Problems in Hemostasis During Open-Heart Surgery: *

II. On the Hypercoagulability of Blood During Cardiac Bypass

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BLOOD is exposed to considerable trauma during cardiac bypass. Subjected as it is to filters, tubing and metal connectors, it is also subjected to the shearing force of oxygen bubbles, the mechanical action of a pump and the action of one or several cardiotomy suckers.

The effect of trauma on blood has been extensively investigated.[7, 10] It has, for instance, repeatedly been shown that during extracorporeal circulation the number of circulating platelets and red cells is greatly reduced. This presumably is the result of damage of these cells. The plasma hemoglobin level invariably rises. These products of blood cell destruction have been related to changes in vaso-motor activity and renal function.

In the present study the effect of the heart-lung machine alone on the blood was investigated. The previously noted changes in platelet number and plasma hemoglobin concentration were confirmed. In addition, it was shown that these changes resulted in the release of large quantities of a thrombo-plastin-like substance. The presence of this substance rendered the blood hypercoagulable. The consequences of the hypercoagulability of this blood are discussed with regard to changes in fibrinogen concentrations which occur in humans during extracorporeal circulation.

Methods and Materials

A. In Vitro Bypass Experiments. Four sets of experiments were performed. Four experiments were done with fresh heparinized dog blood, four with fresh ACD dog blood, two with fresh human ACD blood, and two with human plasma. The human blood was obtained from donors of the same blood type. The fresh human plasma was obtained from the blood bank. In each case the blood was drawn just prior to the start of the experiment.

Two types of oxygenators were used. They were a disposable bag oxygenator††† into which silicone stainless-steel sponges were inserted to aid in debubbling, and a DeWall-Lillehei bubble oxygenator of the type used on the clinical service of this hospital. Sigmamotor pumps were used in both set-ups and these pumps were set just to the point of total occlusion. No significant difference was found in the results obtained from these two oxygenators.

* Submitted for publication April 26, 1961; revised and resubmitted November 7, 1961.

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These studies are supported by U. S. P. H. S. grants.

††† Supplies by Travenol Laboratories.

TABLE 1. *Number of Platelets*

	Specimen No.				
	1	2	3	4	5
Dog blood I	264.000	232.000	120.000	120.000	80.000
Dog blood II	172.000	156.000	120.000	84.000	64.000
Dog blood III	360.000	220.000	160.000	136.000	112.000

Specimen 1—Obtained before starting the pump.
Specimen 2—Obtained 5 min. after starting the pump.
Specimen 3—Obtained 30 min. after starting the pump.
Specimen 4—Obtained 60 min. after starting the pump.
Specimen 5—Obtained 120 min. after starting the pump.

In all experiments the oxygenator was assembled and debubbled in a manner identical to that used in the preparation for open-heart surgery. The oxygenator was then primed with 1,200 to 1,500 cc. of the freshly drawn blood or plasma and the arterial line filled. This line was then connected to the venous inlet of the oxygenating column. The initial blood samples were drawn from the ventricular tubing of the pump-oxygenator and the pump was then started. The blood was recirculated through the oxygenator for two hours, with additional blood samples being drawn five minutes, 30 minutes, one hour and two hours after starting the pump. Flow rates varied from 900 to 1,650 cc. per minute.

B. In Vitro Study of the Effect of Erythrocyte and Platelet Stroma on the Clotting Process. Fresh human blood was obtained immediately before the experiment. Twenty cm.^{3} of the blood was collected in sodium citrate, 5.0 cm.^{3} in sequestrene. The blood was centrifuged and the plasma separated from the red blood cells and platelets. The platelets (obtained from the sequestrene blood) were suspended in 2.0 cm.^{3} of 0.9 per cent saline. The red blood cells (obtained from the citrate blood) in 10 cm.^{3} of 0.9 per cent saline. Both cell suspensions were twice quick frozen and thawed. The experiments were done with citrated plasma, physiological saline solution and disintegrated cell suspensions. Recalcification time and thrombin generation times (*vide infra*) were done on plasma-saline (10:1); plasma-disintegrated platelet suspension (10:1) and plasma-disintegrated red blood cell suspension (10:1).

TABLE 2. *Plasma Hemoglobin Concentrations in Mg. %*

	Sample No.				
	1	2	3	4	5
Dog blood III	0	14	46	89	191
Dog blood IV	5	21	121	158	277
Human blood I	5.5	17	43	81	147
Human blood II	0.5	9.5	36	73	137.5

The blood samples were processed for micro hematocrits, fibrinogen concentrations (K. Jacobsson[5]), plasminogen concentration (Norman[8]), plasminogen activator activity,[4] plasmin activity (Lassen[6]), platelet counts, thrombin times and thrombin generation times (Biggs and McFarlane[1]), plasma hemoglobin (Flink and Watson[3]) and recalcification times (Quick[11, 12]). Platelets counts were done on the heparinized blood samples only. Samples of this blood were drawn up in a white cell pipette and diluted with Reese Ecker solution. Subsequently, the pipette was placed in a mechanical pipette shaker for 15 minutes. Three separate counts were done on each individual blood sample. The average of three counts was taken as the platelet count of the sample.

Results

A. In Vitro Bypass Experiments: *Platelet Counts.* The platelet count invariably declined during the recirculation of blood through the pump oxygenator. The values found during the experiments are summarized in Table 1.

Plasma Hemoglobin Concentration. The plasma hemoglobin concentration increased as the blood continued to be circulated through the system. The values found during the experiments are summarized in Table 2.

Fibrinogen Concentrations. No significant changes were observed in the fibrinogen concentration during these experiments as appears from the fibrinogen values summarized in Table 3.

Plasminogen Concentrations. No significant changes were observed in the plasminogen concentration during the period of recirculation of the blood.

Plasmin and Plasminogen Activator Activity. There was no evidence of activation of plasminogen during the period of recirculation of the blood.

Recalcification Time and Thrombin Generation Time. The recalcification time became shorter during the recirculation of the blood as did the thrombin generation time (Table 4 and 5). These changes were absent when plasma was used instead of whole blood.

Thrombin Time. The thrombin times changed little; occasionally the values became slightly shorter during the course of the experiment.

B. In Vitro Study of Effect of Erythrocyte and Platelet Stroma on Clotting Process: *Recalcification Times.* Mixture of 0.1 cm.^{3}, 0.9 per cent saline with 1.0 cm.^{3} plasma control plasma gave a recalcification time of 187.7 sec. Mixture of 0.1 cm.^{3} platelet suspension with 1.0 cm.^{3} plasma gave a recalcification time of 59.2 sec. Mixture of 0.1 cm.^{3} erythrocyte suspension with 1.0 cm.^{3} plasma resulted in a recalcification time of 55.1 sec.

Thrombin Generation Time. Thrombin generation time of control plasma: 3 min. 16.9″; that of plasma and platelet suspension: 1 min. 12.2″, and that of plasma and erythrocyte suspension: 1 min. 12.2″.

TABLE 3. *Fibrinogen Concentrations in Mg. %*

	Specimen No.				
	1	2	3	4	5
Dog blood I	350	354	347	339	343
Dog blood II	250	250	246	250	238
Dog blood III	240	258	231	236	218
Dog blood IV	384	381	364	377	382
Human blood I	224	190	191	190	191
Human blood II	204	191	188	187	190
Human plasma I	216	210	212	219	219
Human plasma II	202	197	194	195	197

TABLE 4. *Recalcification Times in Seconds*

	Sample No.				
	1	2	3	4	5
Dog blood I	81.4	70.8	69	70.4	50.6
Dog blood II	99.0	58.0	—	20.0	33.0
Dog blood III	160.0	100.6	77.8	93.1	59.9
Human blood I	164.5	145.0	82.0	95.6	103.0
Human blood II	152.2	110.0	112.0	112.2	92.5

Discussion

Blood and plasma were recirculated through a pump oxygenator. During the course of the recirculation of the blood, several changes were observed in the clotting mechanism of this blood.

It was demonstrated that the number of platelets and red cells decreases. These changes were found to be associated with a rise in the plasma hemoglobin concentration. Simultaneously, there was found to be a marked shortening of the recalcification and thrombin generation times. Since the amount of prothrombin remains constant throughout these experiments, the data, summarized in Table 5, indicate the generation of considerable quantity of thromboplastin in the blood.

TABLE 5. *Thrombin Generation Time*

	Specimen No.				
	1	2	3	4	5
Dog blood I	3′38″	1′26″	1′18″	21.6″	24.6″
Dog blood II	3′30″	1′19″	18.5″	—	14.6″
Dog blood III	6′33″	1′28″	1′14″	15.3″	14.2″
Dog blood IV	2′39″	17.2″	13.3″	11.9″	13.2″
Human blood I	5′13″	2 19″	1′29″	1′26″	1′11″
Human blood II	2′46″	2′17	2′24″	2′11″	57″
Human plasma I	2′14″	2′20″	2′10″	2′13″	2′11″
Human plasma II	2′18″	4′20″	3′20″	2′16″	2′11″

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