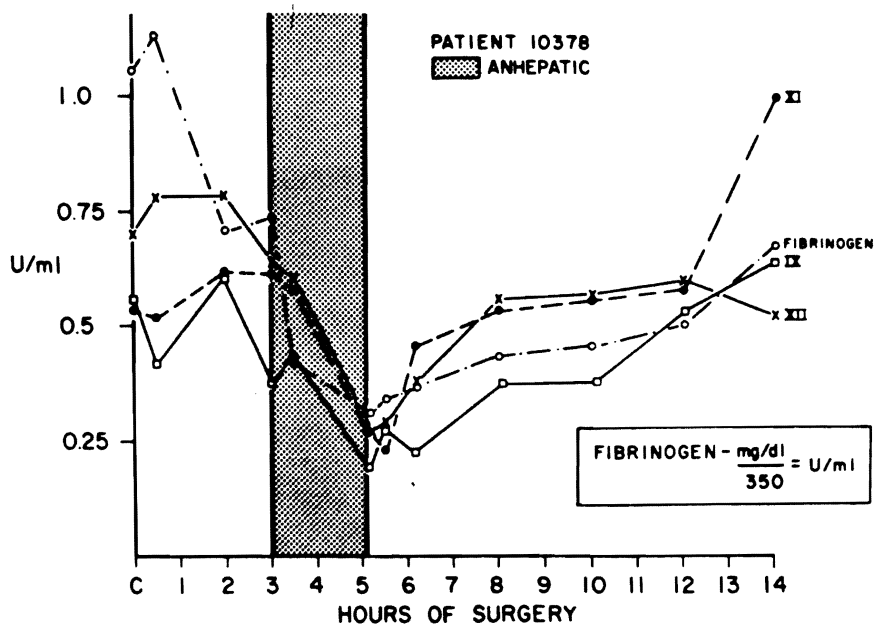


FIGURE 12.2. Intraoperative findings in coagulation factors I, IX, XI and XII.

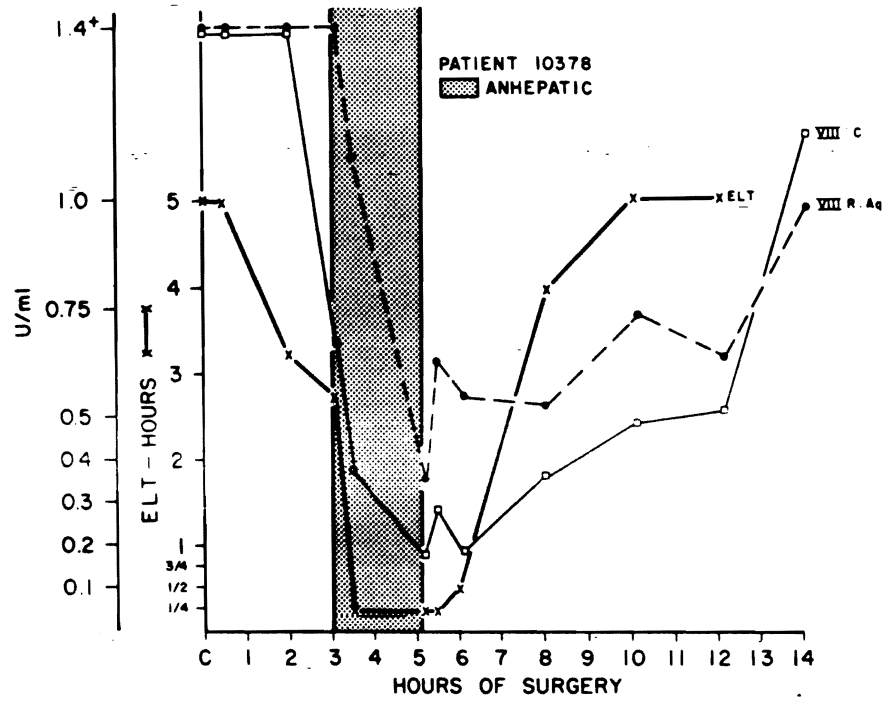
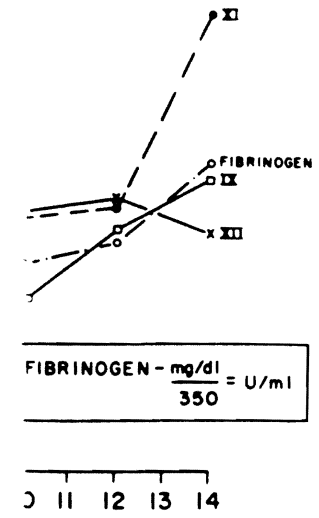


FIGURE 12.3. Euglobulin lysis time (ELT), factor VIII:C and VIIIR:Ag during liver transplantation.



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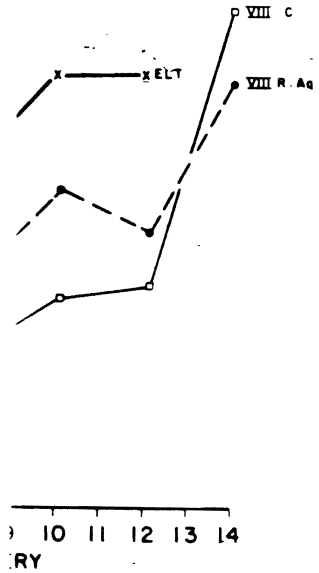

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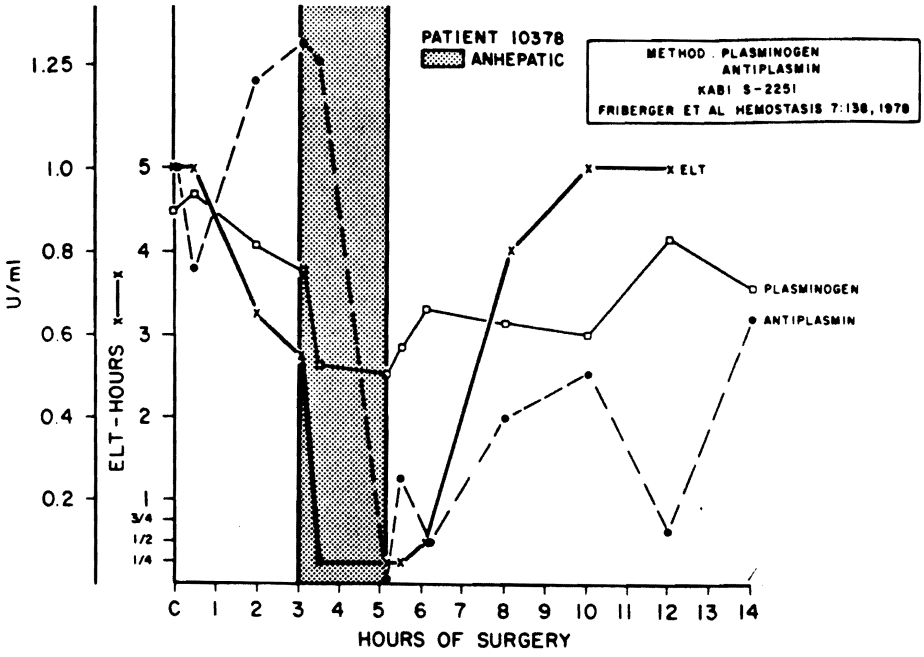

FIGURE 12.4. Euglobulin lysis time, plasminogen and anti-plasmin during liver transplantation.

Figure 12.4 shows the assay results for plasminogen and antiplasmin. Plasminogen showed only a moderate drop during the anhepatic period. However, antiplasmin fell sharply to an undetectable level, then rose when the new liver circulation was established. There appeared to be a direct relationship between activation of the ELT and the subsequent abrupt fall in antiplasmin.

In almost all of the 67 transplant patients, all coagulation factor levels fell during the anhepatic period and usually recovered toward the end of surgery. This pattern was seen with factors II, VII, IX, X, XI, and XII. These changes are described elsewhere (5). The rest of this chapter deals with the fibrinolytic enzyme system and factors V and VIII.

Table 12.2 shows that the euglobulin lysis time became short ($\leqslant$ 105 min.) at some time, often on repeated observations, during 85% of the operations. Very rapid lysis ($\leqslant$ 45 min.) was seen in 43 (64%) of the 67 patients. Preoperatively, this test had shown abnormal fibrinolytic activity in 12 patients (17%).

Table 12.3 shows that the initial F VIII:C levels were high (mean = 1.97) and that they fell approximately 66% to 0.63 U/ml.

TABLE 12.2. Intraoperative Activation of the Fibrinolytic Enzyme System

	Preoperative, active		*Intraoperative, active*	
	No.	*%*	*No.*	*%*
PNC	7	38	16	88
PBC	0	0	16	88
SC	0	0	8	88
MISC	3	33	8	88
CA	0	0	4	50
FUL	2	40	5	100
All	12	17	57	85

and trough levels of factor V:C. The initial levels were low (indicative of severe liver parenchymal involvement). They fell to a mean level of 0.16 U/ml, which was remarkably consistent among different patient categories. Some 38 (56%) reached levels of 0.15 U/ml or lower. Table 12.5 shows that blood use during surgery, which reflects blood loss, is very much greater if factor VIII:C falls to levels $\leqslant$ 0.35 U/ml. The large users of blood are almost all deficient in factor VIII:C.

COMMENT

The fall and subsequent rise in factors II, VII, IX, X, XI, and XII seem to reflect poor or absent synthesis plus dilution due to

TABLE 12.3. Initial and Lowest (Trough) Levels of VIII:C

	Initial F VIII:C (U/ml ± S.D.)	*Trough F VIII:C (U/ml ± S.D.)*	*Decrease (%)*
PNC	1.86 ± 0.84	0.56 ± 0.37	69
PBC	2.25 ± 0.89	0.68 ± 0.41	69
SC	2.00 ± 1.03	0.60 ± 0.45	68
MISC	1.92 ± 0.72	0.58 ± 0.50	69
CA	1.64 ± 0.76	0.73 ± 0.43	54
FUL	1.97 ± 0.84	0.75 ± 0.54	61
All	1.97 ± 0.85	0.63 ± 0.49	66

ibrinolytic Enzyme

Intraoperative, active No.	%
6	88
6	88
8	88
8	88
4	50
5	100
57	85

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VII, IX, X, XI, and XII
plus dilution due to

ls of VIII:C

C	Decrease
	69
	69
	68
	69
	54
	61
	66

TABLE 12.4. Initial and Lowest (Trough) Levels of V:C

	Initial F V:C (U/ml ± S.D.)	Trough F V:C (U/ml ± S.D.)	Decrease (%)
PNC	0.29 ± 0.14	0.15 ± 0.07	48
PBC	0.59 ± 0.22	0.16 ± 0.08	72
SC	0.68 ± 0.50	0.16 ± 0.07	69
MISC	0.39 ± 0.43	0.16 ± 0.10	39
CA	0.71 ± 0.35	0.15 ± 0.06	75
FUL	0.38 ± 0.18	0.17 ± 0.05	46
All	0.49 ± 0.31	0.16 ± 0.07	59

This level is not in the hemorrhagic range, but there were 25 (37%) whose trough levels were ⩽ 0.35 U/ml. Table 12.4 shows the initial hemorrhage and inadequate replacement with FFP and crystalloid solutions. On the other hand, the falls in factors VIII:C and V are more abrupt and persistent, and for F VIII:C in particular seem to involve destruction during an active process such as fibrinolysis. Certainly, these two factors are known to be easily destroyed by fibrinolytic activity.

It is theorized that during liver transplantation, a plasminogen activator appears in the circulation in sufficient strength to activate plasminogen (causing the rapid ELT) and that circulating plasmin cleaves factors VIII and V, making the molecules functionally deficient and, later, structurally abnormal (fall in F VIIIR:Ag shown in Figure 12.3). Activation of Protein C could also result in destruction of factors VIII and V. Future studies will explore this

TABLE 12.5. Patients with Trough Blood Levels of V:C ⩽ 0.15 U/ml and/or VIII:C ⩽ 0.35 U/ml and Blood Use

Factor	Number	"Blood" use mean units	No. used 100
V	18	44	1
VIII	7	99	3
V + VIII	18	106	6
Neither	24	36	1

"Blood" = units FFP + RBC.

possibility. DIC causes multifactor and platelet consumption and the appearance of fibrin split products (FSP). These were found, but in minimal amounts, during liver transplantation. The mechanism of activation of fibrinolysis will require future exploration.

The intraoperative blood use (or loss) is highly dependent on the presence or absence of an abrupt and startling decline in factor VIII:C. When this occurs, the blood use is more than double that which occurs when it does not. Fortunately, plasma fractions high in factor VIII (cryoprecipitate) are available for therapy. However, this may not be effective unless any active fibrinolytic process is stopped by the judicious use of enzyme inhibitors such as epsilon amino caproic acid.

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