Cardiopulmonary bypass and the coagulation system

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Abstract

Cardiopulmonary bypass exerts intended and unintended effects on the enzymatic and formed elements of the coagulation and inflammatory systems. Compared with adults, children are at special risk for known, and unknown, differences in their hemostatic systems. Management of these risks will be presented from a surgical perspective, supporting those strategies with a combination of peer-reviewed data and empiric experience. Preoperatively, strategies discussed are management of preoperative anticoagulants, autologous and directed donation, erythropoietin, and special considerations in the care of pediatric Jehovah’s Witnesses. Intraoperatively, strategies discussed include basic management of cardiopulmonary bypass, heparin and heparin monitoring, protamine, alternative anticoagulant strategies for heparin sensitivity, and intraoperative pharmacologic adjuncts promoting postoperative hemostasis. Postoperative strategies discussed include blood product utilization, recombinant factor VII, the use of thromboelastography to guide therapy, topical strategies, cell saver therapy, and surgical reexploration.

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1. Introduction

Cardiopulmonary bypass was originally pioneered in children. In 1952, F. John Lewis performed the first open heart operation using fibrillatory arrest [1]. C.W. Lillehei was the first to use cross-circulation and hypothermia to repair an atrial septal defect [2]. After developing his prototype “heart lung machine,” John Gibbon repaired an atrial septal defect in 1953 [3]. Although this landmark enabled the performance of intracardiac surgery, disturbances in hemostasis still persist today.

Cardiopulmonary bypass leads to a whole body inflammatory response involving the formed blood elements, coagulation, complement and kallikrein/kinin systems. Hemodilution is directly related to the volume of crystalloid and colloid required to prime the circuit and the patient’s own blood volume and can dilute blood components by as much as 40% [4]. Although children have relatively larger circulating blood volumes when compared with adults (e.g., preterm infants have an estimated blood volume of 90–100 ml/kg compared to 70–80 ml/kg in an adult [5,6]), their low absolute blood volume accentuates their dilutional coagulopathy. Further, their small blood volume creates practical limitations on the use of certain blood conservation strategies such as autologous donation and cell saver.

A profound thrombotic reaction involving both the extrinsic and intrinsic coagulation pathways is initiated by continuous exposure of heparinized blood to the perfusion circuit and to the wound during cardiac surgery. Despite large doses of heparin during cardiopulmonary bypass, heparin does not block thrombin generation; but partially inhibits thrombin after it is produced. Thrombin is continuously generated and a consumptive coagulopathy is initiated [7–9]. If thrombin formation could be completely inhibited during cardiopulmonary bypass, the consumption of coagulation proteins and platelets could largely be prevented.

Seconds after heparinized blood contacts any biomaterial (including heparin-coated surfaces) [9], plasma proteins are
adsorbed onto that surface to form a single layer of proteins [10]. Adsorbed factor XII and fibrinogen undergo conformational changes, triggering activation of the contact pathway and platelet surface adhesion, respectively. Thus heparin is not an ideal anticoagulant during cardiopulmonary bypass, which is indicated by the high concentrations (3–4 mg/kg, initial dose) that are required for efficacy.

Circulating thrombin, surface-adsorbed fibrinogen, complement, platelet activating factor, and cytokines lead to platelet adhesion [4]. Platelets appear to be structurally normal; however, their function is abnormal, as a result of being activated. Hypothermia also exacerbates thrombocytopenia through hepatic sequestration and increased fibrinolysis [12,13]. Bleeding time remains prolonged for several hours after protamine administration [14]. This increased bleeding tendency can be reversed by rewarming [15,16].

Similar changes in complement proteins participate in activation of the complement system [17]. The inflammatory response to cardiopulmonary bypass is mediated by the contact system and consists of four primary plasma proteins [factor XII, prekallikrein, high molecular weight kininogen (HMWK), and C-1 inhibitor] which lead to complement and neutrophil activation. However, when blood contacts a negatively charged surface in cardiopulmonary bypass, small amounts of factor XII are adsorbed and undergo a conformational change to factor XIIa. Factor XIIa in the presence of HMWK activates factor XI and initiates the intrinsic coagulation pathway. Thrombin also activates factor XI, and is the predominating agonist in vivo in pathologic states.

The intrinsic coagulation pathway probably does not generate thrombin in vivo, but is initiated when blood contacts nonendothelial cell surfaces such as the perfusion circuit [18,19]. The extrinsic coagulation pathway is a major source of thrombin generation during cardiopulmonary bypass and is initiated from tissue factor in the surgical wound [20–22]. Tissue factor is a cell-bound glycoprotein that is constitutively expressed by fat, muscle, bone, epicardial, advential, injured endothelial cells, wound monocytes, and many other cells except pericardium [22–24].

Intrinsic and extrinsic tenase complexes catalyze the activation of factor X to factor Xa. The extrinsic tenase complex is formed by the combination of tissue factor, factor V, calcium, and a phospholipid surface to cleave a small peptide from factor X to form factor Xa. Extrinsic tenase also generates small amounts of factor IXa, which greatly accelerates formation of intrinsic tenase and is the major pathway for the formation of factor Xa. The intrinsic tenase is produced by the combination of factor IXa, factor VIIIa, and calcium on the surface of an activated platelet, and catalyzes production of factor Xa 50 times faster than extrinsic tenase. Factor Xa activates factors V and VII in feedback loops.

Blood contact with the biomaterials of the perfusion circuit was initially thought to be the major stimulus to thrombin formation during cardiopulmonary bypass. Increasing evidence indicates that the wound is the major source of thrombin generation during cardiopulmonary bypass [7,25]. This has encouraged the development of strategies to reduce the amounts of circulating thrombin during clinical cardiac surgery by either discarding wound blood or by exclusively salvaging red cells by centrifugation in a cell saver. The reduced thrombin formation in the perfusion circuit has also supported misguided strategies for reducing the systemic heparin dose during first-time coronary revascularization procedures using heparin-bonded circuits. While there is no good evidence that heparin-bonded circuits reduce thrombin generation, there is strong evidence that discarding wound plasma or limiting exposure of circulating blood to the wound (e.g., less bleeding in the wound) does reduce the circulating thrombin burden [26–28].

The coagulopathy induced by cardiopulmonary bypass affects children more profoundly than adults. Neonates are particularly affected, as a result of their unique cardiac lesions, immature hematopoietic and coagulation systems, and small blood volumes [29]. After birth, erythropoiesis is profoundly decreased, accompanied by the cessation of fetal hemoglobin production. This physiologic anemia results in hemoglobin nadirs of 9–11 g/dl at 8–12 weeks of age. Neonates have inherent deficiencies in vitamin K-dependent factors II, VII, IX and X which may be corrected by administering vitamin K at birth [30]. Deficiencies in contact factors (XI, XII, prekallikrein, and high molecular weight kininogen are also present at birth [4,31]). Hepatic immaturity and decreased factor synthesis and accelerated clearance of factors through higher metabolic rates also play a role. Coagulation inhibitors are also low. Protein C, Protein S, heparin cofactor II, and antithrombin III levels are also 40–60% of adult values, slowly achieving adult levels by 180 days [31]. Platelet aggregation may be impaired [32], and fibrinogen exists in a dysfunctional fetal isoform [31]. Notably fibrinogen, platelet counts, and factors V, VIII, von Willebrand factor, and XIII are normal at birth [31]. In spite of the preceding, prothrombin time, and thrombin clotting time are normal within a few days of birth [31]. Thromboelastography has shown that neonates and infants actually develop faster and stronger clots than adults [33].

Acquired coagulation defects have been reported in 58% of children with noncyanotic defects (decreased fibrinogen levels, platelet counts, prolonged bleeding times, and fibrinolytic activity, especially in infants) and 71% of patients with cyanotic defects (prolonged PT, aPTT, decreased levels of fibrinogen, factor II, V, VII, VIII, IX, X, and thrombocytopenia) [34–39].

Older children with cyanotic defects are much more likely to be polycythemic and manifest platelet dysfunction with prolonged bleeding times [35,40]. Polycythemia results in an artificially increased PTT because the heparin dose in specimen tubes is not calibrated for the reduced plasma volume accompanying polycythemia. The high incidence of stroke associated with polycythemia is variably attributed to hypercoagulability or to the poor deformability and sludging
of iron deficient cells [41,42]. Chronic hepatic congestion from the same mechanism or heart failure may lead to liver dysfunction and a decreased production of coagulation factors. Finally, older children are frequently undergoing reoperative surgeries and some are therapeutically anticoagulated. Younger children with polycythemia appear to be hypercoagulable prior to the onset of polycythemia with increased platelets, fibrinogen, and factors V and VIII [34].

Although much of our clinical practice in managing cardiopulmonary bypass in children is extrapolated from adult clinical practice, we will attempt to summarize empiric guidelines and published data where available. The text is organized into issues and strategies encountered before, during and after cardiopulmonary bypass.

2. Before cardiopulmonary bypass

2.1. Management of preoperative anticoagulants before cardiopulmonary bypass

With the increased utilization of anticoagulants and a plethora of new antiplatelet agents it is imperative that the cardiac surgeon be knowledgeable with their mechanisms and duration of action, in order to make appropriate decisions regarding the timing of surgery. In Table 1, a brief summary of agents, mechanisms, and recommended delays in surgery is provided. These topics are covered in more detail in other chapters.

2.2. Preoperative strategies to minimize postoperative blood requirement

2.2.1. Autologous donation

2.2.1.1. Preoperative autologous donation. Preoperative autologous donation was first reported in 1818 [46], and first used for cardiac surgery in the 1980s [47]. While advantages include avoiding the risks of transfusion, disadvantages include the logistical requirements as outlined in the American Association of Blood Bank Guidelines, namely: (1) adequate patient size, (2) adequate time for collection and red cell regeneration (generally 2 weeks per unit of blood in adults or 0.46 units per week [48]), and (3) adequate starting hematocrit (>33%) and red cell mass. Further, patients should be in adequate health and hemodynamically stable enough to withstand phlebotomy, thereby eliminating patients with important left ventricular outflow tract obstruction, congestive heart failure, active endocarditis or systemic infection.

In children, current recommendations are that no more than a maximum of 15% of a patient’s effective blood volume be removed at any given time. Preoperative autologous donation is safe in children over 30 kg, and has even been safely performed in children under 30 kg [49,50]. Iron therapy should be initiated to facilitate red cell regeneration. Smaller children are subject to difficulty with compliance during donation, more difficult venous access, and more hemodilution during cardiopulmonary bypass [50]. Autologous donation has been shown to be safe and effective in the pediatric population, resulting in better postoperative recovery of hemoglobin levels and higher reticulocyte counts [51].

2.2.1.2. Intraoperative autologous donation. As an alternative to preoperative autologous donation, others have sequestered heparinized blood just prior to cardiopulmonary bypass and given the sequestered blood postoperatively. This blood has the advantage of not having undergone clotting factor destruction or platelet activation on cardiopulmonary bypass [52]. Although hematocrit is not allowed to recover prior to surgery and heparin is administered when the blood is returned, this strategy may be a good compromise in small or hemodynamically unstable patients, since hematocrits can be adjusted on cardiopulmonary bypass. This strategy has been shown to be safe and effective in avoiding homologous blood transfusion [52].

2.2.2. Directed donation

Directed donation utilizes blood donated from a relative or family friend screened by the same criteria as regular donors. There is no established medical advantage in using directed donors. Directed donation requires the donor to be of matching blood type, advanced planning to schedule a donor’s blood collection, processing, testing, and shipping, as well as crossmatching at the hospital. Females of childbearing age should not receive donations from husbands or sexual partners because of the risk of sensitization to minor blood group antigens and hemolytic disease of the newborn. Directed donations between blood relatives are gamma-irradiated using 2500 cGy to minimize the risk of transfusion-induced graft-vs.-host disease. Unused units may be “crossed-over” for general use. In Australia, pediatric directed donation served a community need but did have a high wastage rate, was expensive, and was time and labor-intensive when compared with conventional blood [53]. In Canada, similar results led to the conclusion that directed donation was not justified [54].

2.2.3. Erythropoietin administration

Recombinant erythropoietin can be used to accelerate red cell production in anemic patients, (as it is in Jehovah’s Witnesses prior to surgery) but does require a finite period of time to be effective [55]. Allogenic blood transfusions can be reduced with preoperative autologous donation and erythropoietin. In anemic patients undergoing coronary artery bypass grafting, preoperative erythropoietin (vs. control) significantly increased hemoglobin 2.1±0.9 vs. 0.5±0.4 g/dl, respectively, and allogenic transfusion was significantly reduced. Recommended erythropoietin dosing was 500 U/kg once a week for 3 weeks preoperatively [56]. Preoperative erythropoietin significantly increased hemoglobin and avoidance of blood products in pediatric Jehovah’s Witnesses undergoing open heart surgery [57].
a 3 year old Jehovah’s Witness, erythropoietin at 2550 U/week for 4 weeks increased his hemoglobin level from 12.1 to 13.2 g/dl [58]. A larger pediatric study (n = 11) that used erythropoietin at 100 U/kg three times a week for 3 weeks prior to open heart surgery resulted in a median 8% increase in the reticulocyte count and a 6% increase in hematocrit [59]. Another study compared 39 children treated consecutively with erythropoietin (100 U/kg three times a week preoperatively, and IV on the day of surgery) with 39 consecutive age-matched controls who underwent open heart surgery. Allogenic blood was administered to 3/39 (7.7%) children receiving erythropoietin vs. 24/39 (61.5%) controls. They concluded that erythropoietin increased limits of autologous collection and significantly minimized allogenic transfusions [60].

In term infants awaiting heart transplant who require multiple transfusions secondary to iatrogenic blood losses, daily erythropoietin administration helped maintain stable hematocrits and minimized the need for blood transfusion [61]. Adverse effects with recombinant erythropoietin are very rare and include hypertension, rashes, epilepsy, headaches, flu-like symptoms and bone and muscle pains.

### 2.2.4. Jehovah’s Witnesses and cardiopulmonary bypass

The Jehovah’s Witness faith proscribes any allogenic or autologous blood products that have been separated from the body for any period [62,63], based on their interpretation of the Bible (Genesis 9:3–6; Leviticus 17:10; Acts 15:20, 28, 29; 21:25). Major products, i.e., red cells, white cells, platelets, and plasma are not acceptable. Other fractions are

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**Table 1**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Binding</th>
<th>Mechanism</th>
<th>Half-life</th>
<th>Clearance</th>
<th>Recommended delay in surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin unfractionated</td>
<td>Reversible</td>
<td>Binds antithrombin III (AT III) enhancing thrombin—AT III complex formation. Inhibits factor Xa Inhibits platelet function</td>
<td>30 min–2 h</td>
<td>Liver and RES</td>
<td>4–6 h Can be acutely reversed with protamine</td>
</tr>
<tr>
<td>LMW heparin (Enoxaparin)</td>
<td>Reversible</td>
<td>Factor Xa inhibition Binds AT III but too small to bind thrombin Minimal platelet interaction</td>
<td>6 h–10 h</td>
<td>Liver</td>
<td>24–48 h Only partially reversed by protamine</td>
</tr>
<tr>
<td>Warfarin (Coumadin)</td>
<td>Reversible</td>
<td>Inhibits vitamin K-dependent clotting factors II, VII, IX and X</td>
<td>37–89 h</td>
<td>Liver</td>
<td>3–4 days Can be acutely corrected with Vitamin K and FFP administration</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Irreversible</td>
<td>Cyclooxygenase acetylation inhibiting thromboxane A2 (TXA2) production Inhibits release of vitamin K-dependent factors</td>
<td>15 min (Biologic half-life 6–12 h)</td>
<td>Renal</td>
<td>7–10 days (aspirin increases postop CT drainage [43] but does not increase transfusion [44] or reoperation rate) [45]</td>
</tr>
<tr>
<td>Dipyridamole (Persantine)</td>
<td>Irreversible</td>
<td>Platelet adhesion inhibitor, phosphodiesterase and TXA2 inhibition</td>
<td>10 h</td>
<td>Liver</td>
<td>24–48 h</td>
</tr>
<tr>
<td>Clopidogrel (Plavix)</td>
<td>Irreversible</td>
<td>ADP blocker mediated platelet aggregation and subsequent GPIIb/IIa inhibition</td>
<td>8 h</td>
<td>Liver</td>
<td>7 days</td>
</tr>
<tr>
<td>Ticlopidine (Tielid)</td>
<td>Irreversible</td>
<td>ADP blocker</td>
<td>12 h–4 days</td>
<td>Liver</td>
<td>7 days</td>
</tr>
<tr>
<td>Abciximab (ReoPro)</td>
<td>Noncompetitive</td>
<td>GP IIb/IIIa receptor antagonist, inhibition (monoclonal antibody, long binding)</td>
<td>30 min</td>
<td>Binds tightly to platelets for at least 15 days</td>
<td>12 h</td>
</tr>
<tr>
<td>Tirofiban (Aggrastat)</td>
<td>Reversible</td>
<td>GP IIb/IIIa receptor antagonist (nonpeptide fibrin)</td>
<td>2.2 h</td>
<td>Renal</td>
<td>12 h</td>
</tr>
<tr>
<td>Eptifibatide (Integrillin)</td>
<td>Reversible</td>
<td>GP IIb/IIIa receptor antagonist (cyclic peptide)</td>
<td>2.5 h</td>
<td>Renal</td>
<td>12 h</td>
</tr>
</tbody>
</table>

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T. Yeh Jr., M.N. Kavarana / Progress in Pediatric Cardiology 21 (2005) 87–115
and reinfusion by cell-saver [64], as long as the blood products. Jehovah’s Witnesses will generally accept cardiopulmonary bypass, dialysis, intraoperative blood salvage and reinfusion by cell-saver [64], as long as the blood remains in continuous circulation with the patient’s blood. Cell-saver and autotransfusion techniques that maintain a closed circuit with an intravenous line from the collection device to the patient meet this requirement [65,66].

Great effort has been exerted to allow open heart surgery without transfusion [67]. In children, their smaller blood volumes and greater hemodilution make this more difficult [68]. Congenital cardiac surgery without blood products has been performed in Jehovah’s Witness children [69,70]. Recombinant erythropoietin is accepted by most Jehovah’s Witnesses [55], even though it does contain small amounts of albumin. Cardiopulmonary bypass without transfusion has been reported in children under 10 kg using preoperative erythropoietin [59]. Van Son et al. demonstrated an 8% increase in reticulocytes and a 6% increase in hematocrits in children pretreated with erythropoietin (100 U three times a week) and recommended preoperative, intraoperative and postoperative strategies to avoid transfusion [59]. Other strategies include decreasing the priming volume with vacuum-assisted venous drainage [71], hemodilution [72], modified ultrafiltration [73,74] and hemostatic adjuncts to attenuate blood loss in the perioperative period.

Naturally the management of Jehovah’s Witnesses is ethically charged for patients, families, and physicians. Caregivers must balance honoring a family’s religious beliefs with a caregiver’s sworn duty to the best medical interests of their patient, a child who may or may not ultimately accept the Jehovah’s Witness faith for herself. Families should be informed and consented in detail regarding the poorer neurologic outcomes with lower hematocrits on cardiopulmonary bypass and the possible fatality of avoiding transfusions. Many centers prophylactically obtain preoperative court orders to transfuse a patient so a child could be transfused in the case of life-threatening hemorrhage or anemia.

3. During cardiopulmonary bypass

3.1. Routine cardiopulmonary bypass

3.1.1. Surgical vs. coagulopathic causes of bleeding

For surgeons, coagulopathic bleeding is a diagnosis of exclusion. Although beyond the focus of this chapter, no hematologic strategy will effectively overcome true surgical bleeding. Intraoperatively it is incumbent on the surgeon to repeatedly rule this possibility out in a bleeding patient. The importance of well-placed hemostatic sutures remains the best defense against bleeding. Systematically organized inspection of all suture lines, cannulation sites, cut pleural and pericardial edges, and the chest wall is essential.

3.1.2. The role of hypothermia and rewarming

Hypothermia leads to coagulopathy by suppression of platelet aggregation by blocking thromboxane synthesis [75]. Increased transfusion and chest tube output have been documented with a lower core body temperatures in the intensive care unit after cardiopulmonary bypass [75]. Significant prolongation of prothrombin and plasma thromboplastin times has been demonstrated with hypothermia [76]. Some groups have even suggested that platelet transfusion may be beneficial [77,78]. In the ICU, warming blankets and overhead heaters especially in infants are essential.

3.1.3. Bypass circuits: volume, tubings, filters

Advances in oxygenator technology now provide a reduction in the priming volume [79]. Circuit volume can be further reduced by maximizing replacement of the crystalloid prime with autologous blood drained from the arterial cannula into the circuit immediately prior to cardiopulmonary bypass, called retrograde autologous priming (RAP), as well as displacing the venous prime when initiating cardiopulmonary bypass [80]. Leukocyte filters and heparin-bonded circuits reduce the inflammatory response and decrease the requirement for transfusion [81,82]. Priming methods have a controversial effect on blood loss. Some investigators conclude that using 5% albumin, rather than fresh frozen plasma reduced postoperative bleeding [83]. In contrast, another prospective randomized study showed reduced blood requirement when fresh frozen plasma was used in the prime [84].

Heparin-bonded circuits have been shown to reduce the inflammatory response and improve oxygenation in children, suggesting that improved biocompatibility reduces pulmonary complications [85,86] and provides other benefits [85,87]. A prospective randomized study in children revealed that heparin-bonded circuits significantly reduced cytokines and complement generation, lowered interleukin levels, and improved pulmonary and coagulation function after bypass [88].

3.1.4. Modified ultrafiltration

The systemic inflammatory response induced by cardiopulmonary bypass increases morbidity and mortality through capillary leak, fluid overload, poor alveolar gas exchange, and delayed extubation [89]. In children, the relatively more severe hemodilution disproportionately depletes platelets and coagulation factors. Although cell salvage can yield a significant number of red blood cells, in children, ultrafiltration is superior in terms of platelet number and function, and concentration of plasma proteins...
including fibrinogen [90–92]. Others have shown a more negative fluid balance, in addition to preserved platelet number and function, fibrinogen, antithrombin III, total protein and colloid osmotic pressure [93]. Ultrafiltration also removes inflammatory mediators including C3a, C5a, interleukin-6 and tumor necrosis factor-α. Ultrafiltration has been shown to improve early hemodynamics, oxygenation, blood loss, and ventilator days after cardiac surgery [94]. Ultrafiltration is strongly recommended, especially in smaller children undergoing cardiopulmonary bypass.

3.1.5. Importance of maintaining hematocrit on cardiopulmonary bypass

Historically, many centers permitted marked hemodilution on cardiopulmonary bypass to avoid transfusion. Recent studies question that approach and provide evidence of improved neurologic function when higher hematocrits are maintained during cardiopulmonary bypass. Although pigs demonstrate increased cerebral blood flow and metabolism with hemodilution [95], a randomized controlled clinical study in infants undergoing cardiopulmonary bypass demonstrated adverse perioperative and developmental outcomes with hemodilution [96]. Others have shown that increasing hematocrit with modified ultrafiltration improved outcomes after the Norwood procedure [97]. This issue remains controversial, although the clinical data in support of higher hematocrits are compelling.

3.2. Heparin anticoagulation during cardiopulmonary bypass

3.2.1. Heparin variability

The mechanism of heparin’s action is well-described in other chapters; however, one important aspect of using heparin is its variability between individual batches and in a patient’s response.

3.2.1.1. Variability resulting from source (porcine intestinal mucosa vs. bovine lung). The advantages of heparin extracted from porcine intestinal mucosa, or heparin extracted from bovine intestinal or lung tissue have been studied in some detail. In 100 randomized patients, beef lung heparin had greater anticoagulant activity than pork mucosal heparin during a preoperative heparin tolerance test and also during cardiopulmonary bypass [98]. Supplemental heparin was needed in many more of the patients receiving porcine mucosal heparin. Notably less bleeding occurred in patients who received beef lung heparin.

In another study, 113 patients were randomized to receive bovine or porcine heparin [99]. Heparin was infused at 4.5 mg/kg during bypass and administered at the lesser of 70 units/kg or 5000 units/dose at 12-h intervals postoperatively. Platelet counts decreased to 45% of baseline during the first 3 postoperative days (porcine, 44±13%, n=50; bovine, 46±15%), but normalized by day 7. The porcine group had significantly more blood loss than the bovine heparin group (350.7±727.8 ml vs. 1059.6±381.0 ml, respectively, p<0.01). Consequently, the platelet transfusion requirement was greater in the porcine vs. bovine heparin group (1.7±3.9 units vs. 0.5±1.7 units; p<0.05). Except for platelets, blood and blood component transfusion was not different. When patients receiving anticoagulants or anti-inflammatory agents, were compared, four patients in the porcine group received a mean of 8.5 units of packed cells plus supplemental platelets, while seven patients in the bovine group received a mean of 3.0 units of packed cells with no platelets. Porcine heparin resulted in a generalized increase in postoperative bleeding with increased management problems in patients undergoing cardiopulmonary bypass. Additionally, bovine lung heparin has a more reliable protamine neutralization response [100].

Medical patients receiving porcine heparin had a much higher frequency of thrombocytopenia than those receiving bovine heparin [101,102]. Unfortunately, in randomized studies of acute thrombosis, bovine lung heparin was more likely to cause heparin-induced thrombocytopenia (HIT) than porcine heparin [103–107]. Soon porcine heparin became preferred at many medical centers.

In cardiac surgery patients, HIT occurs in 0.75% to 3% [108]. A prospective, randomized study of HIT antibody seroconversion in 98 cardiac surgical patients, found no difference between bovine and porcine heparins (34% vs. 28%, respectively, p=0.74) [109]; however, samples were not tested after postoperative day 5, because it is too early to detect most cases of HIT [110]. A more recent randomized trial found that bovine vs. porcine heparin was associated with a significantly higher seroconversion rate: 49.5% vs. 35.2%; respectively, as well as late seroconversion: 46.8% vs. 32.0% [111]. Now, with the outbreak of bovine spongiform encephalopathy (“mad cow disease”), only porcine heparin is used in the United States and Europe [112].

3.2.1.2. Variability resulting from batch variability and potency standardization. Heparin cannot be prepared with conventional methods. Small-scale batch processing is required and significant batch variability results. The potency of each batch must be standardized using a United States Pharmacopoeia (USP) reference standard yielding units of activity per milligram. A discrepancy of at least 10% in heparin activity was found when the USP reference was compared with the 4th International Standard (IS) [113]. Similarly, a collaborative study by the World Health Organization found that the USP and EP (European Pharmacopoeia) standards differed from their labeled potencies by 10.6% and 2.6%, respectively, when assayed against the 5th International Standard by all methods. Today’s heparin preparations have higher mean molecular weights and narrower molecular weight distributions which yield higher specific activities (180–210 IU/mg). Better agreement is observed when heparins are calibrated against a reference with similar properties.
3.2.1.3. Variability resulting from patient specific factors. The response to a fixed heparin dose varies significantly between patients. A patient’s physiologic state at heparinization is often acute. Increases in acute phase reactant proteins such as factor VIII and fibrinogen commonly shorten the APTT and may appear as heparin resistance [114]. Alternatively, warfarin or factor deficiencies may prolong the APTT. In these cases, less heparin may be required [115]. The common lupus anticoagulant, monoclonal gammopathies, and dysfibrinogenemia may also prolong the APTT but increase the risk of inadequate heparinization [116]. Some acute phase reactants bind heparin, preventing complex formation with ATIII and successful anticoagulation [117]. Weight and age influence the response to heparin through altered intravascular volume and binding of heparin to vascular surfaces.

3.2.2. Heparin monitoring during and after cardiopulmonary bypass

To prevent catastrophic hemorrhagic or thrombosis, heparin requires close monitoring by two complementary modalities: functional assays which monitor clotting time and quantitative assays which monitor heparin concentrations.

3.2.2.1. Activated clotting time (ACT). Development of the ACT clotting time was seminal in managing cardiopulmonary bypass. ACT tests whole blood clotting and protein function. Thrombin time and PTT will not clot at the large heparin doses required for cardiopulmonary bypass and therefore are not useful. ACT monitoring was developed by placing whole blood in a glass or plastic receptacle with premeasured activator [118]; however, variability in measurement led to the development of automated methods. The two most common activators are kaolin (aluminium silicate) and celite-diatomaceous earth (sodium silicate). Kaolin is an artificial product. Celite is isolated from clay deposits that are heavily laden with microskelaxons of diatoms (prehistoric protozoan-like creatures). Both activate Hageman factor which leads to factor IX and then factor Xa production. Kaolin is preferred if aprotinin is being used because kaolin absorbs 98% of aprotinin on contact, therefore negating the effect of aprotinin on the ACT. Celite does not absorb aprotinin and aprotinin significantly prolongs the ACT [119]. Aprotinin, because of its ability to inhibit kallikrein, decreases thrombin–antithrombin III complexes, fibrin-split products, fibrinopeptide 1 and 2, prothrombin fragments, and all markers of thrombin formation, thereby prolonging the ACT [120].

A roughly linear relationship exists between heparin dose and the ACT if certain criteria are maintained [118], namely: normal ATIII and factor XII activities, normothermia, near normal platelet function, a platelet count greater than 50,000, and fibrinogen concentration greater than 100 mg/dl. Before cardiopulmonary bypass, a dose–response curve can be drawn both to monitor the ACT and calculate the protamine reversal dose. An ACT between 300 and 600 s is recommended to prevent clot formation in the oxygenator and minimize bleeding complications [118]. Alternatively, others employ a heparin protocol to reduce heparin rebound and postoperative bleeding [121]: including administration of 300 U/kg heparin IV initially with additional heparin if required to achieve ACT greater than 300 s prior to and during normothermic cardiopulmonary bypass and greater than 400 s during hypothermia (under 30 °C).

3.2.2.2. Heparin levels. Given the variability in the ACT, heparin concentration can also be measured directly. Acceptable levels during cardiopulmonary bypass are 3.5–4 U/ml. Heparin concentration is measured by bubbling air through individual specimens in glass wells, each of which contain incrementally larger amounts of protamine. The first tube to clot contains the optimal ratio of heparin to protamine and yields a heparin concentration.

The combined use of ACT and heparin levels have decreased perioperative bleeding and transfusion when compared with the ACT alone; however, heparin monitoring is expensive [121] and some investigators believe heparin levels correlate well with ACT [122]. Others have shown weak correlation between these modalities [121]. This is particularly true with antithrombin III deficiency and heparin resistance [123] in which 2–3 times the standard heparin dose may be required to achieve the desired ACT of 480 s. If cardiopulmonary bypass were initiated based on heparin levels without benefit of functional (ACT) testing, catastrophic thrombosis may result. The etiology of antithrombin III deficiency is usually a previous dose-dependent exposure to heparin [124]. The treatment is antithrombin III replacement with fresh frozen plasma or antithrombin III concentrate.

3.2.3. Heparin dosing, metabolism, and management on cardiopulmonary bypass

Initial heparin doses range from a 200–400 U/kg bolus before cannulation, 200–400 U/kg in the circuit, and 50–100 U/kg ongoing administration every 30–120 min. Heparin’s peak therapeutic effect occurs within 2 min. Cardiopulmonary bypass may delay the peak effect by 10–20 min from hypothermia or hemodilution. Plasma binds 95% of heparin with some uptake by the extracellular fluid, alveolar macrophages, splenic/hepatic endothelial cells and vascular smooth muscle. The plasma half-life is dose-dependent, i.e., 126 ± 24 min at a dose of 400 U/kg vs. 93 ± 6 min at a dose of 200 U/kg [125]. Heparin is metabolized by the reticuloendothelial system and eliminated by the kidneys. Hypothermia and renal impairment, but not hepatic impairment, delay elimination.

An ACT is measured before heparinization and repeated a minimum of 3 min after giving heparin. A two-point (straight line) dose–response curve assists in judging how much additional heparin to administer. Cardiopulmonary bypass is not initiated until an adequate ACT or heparin
level is confirmed. The optimal ACT for cardiopulmonary bypass is controversial. Although the minimum recommended ACT is 400 s, others recommend 480 s [118], since heparin only partially inhibits thrombin formation. This is done to minimize the consumptive coagulopathy that may result from barely adequate anticoagulation. Failure to achieve a satisfactory ACT may be due to inadequate heparin or to low concentrations of antithrombin III, or “heparin resistance.” If 500 U/kg of heparin fails to achieve an adequate ACT, ATIII deficiency becomes more likely, and fresh frozen plasma or recombinant ATIII [126] is necessary to increase antithrombin concentration.

During bypass, the ACT or heparin level is measured every 30 min and more heparin is given to maintain target levels. Usually one third of the initial heparin bolus is given every hour even when the ACT is therapeutic. Heparin levels are more reproducible than the ACT, but ACT has a long and generally safe track record. Although excessively high ACTs (i.e., >1000 s) may cause bleeding remote from operative sites, low concentrations increase circulating thrombin and risk low grade thrombosis in the circuit and a post-bypass consumptive coagulopathy [127].

One study prospectively evaluated whether heparin and protamine doses administered using a standardized protocol based on body weight and activated clotting time values were associated with either transfusion of hemostatic blood products or excessive postoperative bleeding in 487 cardiac surgical patients. Prolonged duration of cardiopulmonary bypass, lower pre-bypass heparin dose, lower core body temperature in the intensive care unit, combined procedures, older age, repeat procedures, a larger volume of salvaged red cells reinfused intraoperatively and abnormal laboratory coagulation results (prothrombin time, activated partial thromboplastin time, and platelet count) after cardiopulmonary bypass were associated with both increased transfusion and chest tube drainage. Female gender, lower total heparin dose, preoperative aspirin use and the number of hemostatic blood products administered intraoperatively were associated only with increased chest tube drainage. A larger total protamine dose was associated only with perioperative transfusion of hemostatic blood products. Preoperative use of warfarin or heparin was not associated with excessive blood loss or perioperative transfusion of blood products [75].

3.3. Protamine

3.3.1. Heparin reversal

Protamine is a positively charged basic polypeptide isolated from salmon sperm which binds electrostatically to negatively charged heparin and reverses its anticoagulant effect. One to three mg/kg of protamine is given for each 100 units of the initial heparin dose. A randomized study of 26 infants and children compared heparin reversal using standard 1 mg/1 mg ratio of total administered heparin for patients in one group and of the individualized residual heparin concentration in the other group. They found that individualized management of anticoagulation and its reversal results in less activation of the coagulation cascade, less fibrinolysis, and reduced blood loss and need for transfusions [128]. After 1/3 to 1/2 of the planned protamine dose is administered, blood from the surgical field must not be returned to the cardiotomy reservoir to avoid circuit thrombosis. An ACT or heparin level confirms adequate heparin neutralization. More protamine (0.5–1 mg/kg) can be given if either test remains prolonged and bleeding is a problem.

3.3.2. Protamine anticoagulant effect

Although protamine’s neutralizing dose is 1:1 (1 mg to 100 Units), in large doses protamine exerts an anticoagulant and antiplatelet effect that requires an excess of 3:1, by inhibiting the proteolytic activity of thrombin on fibrinogen [129,130]. This prolongation is paradoxically reduced by heparin. Protamine decreases the platelet count by electrostatically adhering to platelet membranes forming micro-aggregates [131] and causes the release of tissue plasminogen activator from endothelium [132].

3.3.3. Protamine reactions

Hypotensive protamine reactions can occur when protamine complexes with heparin because complement is released. This is much less common in children than adults. This hypotension can be attenuated by adding calcium (2 mg/1 mg protamine).

Rarely 0.6%–2% of patients receiving protamine have anaphylactic reactions from antibodies to protamine insulin [133]. Patients who are insulin-dependent diabetics on NPH (neutral protamine Hagedorn), who have undergone vasectomy, or who are allergic to fish are at particular risk.

Pediatric protamine reactions are rare occurring in 1.7–2.8% of patients undergoing cardiopulmonary bypass [134]. Life-threatening reactions to protamine represent true allergic reactions and are classified in Table 2. Protamine reactions are treated with calcium chloride, volume resuscitation, phenylephrine, norepinephrine, and other inotropic support as required. For severe reactions, it may be necessary to readminister heparin and resume cardiopulmonary bypass.

### Table 2

<table>
<thead>
<tr>
<th>Protamine reactions</th>
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</thead>
<tbody>
<tr>
<td>I Hypotension from rapid administration (histamine related)</td>
</tr>
<tr>
<td>II Anaphylactic shock–hypotension, bronchospasm, flushing and edema</td>
</tr>
<tr>
<td>II A IgE and IgG mediated, systemic capillary leak</td>
</tr>
<tr>
<td>II B Immediate nonimmunologic anaphylactoid reaction</td>
</tr>
<tr>
<td>II C Delayed reaction related to complement activation</td>
</tr>
<tr>
<td>III Catastrophic pulmonary vasoconstriction, elevated pulmonary artery (PA) pressures, decreased left atrial (LA) pressures and myocardial depression</td>
</tr>
</tbody>
</table>
3.3.4. Heparin rebound

Heparin rebound is a delayed anticoagulant effect after protamine neutralization due to the rapid metabolism of protamine and to the release of “stored” heparin from lymphatic tissues and other deposits. A significant amount of heparin is nonspecifically bound to plasma proteins and is incompletely neutralized by protamine. Heparin rebound manifests postoperatively by increases in thrombin clotting time, antifactor Xa activity, and protein-bound heparin 1–6 h after surgery [135].

A prospective randomized study of heparin rebound in 300 adults undergoing cardiopulmonary bypass evaluated the effect of a small dose of protamine (25 mg/h for 6 h) on bleeding. Every control patient manifested heparin rebound with increased thrombin clotting time, antifactor Xa activity, and protein-bound heparin between 1 and 6 h after surgery. Heparin rebound was eliminated in the experimental group with normal thrombin clotting times and nearly undetectable heparin levels and protein-bound heparin. Bleeding was reduced by 13%, although transfusions were not changed. No adverse events were attributable to the extra protamine [135].

3.4. Alternative anticoagulants for cardiopulmonary bypass with heparin sensitivity

While heparin-induced thrombocytopenia will be covered in other chapters, Table 3 summarizes alternative anticoagulants that can be used to manage cardiopulmonary bypass when heparin is contraindicated. The alternative direct thrombin inhibitors inhibit fibrin-bound thrombin independent of antithrombin [136], do not require access to the heparin binding site of thrombin, and inhibit both fibrin-bound and fluid-phase thrombin.

3.5. Pharmacologic adjuncts to decrease bleeding after cardiopulmonary bypass

Antifibrinolytic agents are commonly used in cardiac surgery and they act not only by inhibiting fibrinolysis but also by protecting platelets. They are optimally given before the fibrinolysis initiated by cardiopulmonary bypass.

3.5.1. Aprotinin

Aprotinin is a low molecular weight serine protease inhibitor, isolated from bovine lung. Its antifibrinolytic effect is via the inhibition of plasmin and kallikrein. Reversible complexes are formed with various proteases that act against trypsin, plasmin, streptokinase-plasma complex, tissue kallikrein, and plasma kallikrein. Aprotinin intervenes in the coagulation cascade at multiple loci. Aprotinin inhibits propagation of “intrinsic” fibrinolysis through factor XII-mediated kallikrein activation and the generation of plasmin through “extrinsic” or t-PA-mediated activation of plasminogen. Aprotinin reduces thrombin-mediated consumption of platelets by preserving adhesive platelet receptors (GpIb). Aprotinin is excreted via the kidney and raises ACT.

When aprotinin was first used in cardiac surgery, hemostasis was rapidly established in 5 patients manifesting a coagulopathy after cardiopulmonary bypass [148]. The currently accepted regimen of high-dose aprotinin in adults,

<table>
<thead>
<tr>
<th>Table 3 Alternate anticoagulants</th>
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</thead>
<tbody>
<tr>
<td><strong>Generic Name (Trade Name)</strong></td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>Lepirudin (Refludan)</td>
</tr>
<tr>
<td>Bivalirudin (Angiomax)</td>
</tr>
<tr>
<td>Argatroban (Argatroban) [143,144]</td>
</tr>
<tr>
<td>Orgaran (Danaparoid) [145,146]</td>
</tr>
</tbody>
</table>
The efficacy of aprotinin in children is controversial. A small prospective randomized study of cardiopulmonary bypass in children showed no clinical benefit [156]. Two other smaller randomized studies in children found no significant reduction in perioperative blood loss with either low or high dose aprotinin [157,158]. The low dose group received 20,000 units/kg after anesthesia, 20,000 units/kg in the prime, and another 20,000 units/kg given every hour of cardiopulmonary bypass. The high dose group received 35,000 units/kg after anesthesia, 35,000 units/kg in the prime, and an infusion of 10,000 units/kg/min until the end of the operation. Possible reasons why the efficacy of aprotinin could not be demonstrated in these studies are that there exists a known variability of plasma aprotinin levels in children undergoing CPB [159] which often results in subtherapeutic plasma levels, especially in the low-dose group, and that small underpowered studies may have failed to reach significance.

In contrast, several recent studies have shown significant improvements in blood loss and blood product usage with high dose aprotinin [160,161]. Some studies have demonstrated the efficacy of only high dose aprotinin in reoperative and highly complex malformations [162,163]. Patients undergoing repair of ventricular septal defect repair, tetralogy of Fallot, and transposition of the great vessels received low dose (500,000 KIU in the pump prime only) and high dose (50,000 KIU/kg after anesthesia, 50,000 KIU/kg in pump prime, and 20,000 KIU/h continuous infusion) aprotinin [163]. Only complex patients benefited, and of those, only those receiving the high dose regimen benefited. No benefit was seen with the low dose regimen. In reality, there is no true low/high dose regimen but several weight/BSA-based protocols developed to achieve and maintain a plasma level (200 KIU/ml).

Recently, the variability of plasma aprotinin levels was highlighted in children undergoing cardiopulmonary bypass using current weight-based protocols [159]. Neonates and smaller children were at a high risk of reaching subtherapeutic levels of aprotinin. The authors concluded that dosing regimens aimed at achieving “target” aprotinin concentrations for pediatric patients of all weight groups need to be developed to better define the role of aprotinin in blood conservation. Several strategies are summarized in Table 4.

A hypersensitivity phenomenon to aprotinin has been observed. The incidence is <1% during the first exposure, and increases to 5–6% on repeat exposure [164,165]. Children frequently require sequential reoperations and possible risk of an allergic reaction must be considered; however, in children, the risk of hypersensitivity was much lower even after multiple reexposures, ranging from 1% after the first exposure to 2.9% after the third or higher exposures [164,166].

A comprehensive review of pediatric patients undergoing cardiopulmonary bypass suggests that children undergoing reoperative cardiac surgery have improvements in postoperative blood loss, but that blood loss is not reduced in children undergoing primary surgical repair [167]. The potential antiinflammatory and antifibrinolytic benefits are unclear because of the wide range in dosing and plasma levels found in these studies. It is clear that achieving a plasma concentration between 200 KIU/ml and 400 KIU/ml is important [167]. A known discrepancy exists in pediatric dosing because of age-related differences in body surface area to weight ratio. Neonates are particularly affected. In children less than 10 kg, some have recommended that a minimum of 500,000 KIU be added to the pump prime to offset the dilutional effect of priming volume [168].

The current literature suggests that aprotinin be used in high risk and reoperative patients to reduce blood loss and transfusion requirements. Further weight-based dosing regimens need to be developed to achieve plasma levels of 200–400 KIU/ml [167].

Despite an early study suggesting increased graft thrombosis after reoperative coronary artery bypass [169], a meta-analysis on all prospective randomized placebo controlled trials using aprotinin has demonstrated no increased risk of thrombosis in the adult population [170]. In the pediatric population there is no evidence of increased thrombosis in the current literature and to date [167].

### 3.5.2. Epsilon aminocaproic acid (Amicar)

Epsilon aminocaproic acid (EACA) is a synthetic antifibrinolytic agent which forms reversible complexes with either plasminogen or plasmin, saturating the lysine binding sites and displacing plasminogen, and therefore plasmin, from the surface of fibrin. This blocks plasminogen activation and fibrinolysis.

EACA has been used successfully to treat patients undergoing coronary artery bypass grafting with coagulation disorder [171]. It has also been used prophylactically to reduce blood loss in patients undergoing cardiopulmonary bypass, having an impact on both blood loss and transfusion of autologous blood and blood products [172]. Low-dose aprotinin and EACA have shown similar effects on the reduction of intraoperative and postoperative bleeding in the
<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Dosing</th>
<th>Evidence of efficacy</th>
<th>Evidence of risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aprotinin (Trasylol)</td>
<td>Serine protease inhibitor w multifocal effects (see text)</td>
<td>Concentration: 1 cm³ = 1.4 mg = 10,000 KIU Adults: (need 200 KIU/ml plasma level) Hammersmith dosing protocol 5–6 million KIU average total dose 2 million KIU pre-bypass 2 million KIU in the pump prime 0.5 million KIU/h Pediatrics: (no manufacturer or dosing recommendations but a plasma level of 200 KIU/ml is probably advisable)</td>
<td>Strong</td>
</tr>
<tr>
<td>Epsilonaminocaproic acid (Amicar)</td>
<td>Complexes with plasminogen at lysine-binding sites, and blocks adhesion to fibrin</td>
<td>Adults: Load: 100 mg/kg, Infusion: 1 g/hr Load: 150 mg/kg, Infusion: 30 mg/kg/hr Load: 50 mg/kg, Infusion: 25 mg/kg/hr Pediatrics: Load 75 mg/kg, infusion 15 mg/kg/h Load 150 mg/kg, infusion 30 mg/kg/h (this dose was felt appropriate to achieve desired plasma level of 130 mcg/ml) Load 75/mg/kg, 75 mg/kg into pump circuit, Infusion 75 mg/kg/h (to achieve plasma level 260 mcg/ml)</td>
<td>Yes</td>
</tr>
<tr>
<td>Tranexamic Acid</td>
<td>Complexes with plasminogen at lysine-binding sites, and blocks adhesion to fibrin</td>
<td>Adults: Load 10 mg/kg, infusion 1 mg/kg/h 2× and 4× did not change blood loss in adults Pediatrics: Load 100 mg/kg, Infusion: 10 mg/kg/hr 0.3 mcg/kg single dose</td>
<td>Yes</td>
</tr>
<tr>
<td>DDAVP</td>
<td>Stimulates endothelium to release von Willebrand factor, tPA and prostacyclin</td>
<td>None [183,184]</td>
<td>None [180,182]</td>
</tr>
<tr>
<td>Conjugated Estrogens</td>
<td>Unknown</td>
<td>0.6 mg/kg/day × 5–6 days OR 50 mg/day</td>
<td>None</td>
</tr>
<tr>
<td>Steroids</td>
<td>Unknown</td>
<td>Solucortef 100 mg IV</td>
<td>None</td>
</tr>
<tr>
<td>Recombinant factor VII</td>
<td>Activation of factor X via the VⅢa-TF enzymatic complex to the enzyme factor Xa and subsequent thrombin generation</td>
<td>50–60 mcg/kg per dose × 3–4 doses up to 225 mcg/kg</td>
<td>Yes</td>
</tr>
</tbody>
</table>
adult cardiac surgery population [173]. A prospective randomized study compared low dose aprotinin with EACA in the pediatric population and found a significant decrease in perioperative blood loss and transfusion requirement with both drugs but no difference between both drugs [174].

3.5.3. Tranexamic acid

Similar to EACA, tranexamic acid forms a complex with plasminogen through lysine-binding sites, thus blocking their adhesion to fibrin. In contrast to EACA, tranexamic acid is approximately 10 times more potent. A prospective randomized study in children undergoing cardiopulmonary bypass compared tranexamic acid (100 mg/kg, followed by 10 mg/kg/h) with placebo and found significantly decreased blood loss [175]. As with EACA, postoperative bleeding and homologous blood requirements were similarly decreased with the use of tranexamic acid patients undergoing cardiopulmonary bypass [176]. A dose comparison study in children found that a triple dose regimen using 10 mg/kg on induction, once on cardiopulmonary bypass, and after protamine resulted was most effective in reducing perioperative blood loss [177]. Further, in adults undergoing cardiopulmonary bypass pretreated with aspirin, aprotinin was no better than tranexamic acid in curtailling blood loss and was much cheaper [178].

3.5.4. Desmopressin (DDAVP)

DDAVP is a synthetic analogue of vasopressin with decreased vasopressor activity. It stimulates the vascular endothelium to release von Willebrand factor, tissue plasminogen activator and prostacyclin. DDAVP results in a 2 to 20-fold increase in factor VIII levels and mediates platelet adherence to the vascular subendothelium. A prospective randomized study in adults undergoing cardiopulmonary bypass for various indications demonstrated significantly reduced mean operative and early postoperative blood loss (1317 ± 486 ml in the treated group vs. 2210 ± 1415 ml in the placebo group). However the excessive blood loss in both groups and the absence of data on transfusion requirement cast some doubt on their findings [179]. Another nonrandomized study demonstrated a significant decrease in transfusions (especially platelets) in patients treated with DDAVP [180].

In contrast, a prospective randomized double blind study in adults undergoing cardiopulmonary bypass for a variety of indications demonstrated no overall reduction in blood loss or transfusions for patients receiving DDAVP, but did show a significantly lower intraoperative blood loss [181]. Another similar randomized double blind study in adults showed no benefit for DDAVP in routine coronary artery bypass surgery [182].

In children several reports have demonstrated no significant benefit of DDAVP compared with placebo. A randomized double-blind study in children undergoing cardiopulmonary bypass found no difference in blood loss and transfusion requirement between both groups [183]. A similar study demonstrated no difference in blood loss in children undergoing repair of complex congenital heart defects [184].

The current literature in children undergoing cardiopulmonary bypass shows no compelling evidence that DDAVP reduces perioperative blood loss, except in patients with hemophilia, von Willebrand’s Disease, uremic platelet dysfunction, or chronic liver disease.

3.5.5. Conjugated estrogens

Reports have demonstrated shortened bleeding times and reduced bleeding with conjugated estrogen in adult patients with uremia [185]. Although the mechanism is unknown, the effect lasts longer than DDAVP and cryoprecipitate in the setting of uremic platelet dysfunction [186]. One study shows improvement in perioperative blood loss [187], while another showed no reduction in blood loss or transfusion requirement [188]. Conjugated estrogens can be given intravenously or orally. A single daily infusion of 0.6 mg/kg, repeated for 4–5 days, shortened the bleeding time by approximately 50% for at least 2 weeks. A daily oral dose of 50 mg shortened the bleeding time after an average of 7 days of treatment. The pediatric literature offers no support for the routine use of estrogens and the adult evidence is not compelling.

3.5.6. Steroids

Although salutary effects of steroids have been suggested in a few studies in the adult cardiac surgery population [189,190], a recent prospective randomized study in children undergoing cardiac surgery showed no benefit [191]. At the present time there is no compelling data to support the routine use of steroids for the prevention of bleeding after cardiopulmonary bypass.

4. After cardiopulmonary bypass

4.1. Transfusion/blood products

Much literature is dedicated to transfusion medicine and is beyond the scope of this chapter. The brief discussion of conventional products will be given, followed by more detailed discussion of fresh whole blood and new component therapies.

4.1.1. Platelets

Platelets are decreased in number and effectiveness by cardiopulmonary bypass. Hemodilution accounts for most of the decreased platelet count; sequestration, adhesion, and destruction from contact with artificial surfaces account for the rest [193]. In seconds, contact of blood with foreign surfaces leads to platelet adherence, release of cytoplasmic granules, and thromboxane A-2 production. This is mediated by von Willebrand factor which acts as a bridge between a specific glycoprotein on the surface of platelets (GPIb/IX) and collagen fibrils, binding to and stabilizing coagulation factor VIII. Binding of factor VIII by vWF is
required for normal survival of factor VIII (extremely labile otherwise) in the circulation. Plasma levels of thromboxane A-2 and platelet specific proteins rise at onset of bypass. Platelet stores of ADP and ATP are depleted. Microemboli formation contributes to platelet consumption.

Platelet counts decrease to 40–50% of baseline in the first 10–15 min and then stabilize. This is followed by a passivation of foreign surfaces which is characterized by reduced platelet adhesiveness. Platelet counts rarely drop below 40–50% of baseline and usually rise by 50% by postoperative day 2, returning to normal 3–7 days postoperatively, probably from release after sequestration in the liver [193].

Acquired platelet dysfunction may also result from therapeutic platelet inhibitors (e.g., aspirin and clopidogrel). Stopping these agents prior to elective surgery is recommended though not always feasible [194]. In these instances, aprotinin is protective against platelet dysfunction via preservation of platelet membrane bound glycoprotein receptors [195].

Platelet transfusions may be used in the bleeding thrombocytopenic patient. Even when counts are normal, platelets may not be functioning properly. Platelets are frequently the first line of product administration in children because of the general activation that occurs on cardiopulmonary bypass, abnormal function of remaining platelets, and not infrequent use of platelet inhibitors. Single-donor or multiple-donor pooled platelets are available. Single-donor platelets reduce infection and risk of alloimmunization but are more expensive. When pooled, platelets are typically from 5–8 donors. Platelets are not required to be ABO compatible with the recipient; however, Rh negative recipients should receive Rh negative donor platelets, because platelets can contain enough erythrocytes for Rh sensitization.

4.1.2. Fresh frozen plasma (FFP)

FFP is separated from whole blood by centrifugation and stored at −18 °C within 6 h of collection. Fifty percent of factors V, VII, and VIII may be lost from lability, while all other factors are 100% preserved. FFP can be stored at −20 °C for up to 1 year. After cardiopulmonary bypass, FFP is indicated when there is evidence of significant coagulation factor deficiency with a prothrombin time (PT) and plasma thromboplastin time (PTT) more than 1.5 times the control. Ten ml/kg of FFP should raise the factor levels by 2–3%. FFP must be ABO compatible with the recipient’s red cells. The volume of FFP in each pack is stated on the label and may vary between 180 and 400 ml. The traditional dose of 5 to 10 ml of plasma per kilogram body weight may have to be exceeded in massive bleeding. Therefore, the dose depends on the clinical situation and monitoring.

The use of FFP in pump prime has been hypothesized to avoid dilution of fibrinogen, decreasing the need for subsequent product transfusion. Twenty infants less than 8 kg undergoing cardiopulmonary bypass were prospectively randomized to receive 1 unit of FFP in the prime (vs. none in the control group) [84]. Infants receiving FFP in the prime had significantly less dilutional hypofibrinogenemia, need for cryoprecipitate after bypass, and tended to have less mean exposure to blood products [84]. A prospective randomized study from the Mayo clinic found that patients who received 1 unit of FFP in the prime (vs. 5% albumin) had significantly higher total transfusions (8.0±4.2 vs. 6.1±4.5 U, respectively; p=0.035). A post hoc analysis suggested that patients with cyanosis and those requiring complex operations had less blood loss with FFP, than did those receiving albumin in the prime. Conversely, noncomplex, acyanotic patients had fewer transfusions with albumin prime [196].

4.1.3. Cryoprecipitate

Cryoprecipitate is prepared by thawing frozen plasma at 4 °C and recovering the precipitate. The cryoprecipitate derived from one unit of whole blood contains 80–100 units of factor VIII and vWF and 150 mg of fibrinogen. In the bleeding patient after cardiopulmonary bypass, cryoprecipitate transfusion is indicated at a dose of 5 ml/kg if the fibrinogen level falls to less than 100 mg/ml [197].

4.1.4. Packed red blood cells

Packed red cells are indicated in the treatment of postoperative anemia to increase oxygen transport and intravascular volume. One unit contains 300–350 ml and with additives can be stored for up to 42 days. Depending on the type of congenital defect, packed red blood cells are used to maintain hemoglobin levels at optimum levels postoperatively in order to preserve or augment oxygen carrying capacity. A commonly used formula for determining the volume of packed red cells transfusion in infants and children is: (Desired Hgb (g/dl) – Actual Hgb) × Weight (kg) × 3 [197].

4.1.5. Fresh whole blood

To avoid multiple exposures associated with individual component therapy, fresh whole blood has been utilized to replete all components of lost blood with one exposure [198]. In children under 2 years of age and those undergoing complex repairs with fresh whole blood less than 48 h old, perioperative blood loss and exposure were decreased [199]. Mohr et al. compared recovery of platelet count and function in 27 patients who were randomized preoperatively to receive either 1 unit of fresh whole blood (15 patients) or 10 units of platelet concentrates (12 patients) after cardiopulmonary bypass. Platelet thromboxane formation was higher after 1 unit of fresh whole blood than after 10 platelet units (95±25 vs. 46±35 ng/ml, p less than 0.05), as was platelet aggregation response to collagen and epinephrine. The 24-h blood loss was smaller in the fresh whole blood group (560±420 ml vs. 770±360 ml), although the difference was not statistically significant. The authors therefore concluded that one unit of fresh whole blood was equal to 10 units of platelets [198]. Another study compared the effects of fresh vs. old blood in the pump prime and found that although stored blood had a lower pH, a higher lactic acid level, and a higher potassium concen-
tation than fresh whole blood, this resulted in a minimal effect on the final constitution of the priming solution before and during cardiopulmonary bypass in children [200].

A randomized double-blinded study comparing the use of fresh whole blood with combined packed red cells and FFP (reconstituted blood) for priming in 200 children under 1 year of age found no advantage to fresh whole blood. In fact, patients receiving fresh whole blood had a significantly longer stay in the intensive care unit (70.5 h vs. 97.0 h, p = 0.04) and a larger cumulative fluid balance at 48 h (−6.9 ml/kg of body weight vs. 28.8 ml/kg, p = 0.003) [201]. As part of routine management, however, those patients generally received intraoperative autologous donation (sequestration of heparinized blood just upon initiation of cardiopulmonary bypass). Therefore the use of autologous blood in both experimental and control groups may have minimized any added benefit of fresh whole blood in the experimental group.

Many institutions routinely use fresh whole blood during cardiac surgery. The factors limiting its routine use are the availability of donors, and logistical constraints necessary for preoperative screening. Additionally, fresh whole blood is generally stored at 4 °C, a temperature that depresses platelet function when compared with storage at room temperature [202]. Current recommendations are that in neonates and smaller children fresh whole blood may offer hemostatic and antiinflammatory benefits however in larger patients this may not be clinically significant or practical.

4.1.6. Recombinant factor VII

Recombinant factor VIIa has been effective in the treatment of post-bypass bleeding in patients who have a high titer of factor VII inhibitors [203,204]. In congenital heart surgery patients, factor VIIa has been shown to effectively reduce intractable hemorrhage [205,206]. The half-life is at least several minutes and the patient’s prothrombin time is corrected rapidly.

There are several hypotheses as to how recombinant factor VIIa promotes the localized generation of thrombin, a prerequisite for fibrin clot formation [204]. Normal blood clotting depends on the complex formed by factor VIIa with its cofactor, tissue factor. When recombinant factor VIIa is administered, it may saturate the tissue factor expressed at the site of endothelial injury. This complex activates factor X to Xa and initiates thrombin generation [207]. A second line of evidence suggests that recombinant factor VIIa generates thrombin (independent of tissue factor) on the surface of activated platelets accumulating at the site of endothelial injury. In spite of factor VIIa’s low affinity for activated platelets, therapeutically it appears to achieve adequate concentrations to generate local thrombin formation [208]. Finally, evidence in hemophilia suggests that recombinant factor VIIa activates thrombin-activatable fibrinolytic inhibitor, a zymogen which protects fibrin clots from premature lysis; however, no evidence supports this as a clinically important mechanism in patients with normal coagulation systems [209].

The role of recombinant factor VIIa in adult cardiac surgery is unclear. In coronary revascularization, tissue factor released at the anastomoses or unstable coronary plaques may lead to thrombosis and subsequent graft occlusion [210]. Recombinant factor VIIa was studied in children undergoing cardiac surgery with excessive blood loss after failure of conventional treatment [211]. Blood loss significantly decreased (7.8 ml/kg/h), nearly eliminating the need for additional blood products with normalization of the prothrombin time. In two patients with thrombocytopenia, recombinant factor VIIa discriminated surgical bleeding from defects in hemostasis, a further evidence that recombinant factor VIIa is safe and effective when other means fail [211].

To date use of recombinant factor VIIa has been reported in 20 cardiopulmonary bypass patients in the adult population. Hemostasis was achieved in all patients. In 14 patients (70%), rapid hemostasis was achieved following a single dose (mean 57 mcg/kg). In 6 patients (30%) hemostasis was eventually achieved after a mean of 3.4 doses (mean cumulative dose 225 mcg/kg). In 2 patients (10%), thromboembolic complications were noted. One was fatal and in another, intracoronary thrombosis was suspected but was not confirmed [192].

In patients experiencing postoperative hemorrhage with no surgical source and refractory to blood product administration and hemostatic agents, recombinant factor VIIa may be considered; however data are limited and further research is needed to define the role of recombinant factor VIIa in children.

5. Thrombelastography to guide transfusion therapy

Because of the acute nature of bleeding after cardiopulmonary bypass, blood product administration has developed empirically. The thrombelastogram (TEG®) was introduced in 1947 [212] and is now marketed as a proprietary analysis of the dynamics of hemostasis.2 Whole blood clotting is plotted against time from the initial clot formation, through clot acceleration, to maximum clot strength, and ultimately to clot lysis. Parameters derived from this bullet-shaped graph are used to target therapy. Thrombelastography is the single best predictor of post-bypass hemorrhage [213–215] and is useful in decreasing that hemorrhage in children [216–220]. Blood samples on bypass are activated with kaolin (both with and without heparinase) to guide therapy after bypass [216]. Baseline thrombelastograms in children undergoing cardiac surgery have been established and facilitate interpretation [221].

2 This section was developed with the assistance of Phillip Millman who discloses a financial interest in thromboelastography. The proposed management of bleeding herein has been more carefully studied in adults than children and has yet to be completely validated in pediatrics. Nevertheless, a discussion of current thinking with respect to thrombelastography is presented.
Thrombelastography measures dynamic clot formation using a pin suspended in a cup containing 0.36 ml of whole blood and kaolin (with or without heparin) to stimulate the intrinsic cascade. The cup is radially oscillated through an angle of 45° ever 10 s. The torque between the cup and pin is transduced and plotted against time as the clot forms and lysed (Fig. 1).

Interpreting the thrombelastogram requires understanding the sequence of clot formation. Convergence of the intrinsic and extrinsic pathways leads to the formation of one-dimensional thrombin fibers. This creates the initial “split point” (SP) of the thrombelastogram. Thrombin then cleaves soluble fibrinogen into fibrin monomers that polymerize into three-dimensional strands, producing the early acceleration of clot strength after the split point. Thrombin also activates platelets which, via GPIIb/IIIa receptors, form bonds between fibrin strands to produce a rigid, elastic, clot or maximum amplitude achieved by the clot. The strength and stability of this clot to resist the deforming shear stress of flowing blood, determine its ability to impede hemorrhage. Clot strength diminishes as the clot gradually lysed during vascular recovery or more rapidly with fibrinolysis.

Clinically, thromboelastography is directed at restoring a normal tracing by targeting specific coagulation defects, in theory increasing efficacy with fewer transfusion exposures. First normal parameters will be reviewed in Table 5.

---

**Table 5**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal time</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R$</td>
<td>4–8 min</td>
<td>$R$ is the time elapsed from placement of blood in the cup until 2 mm have elapsed graphically from the point where the thrombelastogram first splits (“split point”). $R$ indicates initial thrombin formation and is the best indicator of early factor activation (i.e., conversion of prothrombin to thrombin, prefactor XIII thrombin cross-linking, and cleaving of soluble fibrinogen). If $R$ is prolonged without heparinase and corrects with heparinase, then heparin excess is present. If $R$ is prolonged after heparinase, then hemodilution or heparin excess is likely and factor transfusion can be avoided.</td>
</tr>
<tr>
<td>$R – SP$ [delta]</td>
<td>&lt;1.1 min</td>
<td>If $R$ minus split point ($R – SP$) is normal, hemodilution or heparin excess is likely and factor transfusion can be avoided. Hemodilution: $R$ prolonged, $R$ remains prolonged with heparinase, normal $R – SP$, normal clot strength. Heparin excess: $R$ prolonged, $R$ normalizes with heparinase, normal $R – SP$, normal clot strength. Factor deficiency: $R$ prolonged, $R$ prolonged with heparinase, $R – SP$ prolonged, clot strength (MA low).</td>
</tr>
<tr>
<td>$K$</td>
<td>1–4 min</td>
<td>$K$ is useful as a determination of the initial cross-liking of fibrin strands via factor XIII (after thrombin formation above). While it is not used to guide clinical therapy, it is used to determine $\alpha$ below. $K$ determined from the end of $R$ to the time it takes the angle ($\alpha$) to reach 20 mm.</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>47–74°</td>
<td>$\alpha$ measures the rapidity of fibrin build-up and cross-linking (clot strengthening). The lower the $\alpha$, the poorer the fibrinogen function. A higher angle indicates hypercoagulability.</td>
</tr>
<tr>
<td>MA</td>
<td>55–73 mm</td>
<td>Maximum amplitude is perhaps the most important parameter, indicating the ultimate strength of the clot from fibrin and platelet bonding, and is an important measure of platelet function. If the MA is normal, thrombocytopenia is not problematic unless consumptive coagulopathy is at work.</td>
</tr>
<tr>
<td>EPLY30</td>
<td>0–15%</td>
<td>True percent lysis at 30' is calculated by the formula 100 [MA – A30]/MA, where A30 is the amplitude noted 30 min into lysis. Normal clots do not lose more than 15% of their strength by 30 min. Estimated percent of lysis from maximum amplitude is calculated with proprietary formulas to save time and expedite clinical decision making.</td>
</tr>
<tr>
<td>$G_{\text{max}}$</td>
<td>6.0 k–13.2 kdyn/s²</td>
<td>$G=5000 \text{MA}/(100 – \text{MA})$. This relationship is curvilinear and logarithmic, therefore small changes in maximum amplitude may translate into larger changes in clot strength [222].</td>
</tr>
</tbody>
</table>
Next, typical pathophysiologic tracings are shown in Fig. 2. Table 6 summarizes the stereotypical patterns generated with these pathophysologies. Table 7 provides more detailed clinical recommendations for those abnormalities.

5.1. Example 1

It is common to observe simultaneous clotting abnormalities after cardiopulmonary bypass. Hemodilution, a surgical source of bleeding, excess heparin, clotting factor deficiency, and platelet dysfunction may manifest simultaneously. After cardiopulmonary bypass, thrombelastograms are run with kaolin (plain cup) and kaolin with heparinase (to look for excess heparin). The early parameters reveal:

\[
\begin{align*}
R \text{ (plain cup)} &= 16 \text{ min (prolonged, normal 4–8 min)} \\
R \text{ (heparinase cup)} &= 12 \text{ min (still prolonged, normal 4–8 min)} \\
R - \text{SP (delta)} &= 0.9 \text{ min (normal)}
\end{align*}
\]

Here heparinase normalization of a prolonged \(R\) identifies heparin excess. Nevertheless, the \(R\) is still prolonged in the heparinase cup. The normal \(R - \text{SP}\) (or delta), indicates that hemodilution is present but is not affecting the early function of the clot. If the patient is still bleeding, surgical causes are suggested.

5.2. Example 2

This example illustrates the philosophy of sequential correction of a patient’s coagulopathy. A patient continues to bleed after protamine administration.

\[
\begin{align*}
R \text{ (plain cup)} &= 9.9 \text{ min (prolonged, normal 4–8 min)} \\
R \text{ (heparinase cup)} &= 9.9 \text{ min (prolonged, normal 4–8 min, no excess heparin)} \\
R - \text{SP (delta)} &= 2 \text{ min (prolonged, normal <1.1 min)} \\
G &= 3.0 \text{ kdyn/cm}^2 \text{ (low, normal 6.0–13.2 kdyn/cm}^2\text{)}
\end{align*}
\]

This patient is not simply hemodiluted (because the \(R - \text{SP}\) is prolonged). The patient has no excess heparin on board (as no change occurs in the heparinase cup). Rather, factor deficiency is indicated by the prolonged \(R\) and prolonged \(R - \text{SP}\). FFP is the first product of choice, because the thrombin must be present in order to activate platelets. If \(R\) is corrected but clot strength does not normalize with FFP, then platelets are indicated. In general, algorithmic interpretation of the TEG is sequentially directed at the dynamics of the clotting process.

1. A normal thrombelastogram defect points to surgical bleeding, defective platelet adhesion (with a pump-induced defect or platelet inhibiting drugs as a cause).
2. Simple hemodilution (as indicated by prolonged \(R\), normal \(G\), and normal \(R - \text{SP}\)) requires no treatment but also points to the same etiologies in [1].
3. Heparin excess (as indicate by a prolonged \(R\) that corrects with heparinase) indicates a need for more protamine.
4. Normal clot strength (\(G\)) generally requires no treatment in spite of abnormalities in other parameters (\(R, \alpha, K\)). Surgical bleeding must be evaluated.
5. Low clot strength requires interpretation with other parameters
   (a) Clotting factor deficiency (as indicated by a prolonged \(R\) that does not correct with heparinase and a long \(R - \text{SP}\)) indicates a need for FFP.
   (b) Low \(\alpha\) (and high \(K\)) indicates a need for cryoprecipitate.
   (c) Low MA indicates a need for platelets.
6. Low EPLY30 indicates thrombolysis and indicates that antifibrinolytics should be administered.

We should point out that the use of thromboelastography in children is in its infancy and much of the discussion has been generalized from the adult recommendations. The algorithms presented may have to be modified in children. For instance, one study of thromboelastography in children [217] found that platelet administration alone was sufficient to control bleeding, and return platelet counts and thrombelastogram parameters.
ters to normal in 40% of children. Subsequently cryoprecipitate raised fibrinogen levels to normal and further improved thrombelastograms. Interestingly, fresh frozen plasma did not increase fibrinogen, worsened multiple thrombelastogram parameters, increased ICU chest tube output and transfusion requirement. Smaller children required cryoprecipitate to correct their coagulopathy. This discrepancy is currently being studied in additional pediatric trials.

6. Topical hemostasis

Many topical hemostats have been developed over the years and are summarized in Table 8.

6.1. Oxidized cellulose (Surgicel®)

Surgicel® is a topical hemostatic agent consisting of porous sheets of oxidized cellulose. Its was developed for use in World War II after an American scientist observed that cellulose (indigestible and unresorbable by humans) can, by oxidation, be transformed into an effective, resorbable hemostatic material [223], believed to provide a lattice for clot formation through its ability to bind with hemoglobin. Other hypothesized mechanisms are aggregation of erythrocytes or acceleration of fibrinogen formation [224,225]. Surgicel® consists of two components: a soluble glucuronic acid component cleared by an early degradation and systemic clearance within 18 h, and a fibrous component degraded much more slowly requiring phagocytosis by macrophages at the site of implantation [226,227]. Surgicel® has also been shown to directly activate the extrinsic coagulation pathway [228].

In addition to its hemostatic action it has demonstrated in vitro bactericidal activity against Staphylococcus epidermidis, Staphylococcus aureus, Beta streptococcus, Streptococcus faecalis, Klebsiella aerogenes, Escherichia coli, Proteus vulgaris, Pseudomonas aeruginosa, Bacteroides fragilis and Clostridium perfringens [229,230].

Current evidence suggests that Surgicel® does not adversely affect adhesion formation and in fact may reduce it. In animal studies, surgicel decreased the incidence of peritoneal adhesions in rats [231,232]. In humans, surgicel

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment</th>
<th>$R_{plain}$ cup (kaolin only)</th>
<th>$R_{heparinase}$ (kaolin and heparinase)</th>
<th>$R_{SP}$ difference</th>
<th>$K'/s$</th>
<th>MAG</th>
<th>EPL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical</td>
<td>Sutures</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Hemodilution</td>
<td>No treatment necessary</td>
<td>High</td>
<td>High</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Excess heparin</td>
<td>Protamine</td>
<td>High</td>
<td>Normal heparinase neutralizes residual heparin</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Factor deficiency</td>
<td>FFP</td>
<td>High</td>
<td>High, because thrombin is not formed normally</td>
<td>Low or normal because of antecedent defect</td>
<td>Low or normal because of antecedent defect</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Fibrinogen deficiency</td>
<td>Cryo</td>
<td>Normal</td>
<td>High</td>
<td>Low</td>
<td>Low or normal because of antecedent defect</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Platelets low or dysfunctional</td>
<td>Platelets</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>Fibrinolysis primary</td>
<td>Antifibrinolytic TXA aprotinin</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Fibrinolysis (DIC) Stage 1</td>
<td>Treat DIC</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>Hypercoagulability with fibrinolysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinolysis (DIC) Stage 2 Hypocoagulable after consumption</td>
<td>Treat DIC</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
Table 7
TEG: Detailed Explanation and Clinical Recommendations

<table>
<thead>
<tr>
<th>Thrombelastogram description: likely etiology</th>
<th>Description</th>
<th>Parameter ranges</th>
<th>Adult treatment in OR</th>
<th>Pediatric treatment in OR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal thrombelastogram:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) Surgical Bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) Defective Clot Adhesion: clot forms but bleeding continues</td>
<td>This graph depicts normal hemostasis with normal enzymatic and platelet function and no lysis. Thrombin has cleaved soluble fibrinogen into fibrin and is indicated by normal $R$, $K$, and $x$ values. Platelet function is also normal with a normal MA value. The $G$ value (clot strength) is within normal range and there is no evidence of clot lysis ($EPL=0%$).</td>
<td>See normal ranges above</td>
<td>Treatment is DDAVP (directed at the platelet inhibitors) or cryoprecipitate (directed at factor VIII deficiencies). Incidentally, when using thromboelastography, cryoprecipitate is rarely indicated.</td>
<td></td>
</tr>
</tbody>
</table>

Conventional thrombelastograms are insensitive to platelet inhibitors (aspirin, platelet inhibitors, nonsteroidal antiinflammatory agents), because in vitro thrombin formulation overwhelms this inhibition in vitro. Recently new methodologies have been developed. Lupus anticoagulants are not detected nor has the methodology to assay aprotinin been developed, in part because aprotinin’s mechanism via the P2Y12 receptor or sub ADP receptor is incompletely understood.

If a patient is bleeding with a normal thrombelastogram (or slightly abnormal thrombelastogram with normal clot strength, $G$), then the most likely sources of bleeding are:

1. surgical bleeding
2. defective clot adhesion: i.e., manifests by normal clot formation in chest or chest tube but continued bleeding from failure of the clot to adhere to the injured vessel wall, etiologies are:
   a. von Willebrand’s syndrome (absence of factor VIII)
   b. deficient factor VIII after cardiopulmonary bypass
   c. platelet inhibiting drugs (aspirin, platelet inhibitors such as clopidogrel) are not detected by conventional thromboelastography. A platelet mapping technique has been developed but is beyond the scope of this chapter.

| Prolonged $R$ that corrects with heparinase: | A bleeding patient with a prolonged $R$ in the kaolin cup that corrects with heparinase indicates that heparin is still present. | $R>8$ min (kaolin cup) | 50 mg protamine | 0.5 – 1.0 mg/kg protamine (no clinical data to confirm this dosage) |
| Heparin Excess | $R=4–8$ min (kaolin + heparinase cup) | $R – SP$ normal | Diuretic or do nothing | Unknown (consider diuretic but no clinical data to support this treatment) |

| Prolonged $R$ with normal clot strength ($G$) and normal $R – SP$: | A bleeding patient with hemodilution requires no blood products, but rather requires careful exploration for surgical source. | $R>8$ min (even with heparinase) | 1 FFP | 4 ml/kg FFP |
| Hemodilution | $G$ normal | $R – SP$ normal | 2 FFP | 8 ml/kg FFP |

| Prolonged $R$ that does not correct with heparinase: | A bleeding patient with a prolonged $R$ and $R – SP>1.1$, typically has an enzymatic defect as a source of bleeding, either from excess anticoagulation, factor deficiencies (from pump consumption or hemophilia) which would be best treated with FFP. | $R>14$ | 4 FFP | 10 – 20 ml/kg FFP |
| Clotting Factor Deficiency | $R – SP>1.1$ min | | | |
and thrombin-soaked gelfoam neither increased nor decreased postoperative adhesions [233], while a prospective randomized study of surgicel after laparoscopy for endometriosis revealed significantly fewer adhesions [234].

6.1.1. Gelatin sponge and thrombin (Gelfoam® and thrombin)

Gelfoam® is a water-insoluble, nonelastic, porous, pliable, absorbable sponge prepared by milling absorbable
gelatin sponge from purified pork skin. Though it has no intrinsic hemostatic action, Gelfoam® induces hemostasis through its intense porosity, enabling it to absorb 45 times its weight in blood. As it fills with blood, platelets come into close contact and initiate the extrinsic clotting cascade [235]. The addition of thrombin to gelfoam adds to its hemostatic ability. Absorption is dependent on several factors, including the amount used, degree of saturation with blood or other fluids, and the site of use. In soft tissues, Gelfoam is usually absorbed completely from 4 to 6 weeks, without inducing excessive scar tissue [236]. In fact, studies have shown the contrary [233,234]. Though a mainstay in topical hemostasis, the limited efficacy of surgicel and Gelfoam® led to the development of products that directly activate the clotting cascade.

6.1.2. Microfibrillar collagen hemostat (Avitene®)

Avitene is a microfibrillar collagen hemostat which is available in the form of flour, sheets, or sponge. Avitene® works best when applied dry. When this is not possible the surface to be treated should be compressed with dry gauze, covered with Avitene®, and moderate pressure applied over the Avitene® with a dry gauze. Avitene® should not be used in the closure of skin incisions as it may interfere with the healing of the skin edges due to simple mechanical interposition of dry collagen and not to any intrinsic interference with wound healing. Avitene® is inactivated by autoclaving and should not be resterilized. Moistening it or wetting with saline or thrombin may impair its hemostatic efficacy and it should be used dry. As it is a foreign substance, use in contaminated wounds may enhance infection. Avitene® contains a low, but detectable, level of intercalated bovine serum protein which reacts immunologically as does beef serum albumin. Increases in anti-beef serum albumin titer have been observed. Nearly 2/3 of individuals exhibit antibody titers because of ingestion of bovine food products. Intradermal skin tests have occasionally shown a weak positive reaction to bovine serum albumin microfibrillar collagen but these have not been correlated with IgG titers. Testing has not revealed any significant elicitation of antibodies of the IgG class against bovine serum albumin following use of Avitene®. Care should be exercised to avoid spillage on nonbleeding surfaces, particularly in abdominal or thoracic viscera.

Avitene® (MCH) should not be used in conjunction with autologous blood salvage circuits. Fragments of Avitene® may pass through filters of blood scavenging systems. The reintroduction of blood from cell saver or cardiomyotomy suction of area treated with Avitene® should be avoided. Teratology studies in rats and rabbits have revealed no harm to the animal fetus but the lack of well-controlled studies in pregnant women should restrict its use in pregnant women only when clearly needed. The most serious adverse reactions reported which may be related to the use of Avitene® are potentiation of infection including abscess formation, hematoma, wound dehiscence, and mediastinitis. Other reported adverse reactions possibly related are adhesion formation, allergic reaction, and foreign body reaction.

A randomized clinical study in patients undergoing ascending aortic aneurysm repair and reoperative coronary artery bypass surgery compared the efficacy of Avitene® and surgicel [237]. The group that received Avitene® had significantly decreased chest tube outputs over all and in the first postoperative hour. Another study compared the efficacy of several topical agents after sutured end-to-end aortic anastomoses in rabbits and found that fibrin sealant controlled hemorrhage more effectively than the other agents (Gelfoam®–thrombin, Surgicel®, Avitene®, Floseal®). In addition although all the other agents did significantly reduce blood loss there was no significant difference between the individual topical agents [238].
6.1.3. **Fibrin sealant (Tisseel®)**

Tisseel VH® (Baxter Healthcare Corp., Glendale, CA) is a proprietary, topical protein solution sealer which is sprayed onto hemorrhagic surfaces. This fibrin sealant contains pooled human fibrinogen, thrombin, calcium chloride, and Aprotinin (bovine) and takes 25–45 min to prepare. It was developed as an alternative to fibrin glue. The advantages of Tisseel® over fibrin glue are that it is vapor-heat treated for viral inactivation. When the protein and thrombin solutions are mixed and topically applied, a viscous solution that rapidly sets into an elastic coagulum is produced. Studies have shown that Tisseel® is safe with regard to viral transmission and highly effective in controlling localized bleeding in cardiac operations [239]. It is the only product that can cause clot without a contribution from the patient. Its components are a Sealer protein concentrate (human), heat treated, dried and sterile with a total protein concentration of approximately 130 mg/ml; a fibrinolysis inhibitor (aprotinin) at a concentration of 3000 KIU/ml; bovine, dried; thrombin at a concentration 500 IU/ml and calcium chloride solution, 40 mmol/l.

A multicenter randomized trial of 333 patients in 11 centers in the US undergoing reoperative sternotomy compared the hemostatic ability of fibrin sealant with conventional topical agents and demonstrated a significant reduction in postoperative blood loss and reoperation for bleeding in patients treated with the sealant [239].

Fibrin sealant had a 92.6% success rate in controlling bleeding within 5 min of application, compared to only 12.4% success with conventional topical agents (p < 0.001) [239]. Postoperative blood loss was significantly less (p < 0.05), and there were no documented adverse reactions, or viral transmission of viral infection (hepatitis B, non-A/non-B hepatitis, or HIV). Reexploration for bleeding after redo operations were significantly lower in the fibrin sealant group (5.6%) than in controls (10%) (p < 0.008). There were no significant differences in hospital stay or blood products received between the fibrin sealant group and matched historical controls and no difference in mortality between the fibrin sealant group and nonmatched historical controls. Its disadvantage is that it has to be applied to a dry field and given a chance to cure.

In congenital heart surgery, fibrin sealants have decreased bleeding and transfusion requirements. In a prospective study, patients with postoperative coagulopathy after cardiopulmonary bypass were randomized to receive fibrin sealant on anastomotic sites and microvascular bleeding points or no intervention. Children treated with fibrin sealant, required a significantly less packed red blood cells, FFP and platelets. The operating room time and bleeding during surgery at 4 h, and at 24 h were all significantly reduced. Nevertheless, there were no differences in ventilation time, nor ICU or hospital stays [240].

Similar reduction in bleeding was observed using fibrin sealant in a prospective randomized evaluation of neonates undergoing ECMO [241].

6.1.4. **FloSeal®**

FloSeal® (Fusion Medical Technologies, Inc., Mountain View, CA) is a proprietary, gelatin-based hemostatic sealant which consists of a combination of specially engineered collagen-derived particles and topical thrombin which activates the clotting cascade and simultaneously forms a nondisplacing hemostatic plug. The kit contains a bovine-derived gelatin matrix and a bovine-derived thrombin component. It is composed of a cross-linked gelatin matrix combined with thrombin to produce a highly viscous gel. Although its hemostatic function requires adequate circulating fibrinogen, no platelet activation is required and a bloodless field is not required. It mixes in 1–2 min, is biocompatible and is reabsorbed in 6 to 8 weeks.

The Fusion Matrix Group studied FloSeal® vs. Gelfoam®—Thrombin in cardiac surgical procedures in which standard surgical means were ineffective at controlling bleeding [242]. FloSeal® stopped bleeding in a significantly higher number of patients than conventional therapy with Gelfoam®—Thrombin and showed no differences in adverse events. The major advantage to this product is that it has been formulated for application to an actively bleeding field. Although there have been no reported cases, Floseal® contains animal/bovine products and carries a risk of viral transmission including bovine spongiform encephalopathy.

6.1.5. **CoSeal®**

CoSeal® surgical sealant (Baxter Healthcare Corporation, Freemont, CA) is a proprietary topical agent which contains no pooled human blood components. It consists of two polyethylene glycol polymers. A hydrogel can be prepared and applied in 3 min and the material is completely resorbed in 4–6 weeks after treatment. This agent should be applied to relatively dry surfaces prior to the release of clamps. A multi-center randomized study showed that CoSeal® was superior to conventional topical methods in aortic reconstructive surgery [243]. Another multicenter randomized trial demonstrated that CoSeal® offers equivalent anastomotic sealing performance compared with Gelfoam®/thrombin, and that it provided the desired effect in a significantly more rapid time frame [244]. Since it contains no human or animal proteins, CoSeal® carries no risk of viral transmission. Although it is resorbed within 6 weeks, no long-term data exist with respect to scarring.

6.1.6. **BioGlue® surgical adhesive**

BioGlue® (Cryolife, Inc., Kennesaw, GA) is a proprietary, biological glue initially approved for use in the repair of aortic dissection. It is composed of purified bovine serum albumin (BSA), and glutaraldehyde. The action is almost instantaneous because glutaraldehyde exposure leads to the tenuous binding of lysine molecules, proteins, and tissue surfaces. The glutaraldehyde molecules covalently bond (cross-link) the albumin molecules which polymerize within 20 to 30 s (65% strength) and reaches...
full bonding strength within 2 min. BioGlue® has been used in aortic reconstructive surgery [245] and in the repair of acute aortic dissections [246]. However, there are many cautions in its use, including the avoidance of valve leaflets, intracardiac structures, and circulating blood (as it can result in local or embolic vascular obstruction). Repeat exposure may lead to hypersensitivity reactions. Although this glue has successfully reduced blood loss and achieved hemostasis in congenital heart surgery [247] it should be used with utmost caution as it has been shown to impair vascular growth and cause stricture when applied circumferentially around an aorto-aortic anastomosis in 4-week old piglets [248].

6.2. Mechanical adjuncts

Other blood conservation strategies include acute normovolemic hemodilution, reduced priming volume of cardiopulmonary bypass, blood salvage by filtration or cell processing, modified ultrafiltration and autotransfusion of shed blood. Controlling hypertension (hypotensive hemostasis), reinfusing shed blood and cell saver, minimizing circuit size and ultrafiltration are current mechanical techniques used to attenuate postoperative blood loss after cardiopulmonary bypass.

The first report to demonstrate a less than 10% transfusion rate in Jehovah’s Witnesses was from the Cleveland Clinic in adults which demonstrated transfusion rates of only 6% with a mean of 0.06 units per patient receiving blood. Cosgrove et al. described 6 principal techniques of blood conservation which were, intraoperative autologous donation, nonblood prime, return of all residual cardiopulmonary bypass circuit blood, intraoperative salvage, use of the lowest safe level of anemia during cardiopulmonary bypass as well as in the postoperative period and the reinfusion of shed mediastinal blood [249]. Ovrum et al. in two consecutive studies demonstrated extremely low rates of transfusion (2.4% of patients) using this 6-step blood conservation program and found it to be simple, safe, and cost-effective [250,251].

6.2.1. Controlled hypotension

The concept of controlled hypotensive hemostasis was introduced in the 1940s to reduce intraoperative blood loss and transfusion requirement [252]. A review of 13 prospective studies on multiple surgical specialties, predominately orthopedic patients undergoing total hip replacement demonstrated a 50% reduction in blood loss with this technique [253]. Controlled hypotension is defined as reducing mean arterial blood pressure to 50–75 mm Hg. Although this technique has been widely studied in orthopedic surgery, several reports in adult cardiac and thoracic surgery have shown benefit in reduction of blood loss [254,255]. Modalities that have been used include epidural blockade, inhalation anesthetics, intravenous beta blockade and direct vasodilators.

In the pediatric population reduction in mean arterial pressure to 50–65 mm Hg (or a 30% reduction) did limit intraoperative blood loss and favored sevoflurane and fenoldepam as their agents of choice [256,257]. The benefits of reduced blood loss and transfusion requirement obtained with this technique have to be weighed against the potential for inadequate perfusion of vital organs and may be detrimental over a prolonged period in patients with significant cardiovascular disease, cerebrovascular disease, severe pulmonary disease, renal disease, hepatic disease, pregnancy, anemia and hypovolemia.

6.2.2. Shed blood controversy and cell saver

The concept of using autologous blood transfusion was first introduced in 1818 [46]. In 1968 a known process of collection, washing, processing and reinfusing shed blood was described [258]. After cardiopulmonary bypass, residual blood can be processed by cell saver using centrifugation, ultrafiltration or reinfusion of unprocessed blood. In comparison with cell saver, ultrafiltered blood has higher red cell concentrations and has less platelet and coagulation factor depletion [259]. Shed mediastinal blood has shown to have higher titers of fibrin degradation products and has been implicated in worsening coagulopathy [260] through a potentiation of platelet dysfunction secondary to tissue type plasminogen activator activity [261]. Other studies have found either no difference [262] or higher fibrin degradation titers which did not translate into clinically significant bleeding after washing the infusate [263].

In the pediatric heart surgery population, two studies have demonstrated no increase in coagulopathy with reinfusion of shed blood [262,264]. Although one group has shown increased chest tube drainage with cell saver [261], no studies have been able to conclusively demonstrate increased bleeding in patients receiving shed mediastinal blood. Based on current inconclusive evidence against its use, the reduction in the therapeutic benefit by withholding reinfusion of shed blood is not justified.

6.3. When to reexplore a bleeding patient

As previously mentioned, when a patient is bleeding postoperatively, a surgical cause of bleeding must remain in the differential. When to reexplore is a complex decision that must integrate disparate sources of information. The surgeon who did the case generally has a feel for the likelihood of surgical bleeding based on (1) his intimate understanding of the operation, (2) the operation performed (i.e., complex arterial reconstruction vs. simple atriotomy), (3) whether reoperative surgery was performed, and (4) the appearance of the operative field at the time of the closure. The nature of chest tube output is also an important information. Bright red blood is more likely to be arterial bleeding; dark blood is more likely to be venous. Non-clotting blood in the chest tube implies ongoing coagulop-
athy requiring further correction. Clotting of blood in the chest tube makes surgical bleeding more likely. Guidelines for pediatric reexploration are typically 10–15 ml/kg/h for 3–4 successive hours or 20–25 ml/kg/h total at the end of 4 h with normal coagulation studies and/or hemodynamic instability.

7. Conclusion

Children undergoing cardiopulmonary bypass suffer disproportionate adverse effects because of their size and immature hematopoietic system. Postoperative bleeding is exacerbated by hemodilution, induction of a systemic inflammatory response, along with platelet and coagulation factor activation and depletion. Effective management of bleeding after cardiopulmonary bypass in children requires that physicians understand and are familiar with every technique available to balance competing needs of minimizing blood loss and transfusion, while maintaining good perfusion so that a child’s perioperative and long-term outcome is optimized.

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