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Coagulation Defects Following Extracorporeal Circulation *

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EXCESSIVE postoperative blood loss following open-heart surgery utilizing extracorporeal circulation continues to present a problem during the operative and postoperative period in occasional cases. It has been apparent that as clinical experience increases, the incidence of this distressing complication has decreased, but a review of the coagulation studies carried out among the first 200 open-heart cases at the Presbyterian Hospital has clarified certain aspects of this complication.

There were nine patients who developed major bleeding, requiring administration of fibrinogen during or following extracor-

poreal circulation among 81 perfusions utilizing the bubble oxygenator, as previously described by DeWalt.⁴ Coagulation and fibrinolysin studies were obtained on these nine patients and compared to values from 33 cases without significant fibrinogen depletion. Similar data on the fibrinolytic system obtained from among 119 perfusions carried out utilizing the disc oxygenator of Björk, as modified by Gross,⁶ is presented for comparison.

The report of Ulin²¹ showed a decrease in many clotting factors during cardiopulmonary bypass and after massive transfusions, but he was not able to show significant differences in levels of those patients in whom hemorrhage was a postoperative problem and those in whom it was not. Hoeksema,⁸ Nilsson⁹ and Penick¹⁰ have all shown a decrease in platelets and anti-hemophilic globulin (Factor VIII) during extracorporeal circulation. von Kaulla,²² Nilsson⁹ and Brown² have all stressed the importance of fibrinolysin in the hemorrhagic diathesis following cardiac bypass.

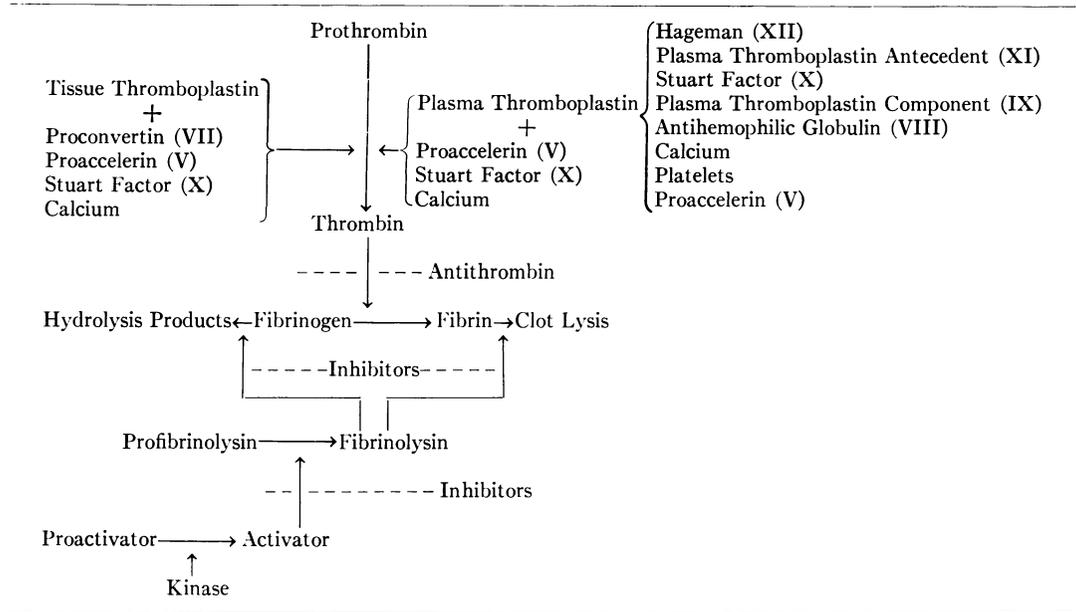
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TABLE 1. Coagulation and Decoagulation Scheme



Methods

The generally accepted scheme for coagulation and decoagulation is presented in Table 1. The coagulation studies carried out among the patients studied measured directly or indirectly the factors shown. The methods utilized were as follows:

Fibrinogen is determined by the method of Ratnoff and Menzie¹⁷ and reported in milligrams per cent. Free profibrinolysin is measured by the hydrolysis of casein by plasma activated by streptokinase. Total profibrinolysin is determined by the hydrolysis of casein by the euglobulin precipitated from plasma and activated with streptokinase. These are reported in arbitrary units.¹² The difference between total and free profibrinolysin is a measure of inhibitors.¹² Clot lysis is estimated by a modification of a method by Coon and Hodgson.³ The euglobulin thrombin time is the clotting time in seconds when 0.01 ml. of thrombin (1,000 U./ml.) is added to 0.2 ml. of re-dissolved euglobulin precipitate prepared for the determination of total profibrinolysin. Euglobulin lysis time

is the time in minutes required for lysis of the above clotted euglobulin fraction. This is similar to a method described by von Kaulla.²³ Quick's¹⁶ method is used for prothrombin time. Stefanini's¹⁹ method is employed for Factor V determination. Prothrombin consumption time is obtained by the method of Sussman.²⁰ The Duckert⁵ modification of the Biggs, Douglas and MacFarlane¹ test for thromboplastin generation is used.

Results

The clotting factors excluding fibrinogen studied during the preoperative, operative and postoperative periods utilizing the bubble oxygenator are summarized in Table 2. All factors were normal in the preoperative period and, during bypass, were abnormal in a manner consistent with the presence of heparin. After heparin neutralization was carried out by administration of protamine sulfate (at a dosage of 2.0 mg. protamine to 1.0 mg. heparin during this initial phase of this study), many factors returned toward normal. In the

early recovery period prothrombin times were slightly prolonged and Factor V somewhat lower than normal. Thromboplastin generation was essentially normal at this time, but prothrombin consumption was poor. This suggests a deficiency either in the number or quality of platelets as a result of the perfusion.

Euglobulin lysis times, which are normally longer than 420 minutes, showed many instances of more rapid lysis during and after perfusion. Approximately 30 per cent of the patients showed less than normal lysis times preoperatively, while 65 per cent demonstrated the same phenomenon by the end of perfusion, and 50 per cent showed it in the recovery room studies. Twelve to 18 hours postoperatively none of the patients showed lysis in less than 420 minutes.

von Kaulla²² has emphasized the importance of increased plasma thrombin times in the production of hemorrhagic phenomenon in these cases. The euglobulin thrombin times reported here are a measure of antithrombin activity. This activity is probably not associated with the presence of heparin, since this substance and any antithrombin which may be associated with the albumin fraction of plasma are removed by the method of iso-electric precipitation. These thrombin times were

found to be prolonged during and immediately after perfusion, but were shorter 24 hours after operation than they had been preoperatively.

It is of interest that the inadequate thromboplastin generation obtained during heparinization could be corrected by substitution of normal serum for the patients' serum, but not by substitution of normal plasma. This suggests an interference of heparin with the development of PTC activity (Factor IX) in the serum, but shows no evidence of a loss of anti-hemophilic factor (Factor VIII) sufficient to produce coagulation abnormalities either during or after perfusion. Shanberge¹⁸ has reported *in vitro* studies indicating such an interference of heparin with PTC activity. Figure 1 shows average thromboplastin generation curves obtained using patients' own plasma and serum at various stages of the operative procedure and by substituting normal plasma or serum.

Particular attention was directed to the alteration occurring in fibrinogen and the fibrinolytic system as a result of cardiopulmonary bypass utilizing the bubble oxygenator described. Fibrinogen, profibrinolysin and antifibrinolysin were determined preoperatively, during bypass and in the recovery period in most of these patients. Table 3 shows the average values for fi-

TABLE 2. Coagulation Changes Utilizing the Bubble Oxygenator Exclusive of Fibrinogen

	Preop.	Perfusion		Recovery Room	18 Hours Postop.
		Early	Late		
Prothrombin time (seconds)	15.8	63.9	82.8	19.4	17.7
Factor V % normal	93	15	20	77	87
Prothrombin consumption time (seconds)	40			18.1	28
Thromboplastin generation at 4 min. (seconds)					
Patients' plasma and serum	13.4	50	45	15.4	13
Normal plasma and patients' serum		40	42	13	
Patients' plasma and normal serum		16	14.5	13	
Total protein Gm. %	6.2	5.7	5.5	5.4	5.4
Albumin Gm. %	4.5	4.1	4.0	4.0	4.0
Euglobulin lysis time (minutes)	331	263	199	269	>420
% Patients with euglobulin lysis time <420	29	47 ↓	64 ↓	47	0
Euglobulin thrombin time (seconds)	17.9	23.6	24.5	20.9	9.1

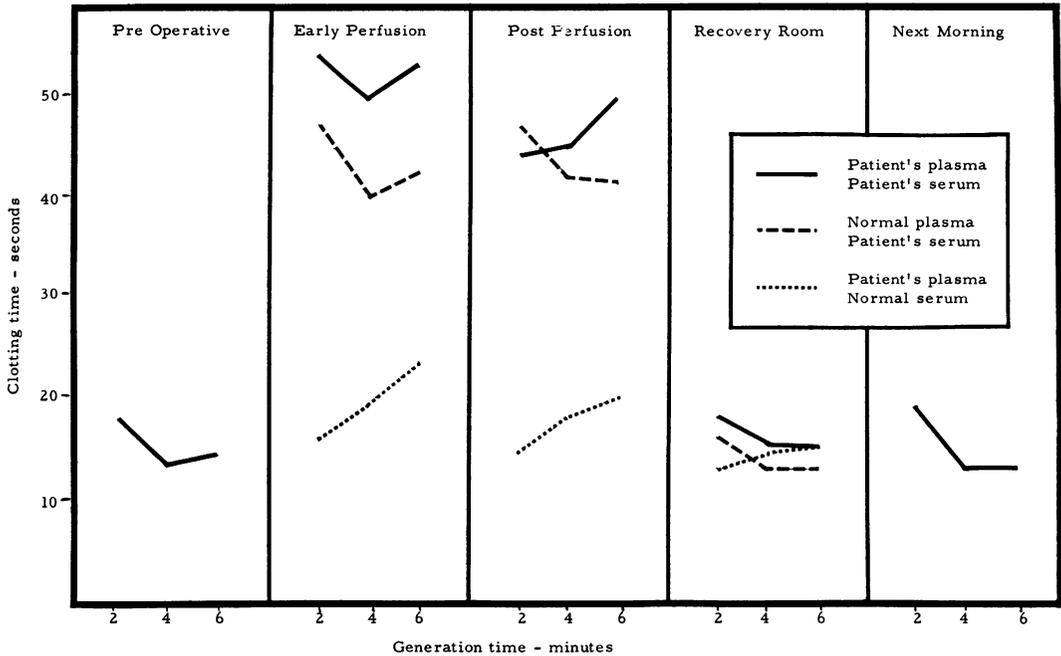


FIG. 1. Average thromboplastin generation curves obtained before, during and after extracorporeal circulation.

brinogen and other determinations in 33 relatively uncomplicated cases, as compared to nine patients who required fibrinogen therapy. The preoperative fibrinogen levels in both groups were essentially the same and there was a similar drop in both groups at the beginning of perfusion. This drop was due partially to a dilution of donor blood with anticoagulant, priming saline and albumin added to the perfusate and possibly to some minute coagulation

of blood drawn for the pump. However, little further decrease was encountered in the control group during bypass and levels returned to normal within 12 to 16 hours. In the group requiring fibrinogen therapy there was a progressive fall in the fibrinogen, profibrinolysin and inhibitor levels during perfusion and, most significant, there was a further decrease in the early recovery period. This continued fall in levels at the termination of bypass was

TABLE 3. Average Fibrinogen System Values Altered by Bypass

	Fibrinogen Administered (9 cases)			No Fibrinogen (33 cases)		
	Fibrinogen	Pro-fibrinolysin	Anti-fibrinolysin	Fibrinogen	Pro-fibrinolysin	Anti-fibrinolysin
Preoperative	249	4.7	3.3	260	4.5	3.1
Early perfusion	191	4.0	2.4	216	4.4	2.9
Post perfusion	152	3.4	2.6	198	4.3	2.8
Recovery room	131	3.0	1.9	196	4.3	3.1
Postfibrinogen	240	3.1	2.0			
18-20 hrs. postop.	290	5.3	2.9	334	4.1	3.1

commonly associated with excessive bleeding. There was a 55 per cent mortality among this group of patients, but it is interesting to note that by the following morning all surviving patients in both groups showed fibrinogen figures above the preoperative values. The inhibitor and profibrinolysin levels of the surviving hypofibrinogenemia group had risen to normal levels with 12 to 16 hours.

The results obtained on 18 patients perfused using the disc oxygenator are essentially the same as those of the control group on the DeWall apparatus. There have been only two episodes of major postoperative bleeding in 119 consecutive patients operated upon utilizing the disc oxygenator, and re-exploration revealed a specific bleeding source in both patients. Data available on the first 18 cases studied utilizing the disc oxygenator is shown in Table 4. It is not within the scope of these data to compare perfusion apparatus, for many modifications of perfusion technic, i.e. moderate hypothermia and low vacuum coronary suction, have markedly reduced blood trauma during the bypass period. Perfusions have been extended to 140 minutes for aortic valve replacement without significant alterations in blood coagulation.

The types of bleeding problems which were encountered in the initial group of patients operated upon utilizing the bubble oxygenator are illustrated with brief clinical summaries and figures to indicate the coagulation changes noted and their response to therapy.

TABLE 4. *Fibrinogen System Changed Utilizing the Disc Oxygenator*

	Fibrinogen (mg.%)	Profibrinolysin (units)	Anti-fibrinolysin (units)
Preoperative	239	5.5	3.9
Pump	206	5.2	3.5
Early perfusion	194	4.8	3.3
Late perfusion	187	5.2	3.7
Recovery Room	202	4.7	3.1

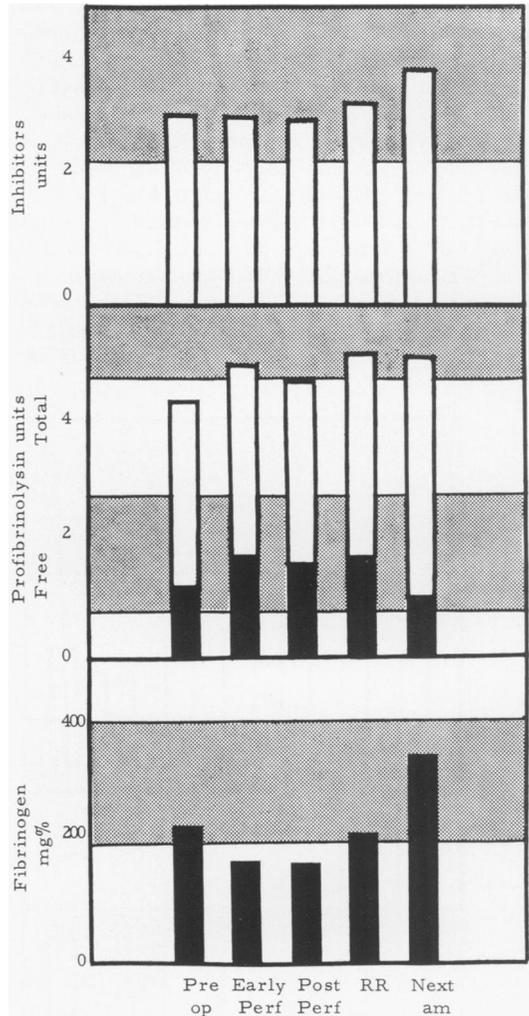


FIG. 2. Case 1 (C. J.): Fibrinolytic enzyme system in a case which was not complicated by excessive bleeding. Shaded areas indicate normal ranges.

Case Reports

Case 1 (C. J.). A 12-year-old boy underwent closure of a secundum atrial septal defect with moderate pulmonary hypertension utilizing 38 minutes of cardiopulmonary bypass. During the first 10 hours postoperatively there was a total blood loss of 950 cc. Coagulation studies, as shown in Figure 2, reveal an essentially normal fall in the fibrinogen level during perfusion, with recovery during the first few hours in the recovery room. The bleeding subsided spontaneously and no specific therapy was indicated. The results shown in Figure 2 are typical of bleeding unaccompanied by a fibrinolytic phenomenon.

Case 2 (E. V.). A 13-year-old boy underwent closure of a ventricular septal defect with moderate pulmonary hypertension utilizing 24 minutes of cardiopulmonary bypass. As seen in Figure 3, the fibrinogen content of blood obtained from the oxygenator at termination of perfusion was 199 mg.%. Two hours following return to the recovery room the fibrinogen had fallen to 147 mg.% and there was approximately 1,200 cc. blood loss from the chest tubes. Fresh whole blood was administered, but blood loss continued and the patient remained hypotensive. Eight hours postoperatively the fibrinogen remained at a level of 150 mg.% and 4.0 Gm. of fibrinogen were ad-

ministered. At 18 hours postoperatively bleeding was again noted from all wounds and the fibrinogen level remained low, despite an additional 6.0 Gm. of fibrinogen and fresh frozen plasma. It is to be noted that there is a continued fall in fibrinolysin inhibitors and evidence of fibrinolysis continued until death, 26 hours postoperatively. It was apparent that during the immediate postoperative period there was evidence of a falling fibrinogen associated with bleeding and general tissue anoxia secondary to hypotension. The fibrinogen was administered late in the course of the bleeding, in the presence of clear evidence of a falling fibrinogen, and the process had become irreversible by the 18th hour postoperatively.

Case 3 (A. M.). A 13-year-old boy underwent closure of a ventricular septal defect with severe pulmonary hypertension utilizing 47 minutes of cardiopulmonary bypass. During the 1½ hours postoperatively there was a 700 cc. blood loss from the chest tube. An additional 25 mg. of protamine were administered and a venous clotting time was recorded of 10 minutes. Platelets were 162,000. Fibrinogen was 196 mg.%. An additional 1,000 cc. blood loss was noted during the next four-hour period and fibrinogen levels, as shown in Figure 4, were falling. At 6 p.m. the fibrinogen was 156 mg.% and the patient received 4.0 Gm. of fibrinogen. The fibrinogen at 8 p.m. was 283 mg.% and no further blood loss was noted. It was apparent that there was a sudden decrease in the amount of bleeding associated with a restoration of fibrinogen level. This response is in sharp contrast to Case 2, where fibrinogen was administered late in the clinical course.

Case 4 (P. M.). A 45-year-old mechanic was previously explored for mitral stenosis and found to have a left atrial tumor. An admission workup revealed a blood group of O positive, Kell negative, Duffy positive, Rh O positive, Rh prime positive, Rh double prime negative. The patient had strong anti-Kidd antibodies to serum and cross-matching was extremely difficult. A left atrial myxoma was excised utilizing extracorporeal circulation. Bypass was prolonged, secondary to the repair of a tear in the inferior vena cava behind the left atrium. A period of 120 minutes of partial and total cardiopulmonary bypass was required to complete the excision and repair, and support circulation until cardiac action improved. On completion of bypass there appeared to be bleeding from all areas of the wound. Coagulation studies at that time revealed evidence of a marked fibrinolysis and a fall in plasma fibrinogen. The patient received 10 Gm. of fibrinogen, albumin

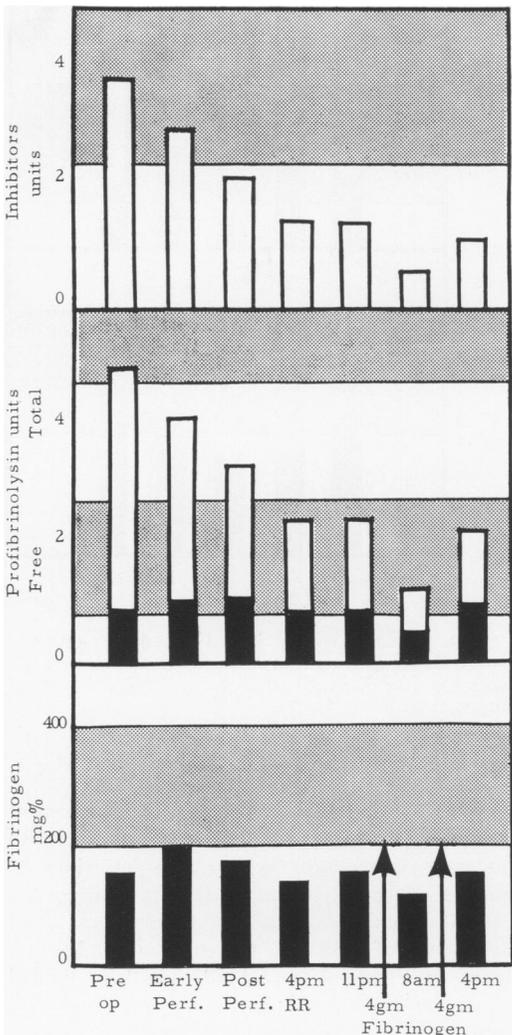


FIG. 3. Case 2 (E. V.): Fibrinolytic enzyme system in a case of severe bleeding which was not controlled by administration of fibrinogen. Shaded areas indicate normal ranges.

and fresh whole blood without response. The patient had received 16 Gm. of fibrinogen at the time of death, without substantially increasing the plasma level. This case illustrates the activation of a strong fibrinolysin, secondary to prolonged cardiopulmonary bypass, and severe tissue destruction. This type of reaction represents the most extreme degree of fibrinolysin and is comparable in all respects to the severe fibrinolysis occasionally seen following general surgical procedures.

Discussion

It is evident that extracorporeal circulation produces many alterations in the coagulation mechanisms of patients undergoing open heart surgery. Some of these alterations are temporary ones, caused principally by the use of heparin as an anticoagulant. The apparent decreases in prothrombin and proaccelerin are due primarily to the antithrombic activity of heparin; however, slightly prolonged prothrombin times may persist after neutralization of the heparin and may require the administration of vitamin K. Interference of heparin with development of plasma thromboplastin component (PTC) activity is, to a great extent, responsible for the inadequate thromboplastin generation during perfusion. Shanberge¹⁸ has shown that such an interference does occur *in vitro*. The correction of generation on addition of normal serum to patient's heparinized plasma, shown in the results presented, is further evidence of this PTC-heparin interference. Following neutralization of heparin at the end of perfusion, the thromboplastin generation returned to normal in all cases. No evidence of loss of anti-hemophilic globulin (AHG), sufficient to produce coagulation abnormalities, was observed in any of the cases studied, either during perfusion or after.

The poor prothrombin consumption in the immediate postoperative period is probably due to either quantitative or qualitative deficiencies in platelets. These deficiencies may be caused by mechanical

factors such as bubbling, passage of blood through tubing, trauma from pumping and coronary sinus suction. In most cases, where platelet counts were performed immediately postoperatively, they were found to be in a low normal range. However, 24 to 48 hours later the count had frequently decreased, suggesting that perfusion may have produced qualitative changes which may affect both function and survival.

It is the fibrinolytic enzyme system

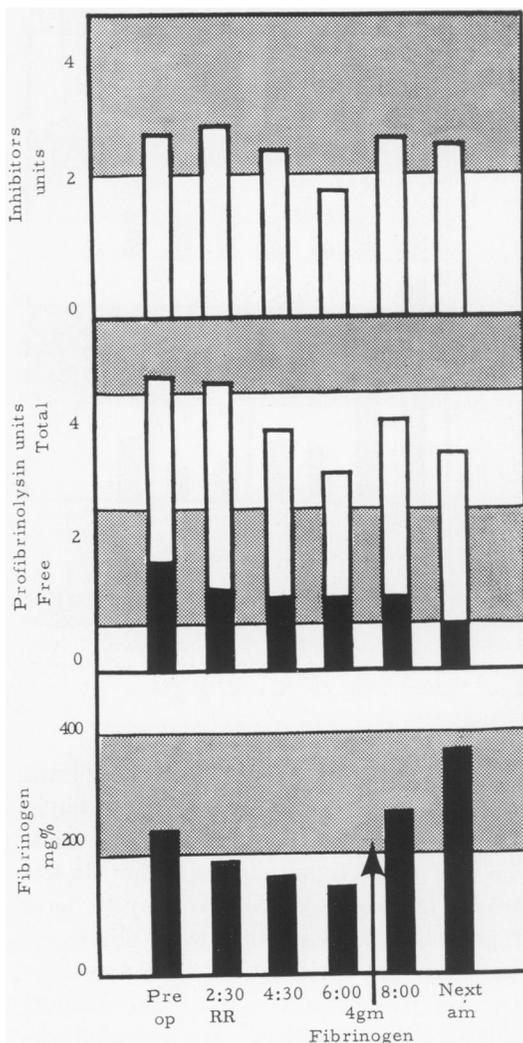


FIG. 4. Case 3 (A. M.): Fibrinolytic enzyme system in a case with severe post-operative hemorrhage which was treated successfully with fibrinogen. Shaded areas indicate normal ranges.

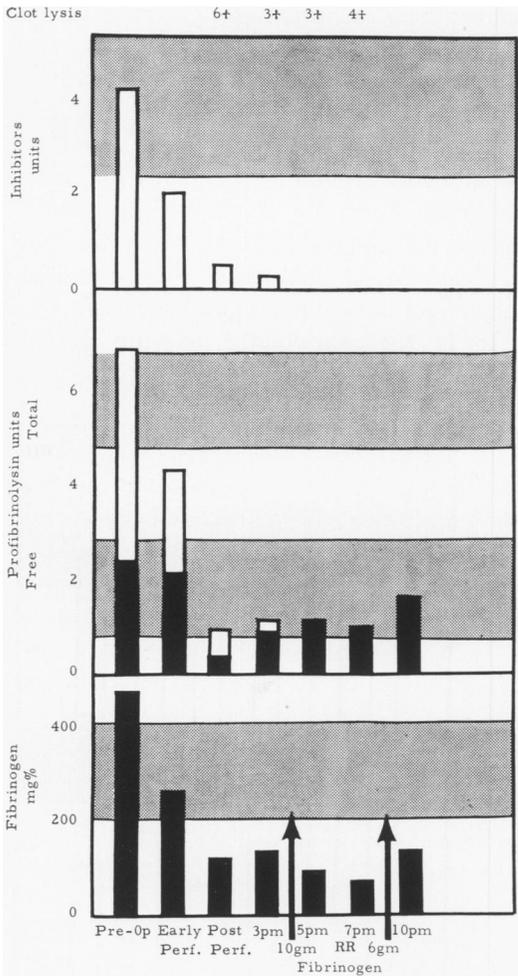


FIG. 5. Case 4 (P. M.): Fibrinolytic enzyme system in a case of fulminating fibrinolysin activation. One part of patient's plasma lysed a clot formed with 32 parts of normal plasma in 2 hours. Shaded areas indicate normal ranges.

which appears to be the most important factor in the production of hemorrhagic difficulties from coagulation dyscrasias. The fact that euglobulin lysis time is decreased in 65 per cent of cases by the end of perfusion suggests that some slight activation of the fibrinolytic system may take place in many cases even where hemorrhage is not a problem. The elevated euglobulin thrombin times are of interest in view of von Kaulla's²² statements that a combination of fibrinolytic and antithrom-

bic activity may be indicative of a poor prognosis following extracorporeal circulation.

In most of the cases of severe bleeding, the drop in fibrinogen began during perfusion and continued in the period between perfusion and admission to the recovery room. In all of the cases where excess bleeding due to hypofibrinogenemia was encountered, the profibrinolysin and anti-fibrinolysin levels were found to be extremely low. The degree of hemorrhage often seems to be a function of the drop or activation of the profibrinolysin to a greater extent than of the reduction in fibrinogen. This was sometimes accompanied by extensive clot lysis or euglobulin lysis, but not consistently so.

This decrease in profibrinolysin and anti-fibrinolysin has been considered indirect evidence that the fibrinolytic enzyme has been activated even in those cases where no direct evidence of clot lysis is available. This picture has been seen in a wide variety of cases of hypofibrinogenemia; i.e. obstetrical accidents such as abruptio placentae and long-standing intrauterine fetal death,¹³ metastatic carcinoma of the prostate,¹⁴ general surgery¹¹ and intravenous injection of streptokinase as an activator of the fibrinolytic system.¹⁵

It is suggested that activation of the fibrinolytic system and subsequent destruction of the circulating fibrinogen is probably initiated by the release of tissue extracts and debris into the coronary sinus chamber of the pump. Most tissues contain potent activators of the fibrinolytic system and continued recirculation of blood through this chamber may be responsible for enormous fibrinolytic activity, as was seen in Case 4.

Treatment

The most important laboratory determinations in evaluating excessive bleeding after extracorporeal circulation are the

venous clotting time, protamine titration, prothrombin time and fibrinogen determination.

Excess protamine sulphate can be as dangerous as insufficient quantities. It is, in itself, an anticoagulant when present in excess and it also acts as an activator of the fibrinolytic system.⁷ It should not be given empirically, because of a prolonged clotting time or because bleeding seems to be excessive, without direct evidence of its need by protamine titration. If prothrombin times are elevated, administration of vitamin K may help to control excessive bleeding.*

When fibrinogen levels are low (less than 150-175 mg.%) and hemorrhage is an acute problem, 1.0 to 4.0 Gm. of fibrinogen, depending upon the weight of the patient, should be given intravenously as a first dose, followed by an additional amount should fibrinogen levels fail to rise. Tolidine blue or albumin may be useful in inhibiting fibrinolytic activity. Epsilon aminocaproic acid, although an efficient inhibitor of the fibrinolytic system, would seem to be contraindicated in these cases, in view of recent reports of subendocardial hemorrhages produced by slow infusion of this substance.** It is to be emphasized that a combination of decreased fibrinogen level and excessive hemorrhage should be demonstrated before fibrinogen therapy is instituted, since there is a definite risk of hepatitis from its use. However, fibrinogen therapy should not be delayed too long since, in this institution, no surgical patients have been saved whose fibrinogen levels have fallen below 100 mg.%.

Whatever other deficiencies in coagula-

tion factors may be present can be corrected by the administration of fresh blood. Therefore, such deficiencies as proaccelerin and antihemophilic globulin are, in most cases, being treated adequately by the usual blood replacement procedures employed in open-heart surgery.

Summary

1. A study has been made of coagulation factors during and after extracorporeal circulation using the DeWall bubble oxygenator and the disc oxygenator.

2. Prothrombin, proaccelerin and thromboplastin generation are impaired during perfusion while the patient is heparinized, but neutralization of the heparin usually restores these factors to normal levels in the immediate postoperative period.

3. Low fibrinogen levels and increased fibrinolytic activity were responsible for the cases of severe hemorrhage noted in this series and had similar features to a wide variety of cases of hypofibrinogenemia reported.

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* At the present time Polybrene is utilized for heparin neutralization in a dosage of one to one.

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