Non-Surgical Hemorrhage Associated with Cardiopulmonary Bypass

by Robert Rodvien, M.D.*

The coagulation disturbances that can occur when cardiopulmonary bypass (CPB) is used for open-heart surgery can best be understood by comprehending the nature of the body’s response to a hemostatic challenge without CPB, and then by considering how the component steps of open-heart surgery may affect the hemostatic response.

I. Components of the Hemostatic Response (See Figure 1)

Blood remains liquid as long as its only exposure is to normal endothelial cells. Blood exposed to any other surface—biologic or otherwise—will alter its own contents to promote vasoconstriction; platelet adhesion, release and aggregation; and fibrinogen conversion to an insoluble latticework of fibrin. This sequence of events is invariant but can be qualitatively modified by a variety of things such as the musculature of the torn arteriole, the quality and quantity of flow, the lipids of the platelet membrane and plasma, the degree of tissue damage, capabilities of fixed and mobile histiocytic cells to remove activated coagulation factors, and the diet and drugs of the individual in whom hemostasis is challenged. The initial events occur in seconds to minutes and will favor platelet participation when the flow is large or turbulent. Sluggish or laminar flow tends to exclude the platelets; and then, the fibrin deposition consists of entrapped leucocytes and erythrocytes without a bridge of platelets between the altered vessel wall and the bulk of the thrombus. Thrombus dissolution normally occurs in days although this time scale can be compressed to hours if the enzymes of fibrinolysis are markedly activated. In the open-heart surgical suite, the focus should be upon the initial response of the blood. One major component of that early response is the platelet.

A. The Platelet

Platelets are small packets of highly active materials which are probably limited to an “all or none” response to any stimulus.1 If platelets are exposed to such diverse stimuli as collagen, thrombin, adenosine diphosphate (ADP), polyvinyl chloride (PVC) tubing, gas bubbles or silicone rubber, they will adhere to the “new” surface and spew out a number of extraordinarily active materials: vasoconstrictors, structural proteins, enzymes, cations, and ADP which prompt more platelets to adhere and undergo the so-called “release action.” Therefore the platelet reaction consists of the physical events of adherence to foreign materials, change in shape and aggregation to each other, and the biochemical reactions are mediated, at least in part, by the “second messengers” common to most cells: the cyclic nucleotides, the intermediates of prostaglandin synthesis, and the divalent cations. As part of this physical and biochemical response by the platelet, the cell’s membrane is altered so that while part of the platelet adheres to the rent in the endothelium, the nonadherent part of the same platelet accelerates the production of thrombin and ultimately fibrin which forms the bulk of the thrombus. The best tests of platelet adequacy are the platelet count and the bleeding time.

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B. The Clotting Factors

Thrombin formation can occur independent of the platelet’s presence. Any abnormal surface, with or without platelets, will cause contact-sensitive proteins in the blood to be retained by the surface, fragmented, and activated to cause another protein in greater amounts to be fragmented and activated. With each different protein’s activation, the amount of the next protein to be activated is increased and the time taken to be activated diminished; hence, the terms “cascade” and “waterfall.” By-products of this activation may modify thrombus formation or have other effects on the blood. The last protein in the cascade is fibrinogen, which is altered to fibrin and which in-turn does not activate other proteins as it forms an insoluble plug against the abnormal endothelium, silicone rubber or gas bubble.

One of the first proteins that interacts with the abnormal tissue or surface—Factor XII—undergoes adherence and proteolysis after which fragments are returned to the circulation. This protein can activate Factor XI or be enzymat-
TABLE 1
FACTORS IN NON-SURGICAL HEMORRHAGE

| 1. Congenital Diseases: | Hyperlipemia, congenital Heart Disease |
| 2. Non-cardiac Diseases: | “Storage Pool” Disease, Liver Disease |
| 3. Drugs: | Anticoagulants, Platelet Suppressive Drugs, Antiarrhythmics, Antibiotics |
| 4. Surgical Procedure: | Site of Incision, Anatomical Repair to be Made, Reoperation (?) |
| 5. Anticoagulation: | Amount of Heparin and Protamine |
| 6. Quality of “Bypass”: | Pump Time, Type of Oxygenator, Quality of the Prime, Extent of Coronary Suction, Hemolysis, Hypothermia |
| 7. Transfusions: | Filter |

ically active in other “cascade” systems; i.e., the kinin, complement, and fibrinolytic systems (see Figure 2). Excessive fibrinolysis is said to occur frequently during CPB (3). When activated, the complement and kinin systems also result in potentially active fragments. Their creation during surgery has not been identified nor have their effects been measured.

II. Components of the “CPB Event” in Man (See Table 1)

CPB is more than using a “heart-lung machine.” In a narrow sense, the term encompasses several intraoperative events in one, all of which can affect the coagulation mechanism. More broadly speaking, comprehension of the events that occur during CPB demands consideration of the preoperative condition of the patient. Rather substantial bleeding is accepted as part of the modality of CPB, and is assumed to be secondary to anatomical bleeding exacerbated by an expected mild coagulopathy. This bleeding is to be distinguished from the nonsurgical causes of hemorrhage in which a hemostatic defect produces diffuse, unexpected and unacceptable bleeding.

Either form of hemorrhage can be enhanced by:

(1) the patient’s non-cardiac ills: the extent of chronic passive congestion, and the complexities of his genetic endowment;

(2) the drugs given to the patient; antiarrhythmics, anti-coagulants, platelet-suppressive drugs, preoperative and anaesthetic agents, and antibiotics;

(3) the variables of surgery: the site of incision, the operation to be done (repair of septal defect, valve replacement, aortocoronary bypass), the number of prior operations on the heart;

(4) the quantity of heparin and the use of protamine sulfate;

(5) the quality of the CPB: time of CPB, oxygenator, quality of the prime, extent of coronary suction, hemolysis, and hypothermia;

(6) the use of blood components with or without a filter; and

(7) the surgical team.

Many, but not all of these parts of the “CPB event” are known to affect the extent of hemorrhage during and after CPB.
It should be emphasized that all individuals who undergo CPB have a major coagulation disturbance. The question is not whether or not a disturbance exists, but rather (1) for the individual patient, which of the disturbances is promoting any excessive bleeding, and (2) for these patients as a group, which of the changes in the components of blood normally necessary for hemostasis are producing more subtle morbidity to the patient by affecting his post-operative mental and physical health. The latter problems will not be dealt with any further in this paper. The question of properly associating a measured coagulation change with unacceptable bleeding is germane to this talk. The mere definition of a change in coagulation status does not mean that the change gives information about why the patient is bleeding.

A. Intraoperative Components of CPB Which Affect Hemostasis
(See Table 2)

In our experience and those of most other observers, thrombocytopenia and a decrease in fibrinogen concentration are essentially universal. A mechanism to account for both these events is Disseminated Intravascular Coagulation (DIC), i.e., thrombin excess. Alternatively, platelets and fibrinogen may be independently altered by CPB and sequestered on foreign surfaces or in the liver. In addition, circulating platelet aggregates theoretically may form as ADP is released from hemolyzed erythrocytes. Such aggregates may cause organ dysfunction wherever they lodge. In the usual CPB, despite the desire to employ Ocham's razor, the independent mechanisms to account for the changes in platelet and fibrinogen levels, is much more likely.

Platelets will adhere to any foreign surface, be it solid or gaseous (see Figure 3). In bubble oxygenators the constantly forming new bubbles continue to alter platelets so that in routine CPB, the longer the bypass, the worse the thrombocytopenia. Those platelets that do circulate may not be maximally competent: those platelets do not perform normally in the glass bead retention test and aggregate poorly. Transient platelet retention and its consequence (intermittent microembolization with endarteriolar occlusion) may be one of the coagulation disturbances induced by CPB which has been difficult to define and yet may have profound long-range effects on each patient's complete health status. Filters have been used in an attempt to prevent the direct consequences of circulating platelet aggregates. One price that is paid when these filters are used is that the
TABLE 2

NON-SURGICAL CAUSES OF BLEEDING DURING OPEN-HEART SURGERY

| A. Thrombocytopenia | B. Platelet Function Defect | C. Heparin Excess/Rebound | D. Fibrinolysis | E. Protamine Excess | F. Thrombin Excess (D.I.C.) |

Thrombocytopenia is more severe. In addition, any material that activates platelets leads to plasma substances that are vasoactive if not toxic to the endothelium. This problem is exacerbated by the added surface of the filter. A blocked filter re-introduced into the circulation can cause transient but profound hypotension, presumably because of released substances from the platelet.

I have emphasized the decrease in platelet numbers (thrombocytopenia), and the impaired function of platelets which circulate (thrombopathy), because platelet problems are the most common cause of non-surgical hemorrhage in the open-heart surgical suite. In individuals with cyanotic congenital heart disease, the thrombocytopenia and thrombopathy may precede the surgery. Therapy consists of component platelet transfusion. The platelet problems are exaggerated by the hemodilution of the prime and usually made worse by the preoperative situation of the patient; specifically, the presence of liver disease or the use of platelet suppressive drugs such as aspirin.

Finally, the quality of CPB may have profound effects on hemostasis in ways that have not been fully explored. Gasliquid interfaces caused by the oxygenator and exaggerated by coronary suction may denature the coagulation proteins producing impaired hemo-

stasis and possibly inappropriate thrombus generation. Sternotomy may expose the blood to tissue factors and lipids which can alter the substrates of hemostasis—the platelet membrane and coagulation factors—to be more or less sensitive to hemostatic challenge.

B. Heparin’s Effects

None of the effects of CPB on the platelet as alluded to above are heparin-sensitive. Heparin is given because without it, the surface-induced activation of the coagulation cascade would clot the blood so that all of the other events would have to be considered theoretical irrelevancies. In our hospital we give 3.5 mg/kg heparin I.V. bolus and will not give any more unless 1) the CPB lasts more than 2 hours and 2) the ACT is less than 400 to 500 seconds. At that time 1 mg/kg heparin is given. The only other heparin that is given is in the blood transfusions given during CPB. The variability in technique from hospital to hospital makes it very difficult to compare the problems of CPB. For all CPB, heparin is absolutely essential. It accelerates the destruction of activated coagulation factors and therefore prevents thrombin production. Any thrombin generation not only insolubilizes fibrinogen as thrombus, but also consumes platelets and generates plasmin. “Thrombin excess” is the most feared of the forms of non-surgical bleeding but it is also relatively uncommon. In this situation—“DIC” if you will—bleeding and clotting occur simultaneously. A working laboratory definition of “DIC” is the documentation of a fall in circulating fibrinogen concentration and platelet numbers associated with a rise in fibrinogen split products. “Thrombin excess” (DIC) and “plasmin excess” (primary fibrinolysis) should therefore be distinguishable because platelets are spared in hyperplasminemia (see Figure 3). Proper management of thrombin
excess requires more heparin. Hence, it must be distinguished from bleeding caused by excess heparin in which the therapy is to reverse the "heparin effect." The distinction is made by laboratory tests alone since the clinical bleeding patterns of too little and too much heparin may be virtually indistinguishable.

Excess heparin, like excess thrombin, is also an unusual cause of bleeding; individuals have variable sensitivities to this anticoagulant. Excess heparin levels can occur after hypothermia is reversed and heparin is released from fat stores, but this event is well-known and rarely results in unexpected bleeding.

Even when the quantity of heparin is not excessive, we believe heparin may contribute to a bleeding diathesis. We have found that heparin can cause loss of platelet function when given in smaller doses than those given in most CPB procedures. The template bleeding time (TBT) is presently the most sensitive indicator of in vitro platelet dysfunction available. As shown in Figure 4, 10 minutes after 100 u/kg I.V. heparin is given the TBT prolongs, and in some instances markedly so. In this short period of time platelet counts after heparin do not change. We have no explanation for this phenomenon, but it may involve the same prostaglandin mechanism that aspirin affects. This effect of heparin may be an important part of the "thrombopathy" of open-heart surgery.

C. Protamine Excess

There are other aspects of intraoperative procedures that can affect the extent of perioperative coagulation problems. Protamine is frequently used to reverse heparin but it too has "anticoagulant" properties. Furthermore, it may exaggerate the thrombocytopenia especially when used in conjunction with heparin.

We have found that protamine excess has been one of the more common causes of non-surgical bleeding following CPB. In our hospital we have recently lowered our dose of protamine to 2.0 mg/kg followed by an optional 1 mg/kgm protamine one-half hour later. This regimen has markedly diminished the extent of chest tube and wound bleeding seen in the post-operative period.

D. Plasmin Excess

Some workers have found that primary fibrinolysis occurs frequently with CPB and advocate that this phenomena is the major contributor to post-operative bleeding. However, mild reductions in plasminogen with the apparent production of plasmin occurs very commonly in CPB, while unacceptable bleeding is unusual. In addition, prevention of fibrinolysis with Amicar® has not decreased the bleeding seen with CPB.

I believe that changes measured in the fibrinolytic mechanism are epiphenomena, akin to elevation of the sedimentation rate with infection, and do not
explain the usual quantity of bleeding or the occasional instance of markedly exaggerated bleeding seen with CPB.

E. Pre-operative Components of CPB which Affect Hemostasis
(See Table 1)

The pre-operative status of the patient is extremely important in determining the extent and quality of CPB bleeding. Congenital abnormalities of the coagulation process sufficient to cause problems are relatively uncommon and can be determined by taking a history and obtaining a partial thromboplastin time (PTT). The “storage pool diseases” of platelets—inflicted or acquired—are being recognized much more frequently and, if suspected from the history, a template bleeding time should be done. There is good reason to suggest that a TBT be done in all patients before CPB. Drugs which are “platelet-suppressive” such as indocin, clofibrate, and sulfipyrazone should be stopped the day before operation, and aspirin should be avoided for the week before surgery because of its prolonged irreversible effect on the circulating platelet. A good screen for these drug effects on platelets is the TBT.

Liver disease secondary to heart failure or from an independent cause can seriously compromise the body’s needed response to surgery in many ways. The thrombocytopenia of CPB can be exaggerated by hepatic and/or splenic sequestration, or impaired folate stores. The vitamin, folic acid, is necessary for the marrow to make platelets. The capacity to restore depleted circulating coagulation factors can also be compromised by impaired hepatic storage and/or synthesis of these proteins. Prior coumadin administration may exaggerate this last problem. The effects of Keflin, Penicillin, Atropine, Quinidine, propranolol, and many other drugs used prior to or with cardiac surgery may not be as insignificant on the platelet as is often presumed.

F. Cyanotic Congenital Heart Disease (CCHD)

The problems posed by cyanotic congenital heart disease (CCHD) deserve special attention. Some investigators have found that the fibrinolytic mechanism is activated. This coagulation disturbance does not explain the low platelet count or abnormal platelet function that is frequently observed. In addition, these patients have a long PTT which can be explained only partially by technical difficulties in determining the proper amount of anticoagulant to use in the test. People with CCHD frequently have elevated venous pressure which persists post-operatively and may cause “anatomical” bleeding independent of a coagulopathy. These same individuals are also often poorly nourished, and frequently need a second or third operation. Re-operation, for any reason, is frequently associated with increased post-operative bleeding which in part reflects the need for dissection of fibrous tissue.

III. What to Do (See Table 3)

For those who have lived with it, hemorrhage during and shortly after CPB really fits the expression: “An ounce of prevention is worth a pound of cure.” A history of significant prior bleeding, the use of drugs, and the extent of hepatic competence, are all important determinants of how hemostatically competent the patient will be. A minimal work-up includes a platelet count and PTT, and I would add a TBT and prothrombin time as well. A simple prophylactic thing to do is to save properly collected blood samples in the lab preoperatively if there is a clinical suspicion of future problems. These tests need not be run unless bleeding occurs at which time compari-
TABLE 3

Potential Coagulation Tests for Use Before, During and After Cardio-Pulmonary Bypass (CPB)

<table>
<thead>
<tr>
<th>BEFORE CPB</th>
<th>WHEN BLEEDING OCCURS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Platelet Count</td>
<td>Y</td>
</tr>
<tr>
<td>B. Template Bleeding Time</td>
<td>Y</td>
</tr>
<tr>
<td>C. Platelet Sizing</td>
<td>?</td>
</tr>
<tr>
<td>D. Prothrombin Time</td>
<td>Y</td>
</tr>
<tr>
<td>E. Partial Thromboplastin Time</td>
<td>Y</td>
</tr>
<tr>
<td>F. Thrombin Time</td>
<td>?</td>
</tr>
<tr>
<td>G. “P.S.” Corrected Thrombin Time</td>
<td>N</td>
</tr>
<tr>
<td>H. Plasminogen/Plasmin Levels</td>
<td>N</td>
</tr>
<tr>
<td>I. Fibrinogen) Split Products</td>
<td>N</td>
</tr>
<tr>
<td>J. Soluble Fibrin Monomers</td>
<td>N</td>
</tr>
<tr>
<td>K. Fibrinogen Level</td>
<td>N</td>
</tr>
</tbody>
</table>

INVITRO EFFECT OF HEPARIN ON COAGULATION TESTS

Figure 5. In Vitro Effect of Heparin on Coagulation Tests
sons can be made with freshly drawn intraoperative specimens.

Intraoperative bleeding is well-described by another adage: "He who hesitates is lost." If non-surgical excessive bleeding is suspected during surgery, collect specimens for a platelet count, prothrombin time, partial thromboplastin time, thrombin time, protamine sulfate corrected thrombin time, fibrin split products, fibrin monomer, and fibrinogen. Check for "risk factors" (such as reoperation) and give platelets. Consider protamine. Heparin and Amicar® are rarely needed and certainly should not be used first. Establish good quick contact with the lab.

The aim of the above tests is to diagnose the reason for bleeding. I have mentioned therapy first because therapy precedes the definitive diagnosis of bleeding in the "open-heart" suite. The tests’ interpretations can be made only in the context of how much heparin and protamine have been given. The PT is relatively unaffected by either drug but is sensitive to rapid thrombin excess, depleting Factor VII. The PTT is more sensitive and the thrombin time most sensitive to heparin (see Figure 5). If protamine corrects the thrombin time, there is heparin excess. We have not found that rapid lysis of the clot observed when doing the thrombin time is a good measure of clinically important fibrinolysis. The presence of fibrin monomers or fibrin split products occurs most frequently with DIC; i.e., thrombin excess. The platelet count is expected to be low but once again, the degree of thrombocytopenia is variable, and the first step in the therapy of uncontrolled non-surgical hemorrhage in the open-heart suite is platelet transfusion.

Post-operative excessive hemorrhage is usually surgical bleeding. There is no doubt, however, that the extent of the bleeding can be greatly influenced by preoperative aspirin and other drugs, or over-utilization of protamine intra-operatively.

The work-up, and therefore therapy, is the same as described above.

IV. Summary

When correction of a ventricular septal defect could first be done 25 years ago, all else was acceptable since the procedure gave the patient life! We should now be thinking about the quality of the life we’re giving. At present we accept a great deal of morbidity—early and late—with this procedure. Much of the morbidity may be due to altered plasma proteins and blood cells of the coagulation system producing distal effects on the brain and other organs. We are only beginning to identify these non-coagulation events medicated by the coagulation proteins and platelets. Excessive morbidity also occurs immediately. We should strive to diminish the coagulopathy of CPB which increases bleeding during CPB. Work is progressing rapidly in new oxygenator designs with less surface area, better non-thrombogenic surfaces, and extremely small transit times. Perhaps in future years, many of the coagulation disturbances of CPB which I’ve discussed here will be non-existent or, at least highly modified so that hemorrhage, DIC, protein denaturation, and platelet embolization and release will be "ancient history."
REFERENCES


