Bleeding and coagulation: Monitoring and management

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Introduction

Manipulations of the coagulation system before, during, and after cardiopulmonary bypass (CPB) are an integral part of the management of patients undergoing cardiac surgery. As the field of pediatric cardiac surgery has progressed toward total corrective or major palliative procedures in younger children with more complex congenital defects, it has become apparent that post-CPB coagulopathies and bleeding are disproportionately greater in these smaller children compared to adolescents or adults and require aggressive intervention to correct. Therefore, in children, management of coagulation during cardiac surgery takes on a magnified importance. The ability to restore hemostasis after CPB in children must begin with a knowledge of their baseline coagulation parameters and an understanding of the coagulation changes associated with CPB. Patient and surgical factors that are associated with post-CPB bleeding as well as coagulation tests that are predictive of this bleeding should be identified. Finally, an appreciation of the consequences of ongoing post-CPB bleeding and an awareness of the transfusion and pharmacologic strategies available to attenuate this bleeding are essential to successfully restore balance to the coagulation system in children after CPB.

Baseline coagulation parameters

The baseline coagulation status of neonates and infants is greatly influenced by maturational factors and by pathophysiologic disturbances that accompany congenital heart defects.

Maturational factors

At birth, the coagulation system is immature and continues in a state of maturation throughout the first year of life. Significant deficiencies in levels of the vitamin K-dependent factors (II, VII, IX, and X) and the contact factors (XI, XII, pre-kallikrein, and high-molecular-weight kininogen [HMWK]) exist at birth. Hepatic immaturity with decreased factor synthesis and accelerated clearance of factors by increased basal metabolic rates in children are cited as causes of these deficiencies. Most of these procoagulant factor levels at birth are only 40% to 50% of those found in adults and do not reach adult levels until later than 6 months of age (Fig. 10.1). Essentially all of the inhibitors of coagulation are also present in low levels during the first year of life. At birth, protein S and C levels are less than 40%, heparin cofactor II levels are 45%, and antithrombin III (ATIII) levels are 60% of adult values and, again, do not attain adult levels until after 6 months of age. Only platelet counts and levels of fibrinogen, factors V, VIII, von Willebrand factor, and XIII are at adult ranges at birth. However, evidence exists that platelet aggregation is impaired and that fibrinogen exists in a dysfunctional “fetal” form in newborns even though these factors are not quantitatively deficient. Thus, qualitative immaturities add further to the precariousness of a newborn’s coagulation system.

In light of these quantitative and qualitative deficiencies, the functional integrity of the coagulation system in young infants could be questioned. Fortunately, however, the results of most coagulation tests, including prothrombin time (PT) and thrombin clotting time, are within normal adult ranges within a few days after birth. Only the activated partial thromboplastin time (aPTT) is prolonged for a substantial time before falling to adult ranges at about 3 months of age. The dependence of the aPTT on the actions of several of the deficient vitamin K-dependent and contact factors may explain its initial prolongation. The maintenance of normal coagulation tests in early infancy may result from a relative balance achieved by the simultaneous immaturities of both the coagulation factors and their inhibitors during this period. If anything, the process tends towards increased coagulability. Thromboelastography (TEG) actually has shown that neonates and infants clot faster and have increased clot strength compared to adults. Despite the maintenance of the functional integrity of the coagulation system in infants,
of coagulation factors. Finally, it should be remembered that drugs with platelet inhibiting properties, such as prostaglandin E₁ (PGE₁) and aspirin, are not uncommonly administered to children with cyanotic heart defects and may further impair their coagulation systems.

Interestingly, young children with cyanotic heart defects appear to develop a hypercoagulable state prior to the onset of polycythemia. Evidence for this is seen in the trend for increased levels of platelets, fibrinogen, and factors V and VIII in these children, and could help explain findings in the early literature of pulmonary thrombi in infants with cyanotic defects who died before the onset of polycythemia. Therefore, children with cyanotic heart defects are subject to the opposite extremes of coagulation problems depending on the progression of their pathophysiology.

Coagulation changes associated with cardiopulmonary bypass

The use of CPB introduces variables that can significantly alter the coagulation status of all patients. The hemodilution encountered upon commencement of CPB can be extreme and can critically modify the delicate hemostatic equilibrium that exists in young children. Furthermore, the extra-corporeal circuit exposes the patient’s blood to a large nonphysiologic surface with the consequent activation of inflammatory and coagulation cascades and the production of further coagulation abnormalities. Therefore, quantitative and qualitative hemostatic alterations accompany the use of CPB.

Hemodilution

The hemodilution associated with CPB produces profound
Thrombin generation

Upon initiation of CPB, thrombin can be generated via several mechanisms. Activation of the intrinsic coagulation cascade through the contact factors is one path of thrombin production. Stimulation of the inflammatory response causes the expression of tissue factor on monocytes and endothelial cells, thus allowing thrombin generation via the extrinsic (tissue factor) cascade as well. Aspiration of blood from the surgical field through the CPB circuit exposes more tissue factor on cell membranes. Heparin is routinely administered prior to CPB in an attempt to attenuate thrombin generation. If anticoagulation were omitted, catastrophic clotting of the quantitative hemostatic changes and may be a principal culprit of the complex coagulation defects that occur after CPB in small children. The priming volume of the CPB circuit can be two to four times the blood volume of this population of patients. With the initiation of CPB, coagulation factor levels have been shown to decrease by 50% and platelet counts by 70% in neonates, despite the use of whole blood in the priming solution (Fig. 10.2). During the course of CPB these factor levels remain relatively constant but then increase somewhat at the end of CPB due to hemococoncentration and/or their increased production as acute phase reactants. However, at the termination of CPB and after the administration of protamine in children under 8 kg, mean fibrinogen levels of 62 mg/dL (29% of baseline level) and mean platelet counts of 64 000/µL (16.5% of baseline) have been reported. This hemodilution-induced reduction of coagulation factor levels combined with the decreased baseline levels in children under 6 months of age creates a situation where factor levels at the conclusion of CPB approach the minimum concentration required for adequate hemostasis (15% for factor V, 30% for all other factors).

**Qualitative coagulation changes**

The extracorporeal circuit provides a huge negatively charged surface that allows for massive activation of the contact factors (XII, XI, prekallikrein, and HMWK) as CPB commences. Contact activation results in the production of factor XIna, kallikrein, bradykinin, and plasmin. Consequently, the intrinsic coagulation cascade, the fibrinolytic system, and the body’s inflammatory response are all massively activated upon the initiation of CPB and all produce significant qualitative changes that contribute to the coagulopathy associated with CPB (Fig. 10.3).
extracorporeal circuit and the patient would occur. Despite the administration of adequate doses of heparin to maintain an acceptable activated clotting time (ACT) and the absence of visible blood clot, thrombin is still generated during CPB. This thrombin goes on to play a significant role in the production of post-CPB coagulopathies.

Fibrinolysis
The fibrinolytic system may be activated by several mechanisms that work in tandem during the process of cardiac surgery. Endothelial cells can be stimulated to release tissue plasminogen activator (tPA) by thrombin, by bradykinin generated through the contact activation system, and by the stimuli of skin incision and sternotomy. Tissue plasminogen activator stimulates the conversion of plasminogen to its active form plasmin. Plasmin then causes fibrinolysis by breaking arginine and lysine peptide bonds in fibrinogen and fibrin. Plasmin also can be generated by the direct actions of factor XIIa and kallikrein on plasminogen. Potentiating these mechanisms that activate the fibrinolytic system is a decrease in the levels of the inhibitors of plasmin during CPB. This combination of enhanced activation and decreased inhibition of plasmin sets the stage for fibrinolytic activity during CPB. Indeed, measurements of fibrin split products and clot lysis activity as well as modified thromboelastograms have demonstrated the occurrence of fibrinolysis during CPB in both adults and children. This fibrinolytic activity usually resolves without intervention within 90 minutes of the termination of CPB, possibly because of significant and persistent increases of plasminogen and plasmin inhibitors during this time. The contribution of fibrinolysis to post-CPB bleeding is not clear since several studies have found no correlation between postoperative blood loss and the intraoperative occurrence of fibrinolysis. However, the products of the fibrinolytic system, plasmin and fibrin split products, may play a role in the creation of other qualitative coagulation defects during CPB.

Platelet dysfunction
Platelet function abnormalities are deemed to be the most common etiology for excessive postoperative bleeding in adult cardiac surgical patients. Exposure to the CPB circuit alters the ability of platelets both to adhere to exposed subendothelial surfaces and other platelets and to aggregate with each other. Platelet adhesiveness is achieved through the glycoprotein Ib (von Willebrand) receptor. Plasmin generated by activation of the fibrinolytic system during CPB and the turbulence and shear stresses imposed by CPB have both been shown to destroy this important platelet adhesive receptor. Platelet aggregation after CPB is impaired after the platelets are "activated" during CPB. Activation of platelets leads to a depletion of their granules and a reduction of their ability to "stick" to each other afterward. Thrombin generated during CPB, fibrin degradation products resulting from plasmin's action on fibrin during CPB, and plasmin itself may all be responsible for this platelet activation during CPB. The subsequent impairment of the platelets' abilities to adhere and aggregate results in severe platelet dysfunction after CPB (Fig. 10.4).

Anticoagulation
Anticoagulation is a coagulation change mandated, rather than produced, by CPB in order to attenuate thrombin generation with subsequent clotting and promotion of qualitative coagulation defects. Because of its instant action and ease of neutralization, heparin is used to achieve this anticoagulation. Heparin exerts its anticoagulant effect by combining with ATIII and consequently greatly accelerating ATIII's inhibition of thrombin and other activated coagulation factors. In adults and older children, the response to heparin is proportional to ATIII levels. However, this relationship is complicated in infants because, despite their lower ATIII levels, their response to heparin is not diminished. Fortunately, an initial dose of heparin standardized to body weight usually achieves acceptable levels of anticoagulation not only in adults and older children but also in infants. A significant variability in heparin’s anticoagulant effect has been noted in adults and found to be even more pronounced in young children. Furthermore, heparin's half life is considerably shorter in children than adults. Because of these variations, the degree of heparin-induced anticoagulation must be assessed continually during and immediately after CPB. This can be accomplished by measuring heparin
levels or by measuring its anticoagulant effect. Arguments exist as to which of these methods is more appropriate because measurement of heparin levels does not take into account the tremendous variability in individual patients’ responses to heparin, whereas measurement of the ACT to assess heparin’s anticoagulant effect is influenced by factors other than heparin. While heparin levels decline upon the commencement of CPB in all patients, these levels are significantly lower during CPB in children than adults even in the presence of acceptable ACT levels. These lower heparin levels may be the result of a higher blood volume to body weight ratio in children thus effectively allowing heparin dosing calculations based on body weight to underestimate the needed dose for children. On the other hand, ACT values may remain high despite lower heparin levels because of the interplay of other factors that influence ACT values. Hypothermia and hemodilution synergistically prolong the ACT after heparin administration. The complexity of the surgical procedures performed on young children often necessitates much lower temperatures than are routinely used in adult patients. Additionally, hemodilution upon the commencement of CPB in small children can be profound, as previously discussed. Therefore, it is not surprising that despite the maintenance of acceptably prolonged ACT values during CPB, the coagulation system is not totally inhibited as evidenced by the occurrence of thrombin generation and fibrinolysis. However, data defining required heparin levels for complete inhibition of the coagulation system during CPB in children are lacking. In clinical practice, the ACT is most often used to document what is felt to be adequate levels of anticoagulation during CPB. As can be predicted, ACT measurements are usually significantly prolonged during the hypothermic period of CPB and require no further heparin administration during this time for maintenance of acceptable measurements. However, during the period of rewarming, the ACT values may fall rapidly thus necessitating their constant monitoring and the not infrequent administration of additional heparin prior to terminating CPB.

With the termination of CPB, the ACT becomes a very useful test in confirming the adequacy of heparin neutralization with protamine. At this point, however, ACT values continue to be influenced by factors other than heparin and its reversal with protamine. Even after adequate protamine dosing, the ACT can remain prolonged because of abnormally low coagulation factor levels, especially low levels of fibrinogen and factors VIII and XII. On the other hand, normal ACT values can exist in the presence of platelet abnormalities or factor VII deficiency and continued bleeding. Therefore, while return of the ACT to baseline levels is a very good indication that heparin has been completely neutralized, the ACT is not a sensitive test for predicting the presence of post-CPB coagulopathies and the likelihood of continued bleeding.

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Managing coagulopathies associated with cardiopulmonary bypass

Managing the coagulopathies associated with CPB is critical in order to minimize the consequences of ongoing bleeding (Table 10.1). Identification of risk factors associated with post-CPB bleeding in children allows the anticipation of bleeding as CPB is concluded and thus permits adequate preparation for its management. Knowledge of which coagulation tests can help predict those children who will experience ongoing bleeding after CPB and establishment of an institutional infrastructure that allows the rapid acquisition of these tests is important. A blood bank service that is able to provide a variety of products ranging from whole blood and packed red blood cells to pheresed platelet units, individual platelet units, fresh frozen plasma (FFP), and cryoprecipitate as well as concentrated individual coagulation factors is an absolute necessity. The ability to concentrate, wash, leukoreduce, and irradiate blood products should also be available. The blood bank should be staffed with personnel who have a thorough knowledge of transfusion medicine and can provide timely advice to clinicians. Preoperative communication with this staff is mandatory in order to insure the availability of necessary blood products prior to any surgery. Pharmacologic agents known to attenuate or help treat post-CPB coagulopathies should be available as should equipment used in blood conservation techniques such as cell salvage and ultrafiltration. Finally, the potential for late postoperative thrombotic complications should be appreciated in certain subsets of children.

Risk factors

Associations have been found between several patient, laboratory, or surgical characteristics and post-CPB blood...
loss and transfusion requirements in children. Patient age appears to be the variable with the most significant association. Post-CPB blood loss and blood product administration varies inversely with age, with children younger than 1 month being at greatest risk.40 Since age is a continuous variable, further work has found 12 months to be the age below which greater blood loss should be anticipated.31 Body weight has also been found to be a predictor of post-CPB bleeding. Children weighing less than 8 kg have been found to have significantly more bleeding and transfusion requirements than larger children.13 Therefore, children less than 1 year of age or 8 kg body weight should be considered at high risk for significant post-CPB coagulation problems.

Batteries of preoperative laboratory tests have also been examined to determine their abilities to predict excessive post-CPB bleeding. Preoperative hematocrit level, aPTT, and certain TEG parameters (α and shear modulus) have been found to be associated with 12-hour chest tube drainage in one study of 482 children.42 This study found no association between preoperative ACT, PT, platelet count, fibrinogen level, or other TEG parameters (R, K, and MA, see p. 163) and postoperative chest tube drainage. Based on their findings, these authors proposed that children may be at increased risk for postoperative bleeding if any of the following preoperative laboratory values are found: hematocrit > 45%, aPTT greater than or equal to 49 s, or TEG α less than or equal to 34°. Another investigation, however, found no preoperative coagulation test, including all of those noted above, to be predictive of or to correlate with 24-hour chest tube drainage in a study of 75 children.13 Despite the differences in these findings, the conclusions of the one study justify obtaining coagulation tests preoperatively in children scheduled for cardiac surgery. Values that lie outside of the guidelines previously mentioned should alert one to the upcoming possibility of excessive bleeding after CPB.

Several factors associated with surgical technique also show correlations with post-CPB blood loss and transfusion requirements. In children less than 1 year of age, the degree of hypothermia during CPB and the use of deep hypothermic circulatory arrest are significant factors; whereas, in children older than 1 year, the duration of CPB, the complexity of the surgical procedure, and repeat sternotomy are significant factors. The surgeon performing the procedure has also been found to be a correlating variable. Finally, the presence of either preoperative congestive heart failure or polycythemia is associated with higher post-CPB blood loss, and children who bleed significantly after chest closure in the operating room are at risk to continue this excessive bleeding in the postoperative period.81

Coagulation tests

While the presence of a significant coagulopathy in infants at the conclusion of CPB is almost always abundantly clear from the appearance of the surgical field, an elusive task after CPB in older children is the determination of the significance of any ongoing bleeding and the specific etiologies of the coagulopathy involved. Multiple coagulation tests obtained during and after CPB have been examined in attempts to identify a test that can be deemed the “gold standard” for delineating significant coagulopathies and children who will bleed excessively after CPB.

During CPB, platelet counts and TEG MA values have been found to be associated with postoperative chest tube drainage in children.42 The platelet count during CPB yielded the best association to allow one to distinguish those children who will bleed excessively. Values less than or equal to 108,000/µL provided a sensitivity of 83% and a specificity of 58% in distinguishing these children. The TEG MA value, on the other hand, was the only coagulation test significantly associated with total blood products transfused during the first 24-hours postoperatively. Both platelet count and fibrinogen level were found to correlate with the TEG MA value during CPB in this study.

After CPB and heparin neutralization with protamine, platelet counts, fibrinogen levels, and TEG α and MA values have been found to correlate independently with postoperative chest tube drainage in pediatric patients.13 Platelet count and fibrinogen level correlated with the TEG α and MA values as well. As was noted during CPB, the platelet count and the TEG MA value after CPB were again the tests that were most consistently associated with postoperative bleeding. Another investigation also found post-CPB TEG MA as well as K values to be associated with 24-hour chest tube drainage in children. The-post-CPB TEG was 100% accurate and 73% specific in its ability to predict increased postoperative bleeding in this study. It seems, therefore, that platelet counts, fibrinogen levels, and TEG parameters provide useful data to help define coagulopathies after CPB in children.

In adults, algorithms have been established to guide the management of post-CPB coagulopathies and have been based on ACT values, PT, aPTT, platelet counts, fibrinogen levels, and TEG values. Use of these algorithms has resulted in a decrease in postoperative chest tube drainage and blood product usage when compared to therapeutic interventions based solely on clinical judgements of the appearance of the operative field.44–46 Constructing and testing comparable algorithms for children remains to be accomplished. Pediatric algorithms should probably be built around platelet counts, fibrinogen levels, and TEG parameters. Transfusion thresholds for each of these parameters will need to be established. The influence of many factors independent of the coagulation system, however, must always be considered when managing post-CPB coagulopathies in children. Patient demographics, CPB techniques, and extensive extracardiac suture lines will all contribute to postoperative bleeding in pediatric patients independent of any coagulopathy that may or may not simultaneously exist.
In order to use an algorithm to guide the management of post-CPB coagulopathies, the results of coagulation tests must be rapidly available to clinicians. Technology currently exists to allow on-site measurements of whole blood PT, aPTT, and platelet counts in the operating room. The use of TEG for this purpose has also been growing. Thromboelastography is a unique test in that it allows assessment of the global coagulation picture from the initiation of clot formation to clot lysis or retraction. Five parameters are measured from a TEG tracing and other parameters can then be calculated from these measurements. (Fig. 10.5) The reaction time, or R value, is measured from the beginning of the tracing until an amplitude of 2 mm is reached and is expressed either in millimeters of chart distance or in minutes. The R value is similar to whole blood clotting time and reflects the function of the intrinsic coagulation pathway. Coagulation factor deficiencies and the presence of heparin result in prolongation of the R value. The coagulation time, or K value, is the interval from the end of the R value (2 mm amplitude) until the tracing reaches an amplitude of 20 mm and is also measured in millimeters or minutes. The angle (α) is measured as the slope of the outside divergence of the TEG tracing from the point of the end of the R value. The K and α values assess the rate of clot formation. Thrombocytopenia, platelet dysfunction, and hypofibrinogenemia will prolong the K value and reduce the α value. The maximum amplitude (MA) is the width of the TEG tracing (in millimeters) at its widest point. The MA is a reflection of the maximum strength of the clot and is influenced most importantly by fibrinogen levels, platelet counts, and platelet function as well as by factors VIII and XIII. Abnormalities of any of these will diminish MA values. The A-60 value is the amplitude of the TEG tracing 60 minutes after the MA value has been reached. This value is useful in measuring clot retraction or destruction by comparing it to the MA value. An A-60 : MA ratio (whole blood clot lysis index) of less than 0.85 has been used to define fibrinolysis. The elastic shear modulus (G) is calculated from the MA value by the equation:

\[ G = \frac{(5000 \text{ MA})}{(100 - \text{MA})} \]

The shear modulus is reported in dynes/cm² and is affected by platelet counts and fibrinogen levels. Analysis of a TEG tracing permits an assessment of the entire coagulation process at a given time and gives an overview of the interplay of all the components of coagulation as they work together to form and maintain a clot. Delay in clot initiation, slow build-up of the clot, weakness of the formed clot, and fibrinolysis can all be detected by TEG.

The TEG can be modified to become a rapid point-of-care test. Activation of blood with either celite or tissue factor in children allows MA values to become evident within 6–15 minutes of starting the test. These MA values are 30% greater than unactivated values; however, platelet counts and fibrinogen levels continue to correlate with these activated values. Adding heparinase or protamine to blood samples neutralizes circulating heparin and allows TEG data to be obtained during CPB. After CPB, heparinase-modified TEGs can also be helpful in discerning the contribution of residual circulating heparin to persistently prolonged ACT values after initial protamine administration. Therefore, TEG is poised to become a very useful coagulation monitor in children should algorithms be built to help manage their post-CPB coagulopathies.

**Blood product therapy**

Since infants will have an obvious coagulopathy at the conclusion of CPB, the first point to be considered in blood product therapy is the use of whole blood vs. individual coagulation products. Whole blood less than 48 hours old has been shown to better limit post-CPB blood loss in children under 2 years of age and, more specifically, in patients of this age undergoing complex surgical procedures (arterial switch, Glenn, Fontan, truncus arteriosus repair, stage I palliation for hypoplastic left heart syndrome [HLHS]) when compared to the use of a reconstituted product composed of 1 U each of packed red blood cells, platelets, and FFP. This improvement in hemostasis was felt to be secondary to the presence of better functioning platelets in the whole blood as assessed by platelet aggregation tests. Children older than 2 years and
those of any age undergoing less complex procedures did not show this benefit. Despite this hemostatic benefit of fresh whole blood and its advantage of reducing donor exposures, its use must be supplemented at times with the transfusion of individual coagulation products to optimally control post-CPB blood loss, especially in younger patients. One study of 30 neonates found that despite the use of fresh whole blood, 70% of the neonates also received platelet transfusions, 37% received cryoprecipitate, and 17% received FFP as second-line treatments for inadequate clot formation and excessive transfusion requirements.3 Additionally, whole blood less than 48 hours old is not readily available at all pediatric cardiac surgical centers and, when it is, it usually has been stored at 4°C, a factor which significantly depresses platelet function compared to storage for similar lengths of time at room temperature.29 Therefore, the transfusion of separate component products plays a primary role in treating post-CPB coagulopathies in children in many institutions.

The effects of different coagulation products in correcting abnormalities of TEG parameters, platelet counts, and fibrinogen levels after protamine administration in children have also been investigated.13 Since abundant evidence that qualitative platelet dysfunction4,12,28,31,44,50 as well as severe quantitative platelet deficiencies3,12 exist after CPB, initial treatment of ongoing bleeding after adequate heparin neutralization was with platelet transfusions. Platelet administration substantially improved the TEG parameters in addition to the platelet count. Approximately 40% of children were found to need only platelet transfusions to adequately control bleeding and, in these patients, TEG parameters were returned to baseline values by the platelet transfusion alone. The use of cryoprecipitate or FFP to manage continued bleeding and abnormal TEG values after adequate platelet transfusion was then compared. Cryoprecipitate administration raised fibrinogen levels to normal and significantly further improved TEG parameters, whereas FFP not only failed to increase fibrinogen levels but also worsened all TEG parameters. Patients given platelets followed by FFP had substantially more 24-hour chest tube drainage than those receiving cryoprecipitate. Additionally, patients receiving FFP required more coagulation product administration in the intensive care unit (ICU) than did those receiving cryoprecipitate. Therefore, it was advocated that when using component therapy to treat post-CPB coagulopathies in children, platelet transfusion followed by cryoprecipitate, if needed, seems the better approach to restore hemostasis, and it was noted that smaller children required this additional administration of cryoprecipitate more often to adequately control their post-CPB coagulopathies.13

**Pharmacologic strategies**

An even more effective method of combating post-CPB coagulopathies would be their prevention. While priming volumes of extracorporeal circuits are continually being adjusted to minimize the quantitative defects caused by hemodilution, many investigators have attempted to attenuate the qualitative defects with pharmacologic therapies. Desmopressin acetate, antifibrinolytics (e-aminocaproic acid and tranexamic acid), and aprotinin have been evaluated for their abilities to accomplish this during CPB.

**Desmopressin acetate**

Desmopressin acetate (1-deamino-8-D-arginine vasopressin [DDAVP]) is a synthetic analogue of the posterior pituitary hormone, vasopressin. Administration of DDAVP has been shown to increase plasma levels of the procoagulant factor VIII:C and of the von Willebrand factor.50,51 Importantly, the plasma level of the larger, more hemostatically active, multimers of von Willebrand factor have been shown to increase after DDAVP.52 The von Willebrand factor plays a major role in mediating platelet adhesion to exposed subendothelium by binding to adhesive glycoprotein Ib receptors on the platelet membrane and to the exposed subendothelial collagen.50 DDAVP may also improve hemostasis by a direct effect on blood vessel walls to increase platelet adhesiveness and promote platelet spreading at sites of vessel injury.52 Since DDAVP seems to improve hemostasis by enhancing platelet function and since platelet dysfunction has been incriminated as a cause of post-CPB bleeding, DDAVP has been used in an attempt to curb blood loss after cardiac surgery.

Studies involving the routine prophylactic administration of DDAVP (0.3 µg/kg) to adults undergoing primary coronary artery bypass grafting have shown no reduction in post-CPB blood loss or transfusion requirements.53,54 When given to adults undergoing more complex procedures, such as valve replacements or repeat sternotomies, DDAVP has been shown to decrease blood loss during the first 24 postoperative hours.51 Additionally, when DDAVP has been given to adult patients with documented platelet function abnormalities (prolonged bleeding times and decreased TEG MA values) and continued bleeding after CPB, the bleeding and the amount of blood products transfused have been significantly reduced compared to patients not receiving DDAVP.50,55 Two studies have investigated the prophylactic administration of DDAVP (again, 0.3 µg/kg) to children after cardiac surgery, in many cases after complex procedures, and neither has shown a reduction in blood loss or transfusion requirements with this therapy.56,57

Potential complications following the use of DDAVP could relate to its endocrine functions; however, no evidence of vasoconstriction (smooth muscle effects) or of alterations in water balance (antidiuretic hormone effects) have been noted.50,51,53,55,57 Although tPA is released by DDAVP, no fibrinolysis has been demonstrated with its use.52,54 No evidence of an increased risk of thrombosis has been found after the use of DDAVP.50,53
The routine prophylactic use of DDAVP after CPB in children and adults does not seem to improve hemostasis. Administration of DDAVP to select patients with documented platelet function abnormalities (prolonged bleeding times or decreased TEG MA values) in the face of ongoing bleeding may prove beneficial.

### Antifibrinolytics

Epsilon-aminocaproic acid (EACA) and tranexamic acid (TA) are the two clinically available antifibrinolytic drugs. The antifibrinolytic actions of EACA were discovered in 1959 and the subsequent research for more potent drugs with similar actions found TA in 1962. Epsilon-aminocaproic acid is a synthetic monoaminocarboxylic acid whose structure is closely related to the amino acid lysine. Tranexamic acid is the trans isomer of 4-amoenoethylcyclohexane carboxylic acid. Both exert their antifibrinolytic effect most importantly by competitively binding with the lysine binding sites of plasminogen, thus altering plasminogen’s conformation and thereby preventing plasminogen activators from converting the plasminogen to its active form, plasmin. At significantly higher concentrations, these drugs bind directly to plasmin that has already formed, thus directly inhibiting the plasm’s activity. Both drugs are fairly rapidly excreted by the kidneys, although TA has a longer half-life. Tranexamic acid is six to 10 times more potent than EACA.20,58

Both EACA and TA have been shown to inhibit fibrinolytic activity when used prophylactically during CPB.19,59 Although some postulate that fibrinolysis is not a major contributor to post-CPB bleeding,14,22,25,26 a reduction in post-CPB blood loss and transfusion requirements has been demonstrated with the prophylactic use of these drugs in adults.34,58–60 The contribution of the products of fibrinolysis to the generation of post-CPB platelet dysfunction no doubt plays a role. Indeed, studies with TA have shown not only that TA preserves platelet function after CPB but also that the amount of postoperative bleeding correlates with the post-CPB platelet function and not with the occurrence of fibrinolysis.32,61 Other adult studies, however, have failed to show any beneficial hemostatic effect with the use of these antifibrinolytic agents.62,63 Several investigations focusing only on children have revealed no reduction in bleeding or blood product transfusions during the first 24 hours after CPB with the prophylactic use of either EACA or TA.64–66 However, when the children with cyanosis were analyzed separately in these studies, both EACA and TA significantly reduced postoperative blood loss and transfusion requirements.64,65 Additionally, another study has indicated a significant reduction in 24-hour blood loss and transfusion requirements in children undergoing repeat sternotomies who were prophylactically given TA.67 Therefore, the prophylactic use of antifibrinolytic agents to attenuate post-CPB bleeding may be efficacious in children with cyanotic heart defects and in those undergoing repeat sternotomies.

Multiple dosing regimens have been reported for each of these antifibrinolytics in adult patients and then have been extrapolated to the pediatric population. For EACA, a plasma level of 130 µg/mL is needed to inhibit fibrinolysis.68 Since EACA that is administered intravenously is rapidly excreted by the kidneys, successful dosing protocols have used a loading dose followed by a continuous infusion. Published schedules for intravenous administration of EACA to adults include a loading dose of 100 mg/kg followed by an infusion of 1 g/hour,20 a loading dose of 150 mg/kg followed by an infusion of 30 mg/kg/hour,69 and a loading dose of 50 mg/kg loading dose followed by an infusion of 25 mg/kg/hour. All of these doses achieve plasma levels of at least 130 µg/mL. Published pediatric dosing regimens include a loading dose of 75 mg/kg followed by an infusion of 15 mg/kg/hour64 and a loading dose of 150 mg/kg followed by an infusion of 30 mg/kg/hour.66 The higher of these doses was felt by the investigators to be appropriate to achieve the desired plasma levels of 130 µg/mL after comparison to adult protocols.66 A recent pharmacokinetic study in children undergoing repair of congenital heart defects with bypass used a best-fit two-compartment model, and recommended a loading dose of 75 mg/kg, 75 mg/kg into the bypass circuit, and an infusion of 75 mg/kg/hour in the pre- and post-bypass periods, in order to achieve predicted plasma levels of 260 µg/mL in 95% of patients.67

Dosing regimens for TA have been analyzed more on a pharmacodynamic basis. Again, most regimens employ a loading dose followed by a continuous infusion because of rapid renal elimination of TA. Although lower doses of TA have been shown to attenuate the fibrinolysis associated with CPB in adults, a loading dose of 10 mg/kg followed by an infusion of 1 mg/kg/hour is needed to reduce post-CPB blood loss. Higher doses (double and quadruple this amount) have been found not to further reduce postoperative blood loss in adults.61 A dosing protocol using a loading dose of 100 mg/kg after induction followed by another 100 mg/kg dose in the pump prime and an infusion of 10 mg/kg/hour has proven beneficial in pediatric patients.68 It has been emphasized with both antifibrinolytics that since the initiation of fibrinolysis begins with skin incision and continues with sternotomy, pericardiotomy, and the initiation of CPB, administration of these drugs starting prior to skin incision results in significantly more reduction of fibrinolysis, platelet dysfunction, and blood loss than administration after CPB and protamine infusion.32,71

Much concern has been voiced about potential thrombotic complications after the use of antifibrinolytics, although none of the previously cited reports found any significant increase in thrombotic or embolic problems in either adults or children. These complications are of more concern when antifibrinolytics are used incorrectly during a hypercoagulable
state with compensatory fibrinolysis (disseminated intravascular coagulation [DIC]) rather than during the primary fibrinolysis that may occur after CPB.72

Aprotinin

Aprotinin is a serine protease inhibitor isolated from bovine lung. Its ability to inhibit trypsin, plasmin, and kallikrein has been known since the 1930s, with its clinical use first reported in 1953 for the treatment of acute pancreatitis.73,74 High doses of aprotinin were found in 1987 to be useful in reducing blood loss and transfusion requirements in adults undergoing repeat cardiac surgery as well as primary coronary artery bypass graft (CABG).75-76 Since then, multiple investigations have explored the use of aprotinin in a variety of patient populations requiring CPB.

Aprotinin’s antagonism of kallikrein and plasmin leads to its beneficial hemostatic effects after CPB.73 Kallikrein is the central component of the contact activation cascades and thus stimulates thrombin formation via the intrinsic coagulation pathway, generates bradykinin from HMWK, and cleaves plasminogen to form plasmin.15 Thrombin, bradykinin, and plasmin are all involved in the initiation of fibrinolysis and the production of platelet dysfunction associated with CPB: thrombin stimulates tPA release and “activates” platelets thus diminishing their future ability to aggregate,14 bradykinin stimulates tPA release, and plasmin not only lyases fibrinogen and fibrin but also cleaves the adhesive glycoprotein IIb receptor from platelet surfaces thus decreasing the platelets’ ability to adhere to exposed subendothelial surfaces. Plasmin also interferes with the subsequent binding of fibrinogen to the aggregatory glycoprotein IIb-IIIa platelet receptors.28,76 Plasmin, kallikrein, and thrombin are all also involved in perpetuating the inflammatory response that accompanies CPB by activating the complement cascade, neutrophils, and endothelial cells. Aprotinin is able to inhibit plasmin at plasma levels of only 50 KIU/mL and does so by rapidly forming an almost irreversible complex with it. At much higher plasma levels (200 KIU/mL), aprotinin also inhibits kallikrein formation thus attenuating its central role in the production of post-CPB coagulopathies and the activation of the inflammatory response.77

Abundant evidence exists documenting aprotinin’s ability to decrease blood loss and transfusion requirements after CPB in adults undergoing CABG or valve surgery both as primary or redo procedures.73,75,76,78 These beneficial effects seem even greater in adults considered at high risk for post-CPB bleeding such as those undergoing repeat sternotomies, those with acute bacterial endocarditis, and those with recent aspirin ingestion.74,79 Conflicting reports have been published concerning aprotinin’s effects on blood loss and transfusion requirements after CPB in children. Several factors probably combine to create the dichotomy in these studies. The children included in most investigations were very heterogenous in their ages and sizes as well as in their cardiac defects and the subsequent surgical procedures they underwent. Furthermore, a vast array of aprotinin dose regimens were used as were a variety of heparin and protamine protocols, CPB circuit primes, and transfusion triggers. However, almost all currently available data indicate that in children undergoing primary sternotomies, the administration of aprotinin does not decrease blood loss or transfusion requirements.80,81 Blood loss 6 hours postoperatively was found in one study to be significantly reduced in children undergoing primary sternotomies who received a “high dose” of aprotinin, but even in these children the 24-hour blood loss and the transfusion requirements were not reduced by aprotinin.23 However, reproducible evidence exists that aprotinin is beneficial in children undergoing repeat sternotomies. Reductions in transfusion requirements and attenuation of post-CPB TEG abnormalities have been demonstrated with the use of aprotinin in studies comprised exclusively of this subset of children.82,83 In addition, the time required for chest closure in the operating room and the durations of postoperative mechanical ventilation, ICU stay, and total hospitalization were reduced in these children, possibly reflecting the attenuation of the inflammatory response to CPB by aprotinin. Despite the significant cost of aprotinin, savings of several thousand dollars were realized in the hospital charges for each of these children thus proving aprotinin to be cost effective as well as hemostatically efficacious. These beneficial effects of aprotinin were dose dependent with greater hemostatic and economic advantages found with the use of higher doses.

Another homogeneous group of children that has been found to benefit from the use of aprotinin is neonates undergoing arterial switch procedures. An early study found a significant reduction in the time required for chest closure in the operating room when aprotinin was administered to these patients.84 Subsequently, an investigation that included a group of 56 neonates undergoing arterial switch procedures found reductions in 24-hour chest tube drainage and transfusion requirements, again in a dose dependent fashion.81 A wide range of dosing regimens have been used when administering aprotinin to children, and, as indicated, the beneficial effects of aprotinin are greater with higher doses. The adult literature indicates that achieving aprotinin plasma levels of 200 KIU/mL is of paramount importance since this level is necessary for the inhibition of kallikrein and the subsequent blockade of kallikrein’s activation of the coagulation, fibrinolytic, and inflammatory systems.73 This blockade of kallikrein is deemed the pivotal difference between aprotinin and the anti-fibrinolytic agents. The only pediatric study to measure plasma aprotinin levels found maximum levels of 99 ± 25 KIU/mL 30 minutes after the initiation of CPB in children receiving a 30 000 KIU/kg loading dose of aprotinin after the induction of anesthesia with another 30 000 KIU/kg placed in the pump prime. No infusion of aprotinin was
used.23 Other pediatric studies have used higher aprotinin doses in children but have not measured plasma levels.80–83 Doses in these studies have been based either on body weight or body surface area. Weight based regimens have originated as extrapolations from adult dosing protocols and have included a loading dose and pump prime dose of 35 000–50 000 KIU/kg accompanied by an infusion of 10 000–20 000 KIU/kg/hour. Body surface area based regimens apparently evolved from discussions with the manufacturers of aprotinin and have used a loading and a pump prime dose of 240 mg/m² with an infusion of 56 mg/m²/hour.84 However, no pediatric dosing recommendations are included in the manufacturer’s product insert. Dosing calculations based on body surface area result in the administration of much larger amounts of aprotinin than those based on body weight. Studies to determine the plasma level of aprotinin reached with each of these various doses are needed before a definitive pediatric dosing protocol can be advocated.

Several potential problems have been reported in adults receiving aprotinin, but pediatric studies have not conclusively related any adverse events with the administration of aprotinin. Concern about renal impairment following the use of aprotinin in adults exposed to periods of deep hypothermic circulatory arrest has not borne out in children.23,83 Reports of dysrhythmias,82 neurologic events,82 and thrombotic problems83 either have been found not to differ significantly between control groups and those children receiving aprotinin or have been felt to be multifactorial in origin. Since aprotinin is derived from bovine lung, it represents a foreign protein and, therefore, carries a risk for allergic reactions on repeat exposures. The incidence of this occurring has been found to be 2.5–2.8%85,86 and is significantly related to the length of time between exposures to aprotinin. Patients with a re-exposure interval of less than 200 days have demonstrated a 4.5% incidence of adverse reactions whereas the incidence falls to 1.5% in those with a longer interval.85 Those manifesting these adverse reactions have been found to possess very high antiaprotinin immunoglobulin G (IgG) antibody concentrations. Unfortunately, the occurrence of high antiaprotinin IgG antibody levels is only 60% predictive of adverse reactions upon repeat exposures; however, no adverse reactions have occurred when these IgG levels were low or undetectable preoperatively. Interestingly, skin prick tests to assess immunoglobulin E (IgE) antibody-mediated hypersensitivity have not been found to be predictive of subsequent adverse reactions to re-exposure to aprotinin.86 Based on this knowledge, the following recommendations have been made for situations when a repeat exposure to aprotinin is being contemplated: (i) re-exposure should be avoided within 6 months of a previous exposure; (ii) a test dose of 1 mL (10 000 KIU) of aprotinin should be administered prior to the loading dose; (iii) test and loading doses should be delayed until conditions for rapid commencement of CPB are present; (iv) the addition of aprotinin to the pump prime should be delayed until after the loading dose has been safely given; (v) H1 and H2 blockers as well as standard treatments for hypersensitivity–allergic reactions (epinephrine, corticosteroids) should be readily available. Should an exceptional situation arise where the clinical benefit of readministering aprotinin within 6 months of a previous exposure is felt to outweigh the risk of an allergic reaction, preoperative testing for antiaprotinin IgG antibodies should be performed and the use of aprotinin should proceed only in the absence of these antibodies and still with utmost caution.85,86

Finally, care must be taken to insure a safe level of anticoagulation when aprotinin is used. Through its inhibition of kallikrein and the subsequent activation of factor XII, aprotinin inhibits the intrinsic coagulation cascade. This inhibition acts synergistically with that produced by heparin to augment the prolongation of celite ACTs.87 Although some feel this synergy is helpful in preventing thrombin generation, others feel that celite ACT measurements can not be depended upon to reflect adequate anticoagulation in the presence of aprotinin. On the other hand, kaolin, a negatively charged molecule, binds aprotinin, a positively charged molecule, thus preventing aprotinin from inhibiting intrinsic coagulation. Kaolin ACTs, therefore, are not influenced by the presence of aprotinin.88 To insure adequate anticoagulation when aprotinin is being used, it is suggested that celite ACTs be maintained greater than 750 s, kaolin ACTs be maintained over 480 s, heparin levels be monitored, or supplemental heparin be administered at a routine interval (usually hourly) during CPB even in the presence of adequate ACT measurements.89,90

### Blood conservation

Measures to conserve autologous blood during pediatric open heart surgery are worthwhile because of the severity of post-CPB coagulopathies and the resultant blood loss. Several blood conservation options are possible and success is likely to be enhanced if multiple measures are employed. The efficacy of some blood conservation techniques varies with the child’s age (Table 10.2). Preoperatively, the patient’s likelihood of bleeding should be assessed and a blood conservation strategy chosen that has a favorable ratio between potential benefit and risk. Techniques of proven value in children that are not discussed elsewhere in the chapter will be emphasized.

### Preoperative considerations

Preoperative autologous donation (PAD) is the collection and anticoagulation of whole blood from a patient for anticipated perioperative transfusion. It eliminates the risk of bloodborne infections and incompatibility issues, including graft-vs.-host disease, and diminishes immune modulation.
The amount of blood collected from a single donation is typically limited to 10% of the child’s total blood volume. Most pediatric patients selected for PAD are more than 7 years old or weigh more than 40 kg. The rate of donation reactions is 2–5% and increases with decreasing age and weight. Limited venous access is an additional concern. The use of PAD for cardiac surgery remains controversial because of safety concerns and the risk of delaying surgery. Adults with unstable coronary artery disease, aortic stenosis, or congestive heart failure are generally excluded from PAD. Suitability of PAD in children with congenital heart disease depends on the anticipated consequences upon a patient’s cardiac pathophysiology. Although PAD has been safely performed in children weighing less than 20 kg with simple cardiac anomalies, the technique is usually limited to teenagers and is performed infrequently.

Recombinant human erythropoietin α (EPO), the primary growth factor for red blood cells, is approved in the USA, Canada, Japan, and Europe for use in patients donating autologous blood before surgery. Treatment with EPO (100 U/kg subcutaneously three times a week for 3 weeks and intravenously on the day of surgery) increased the amount of autologous blood that could be collected and minimized allogetic blood exposure in children (age range 2–14 years) undergoing repair of atrial or ventricular septal defects. The combined use of EPO and PAD for pediatric cardiac surgery is new and has potential. However, it is expensive, invasive, and probably will be limited to children undergoing elective non-complex cardiac surgery. Platelet count increases with EPO therapy. While this may be an advantage in some cases, it would be a concern in prothrombotic patients, including those with single ventricle physiology.

### Intraoperative considerations

The influences of differing anesthesia techniques or agents on bleeding during pediatric cardiac surgery are poorly known. Basic principles would suggest avoidance of high blood pressure and venous congestion. Of interest, patients undergoing unifocalization of aortopulmonary collaterals may be at greater risk for hemorrhage from postoperative liver dysfunction. Intraoperative measures to preserve hepatic blood flow could be worthy of consideration.

Acute normovolemic hemodilution (ANH) is the removal before CPB of whole blood from the patient while maintaining isovolemia by crystalloid or colloid infusion. The patient’s blood is reinfused after CPB. Although safe, the technique is seldom indicated during pediatric cardiac surgery because children undergo substantial hemodilution during CPB and consequently have less red cell mass available for ANH. Additionally, the platelets in ANH blood are often insufficient to correct post-CPB deficits in platelet number and function. Indeed, the efficacy of ANH even in adult cardiac surgery is questionable.

Platelet-rich plasma can be obtained by plateletpheresis after induction of anesthesia and transfused after CPB. Recent reviews conclude that the current technology is clinically ineffective and plateletpheresis should not be considered for routine use.

Fibrin glue has been used in children undergoing repair of congenital heart defects and is most efficacious in controlling low pressure venous bleeding. Exposure to topical sealants that contain aprotinin results in an antibody response similar to that observed after intravenous aprotinin administration. When exposed to fibrin glue of bovine origin, patients may develop antibodies against bovine factor V or X. These

### Table 10.2 Blood conservation techniques. Possible means for reducing allogetic blood transfusions during pediatric cardiac surgery.

<table>
<thead>
<tr>
<th>Management strategy</th>
<th>Neonate</th>
<th>Teenager</th>
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<tbody>
<tr>
<td>Preoperative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autologous blood donation</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Erythropoietin, iron</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Plateletpheresis</td>
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<td>-</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limit hypothermia</td>
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<td>+</td>
</tr>
<tr>
<td>Limit duration of CPB</td>
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<td>+</td>
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<tr>
<td>Avoid circulatory arrest</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Meticulous hemostasis</td>
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<td>+</td>
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<td>Topical sealants</td>
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<tr>
<td>Anesthesia</td>
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<tr>
<td>Normothermia after CPB</td>
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<td>+</td>
</tr>
<tr>
<td>Transfusion algorithm</td>
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<td>+</td>
</tr>
<tr>
<td>Antifibrinolytic agents</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acute normovolemic hemodilution</td>
<td>-</td>
<td>?</td>
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<tr>
<td>Anesthetic technique and agents</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>DDAVP</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Cardiopulmonary bypass</td>
<td></td>
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<tr>
<td>Limit prime volume</td>
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<td>+</td>
</tr>
<tr>
<td>Nonsanguinous prime</td>
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</tr>
<tr>
<td>Defined target hematocrit during bypass</td>
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<td>+</td>
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<tr>
<td>Ultrafiltration</td>
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<tr>
<td>Heparin coated circuit</td>
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<tr>
<td>Blood substitutes</td>
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<tr>
<td>Centrifugal pump</td>
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<td>?</td>
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<tr>
<td>Reinfuse circuit residual fluid</td>
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<td>-</td>
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<td>Postoperative</td>
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<tr>
<td>Transfusion algorithm</td>
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<td>+</td>
</tr>
<tr>
<td>Reinfuse shed blood</td>
<td>-</td>
<td>?</td>
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CPB, cardiopulmonary bypass; DDAVP, 1-deamino-8-D-arginine vasopressin.
antibodies can then cross-react to inhibit the patient’s own factor V or X.

Perfusion considerations

Unfortunately, the degree of hemodilution incurred by small infants during CPB is extreme. Although perfusionists have devised methods of limiting hemodilution, almost all neonates require a blood-containing prime. The optimum hematocrit during CPB remains undefined and probably is influenced by factors such as blood flow, degree of hypothermia, and the type of cardiac anomaly.

Ultrafiltration has been repeatedly demonstrated to be useful during pediatric open heart surgery. This technique uses convection transport across a semipermeable membrane under a hydrostatic gradient to remove water and low molecular weight solutes from blood. Effects include hemococoncentration of the patient, removal of inflammatory mediators, and an ability to manipulate plasma electrolytes and colloid osmotic pressure. Ultrafiltration reduces the requirement for allogenic blood products by increasing the patient’s hematocrit, concentrating coagulation plasma proteins, and modulating the systemic inflammatory response to CPB.93 Heparin blood concentration increases because it is highly protein bound and hence not filtered.94 There are several methods of ultrafiltration. A blood-containing CPB prime can be ultrafiltered prior to initiation of CPB; conventional ultrafiltration is performed during CPB; modified ultrafiltration (either arteriovenous or venovenous) occurs after separation from CPB. The amount of ultrafiltrate obtained can be increased by adding fluid to the CPB circuit to maintain isovolemia. It is unclear which of the ultrafiltration variants provides maximal clinical benefit.

Blood shed intraoperatively can be collected into an automated centrifuge-based blood salvage instrument that produces a suspension of washed, concentrated red blood cells containing little or no heparin. Likewise, red cells present in the CPB circuit after separation of the patient from CPB can be salvaged. Red cell salvage has been found to be a useful blood conservation technique during pediatric cardiac surgery.95 Washed red cells lack plasma proteins and will lead to coagulation factor depletion if transfused in large volumes.

Unprocessed residual CPB fluid can be returned to the patient. However, this is not optimal because the fluid has a low hematocrit and contains heparin, fibrinolysis byproducts, and cellular debris. Mediastinal and pleural shed blood can be collected postoperatively and reinfused but the technique is seldom used in pediatric cardiac surgery. There is concern that reinfused shed blood promotes a coagulopathic state because shed blood not only contains decreased amounts of coagulation factors and increased levels of fibrin degradation products but also stimulates tPA. Additionally, the hematocrit of shed blood is usually less than 20%.

Postoperative thrombosis

Children, especially neonates, can become hypercoagulable postoperatively as a consequence of the coagulation changes associated with CPB and the treatment of post-CPB coagulopathies. After CPB, there is ongoing thrombin generation, but fibrinolysis is reduced because of increased plasminogen activator inhibition. Furthermore, anticoagulant capacity is diminished with decreased protein S, protein C, and ATIII activities. Additionally, factors predisposing to clotting are present, including low blood flow, exposure to foreign materials, and the presence of central venous catheters. Children who have undergone a Glenn anastomosis or a Fontan procedure are at an increased risk for venous thrombosis, probably because of the simultaneous presence of many of these factors. Other procoagulant concerns postoperatively include the relatively common prevalence of activated protein C resistance from the factor V Leiden mutation96 and the infrequent occurrence of heparin-induced thrombocytopenia.

It is important to monitor the postoperative pro and anticoagulant status of children at high risk for venous thrombosis and to remove central venous lines as soon as possible after surgery. Mortality rates of 33–50% after postoperative clinical venous thrombosis are reported.97 Neonates have a 10-fold risk compared to older children. Correction of factor deficiencies, anticoagulant therapy with heparin and/or warfarin, thrombectomy, and thrombolysis may be necessary in preventing or managing postoperative hypercoagulable states.

Summary

Ongoing bleeding after cardiac surgery in children produces significant morbidity and thus demands that clinicians caring for these children be knowledgeable about the etiologies and management of post-CPB coagulopathies. Risk factors and coagulation tests have been identified that permit one to anticipate and then treat bleeding after CPB. Pediatric investigations have defined the utility of specific blood products in restoring hemostasis and the appropriate use of pharmacologic therapies for attenuating postoperative blood loss. However, much work remains to be done in children in this arena. Continued manipulations of extracorporeal circuits to minimize quantitative and qualitative hemostatic derangements, development of pharmacologic agents to inhibit the inflammatory response to CPB and to provide better anticoagulation during CPB, and development of blood substitutes and more targeted coagulation products remain a few of the goals that will further enhance our ability to safely care for these children. Meanwhile, recognition of the significance of this aspect of pediatric cardiac surgery will allow clinicians to minimize one source of morbidity associated with these procedures.
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