Practical control of hemostasis

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Hemostasis is a tripartite function depending on vascular integrity, platelet function, and coagulation factors. Bleeding represents a defect in hemostasis, and abnormal bleeding represents blood loss in excess of what could be expected in a given patient at that stage in the procedure. For example, during cardiopulmonary bypass the hemostatic mechanism is essentially totally paralyzed by heparin and that is to be expected. Following bypass termination and heparin reversal, total hemostatic paralysis is not to be expected and would require evaluation and treatment before the chest could safely be closed. Evaluation of abnormal bleeding must include an examination of all three parts of the hemostatic mechanism.

This review is divided into four parts: (1) preoperative evaluation; (2) intraoperative period, prebypass and intrabypass; (3) intraoperative period, bypass, and postoperative period; and (4) an approach to the bleeding patient.

Preoperative evaluation

The best method for detecting hemorrhagic diathesis is a properly taken history. One of the most important items to be checked in the history is the hemostatic response to a prior surgical experience. With respect to any bleeding episode, the history

should establish severity, site, duration, and etiology as well as similar episodes, age at onset of symptoms, family history, and any related information the patient may think relevant. Especially important in the history is a detailed record of drug ingestion. In addition to asking about the use of aspirin, drug history should include details about occupation and exposure to toxic agents or ionizing radiation. The age at onset is an equally important clue with bleeding problems starting in infancy or early childhood, suggestive of a congenital defect.

Physical examination may detect evidence of a hemorrhagic diathesis. Petechiae or prolonged bleeding following superficial trauma are usually due to vascular or platelet abnormalities. In contrast, the subcutaneous bleeding that occurs in deficiencies of coagulation factors is usually an ecchymosis as opposed to discrete petechiae seen with vascular or platelet abnormalities. Hemarthrosis or deep bleeding into muscles is more likely to occur with a coagulation factor deficiency.

A screening coagulation profile on any patient scheduled for cardiovascular surgery, or any patient whose history is suggestive of hemorrhagic diathesis, is essential. One such profile includes prothrombin time (PT), activated partial thromboplastin time, platelet count, fibrinogen level, and bleeding time. In the operating room a baseline whole blood coagulation or an automated activated coagulation time may be performed. Although the yield from such a profile may be low, the advantage of not having to include a preexisting defect in the differential diagnosis of a bleeding disorder that occurs intraoperatively justifies the effort. With a negative history and a normal screening coagulation profile this is a valid assumption.[1]

The first step in laboratory analysis of hemostasis is obtaining a blood specimen, which must be done with the same attention to detail as performing the actual test. Venipuncture should be accurate and atraumatic to avoid introducing tissue juice. One way to insure this is to use a two-syringe technique in which the first syringe is discarded after 2 ml is obtained; a second syringe is attached to the indwelling needle to collect the sample. An alternate approach is the use of indwelling arterial or central venous lines. These lines may contain heparin flush solutions; the frequent contamination of samples of heparin has prompted many laboratories to proscribe samples for coagulation tests being obtained from such lines. This proscription is not necessary if samples are collected with the same attention to detail as with venipuncture collection. It is particularly important to withdraw an adequate aliquot before collecting a sample. In an arterial line with a deadspace of 2.0 cc between patient and sampling port, withdrawing 4.0 cc before collecting the sample will eliminate the chance of heparin contamination.[2] Additionally, the use of indwelling lines around which hemostasis has been secured will obviate the need for venipuncture, with its attendant introduction of another defect in vascular integrity.

An increasing number of mechanical devices are available to perform coagulation tests, with the end point being measured by electrical, magnetic, mechanical, or optical methods. Although these machines have the advantage of reducing human variability in a given test, they are more expensive except in large volume laboratories. However, an

automated activated coagulation time device, and a machine for measuring thrombin time are being used in the operating room with success.[3, 4]

Intraoperative period, prebypass and intrabypass

The use of heparin to prevent blood from clotting on exposure to the foreign surface of the heart-lung machine is essential. Bull et al[5] clearly showed the value of individualizing heparin dosage when they demonstrated a threefold variation in patient sensitivity, i.e., the degree of prolongation of coagulation in response to a given dose of heparin and a fourfold variation in heparin decay rates. The administration of heparin via a central line, aspirating before and after the heparin injection, and demonstrating the heparin effect with some coagulation parameter are recommended to insure that the potentially lethal complication of intrabypass clotting does not occur.

What constitutes the therapeutic range for cardiopulmonary bypass remains controversial. In long-term use of the extracorporeal membrane oxygenator for treatment of respiratory insufficiency, there is minimal introduction of damaged tissues or tissue juice into the circulation, and an activated coagulation time in the range of 180 to 200 seconds has proved to be a safe lower limit.[3] In routine cardiopulmonary bypass, Bull et al[6] have found that with a manual activated coagulation time in excess of 300 seconds, blood does not form even small clots after the conclusion of bypass, and have recommended that level as a safe limit.

More recently Young et al[7] advocated keeping the automated activated coagulation time above 400 seconds, using as their criteria the appearance of fibrin monomer and suggesting that monitoring the appearance of fibrin monomer is a more sensitive microscopic method for activation of the coagulation process than looking for formation of gross clots. Heparin levels that prolong the activated coagulation time to >300 to 400 seconds do not render the blood infinitely incoagulable, and care must be taken to ensure that heparin levels remain sufficiently elevated throughout bypass. The best means of ensuring this is serial measurement of any of several coagulation parameters.

Among the factors that may affect heparin requirements, the confusion of milligrams versus units of heparin and temperature are perhaps the most common. A unit of heparin is defined as the amount required to prolong the coagulation of 1.0 cc whole blood for 3 minutes. Beef lung heparin contains not less than 140 μ/mg and porcine mucosa heparin contains not less than 120 μ/mg. To minimize confusion heparin doses should be expressed in terms of units, not milligrams. With respect to temperature, Cohen et al[4] have confirmed the suggestions of others that the half-life of heparin is prolonged with cooling and, in fact, with temperatures below 25 C heparin decay is almost totally arrested. For this reason doses of heparin need not be administered as frequently, if at all, during total body hypothermia. Equally important, with rewarming, heparin levels must be monitored in some way to ensure heparin effect.

Intraoperative period, postbypass, and postoperative period

The six "Ps" of hemostasis in patients following cardiopulmonary bypass in order of decreasing importance are prolene, protamine, platelets, plasma, pressure/patience. In addition, fibrinolysis, disseminated intravascular coagulation and breaks in technique are other potential causes of defective hemostasis.

Protamine-heparin interaction. Al-

though much of the confusion surrounding heparin requirements was eliminated with demonstration of the need for individual variation of dose, protamine requirements remain a confused and controversial area. There are two principal areas of confusion. The first area deals with the failure, when giving heparin:protamine formulas, to specify how much heparin is to be neutralized; the initial dose, the initial plus any supplemental doses, the initial and supplemental plus any heparin added to the pump prime.[8] The second area of confusion is the question of the anticoagulation properties of protamine. In vitro, protamine will retard clot formation. Following cardiopulmonary bypass in patients, Guffin et al[9] have shown that excessive doses of protamine produce increased chest bottle drainage, as well as prolonged closure time, the latter presumably being related to the increased oozing seen with excess protamine. In vitro, protamine has been shown to impair platelet aggregation in response to adenosine diphosphate, and this may explain the bleeding problems that occur after excessive doses of protamine.[10] Individualization of protamine doses is just as essential as individualization of heparin doses. Using a 1.0:1.0 heparin: protamine ratio based on the total dose of heparin administered to the patient, but not to the pump prime, and then checking for heparin effect is an effective, conservative way of neutralizing heparin. If heparin effect is noted, additional protamine is administered and blood is again checked for heparin effect.

Should excessive bleeding, which is not due to obvious inadequate surgical hemostasis, occur later in the closure, or postoperatively, blood should again be checked for heparin effect. Heparin rebound, which is defined as the recurrence of heparin effect in blood after laboratory-demonstrated adequate neutralization with protamine, has been described up to 24 hours after heparin neutralization, and is especially likely to occur in the first 4 to 6 hours after neutralization.[11] Although the occurrence of heparin rebound is probably a relatively rare event in the usual clinical setting, the diagnosis is easily made by means of an activated coagulation time and a protamine titration; and specific, simple treatment with protamine is readily available.

Platelets. A consistent finding in studies of hemostasis has been a decrease in the platelet count during cardiopulmonary bypass. The major portion of this decrease occurs during the first 2 to 5 minutes of bypass, and has been shown to be associated with a decrease in platelet adhesiveness.[12] This thrombocytopenia, which is the most dramatic and consistent change in hemostasis associated with cardiopulmonary bypass, may in part be due to hemodilution. However, platelet aggregation on foreign surfaces (mechanical equipment), platelet sequestration, and/or platelet destruction may also be factors contributing to the drop.[13, 14]

In addition to the reduction in platelet counts, studies in some patients have shown a change in platelet function. Bachmann et al,[15] in a prospective study of hemostasis and extracorporeal circulation found inadequate surgical hemostasis to be the principal cause of excessive bleeding. In those cases where there was a generalized hemostatic defect, they frequently found a qualitative platelet function defect, which did not correlate with bypass duration, drop in platelet count, or concentration of circulating fibrin split products.[16]

The management of patients in whom platelet quantity or quality may be contributing to excessive bleeding postbypass requires the administration

of platelet concentrates. However, the routine use of this blood product following open heart surgery is both unnecessary and wasteful of a blood component in short supply.[17] In patients who have platelet counts less than 50,000 to 70,000, and in whom there is excessive bleeding, the use of platelet transfusion to raise the count is indicated. Although the increment in platelet count per unit of platelets infused is extremely variable, an increase of 5,000 to 10,000 platelets/mm^3 for each unit of platelet concentrate infused is a reasonable estimate. Platelets stored at 22 C have been reported to survive longer after transfusion. However, platelets stored at 22 C do not function as well for the first few hours after infusion and, therefore, platelets stored at 4 C would appear to be indicated to treat patients who are bleeding due to a qualitative or quantitative platelet defect.[18]

Plasma. Fresh frozen plasma is one blood product which, because of its long shelf life, is in abundant supply and often used. However, the need for fresh frozen plasma on a routine basis has never been demonstrated.

Fibrinogen, fibrinolysis, and disseminated intravascular coagulation. Fibrinogen levels usually decrease to some degree during bypass, and this decrease is associated with an increase in fibrin split products. Together with the aforementioned decrease in platelets, this triad would suggest that at least limited disseminated intravascular coagulation occurs, which may be due to inadequate heparinization, inadequate perfusion, or other causes. Other potential causes for this triad include (1) hemodilution with nonblood product primes, (2) mechanical destruction of platelets and clotting factors by the oxygenators and pumps, and (3) effects related to a primary fibrinolysis associated with cardiopulmonary bypass.

Many studies have demonstrated an increase in fibrinolytic activity in association with extracorporeal circulation, though not necessarily associated with pathologic bleeding, and some investigators have advocated the regular use of epsilon aminocapoic acid in these cases on the basis that primary fibrinolysis routinely occurs.[19] If the case is one of primary fibrinolysis, then the use of epsilon aminocapoic acid is logical. However, if the case is one of secondary fibrinolysis, then the use of epsilon aminocapoic acid may result in a thromboembolic catastrophe.[20] Since the incidence of primary fibrinolysis is low, and that associated with extracorporeal circulation is infrequently associated with excessive bleeding, withholding epsilon aminocapoic acid therapy is both logical and conservative.[1]

Breaks in technique. The diagnosis of a break in technique may present a particularly difficult diagnostic problem in the first of what can become a series of cases. Diligent investigation may be necessary to identify the problem. Brooks and Bahnson[21] reported an "epidemic of hemorrhage following cardiopulmonary bypass" in which six consecutive patients averaged 2852 cc blood loss versus an average of 562 cc for patients before and after the epidemic. The epidemic ceased abruptly when soaking in 20% sodium hydroxide was added to the technique of cleaning a reusable pump oxygenator. Although unable to identify precisely the cause of the outbreak, they suggested that contamination with a sterile pyrogenic plasminogen activator may have been the cause. Examples of other breaks in technique include the use of the wrong concentration of heparin, and the wrong

conversion factor for milligrams of heparin to units of heparin.

Pressure/patience. Reduction in pressure to decrease bleeding is a well-accepted technique. Equally important is the avoidance of hypertension with its threat of stressing vascular suture lines with possible catastrophic results.

A definite cause for excessive bleeding may not be identified. Patience in the management of these cases, and the administration of appropriate fluids and blood components in adequate volumes occasionally may be necessary for many hours to achieve a favorable outcome.

Prolene (inadequate surgical hemostasis). If a patient has been adequately heparinized during bypass to prevent consumption of coagulation factors and platelets necessary for hemostasis postbypass, if the heparin has been adequately neutralized with protamine as measured by a protamine titration, and if a repeat coagulogram is normal in the face of continued excessive bleeding, reexploration with the anticipation of finding a break in vascular integrity is indicated.[15] The possibility of inadequate surgical hemostasis must not be ignored even when there are other reasons for abnormal hemostasis. It should be emphasized that in surgical bleeding clots do form and may plug the chest tubes, leading to a hidden blood loss greatly in excess of the measured loss. However, even when coagulation test results are normal, it is not rare to fail to discover a discrete bleeding vessel on reexploration even in the presence of moderate bleeding.

Summary. Adequate preoperative evaluation, heparin administration with demonstration of its effect before and throughout bypass, protamine neutralization of heparin postbypass, and meticulous surgical hemostasis will prevent most cases of excessive bleeding. However, when excessive bleeding does occur despite these precautions, several tests will facilitate rapid evaluation and guide to therapy (*Table*).

These tests can be performed quickly and reliably. The whole blood coagulation time can be readily performed in the operating room or intensive care unit while blood is being transported to the laboratory for other tests. No elaborate equipment or special reagents are necessary for whole blood coagulation time, which can yield meaningful results if properly performed. The clot can then be observed for retraction (a rough measure of platelet function) or lysis. Care must be taken not to confuse the dissolution after vigorous shaking of a weak, friable clot due to hypofibrinogenemia from true fibrinolysis. A fibrinogen level obviously assists in making this distinc-

Table. Tests to evaluate excessive bleeding

Test	Comment
Whole-blood coagulation time or activated coagulation time	Can be done in operating room; observe for clot retraction and lysis
Fibrinogen level	Depressed in disseminated intravascular coagulation
Prothrombin time	Prolonged in hepatic disease; vitamin K deficiency, coumarin anticoagulation, disseminated intravascular coagulation
Activated partial thromboplastin time	Prolonged in Factors V and VIII deficiences (massive transfusion), the hemophilias, or in the presence of heparin
Platelet count	
Bleeding time	Platelet function

tion, and forms part of the triad of screening tests for disseminated intravasculature coagulation (along with the prothrombin time and platelet count). In addition to its value in screening for disseminated intravascular coagulation, the prothrombin time is of value in diagnosing hepatic disease, vitamin K deficiency, or small doses of coumarin. The activated partial thromboplastin time and prothrombin time will be abnormal with higher doses of coumarin. Similarly, the activated partial thromboplastin time will be prolonged with small doses of heparin, and both the prothrombin time and activated partial thromboplastin time will be prolonged with higher doses of heparin. The bleeding time is especially valuable in these instances where the quality rather than the quantity of platelets is in question.

As with any laboratory determination, serial tests are of value in making a diagnosis and in assessing the response to therapy. This is especially true when initial screening test results were obtained preoperatively to serve as baseline values. Goal-directed therapy is dependent on accurate diagnosis. With the development of specific factor concentrates eliminating the need for a shotgun approach with fresh frozen plasma, and the danger of volume overload, the need for a specific diagnosis is essential. With the tests available today, such a specific diagnosis is almost always possible.

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