REVIEW ARTICLE

Dennis M. Fisher, M.D., Editor

Anesthesiology
1999; 91:1122–51

Anticoagulation Monitoring during Cardiac Surgery

A Review of Current and Emerging Techniques

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AFTER almost two decades of relative stability in anticoagulation practice and monitoring for cardiac surgery, recent developments call for review and reconsideration of these issues. The introduction of aprotinin in 1994 and the development and use of new thrombin (*e.g.,* hirudin, argatroban), Xa (*e.g.,* low-molecular-weight heparin compounds), and platelet (*e.g.,* abciximab, eptifibatide, tirofiban) inhibitors and new fibrinolytic agents (*e.g.,* recombinant tissue plasminogen activator) has complicated clinical management. Also, the introduction of antithrombin III (ATIII) concentrates has opened a new pathway to manage heparin resistance. The availability of heparin-bonded extracorporeal circuits has engendered clinical management controversies that test the clinician's knowledge and judgement.

This review describes and interprets the literature on these topics and includes a survey conducted in 1993 of heparin and protamine dosing and monitoring practices in the United States. Clinical scenarios involving either newer antithrombotic agents or disease states that render traditional monitoring obsolete are also discussed.

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Received from the Departments of Anesthesiology and Pathology, Washington University School of Medicine, St. Louis, Missouri; the Department of Anesthesiology, Allegheny University Hospitals–Allegheny General, Pittsburgh, Pennsylvania; the Department of Anesthesiology and Critical Care Medicine, University of Patras School of Medicine, Patras, Greece; and the Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia. Submitted for publication November 17, 1997. Accepted for publication April 13, 1999. Research support, honoraria, or consulting fees were provided from one or more of the following corporations: Rhone-Poulenc Rorer Pharmaceuticals, Inc., Collegeville, Pennsylvania; Acumetrics, Inc., San Diego, California; Genzyme Corporation, Cambridge, Massachusetts; Medtronic Blood Management, Parker, Colorado; International Technidyne, Edison, New Jersey; Boehringer Mannheim, Indianapolis, Indiana; Ciba Corning Diagnostics Corporation, Indianapolis, Indiana; Bayer Corporation, West Haven, Connecticut; and IBEX Technologies, Montreal, Canada.

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Key words: Aprotinin; bleeding; cardiopulmonary bypass; heparin; protamine.

Overview of Coagulation in Cardiac Surgery

The hemostatic system limits hemorrhage when vascular integrity is compromised and includes several major components: platelets, von Willbrand factor (vWF), coagulation and fibrinolytic factors, and the blood vessel wall. The endothelium normally serves as a protective layer against hemostatic activation. When endothelium is denuded, activated platelets adhere to exposed subendothelium, a reaction largely mediated by vWF, and then aggregate to provide initial hemostasis. Platelets also provide an active phosholipid surface for interaction with coagulation factors. The coagulation system consists of a number of clotting active zymogens and cofactors and is subdivided into three pathways (*i.e.,* intrinsic, extrinsic, and common) that ultimately lead to formation of a fibrin clot (fig. 1). Tissue factor activates the extrinsic pathway to form fibrin, which stabilizes the hemostatic platelet plug. Several important physiologic mechanisms counterbalance the propensity of both platelets (*i.e., via* prostacycline [PGI_2], nitric oxide)

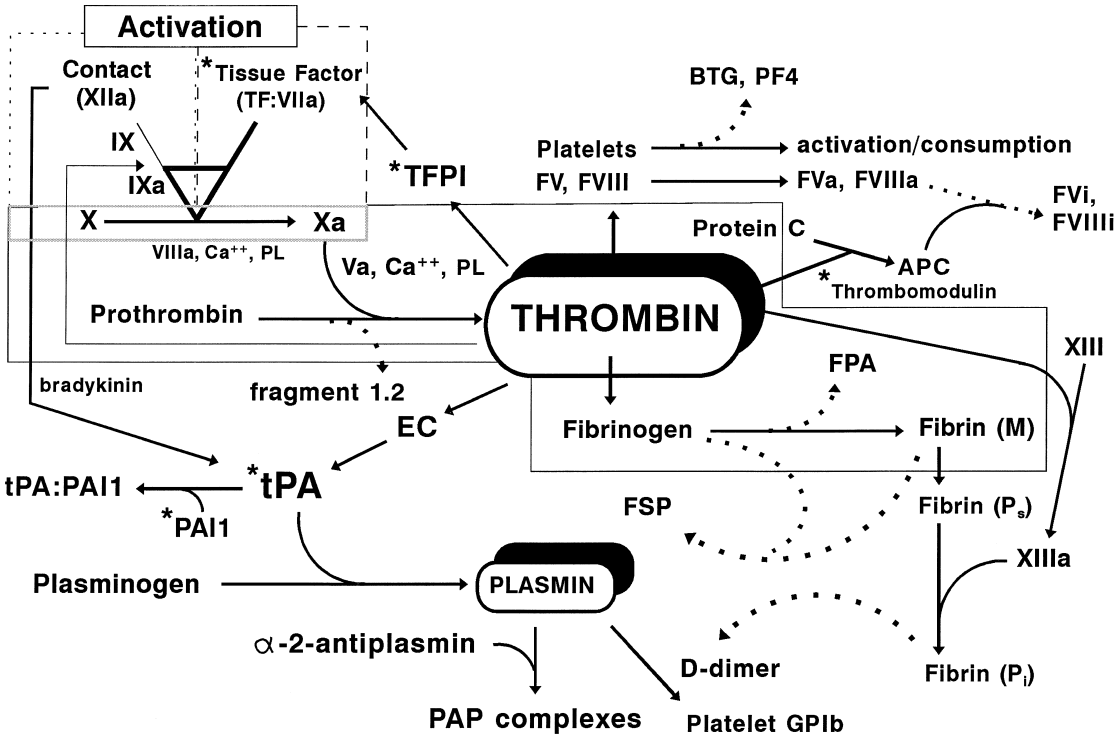

Fig. 1. Mechanisms and effects of excessive hemostatic activation with cardiac surgery. The coagulation system, a complex web of interactions, is subdivided into three pathways: intrinsic or contact (enclosed by small dashed line), extrinsic or tissue factor (enclosed by a large dashed line), and common (enclosed by a solid line); the conversion of Factor X to Xa is within all three pathways (enclosed by a solid, thick line). Dashed lines designate release of protein cleavage by-products. Activated factors are designated using a small "a," whereas inactivated factors are designated using a small "i." XII = Factor XII; VII = Factor VII; X = Factor X; VIII = Factor VIII; IX = Factor IX; V = Factor V; XIII = Factor XIII; PT 1.2 = prothrombin fragment 1.2; Ca^{++} = calcium ions; FPA = fibrinopeptide A; PL = phospholipid; PAP = plasmin–antiplasmin complexes; EC = endothelial cells; tPA:PAI1 = tPA–PAI1 complexes; fibrin (m) = fibrin monomer; fibrin (p) = fibrin polynomer; fibrin (L) = fibrin cross-linked polymer; PAI1 = plasminogen activator inhibitor; tPA = tissue plasminogen activator; FDP = fibrinogen–fibrin degradation products; D-dimers = polymerized fibrin degradation products. *Designates endothelial cell related.

and coagulation (*e.g.,* proteins C and S, ATIII, heparin cofactor II (HCII), and tissue factor pathway inhibitor) to form clot. The fibrinolytic system consists of several plasmatic factors (*e.g.,* tissue plasminogen activator [tPA], plasminogen) that interact to produce plasmin, which lyses clots and potentially prevents vasocclusion at the site of vessel injury; the fibrinolytic system is regulated by other factors, such as plasminogen activator inhibitor and α_1 antiplasmin that bind tPA and plasmin, respectively.

Cardiac surgery with cardiopulmonary bypass (CPB) places patients at risk for excessive perioperative blood loss. This risk is influenced by the type of procedure[1,2] and the duration of CPB.[3,4] Although preexisting[5] or acquired[6] hemostatic abnormalities occasionally cause excessive perioperative bleeding, more often, CPB impairs the hemostatic system, which results in excessive bleeding (fig. 2). Crystalloid or colloid solutions used to prime the CPB circuit and as a component of cardioplegia significantly dilute coagulation factors and platelets,[2,7] and excessive activation of the hemostatic system can also consume them. This activation results from stimulation of both the intrinsic[8] and the extrinsic[9,10] pathways from blood contact with extracorporeal and pericardial surfaces, as well as from the subatmospheric pressure of cardiotomy suction. Excessive fibrinolysis can be triggered by CPB-mediated activation of Factor XII, kallikrein[11] and thrombin, hypothermia,[12] retransfusion of tPA that has been released into the surgical field,[13] or intravascular release from injured endothelial cells.[14] Even after "complete" protamine neutralization, heparin can potentially inhibit coagulation[15] and platelet function.[16,17] Similarly, excess protamine can inhibit coagulation[18] and affect platelet function.[19–21] Finally, elastase release from polymorphonuclear leu-

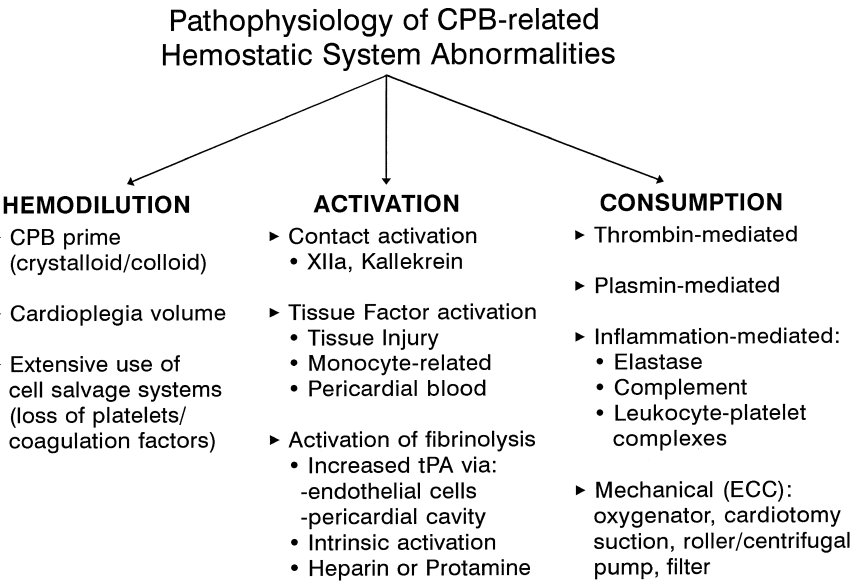

Fig. 2. Pathophysiology of hemostasis abnormalities with extracorporeal circulation. Cardiopulmonary bypass crystalloid prime refers to the crystalloid solution necessary to prime the cardiopulmonary bypass circuit, whereas cardioplegia volume refers to the volume of crystalloid necessary for cardioplegic myocardial arrest. Contact activation *via* extracorporeal circulation (ECC) refers to contact activation related to interface of blood with nonendothelial surface of the ECC. Pericardial activation refers to activation of the hemostatic system *via* the tissue factor pathway mediated by transfusion pericardial blood containing tissue thromboplastin. Mechanical ECC refers to shear forces imposed by some of the components of the ECC circuit as listed tPA = tissue plasminogen activator; Gp = platelet glycoprotein receptors (*e.g.*, IIb/IIIa or Ib).

kocytes[22] and tumor necrosis factor[23,24] may impair hemostasis.

Increased thrombin and plasmin activity are important because they each mediate several reactions (fig. 1). In addition to generating fibrin monomer, thrombin activates Factors V, VIII, and XIII and platelets. At the same time, thrombin downregulates hemostasis by releasing tPA and tissue factor pathway inhibitor and by activating protein C, which, when complexed with endothelial-bound thrombomodulin, clears activated Factors V and VIII. Thrombin-mediated consumption of these factors was suggested recently by inverse relations between Factor V levels and markers of thrombin generation (*e.g.,* prothrombin fragment 1.2: $r = -0.57$) or activity (*e.g.,* fibrinopeptide A: $r = -0.53$) at the end of CPB.[25] Despite relatively high doses of heparin during CPB, thrombin and plasmin are generated progressively,[9,26] as shown by the increasing concentrations of prothrombin fragment 1.2 (F1.2), thrombin–antithrombin complexes, fibrin monomers,[27] and fibrin degradation products (*e.g.,* D-dimers).[25,28,29] Excessive plasmin activity can lead to platelet dysfunction from fibrinogen–fibrin degradation products (FDP),[16] degradation of Factors V, VIII, and XIII,[30] and, rarely, hypofibrinogenemia.[2,31–33] Plasmin can also either lyse[34] or internalize[35,36] platelet membrane glycoproteins (GP Ib), impair the *in vitro* response of platelets to various agonists,[37] and enhance platelet response to thrombin at lower temperatures.[35]

The exact effects of hypothermia on the hemostatic system during CPB are not well-characterized. Better suppression of thrombin activity during hypothermia[38] by higher heparin concentrations may preserve coagulation factors and platelets even though platelet reactivity increases.[39] If thrombin activity decreases at hypother-

Table 1. Summary of Hemostatic Abnormalities Associated with Cardiac Surgery Involving Extracorporeal Circulation

Decreased or denatured coagulation factors[2,7,42,174,283–287]
Decreased physiologic inhibitors (ATIII, protein C, protein S)[25,28,63–68,174,286,288–294]
Decreased fibrinolysis inhibitors (PAI1, α-2 antiplasmin)[295,296]
Disseminated intravascular coagulation[297,298]
Primary fibrinolysis[299]
Platelet related
Thrombocytopenia[2,11,286,294,300–302]
Platelet activation/desensitization[3,11,25,42,43,283,303–309]
Prolonged bleeding time[3,157,283,284,301,310]
Decreased platelet reactivity[3,42,251,252,284,301,305,307,308,311,312]
Loss of platelet glycoprotein receptors
Fibrinogen (Gp IIb/IIIa)[302–304,313,314]
von Willebrand factor receptor (Gp Ib)[303,304,314–316]
Platelet degranulation (BTG, PF4, ADP)[3,22,25,32,42,43,67,145,157,229,304,305,308,312,317,318]
Changes in platelet signaling/adhesion molecule expression[19,304,305,311,318–322]
Hypothermia-related effects[3,35,39,323–325]
Heparin-related inhibition[16,17,21,52,53,95,144,146–148,226]
Heparin-related activation[17]
Protamine-related platelet dysfunction[19–21,156,157]

ATIII = antithrombin III; PAI1 = plasminogen activator inhibitor 1; Gp = glycoprotein; BTG = β-thromboglobulin; PF4 = platelet factor 4; ADP = adenosine diphosphate.

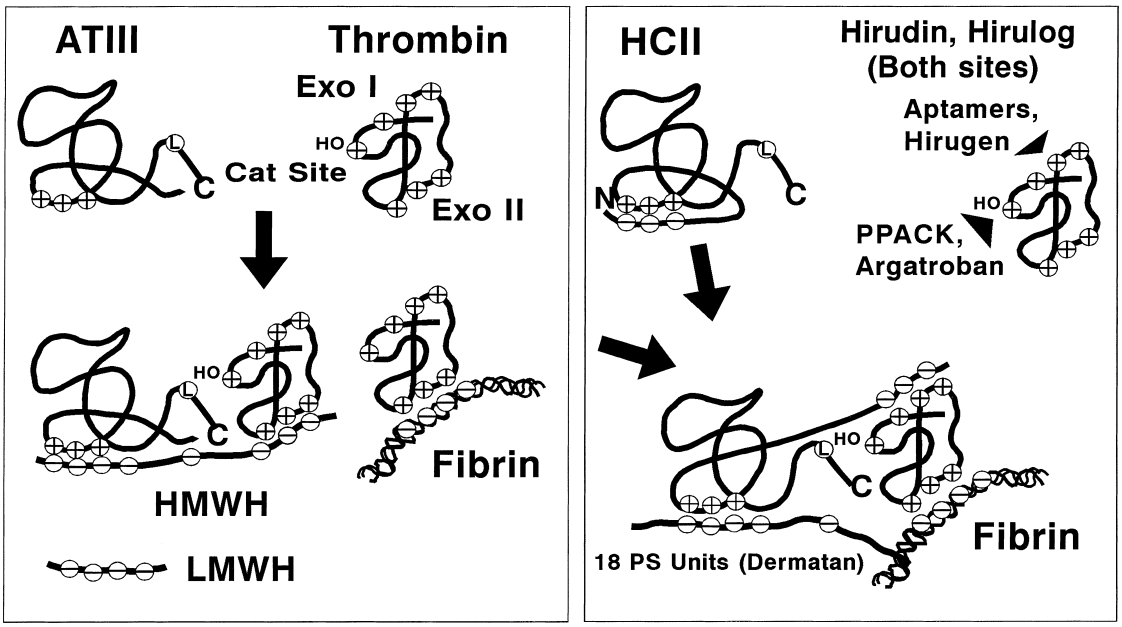

Fig. 3. Inhibition of thrombin activity. (*Left*) Depiction of normal physiologic inhibition of fluid-phase thrombin by high-molecular-weight (HMW) heparin molecules and the limitations of heparin in inhibiting clot-bound thrombin. The thrombin molecule has three major binding sites: (1) the fibrinogen binding site (Exo I), (2) the fibrinogen catalytic site (Cat Site), and (3) the fibrin binding site (Exo II). After binding of heparin to the antithrombin III (ATIII) molecule *via* a critical pentasaccharide sequence, a conformational change in the C-terminal portion of the ATIII molecule is induced. Inhibition of the thrombin molecule requires heparin molecules with a critical oligosaccharide chain length of 18 U that serve as a template for the binding of ATIII with thrombin. However, thrombin inhibition *via* the ATIII–heparin mechanism is limited by availability of the Exo II site, which can also be occupied by fibrin. Although low-molecular-weight (LMW) fractions of heparin induce a conformational change in the C-terminal portion of the ATIII molecule, they cannot serve as a template for ATIII and thrombin because of their short chain length. (*Right*) Depiction of the normal inhibition of clot-bound thrombin by the heparin cofactor II (HCII)—heparin complex and the sites of action of various direct thrombin inhibitors. A minimum chain length of 6 U for the heparin oligosaccacharide is required to activate HCII; however, 20–24-U chain lengths result in a substantially greater thrombin inhibition *via* HCII. Direct thrombin inhibitors, such as hirudin and hirulog, bind to both the Exo I and the catalytic sites of the thrombin molecule. In contrast, polypeptide aptamers and hirugen bind to the Exo I site, whereas argatroban binds to the fibrinogen catalytic site of thrombin. As modified from Tollefson DM: Insight into the mechanism of action of heparin cofactor II. Thromb Hemostas 1995;74:1209–14. Reprinted with permission.

mia, like that of most enzymes, an *in vitro* monitoring system reflecting thrombin activity directly may better represent physiologic conditions.

In summary, activation of coagulation and fibrinolysis with consumption of platelets and labile coagulation factors can occur even with standard high-dose heparin-induced anticoagulation. Although several hemostatic aberrations have been reported after CPB (table 1), platelet dysfunction is considered to be the most important abnormality in the early postoperative period.[3,5,40–43]

Overview of Heparin in Cardiac Surgery

Anticoagulation is used during cardiac surgery to prevent overt thrombosis of the extracorporeal circuit and to minimize excessive CPB-related activation of the hemostatic system. Heparin is used routinely because it is effective, immediately reversible, generally well-tolerated, and inexpensive. Unfractionated heparin is a polysaccharide mixture of low- and high-molecular-weight fractions (*i.e.,* molecules ranging from 1,000–50,000 d) that differ functionally. Fractions with minimum chain length of 18 oligosaccharide units and a molecular weight of approximately 4,500 d or higher preferentially inhibit thrombin (*i.e.,* Factor IIa).[44] Oligosaccharide chain length is important because thrombin inhibition requires simultaneous binding of thrombin and ATIII by heparin, which acts as a template (fig. 3). A minimum chain length of 6 oligosaccharide units is essential for heparin to catalyze the inhibition of thrombin by HCII, another important *in vivo* inhibitor of the hemostatic system (fig. 3). However, inhibition (*e.g.,* 10,000-fold increase) of thrombin *via* HCII is optimal with a chain length of 20–24 oligosaccharide units.[45] The ability of

HCII to inhibit clot-bound thrombin may be important during CPB as well.[46,47]

Because inhibition of Factor Xa does not require simultaneous binding of Xa and ATIII *via* a heparin template, lower molecular weight fractions of unfractionated heparin easily inhibit Factor Xa. The antithrombotic properties of heparin are predominantly mediated by the binding of heparin to ATIII through a specific pentasaccharide sequence. This complex then inhibits Factor Xa (*i.e.,* all molecular weight fractions) and thrombin (*i.e.,* higher molecular weight fractions of unfractionated heparin).[48] Only one in three unfractionated heparin molecules has the critical pentasaccharide sequence necessary for binding to ATIII.[48] Although binding of heparin to ATIII inhibits thrombin and Factor Xa,[49] this complex also inhibits several other sites in the intrinsic pathway. In addition, the extrinsic pathway can be attenuated by heparin-mediated release of tissue factor pathway inhibitor[50] that inhibits activation of the extrinsic pathway.[51] Heparin may also inhibit[16,17,52,53] or activate[17] platelets and has been shown to initiate fibrinolysis.[16]

Although unfractionated heparin is metabolized in the reticuloendothelial system and in the liver, at least 50% is eliminated unchanged *via* the kidneys. Plasma elimination half-life of unfractionated heparin varies with dose, increasing from 60 min with 100 U/kg to 150 min with doses of 400 U/kg.[54–56] Low-molecular-weight heparin (LMWH) compounds, such as enoxaparin (Rhone-Poulenc Rorer, Collegeville, PA) or dalteparin (Pharmacia & Upjohn Co., Kalamazoo, MI) have a more consistent pharmacokinetic profile between patients because of the lower protein binding,[57] less affinity for platelets,[52] vWF[52] and endothelial cells,[58] and clearance, which is primarily renal.[59]

There is substantial variability of heparin anticoagulant responsiveness, as illustrated by a wide range of heparin dose–response test-derived slope values in patients undergoing cardiac surgery (median, 79; 95% confidence interval, 58–114 $s \cdot U^{-1} \cdot ml^{-1}$)[60] and in normal volunteers (median, 92; 95% confidence interval, 77–117 $s \cdot U^{-1} \cdot ml^{-1}$).[61] Impaired heparin responsiveness (*i.e.,* also called *heparin resistance*) often is attributed to ATIII deficiency.[61] ATIII activity levels as low as 40–50% of normal, which are similar to those observed in patients with heterozygotic hereditary deficiency,[62] are commonly seen during CPB.[25,63–67] Acquired perioperative reductions in plasma ATIII concentrations have been related to preoperative heparin use,[65–68] hemodilution,[64–66] or consumption during CPB.[25] The importance of ATIII in controlling platelet and coagulation activation is supported by recent findings that large increases in markers of platelet activation (*e.g.*, β thromboglobulin and thrombin activity, such as fibrinopeptide A [FPA], occurred when ATIII concentration was < 0.6 U/ml (normal, 0.8–1.2 U/ml).[61] Significant variability in heparin anticoagulant response[60,61] may also result from interpatient differences in heparin binding to endothelial cells,[58] leukocytes,[69] platelets,[70,71] or proteins,[15,49,72,73] such as vitronectin,[74] vWF[52] or histidine-rich glycoprotein.[57] The heparin tissue source (*i.e.,* intestinal *vs.* lung, porcine *vs.* bovine), method of preparation, molecular weight distribution of heparin used,[15,75] and possibly the use of nitroglycerin infusions[68,76] (for which the mechanisms are unknown) may also contribute to impaired responsiveness. Unfortunately, no currently available tests can help clinicians identify the specific cause of heparin resistance.

Current Monitoring methods

Monitoring Hemostasis during CPB: Current Practice and Fixed Dosing Regimens

A survey in 1993 of anticoagulation practices (Appendix) indicates that heparin administration for CPB is predominantly based on an initial dose followed by activated clotting time (ACT) monitoring, although some centers still use fixed dosing schemes. The limitations of fixed dosage regimens without monitoring include the lack of confirmation of adequate anticoagulation and the inability to maintain a consistent heparin concentration for individual patients. However, one blinded study using fixed doses found no relation between ACT values during CPB and bleeding outcomes.[77] In addition, Jobes *et al.*[78] did not find reduced bleeding or transfusion requirements when heparin concentration monitoring was compared to fixed dosage protocols. As discussed later, inconsistent outcomes (*i.e.,* some showing improved transfusion outcomes, others not) have been observed when ACT monitoring was compared to fixed dosing regimens (table 2). Available point-of-care instruments can facilitate the monitoring of heparin's antithrombotic properties and its circulating concentration.

Monitoring Heparin's Anticoagulant Properties: Instruments that Measure ACT

The ACT assay represents a modification of the Lee-White whole blood clotting time and uses an activator, either clay (kaolin) or diatomaceous earth (celite), to accelerate coagulation by activating the contact path-

Table 2. Summary of Studies That Have Examined the Effect of the Method of Anticoagulation Monitoring (Activated Clotting Time) *versus* No Monitoring on Perioperative Blood Loss and Transfusion Outcomes

Reference	No. of Patients	Blood Loss	Transfusion Requirements	Study Design
Babka *et al.,* 1977[134]	20	ACT < NM	NE	Prospective, randomized
Verska *et al.,* 1977[133]	114	ACT < NM	ACT < NM	Historical control group
Roth *et al.,* 1979[135]	56	ND	ND	Historical control group
Akl *et al.,* 1980[141]	120	ND	ACT < NM	Historical control group
Papaconstantinou *et al.,* 1981[136]	126	ACT < NM	ACT < NM	Historical control group
Jumean *et al.,* 1983[137]	77	ACT < NM	NE	Historical control group
Dearing *et al.,* 1983[142]	648	ACT < NM	ACT < NM	Retrospective, sequential grouping
Niinikowski *et al.,* 1984[138]	100	ACT < NM	ND	Retrospective, sequential grouping
Lefemine *et al.,* 1985[139]	61	ND	NE	Not specified
Preiss *et al.,* 1985[140]	350	ND	ACT < NM	Retrospective
Metz *et al.,* 1990[77]	193	ND	NE	Prospective

Heparin doses were either administered based on activated clotting time values or empiric dosing regimens or no monitoring. Anticoagulation factors that help explain the discrepant results between studies are included.

ND = no difference, NE = not examined; ACT = activated clotting time; NM = no monitoring.

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way. Test tubes or cartridges can be inserted into respective instruments for prewarming 1 min or more before test initiation because failure to prewarm prolongs ACT values.[79] Hemochron (International Technidyne Inc., Edison, NJ) automated instruments permit measurement of celite or kaolin ACT values. Blood (2.0 ml) either devoid of heparin or containing heparin up to 8 U/ml (higher levels prolong ACT values beyond the 1,000-s detection limit) is transferred into an ACT tube that contains either celite or kaolin (or less commonly, saline) and a magnetic rod. The blood is then mixed by a manual, gradual shaking of the tube. After the tube is inserted into a 37°C heat block chamber, it rotates automatically until a formed clot engages the rod, at which time a sensor detects a change in magnetic attraction and stops a timer to yield an ACT value. This value relates linearly to the concentration of heparin in the blood specimen.[80]

Hepcon or ACT II (Medtronic Blood Management, Parker, CO) automated instruments use kaolin or, less commonly, celite as the activator. Blood specimens (0.4 ml) are either automatically (Hepcon) or manually (ACT II) inserted in each of the two (ACT II or Hepcon) wells of a cartridge. Each instrument then lifts a plunger–flag assembly that facilitates mixing and activation of blood by kaolin or celite. The presence of a clot is based on optical detection of a decreased rate of descent of the plunger–flag assembly.

Activated clotting time can also be measured using the Sonoclot instrument (SonACT, Sienco Corp., Wheat Ridge, CO), which detects viscokinetic changes of blood as it undergoes coagulation. Whole blood or platelet-rich plasma obtained *via* differential centrifugation (0.4 ml) is placed in a cuvette in which a vibrating plastic probe is suspended. The changes in mechanical impedance to vibration exerted on the probe are recorded in a tracing called a Sonoclot signature. As fibrin strands form, impedance increases to a peak. The onset time (T1, normally 80–130 s) reflects the beginning of a fibrin (clot) formation and corresponds to the ACT (*i.e.,* called SonACT). Although the SonACT potentially may be used to monitor anticoagulation, evaluations of this test during CPB are lacking.

One recently developed ACT test (Array Medical, Edison, NJ) uses either celite or kaolin activation and 2-ml blood sample volumes. However, insufficient data are available to comment on its performance.

Celite ACT and kaolin ACT correlate well ($r = 0.91$, $r = 0.93$, respectively) with laboratory-derived anti-Factor Xa heparin concentration values in the pre-CPB period[81] and are commonly used during CPB to monitor anticoagulation. However, ACT prolongation during CPB is not necessarily caused by heparin.[78] This may relate to the intrinsic variability of ACT measurements,[82,83] to other factors associated with CPB, such as hypothermia,[81,82,84] quantitative and qualitative platelet abnormalities,[85–87] aprotinin (*i.e.,* when celite is used as an activator),[88–92] or hemodilution.[81] An inverse, independent relation between core body temperature and ACT values (*i.e.,* using multivariate statistical analyses) observed in one study may reflect inadequacy of specimen warming by the respective instruments.[81] What remains unclear is the degree to which this divergence (*i.e.,*

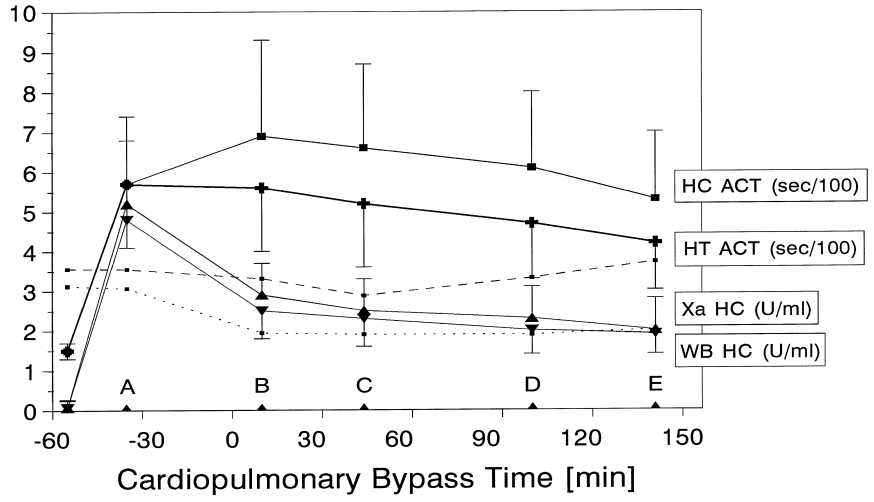

Fig. 4. Limitations of activated clotting time (ACT) in heparin monitoring with cardiopulmonary bypass (CPB). Comparison of ACT values obtained with two different contact-activating agents and heparin concentration measurements using a laboratory-based and point-of-care method obtained in 32 patients during CPB. Mean values of ACT are expressed as seconds per 100 (s/100) for both celite Hemochron (HC) ACT and kaolin Hemotec (HT) ACT assays. Plasma equivalent heparin concentration (WB HC) and anti-Xa plasma heparin concentration (anti-Xa HC) are expressed as units per milliliter (U/ml). Hematocrit values (dotted line) are expressed as percent values divided by 10, and core body temperature (dashed line) is expressed as degrees centigrade divided by 10. Blood specimens were obtained before heparin administration and 10 min after (A) heparin administration, (B) initiation of CPB, (C) achievement of hypothermia, and (D) rewarming, as well as (E) immediately before discontinuation of CPB. T-bars represent SD. From Despotis GJ, Summerfield AL, Joist JH, Goodnough LT, Santoro SA, Spitznagel E, Cox JL, Lappas DG: Comparison of activated coagulation time and whole blood heparin measurements to laboratory plasma anti-Xa heparin concentration in patients having cardiac operations. J Thorac Cardiovasc Surg 1994; 108:1076–82. Reprinted with permission.

between ACT and heparin concentration values) reflects an increased sensitivity of coagulation proteins to heparin-induced anticoagulation in the presence of hypothermia. Unfortunately, no investigation has specifically assessed the relation between ACT and blood–heparin concentrations at various constant levels of hypothermia.

By affecting the ACT method, CPB-related factors (*i.e.,* hemodilution and hypothermia) ultimately may contribute to variability in heparin levels during CPB when this test is used to guide heparin therapy.[77,81,84,93] Variability in heparin concentration was recently assessed by calculating the absolute deviation of heparin levels during CPB from the target pre-CPB heparin levels (*i.e.,* obtained after heparin administration but before initiation of CPB) for each of 32 patients.[81] When heparin dosing was guided by ACT values (*i.e.*, $<$ 480 s for additional heparin) during CPB, heparin concentration (*i.e.*, anti-Xa activity) varied substantially (2.7 U/ml = mean absolute deviation for 32 patients) from those concentration values that were present at similar ACT values before CPB.[81] In most cases, the CPB heparin concentrations were lower than those observed before initiation of CPB. Mean absolute deviation was smaller (0.75 U/ml, $P <$ 0.001) when heparin was infused continuously in another study.[94] Figure 4 shows the typical divergence between mean ACT and heparin concentration (*i.e.*, both anti-Xa heparin activity and whole blood heparin concentration) values that occurs during hypothermic CPB.[81]

Heparin Concentration Assays

Automated Protamine Titration Method and Fluorometric Assay. To provide an ACT alternative that is potentially unaffected by CPB-related hypothermia and hemodilution, several methods have been developed to measure whole blood heparin concentration. These techniques use either neutralization techniques (*e.g.*, automated protamine titration method, heparin-responsive sensor) or heparin activity (*e.g.*, fluorometric assay, HepTest [Haemachem, St. Louis, MO] whole blood anti-Xa/IIa activity). All of these techniques offer the advantage over ACT-based or empiric protamine dosing regimens of basing protamine doses on whole blood heparin concentrations present at the end of CPB. However, each one is limited by the need to use standard algorithms to calculate blood volume in a patient population in which blood volume is likely to be highly variable. Other limitations include discontinuous measurements and the use of clotting as a surrogate endpoint rather than direct measurement of heparin concentrations. Alternatively, basing protamine on administered heparin doses or ACT-based estimates of heparin concentration may result in administration of larger protamine doses. The inability of assays that measure only heparin concentration to detect the antithrombotic properties of heparin constitutes a major limitation of this approach. This is important in patients who have a theoretically adequate blood heparin concentration but who also have an increased risk for thrombosis because of resistance to heparin-induced an-

ticoagulation. Accordingly, because heparin concentration monitoring only assesses the amount or concentration of heparin that do not necessarily correlate with the anticoagulant effects of heparin, it may mislead the clinician regarding anticoagulant activity. The optimal monitoring system would therefore accurately assess *in vivo* thrombin activity, yet not be artifactually affected by the effects of hemodilution or hypothermia unless these factors directly affect *in vivo* thrombin activity.

Whole blood heparin concentration measurements can be performed at the bedside using an automated heparin protamine titration method (Hepcon Instrument, Medtronic Blood Management, Parker, CO).[38,78,95,96] With this method, a thromboplastin reagent is used to accelerate coagulation *via* the tissue factor pathway, and the device then measures clotting times in several channels that contain varying amounts of protamine. The principle behind this test is that clotting occurs first in the chamber in which the protamine-to-heparin ratio is nearest the neutralization point.[78] Because the first channel to clot, and not absolute clot time, is the endpoint, this method is unaffected by reductions in clotting factors and platelets during CPB.[97–99]

Heparin levels determined by this automated protamine titration method have been shown to correlate well with anti-Xa plasma heparin measurements (*i.e.*, a laboratory-based method)[81,99] even when aprotinin is present.[100] Hardy *et al.* found a large bias (mean ± SD difference between values was 1.45 ± 1.65 U/ml) between measurements derived from the automated protamine titration method and from anti-Xa measurements.[101] However, the findings of Hardy *et al.*[101] were not confirmed in two subsequent studies[98,99] in which the bias between Hepcon and anti-Xa levels was lower, 0.002 ± 0.53 (range, −1.78–1.72) and 0.715 ± 0.99 U/ml, respectively. Although the exact relation between whole blood (automated protamine titration assay) and plasma (anti-Xa chromogenic) heparin levels needs further investigation, another recent study showed that patient-specific heparin concentrations can be maintained using the automated protamine titration assay.[94]

The Protopath (Dade division, American Hospital Supply Inc., Chicago, IL) system measures heparin activity by its ability to inhibit the action of thrombin on a synthetic fluorogenic substrate.[102,103] A plasma separator produces 0.5 ml plasma in 1 min by pneumatic filtration rather than centrifugation. The Protopath system assay is not influenced by fibrinogen or other procoagulant levels, by decreases in ATIII, or by hypothermia,[93] all of which can affect the ACT method. This assay appears to be sensitive solely to the concentration of heparin in the plasma. As a result, ATIII deficiency or other causes of heparin resistance will not be detected. Heparin levels can be measured accurately in approximately 5 min, so that additional doses of heparin can be given or withheld appropriately. In one study during CPB, Protopath use decreased protamine doses by an average of 64.7% without causing clotting or bleeding problems.[103] Although the Protopath system provides accurate plasma heparin concentration measurements,[104] its clinical usefulness is limited by the lack of clot-formation detection, the need for considerable technical expertise in assay standardization, the need to convert plasma heparin concentration values to whole blood equivalent values when determining protamine dose, and by equipment calibration and maintenance requirements. These limitations may account for the lack of its widespread use. Limitations common to both methods (*i.e.,* automated protamine titration and Protopath) include the inability of measurements to assess actual molecular species (*e.g.,* high-molecular-weight heparin *vs.* LMWH), to evaluate the anticoagulant properties of heparin or to detect heparin resistance.

Newly Developed Monitoring Techniques

Monitoring Heparin's Anticoagulant Properties: HMT, LHMT, HiTT, HiPT

The thrombolytic assessment system (TAS; Cardiovascular Diagnostics, Raleigh, NC) is a portable, lightweight instrument initially designed for bedside monitoring of prothrombin time (PT) and activated partial thromboblastin time (aPTT). The TAS rapidly performs measurements on citrated whole blood or plasma. Disposable test cards, the size of a credit card, contain a reaction chamber with all the reagents necessary for a particular test. These cards detect the onset of clot formation or lysis in an analyzer maintained at 37°C. The reagents are dry, which extends room temperature shelf life. Test cards also contain celite, calcium chloride, modifiers–stabilizers, and paramagnetic iron oxide particles. The heparin management test (HMT) and low-range heparin management test (LHMT) are used to monitor the anticoagulant properties of heparin in whole blood with heparin concentrations between 1 and 10 U/ml or between 0 and 4 U/ml, respectively. When 30 μl blood is added to the reaction chamber on the test card, it mixes with the reagent in a reaction chamber, thereby dissolving the dry reagent and changing the light reflection pattern detected by a photodetector to automatically

begin the test. With the HMT and low-range heparin management tests, celite activates coagulation. Coagulation is measured by optically monitoring the impedance of the movement of the iron oxide particles in an oscillating magnetic field. Clotting causes particle movement to cease, whereas clot lysis causes them to resume movement. HMT measurement values should be affected by *in vitro* hypothermia based on the equilibration of the relatively small volume of blood (30 μl) used in the test and the room temperature reagents within the nonheated chamber in the TAS system, which ultimately lowers the temperature of the blood specimen. Preliminary evidence suggests that correlations between HMT and heparin concentration values are slightly better than Hemochron and ACT II versions of the test,[105,106] Gibbs *et al.*[106] demonstrated that the coefficient of variation was less for HMT values (7.3–14.2%) when compared to celite ACT (10.2–37.8%), and Slaughter *et al.* demonstrated a better correlation ($P < 0.05$) between HMT values and anti-Xa values ($r = 0.84$) when compared to kaolin ACT values ($r = 0.75$).[105]

Another assay for monitoring heparin's anticoagulant properties during CPB is the high-dose thrombin time (HiTT; International Technidyne) that can be measured using Hemochron instruments. The HiTT assay measures heparin–antithrombin activity indirectly by using the final common pathway of the coagulation cascade. Because fibrin is formed when thrombin enzymatically cleaves fibrinogen in this test, the rate of fibrin formation relates to the concentration and qualitative function of fibrinogen and thrombin activity. In addition to the concentration of thrombin, the presence of thrombin inhibitors (*e.g.*, heparin) or fibrin-split products influences HiTT measurements. Because fibrinogen levels more than 80 mg/dl generally do not affect the rate of fibrin formation and the HiTT assay contains a high concentration of thrombin (3 U/ml), fibrin formation (clot detection) should relate linearly to heparin concentration. Although this assay may have clinical usefulness for monitoring anticoagulation during CPB, in part because it is unaffected by aprotinin,[107] recent evidence indicates that HiTT values have a poor relation to whole blood heparin concentrations (Hepcon automated protamine titration method) before and during CPB.[91] Another limitation of this assay includes the instability of dissolved thrombin, necessitating fresh preparation of reagents. More extensive validation in controlled clinical studies is needed to compare HiTT values to ACT and heparin concentration values and to sensitive markers of coagulation activation during CPB.

Another assay that can be performed using a Hemochron instrument is the high-dose prothrombin time (HiPT), which evaluates activation *via* the extrinsic pathway. This whole blood measurement is activated by rabbit brain thromboplastin. A stepwise HiPT response to incremental heparin concentrations was recently demonstrated by Tabuchi *et al.*,[108] but more evaluations are needed to adequately evaluate this assay's relation to heparin concentration values (anti-Xa chromogenic assay), markers of hemostatic activation (*e.g.*, FPA or fibrin monomer levels), and clinical usefulness.

Although assays developed as alternatives to the ACT-based tests potentially offer distinct advantages, inability to specifically assess suppression of thrombin activity as an endpoint is common to all of the tests described. As previously addressed, two important goals of anticoagulation monitoring during cardiac surgery are to prevent thrombosis of the extracorporeal circuit and to minimize excessive CPB-related activation of the hemostatic system. Therefore, an ideal method would directly assess the antithrombotic properties of heparin using a thrombin activity (*e.g.,* fibrinopeptide A) or fibrin generation endpoint. Measurement values from such a system would ideally be affected only by other CPB-related factors, such as hypothermia, hemodilution, or aprotinin if these variables affected *in vivo* thrombin activity.

Heparin Concentration Assays

Heparin-responsive Sensor, Whole Blood Anti-Xa/IIa Heparin Activity. The heparin-responsive sensor (HRS), which consists of a heparin-sensitive membrane (critical components of membrane from Fluka Chemical Corp., Ronkonkoma, NY), measures heparin concentration by a potentiometric signal generated by the heparin molecule's negative charge. A polymer membrane-type ion-selective electrode detects a change in electrical potential induced by a quantitative titration of protamine.[109–111] If protamine added in a blood sample does not completely neutralize the heparin present, the electrical potential changes in proportion to the amount of excess heparin present. If protamine effectively neutralizes heparin, no potential change will occur. The HRS method correlates well with the Hepcon method ($r = 0.942$) and has only a small bias (0.211 IU/ml).[98] The bias between the HRS and anti-Xa assays is also small (0.102 IU/ml) when compared to the bias between plasma-equivalent Hepcon values and anti-Xa assays (0.715 IU/ml).[98] Potential advantages of the HRS system over the Hepcon system include the absence of a need for clot formation (*i.e.,* assay is accurate in solutions that contain

no coagulation factors) and the ability to report heparin concentrations over a wider range of values. HRS has not yet been tested in a large number of patients and has the theoretical limitations of influence by other anions, such as salicylates, iodide, bromide, or nitrate, as well as cost.

The HepTest, a recently developed commercial clotting test, monitors the anticoagulant properties of unfractionated and LMWH based on the inhibition of either Factor Xa or IIa.[112,113] This method measures heparin's potentiation of ATIII-mediated inhibition of exogenous Factors Xa or IIa using an electrochemical clot detection endpoint.

Early studies showed that calculated values for LMWH pharmacokinetic parameters were similar using Heptest and either anti-Xa chromogenic or amidolytic assays.[113,114] Although another study showed that Heptest-measured Xa-like activity levels using finger-stick specimens were comparable to those measured with a chromogenic substrate assay using venous blood specimens,[115] a subsequent study from the same investigators showed that Heptest values were 10–20% larger than those from the chromogenic (*i.e.*, S 222) method.[116] Data from more recent studies indicate that Heptest measurements accurately reflect anti-Xa with LMWH and anti-Xa and anti-IIa activity with unfractionated heparin.[117] Heptest measurements have also been shown to reflect the anticoagulant tissue pathway factor inhibitor properties of tissue pathway factor inhibitor released by heparin.[118] This test also has been recently evaluated for potential use as a point-of-care method[119] and has been adapted for use with a fully automated, coagulation-dedicated analyzer.[120] Studies that evaluate the potential usefulness of this assay in monitoring anticoagulation during cardiac surgery are needed. Because this method assesses heparin concentration using a heparin activity endpoint, measurements could potentially vary, independent of molecular weight (*i.e.*, anti-Xa *vs.* anti-IIa activity). This limitation may be potentially overcome by assessing the differential inhibition of two important substrates (*e.g.*, thrombin and Factor Xa).

Monitors that Predict Heparin Resistance

If heparin resistance is secondary to ATIII deficiency, detection and treatment of heparin resistance is potentially important to the preservation of coagulation factors and platelets during CPB. Hereditary or acquired ATIII deficiency renders heparin less effective in suppressing thrombin generation or activity during extracorporeal circulation.[64,66,121] Because of this and the well-documented substantial interpatient variability in the ACT response to heparin,[60,61,122,123] Bull *et al.*[124] advocate a dose–response plot to predict the heparin requirements of individual patients.

Accordingly, assays such as the heparin dose–response test (HDR; Medtronic Blood Management, Parker, CO) based on the kaolin ACT, and the Heparin Response Test (HRT; International Technidyne Inc.), based on the celite ACT, have been developed. These automated or semiautomated tests add heparin to the patient's blood *ex vivo* to determine ACT responsiveness to heparin. In addition to estimating heparin requirements for individual patients before surgery, these tests should be able to identify patients with significant heparin resistance secondary to decreased ATIII levels. Although a targeted ACT of 480 s was achieved from the initial heparin dose predicted by the HDR test in 40 of 41 adult patients,[122] further studies are needed to validate this test's ability to project the heparin dose needed to achieve any target ACT.

Potential use of these tests to identify patients with ATIII-mediated heparin resistance is supported by the demonstration of a progressive reduction in the responsiveness of whole blood to heparin (*i.e.*, at high concentrations used with CPB) when ATIII concentration is $<$ 80 U/dL.[61] In this study,[61] there was a strong linear relation between kaolin (slope = 1.04ATIII − 2; r^2 = 0.78) and celite (slope = 1.36ATIII + 6; r^2 = 0.77) ACT slopes and AT III concentrations $<$ 80 U/dl. These tests were used as part of anticoagulation management protocols in two recent studies showing that precise patient-specific control of heparin and protamine administration decreased blood loss (15 and 50%, respectively) and transfusion requirements (50 and 80%, respectively).[60,125] The protamine response and HRT tests were used in these studies to determine the heparin dose necessary to attain the target ACT value (*e.g.*, 400 or 480 s, respectively) before CPB. In the study by Despotis *et al.*,[60] the heparin concentration required to reach that target ACT value was maintained throughout CPB even if ACT values exceeded the target values.

Monitoring Heparin after Cardiopulmonary Bypass: Detection of Residual Heparin or Heparin Rebound

Persistent circulating heparin from inadequate neutralization[126,127] or release of heparin from heparin-binding proteins, from heparin-protamine complexes, or from other sites[49,128] can contribute to excessive bleeding after CPB. *Heparin rebound* is defined as the recurrence of heparin activity after complete neutralization by pro-

tamine. One study revealed that chest tube drainage is reduced if heparin rebound is detected using ACT values then treated with additional protamine.[95] The 1993 survey detailed in the Appendix also reveals that most centers were using ACT measurements as an index of adequate heparin reversal. However, the ACT is probably not the most appropriate test for diagnosing heparin rebound because it is relatively insensitive to heparin concentrations $<$ 0.6 U/ml.[80,129] Murray *et al.*[129] showed that Hepcon whole blood heparin concentration measurements detected heparin rebound better than the ACT, even though, at the time of the study, the Hepcon cartridge detection threshold was 0.4 U/ml. Because a cartridge (TheraCon, Medtronic HemoTec, Parker, CO) with a detection threshold of 0.1 U/ml is now commercially available, presumably this would further enhance the Hepcon device's diagnostic sensitivity advantage over ACT values in this application.[130] The heparin responsive sensor or the Heptest can also be used to detect low circulating levels of heparin after protamine administration.

Alternatively, heparinase (IBEX Corp., Montreal, CA), an enzyme that degrades heparin to smaller, inactive fragments, has been used to improve the sensitivity of various test systems to low heparin concentrations. Specifically, heparinase has been used with the ACT,[131] laboratory-based and point-of-care whole blood[132] PT and aPTT assays (Boehringer Mannheim Diagnostics, Indianapolis, IN) by comparing neutralized and un-neutralized specimens. In the heparinase ACT method, heparinase is included in one of the cartridge channels of a dual-channel high-range ACT (HR ACT) test to eliminate the anticoagulant properties of heparin. In addition, a whole blood thrombin time assay with protamine neutralization (HNTT, International Technidyne) has been evaluated for its ability to assess residual heparin or heparin rebound in the post-CPB period.[125] Although these tests may be clinically useful with respect to detection of un-neutralized heparin or heparin rebound, studies are needed to compare these assays to standard laboratory measurements of heparin activity and to define the heparin detection threshold.

Impact of Monitoring on Clinical Practice

Impact on Blood Loss and Transfusion of Blood and Blood Components

Our survey reveals that the ACT is the most commonly used method to monitor heparin anticoagulation during CPB (Appendix). This finding probably relates to the ease of use of the ACT and studies from the late 1970s and early 1980s showing a reduction in postoperative chest tube drainage when the ACT test was used. When compared to no monitoring, the impact of heparin–protamine dosing guided by ACT-based protocols on chest tube drainage and transfusion outcomes has varied (table 2).[77,133–142] Of 11 studies, 6 showed a reduction in chest tube drainage and 5 showed no difference. Only seven of the studies investigated transfusion outcomes, and five of these showed that ACT-based protocols reduced transfusion requirements. Only 2 of these 11 studies were prospective,[77,134] and neither of these 2 involved a randomized, blinded study design, which may limit the accuracy and reliability of the findings.

Likewise, when compared to either fixed-dose[78] or ACT[38,60,95,143] protocols, the impact of heparin concentration monitoring protocols on bleeding and blood conservation has varied. Although some authors suggest that excessive bleeding relates to use of larger doses (*i.e.*, doses greater than those typically administered using ACT methods) of bovine heparin during CPB,[38,144] other studies found no differences in blood loss when either bovine[95,145] or porcine heparin were used.[4,60,125,143] Table 3 summarizes important factors that help explain the differences in outcomes using several heparin monitoring protocols. To determine whether heparin dose, as directed by an ACT-based protocol, relates to either blood loss or transfusion requirements, a multivariate analysis of 487 consecutive patients was recently performed.[4] Although this analysis was limited by its retrospective design, significant associations were demonstrated between lower initial–total heparin dosage and increased blood loss and transfusion requirements.

In a subsequent prospective randomized trial from the same institution, the impact of heparin and protamine administration as directed by a point-of-care whole blood (WB) hemostasis system (Hepcon, Medtronic Blood Management, Englewood, CO) on bleeding and blood transfusion when compared to an ACT-based protocol was evaluated in 254 patients.[60] An empiric dosing regimen for heparin and protamine was used for control patients using ACT values, whereas the anticoagulation–reversal protocol for intervention patients was based on HDR, ACT, and whole blood heparin concentration values. A patient-specific, reference heparin concentration (*i.e.*, pre-CPB whole blood heparin concentration associated with kaolin ACT of 480 s; median, 3.4 U/ml; 95% confidence interval, 2–5.4 U/ml) was maintained during CPB, and the protamine dose was calculated from the mea-

Table 3. Summary of Studies That Have Examined the Effect of Higher Heparin Doses and Method of Anticoagulation Monitoring on Perioperative Blood Loss and Transfusion Outcomes

Heparin Protocols Used	No. of Patients	Heparin Dose (U/kg)	Heparin Source (Bovine *vs.* Porcine)*	Patient-specific Monitoring	Heparin Rebound Monitoring	CPB Time (min)	Transfusion Requirements	Blood Loss (ml of CTD in 24 h)
Heparin concentration *vs.* fixed dose								
Jobes *et al.,* 1981[78]	46	318 *vs.* 307	?	?	No	?	NE	1,057 *vs.* 953
High *vs.* low fixed heparin dose								
Boldt *et al.,* 1994[144]	60	640 *vs.* 354	Bovine	No	No	107	↑	1,150 *vs.* 700†
Okita *et al.,* 1997[145]	94	440 *vs.* 286	?	No	No	168	ND	907 *vs.* 1,126
Heparin Concentration *vs.* ACT								
Gravlee *et al.,* 1990[38]	21	564 *vs.* 442	Bovine	No/yes	No	105	NE	1,104 *vs.* 699†
Gravlee *et al.,* 1992[95]	63	740 *vs.* 354	Bovine	No/yes	Yes	115	ND	1,035 *vs.* 901
Despotis *et al.,* 1995[60]	254	612 *vs.* 462	Porcine	Yes/yes	Yes	145	↓	840 *vs.* 924†
Sakurada *et al.,* 1997[143]	34	690 *vs.* 300	?	Yes/yes	No	71	ND	563 *vs.* 595

Generally, studies implementing protocols that direct higher doses of heparin to be administered are summarized on the left side of each column; these included protocols in which heparin was administered based on either heparin concentration monitoring or empirically with time-dependent, heparin bolus/infusion techniques (high fixed heparin dose). Studies that implemented protocols that directed lower doses of heparin to be administered are summarized on the right side of each column; these included protocols in which heparin was administered empirically based on time-dependent, bolus/infusion regimens (low fixed heparin dose) or ACT monitoring. Anticoagulation factors that help explain the discrepant results between studies are included. Patient-specific dosing of heparin based on monitoring of either ACT values (anticoagulant response) or heparin concentration *vs.* empiric regimens are summarized for each study. Numeric values in this table represent mean values for each group.

CPB = cardiopulmonary bypass; NA = not applicable; NE = not examined; ND = no difference; CTD = chest tube drainage; ? = inability to discern from study; ACT = activated clotting time.

* Bovine lung source *vs.* porcine mucosal source.

† $P \leq 0.05$.

sured, residual heparin concentration. Patients in the intervention cohort received 25% larger total doses of heparin and had smaller protamine-to-heparin ratios (*i.e.*, by 25%) when compared to control patients. A greater percentage of patients in the control cohort required platelet (34 *vs.* 22%, $P = 0.03$), plasma (31 *vs.* 11%, $P < 0.001$) and cryoprecipitate (5 *vs.* 0%, $P = 0.01$) units when compared to the intervention cohort. Control cohort patients also had 10% longer operative post-CPB closure times ($P = 0.02$), 15% more mediastinal chest tube drainage ($P = 0.05$) in the first 4 h postoperatively, and twice as many control patients required hemostatic (*e.g.*, platelets, fresh frozen plasma, and so on) transfusion (17% *vs.* 33%, $P = 0.005$).

Because generation of FPA[38,64] and inhibition of clot-bound thrombin[47] have been shown to relate inversely to heparin concentration, maintenance of heparin concentrations that more effectively inactivate thrombin may preserve hemostasis during prolonged CPB. This is supported by findings from two additional studies. The first study evaluated 31 patients requiring repeat or combined cardiac procedures (*i.e.*, coronary revascularization plus valve repair/replacement) and thus at increased risk for excessive bleeding.[25] Maintenance of higher heparin concentrations better preserved consumable ATIII and Factors I, V, and VIII most likely related to better suppression of thrombin (65% reduction in FPA levels) and fibrinolytic (*i.e.*, 50% reduction in D-dimers) activity. The second study showed that larger heparin doses can better suppress thrombin (*i.e.*, lower TAT complexes) and fibrinolytic activity (*i.e.*, lower D-dimers) in patients undergoing deep hypothermic circulatory arrest.[145] These studies suggest the superiority of higher heparin concentrations for procedures involving prolonged or complicated CPB. These findings may relate to the propensity of hemodilution and hypothermia to prolong ACT, independent of blood heparin concentration, thus resulting in smaller heparin doses.

Higher stable heparin concentrations during CPB can also preserve platelet function during prolonged CPB. In a recent trial, less platelet activation (*i.e.*, lower platelet factor 4 and β thromboglobuloin levels) was shown in patients who received larger heparin doses.[145] Preservation of platelets by higher heparin levels during CPB is supported by more prolonged bleeding times in patients who received less heparin during CPB;[25] in addition, a significant correlation ($r = 0.51$, $P = 0.004$) between FPA and BTG levels in that study suggests that platelet activation may relate directly to thrombin activity. Inhibition of platelet function by hepa-

Table 4. Summary of Studies that Have Examined the Effect of Protamine Dose on Perioperative Blood Loss and Transfusion Outcomes

Reference	No. of Patients	Blood Loss	Transfusion Requirements	Protamine:Heparin Ratio*		
				MON	EMP	% Reduction†
Berger *et al.,* 1968[149]	64	MON < EMP	NE	0.7:1	1.4:1	43
Guffin *et al.,* 1976[150]	60	MON < EMP	NE	0.4:1	1.2:1	67
Moriau *et al.,* 1977[151]	20	NE	MON < EMP	1.1:1	2.5:1	56
Jobes *et al.,* 1980[78]	46	ND	NE	1.1:1	1.7:1	35
Ottesen *et al.,* 1984[152]	20	ND	NE	1.0:1	1.6:1	38
Keeler *et al.,* 1991[153]	40	ND	ND	1.2:1	1.8:1	33
Jobes *et al.,* 1995[125]	46	MON < EMP	MON < EMP	0.5:1	1.1:1	55
Shore-Lesserson *et al.,* 1998[154]	20	ND	ND	0.8:1	1.1:1	27

Protamine doses were either administered based on empiric dosing schemes using initial or total heparin doses used or monitoring protocols.

ND = no difference; NE = not examined; EMP = empiric dosing schemes; MON = monitoring protocols.

* Protamine (mg) to heparin (mg) ratio calculated based on total heparin administered for cardiopulmonary bypass.

† Refers to percent change in protamine-to-heparin ratio between cohorts.

rin[16,17,21,52,53,95,144,146–148,226] may relate to suppression of Factor VIII-mediated platelet aggregation[53] or von Willebrand factor–related mechanisms.[52] However, other studies indicate that inhibition of platelet function by heparin may be detrimental, based on the lack of reversibility by routine doses of protamine,[147] which may relate to the degree of platelet inhibition.[17,148] In one study, 59% of patients displayed mild-to-moderate inhibition, whereas 33% of patients displayed severe inhibition, and the degree of platelet inhibition by heparin correlated with blood loss.[148] Although these findings explain how platelet inhibition can be interpreted as being synonymous with platelet dysfunction,[16] the duration of this inhibition by heparin has not been well-characterized, and it is uncertain whether the inhibition by heparin is dose-dependent within the range of heparin concentrations used clinically (1–5 U/ml). In addition, these studies did not evaluate whether heparin-mediated platelet inhibition was influenced by the dose of heparin required to obtain a therapeutic anticoagulant response for a given patient. Until these issues are resolved, maintenance of higher patient-specific heparin concentrations should be considered to reduce thrombin-mediated activation and consumption of platelets in patients requiring longer CPB intervals.

Monitoring protocols can markedly influence protamine doses used to neutralize heparin.[78,125,149–154] Two recent studies prospectively compared the use of a new, point-of-care hemostasis system (RxDx System, International Technidyne Corp.) to standard ACT-based empiric regimens in adult patients undergoing cardiac surgical procedures.[125,154] The RxDx system estimates patient-specific anticoagulant response to heparin (*e.g.*, HRT), determines celite ACT values, and calculates protamine dose by using ACT-based approximations of heparin concentration (*e.g.,* protamine response test). When compared to control patients whose anticoagulation and reversal were based on empiric regimens, Jobes *et al.*[125] demonstrated that RxDx produced a 50% reduction in the protamine dose ($P < 0.01$), which resulted in 50% less chest tube drainage ($P = 0.01$) and 80% fewer transfusions ($P = 0.02$) in the first 24 h postoperatively. In contrast, Shore-Lesserson *et al.*[154] did not observe a reduction in blood loss and transfusion requirements, nor was the protamine dose substantially decreased by use of the RxDx system.

Of eight published studies that specifically evaluated the clinical impact of reducing protamine dose, four showed either reduced blood loss or transfusion requirements,[125,149–151] whereas four did not.[78,152–154] However, a reduced protamine dose was not associated with increased blood loss or transfusion in any of these studies. The discrepancy in outcomes between these studies probably relates to differences in the relative extent of reduction in protamine dose and the overall protamine-to-heparin ratio in the intervention cohorts within these studies. Thus, in the four studies that showed a favorable difference in outcome, better bleeding or transfusion outcomes occurred when the reduction in protamine dose was approximately 50% or greater and when the protamine-to-heparin ratio was less than 1.[125,149–151] The four negative studies either had smaller reductions in protamine dose (27–38%) or protamine-to-heparin ratios consistently that were more than 1, or both (table 4). The decreases in perioperative

blood loss associated with reduced doses of protamine may result from less complement activation[155] or from reduced protamine-induced platelet dysfunction.[19–21,156,157] Based on our survey results (Appendix), 48% of clinicians polled probably administered excessive doses of protamine as a result of using empiric regimens based on a fixed ratio (*e.g.*, 1:1 or greater) of protamine to the total heparin dose administered.

In summary, because several studies reveal limitations of ACT monitoring during CPB[78,81–90] and the detrimental effects of excessive protamine on platelet function (*e.g.*, 50% reduction in the percentage of platelets expressing P-selectin after stimulation with thrombin receptor agonist peptide, or TRAP),[21] blood loss (*e.g.*, increased by 100%), and transfusion requirements (increased by 100–400%),[60,125,133,149–151] significant refinements of the clinical practices used for determining heparin and protamine doses should be considered. New agents, such as recombinant platelet factor 4 (rPF4),[158,159] lactoferrin,[69] or the enzyme heparinase,[21,160] are being investigated as therapeutic alternatives to protamine for patients with known hypersensitivity to or history of catastrophic reactions to protamine. However, the finding that heparinase does not produce platelet dysfunction, (*e.g.*, reduced thrombin receptor agonist peptide–mediated expression of P-selectin) suggests that these alternatives may also reduce bleeding.[21]

Monitoring for Special Clinical Circumstances

Monitoring the Antithrombotic Properties of Heparin in Patients with Acquired or Hereditary Coagulation Factor Deficiency

Heparin monitoring during CPB can pose particular difficulties in patients with acquired coagulopathies, such as warfarin therapy, or congenital deficiencies of the coagulation, contact Factor XII,[161–168] high-molecular-weight kininogen, or prekallikrein. The latter three deficiencies are not associated with abnormal bleeding even when the hemostatic system is challenged with surgical wounds. Baseline (*i.e.,* prior to heparin administration) ACT values were substantially prolonged (*i.e.*, 522 ± 43 s) in five asymptomatic patients with Factor XII deficiency.[164,165,167–169] Heparin monitoring can also be compromised in patients with congenital Factor XI deficiency, approximately half of whom have no increased risk of abnormal bleeding in daily life.[170] Monitoring heparin therapy with routinely used methods may also be challenging in patients with antiphospholipid antibodies.[171,172] In all of these situations, heparin cannot be monitored during CPB with the ACT[165] or with any other assay that depends on contact pathway activation (*e.g.*, aPTT, HMT, SonACT). Although there is little published data about such patients, heparin can be monitored with on-site measurements of HiTT or HiPT, with whole blood heparin concentrations, or with a modification of the ACT method using plasma from an unaffected individual (*e.g.,* FFP).[169]

Therapeutic warfarin anticoagulation has been shown to enhance the antithrombotic properties of heparin during CPB while paradoxically decreasing postoperative bleeding,[67] presumably by reducing activation and consumption of clotting factors during CPB. Heparin is still required because the warfarin-induced anticoagulation is insufficient for conducting CPB. Although there are no published studies to support this approach, it may be advantageous to use smaller doses of heparin in the presence of warfarin because these agents appear to be complementary or synergistic in reducing hemostatic system activation and inhibition of platelet function.[17,148] HiPT results would likely be misleading as a judge of adequate heparinization in the setting of therapeutic warfarin anticoagulation because of preexisting reduction in Factor VII by warfarin. Because the optimal dose of heparin with warfarin is unknown, we recommend a standard initial dose of heparin (*e.g.*, 300 U/kg) because ACT and ACT-based tests (*e.g.*, HDR and HRT assays) may be misleading in this setting. For heparin dosing during CPB, it is unclear whether it is preferable to use ACT values or a time-dependent, fixed dosing regimen or to maintain a reference whole blood heparin concentration obtained after administration of the standard initial dose of heparin.

Anticoagulation Monitoring and Neutralization in Pediatric Cardiac Surgery

Despite a physiologic impact of CPB exceeding that for adults (*e.g.*, more hemodilution), heparin anticoagulation and monitoring in children undergoing cardiac surgery has received relatively limited attention from clinical investigators.[173,174] Consequently, in most centers, CPB anticoagulation practices for children are extrapolated from those in adults.[173–175]

In children undergoing CPB, Andrew *et al.*[173] demonstrated that neither celite ACT nor kaolin ACT values correlated with heparin concentration, probably related to the deterioration in the ability of ACT values to reflect

heparin concentrations in the presence of more pronounced hemodilution in children. This contrasts with the weak correlation between either celite (r = 0.34) or kaolin ACT (r = 0.59) values and heparin concentration in adults.[81] As with the adult series, these investigators also observed higher celite ACT values throughout CPB compared to kaolin ACT values that may reflect the relative potency of these two activators or the concentrations chosen for the available test cartridges and tubes.[173] Whereas 94% of celite ACT values throughout CPB were more than 450 s, only 27% of kaolin ACT values exceeded 450 s.[173] The investigators reasoned that all patients would have received larger heparin doses during CPB if only kaolin ACT values had been used to guide heparin therapy. Therefore, it appears that ACT values (*i.e.*, celite more than kaolin) are prolonged to a greater extent during pediatric CPB, that this prolongation is most likely related to more pronounced hemodilution, and that this may lead to underdosing of heparin.

Heparin concentrations were assessed in three studies, although in each study the authors used ACT values alone to guide heparin dosing during CPB.[173,174,176] After the initial heparin dose (300 U/kg) and before starting CPB, *ex vivo* plasma heparin concentrations (using a thrombin clotting time assay), were similar (*e.g.*, 3 U/ml) to values observed in adults.[173] However, heparin levels decreased by approximately 50% at the onset of CPB despite administration of heparin in the CPB prime, suggesting the importance of the larger ratio of CPB circuit volume to blood volume in children *versus* adults with respect to hemodilution and heparin therapy during CPB.[173,174] In the second study, heparin concentrations were assessed by antithrombin and by anti-Factor Xa assay.[174] Anti-IIa heparin levels were lower than anti-Factor Xa levels ($P < 0.001$) throughout CPB, suggesting faster clearance of larger molecular weight fractions of heparin.[174] A good correlation (r = 0.9) was observed between the assays throughout CPB, and both assays displayed a significant decrease in heparin levels immediately after starting CPB. In the third study,[176] larger doses of heparin in the CPB prime (3 *vs.* 1 U/ml) caused higher heparin levels after initiation of CPB, and this was accompanied by D-dimer levels that tended to be lower ($P = 0.06$). This finding suggests that children require heparin concentrations in the CPB prime that either approximate or exceed those used for adults.[176]

D'Errico *et al.*[177] used the HDR assay to estimate heparin requirements in children before the start of CPB and to determine the sensitivity to heparin in four age groups: (1) infants (younger than 1 yr), (2) preschool (1 to 5 yr), (3) school age (5 to 14 yr), and (4) adults (more than 14 yr). The target heparin concentration (THC) required to achieve a kaolin ACT of 480 s in preschool children was approximately 30% more than in adults, whereas the initial heparin dose (as measured in U/kg) required to achieve this THC was 50% more than that needed to achieve the same ACT in adults.[177] The THC needed for school-aged children did not differ from that needed for adults. However, although the THC in infants was similar to that for adults, the initial heparin dose needed to achieve it involved significantly larger values (*e.g.*, 578 ± 220 U/kg) compared to that needed for school-aged children and adults.[177] These results suggest that either the Hepcon system did not calculate an accurate blood volume for these children or preschool children have increased heparin binding by endothelial cells or heparin binding proteins. In addition, all children younger than 5 yr require significantly larger total heparin doses to achieve a given THC, which may relate to lower ATIII levels, especially in infants younger than 6 months of age.[175]

Although this reduced responsiveness to heparin does not necessarily relate to ATIII concentration, the findings observed by Hashimoto *et al.*[64] indicate that ATIII supplementation can reduce thrombin activity during CPB when ATIII levels decrease because of hemodilution or consumption. More clinical studies that evaluate anticoagulation and the hemostatic system in children undergoing CPB are needed to identify anticoagulation and monitoring strategies that optimize thrombin suppression while minimizing bleeding and transfusion.

Monitoring in Patients Undergoing Procedures Involving Use of Heparin-bonded Circuits

In an attempt to simulate the antithrombotic properties of the normal endothelial surface, heparin has been bonded to the extracorporeal circuit. Although not universal,[178] several studies have shown that this approach attenuates the inflammatory response to CPB as reflected by reduced complement[179–185] and granulocyte activation.[180,182,183,185,186] Numerous studies evaluating the potential for heparin-coated circuits to preserve hemostasis have not shown consistent reduction in sensitive biochemical markers of hemostatic system activation.[178,180,182,183,185,187–197] Some studies using reduced systemic heparin doses showed increased activation with heparin-coated circuits (as evidenced by increases in prothrombin fragment 1.2, FPA, D-dimer, and β thromboglobulin values).[192,198,199] However, others

showed either no significant differences[195,200] or reductions in these markers both in *ex vivo*[200] and in simulated CPB models.[201] Use of heparin-bonded circuits has been associated with reduced platelet activation when small doses of heparin are used.[198,199] However, findings have been inconsistent when routine doses of heparin are used, some showing lower platelet activation,[180,195] whereas others show no difference.[190,193] Smaller heparin doses and ACT thresholds have been advocated when heparin-coated circuits are used based on data from a few studies that demonstrated reduced blood loss, transfusion requirements, and a seemingly similar risk of perioperative thrombotic complications.[180,187–191]

However, the majority of these studies summarized in table 5, used short CPB intervals and were not powered adequately to clearly address safety of lower heparin doses with heparin-coated circuits with respect to thrombotic complications. In addition, some of these studies showed larger increases in markers of coagulation activation in patients who receive lower heparin doses during use of heparin-bonded circuits,[192,198] and others described thrombotic events when extracorporeal life support was used without systemic anticoagulation[202] or with lower doses of heparin.[203] This has led Edmunds[204] to suggest that lowering heparin dose with heparin-coated circuits is inappropriate because of the lack of adequate safety data. In the absence of large-scale trials that address conclusively this important safety issue, we agree with his conclusion.

New Drugs and Monitoring Implications

Aprotinin. Aprotinin, a nonspecific serine protease inhibitor that inhibits trypsin, plasmin, and kallikrein, markedly decreases bleeding after cardiac procedures involving extracorporeal circulation.[205] Aprotinin can reduce activation of the hemostatic system by inhibiting the contact,[206–210] and possibly tissue factor,[211] pathways, as reflected by decreased thrombin generation and activity during CPB.[209,212] However, it may potentially lead to a hypercoagulable state caused by inhibition of plasmin,[206] protein C, or both.[213,214] Because inhibition of protein C may more likely occur at plasma concentrations more than 250 KIU/ml,[214] weight-adjusted dosing regimens should be considered, especially in smaller patients when a full dose (*i.e.*, Hammersmith regimen, package insert, Bayer Corporation, West Haven, CT) is used. Because thromboembolic complications initially were reported in cardiac patients whose heparin administration was based on celite ACT protocols,[215–217] several investigations have assessed the impact of aprotinin on coagulation assays.

Initial investigations showed that celite ACT values are prolonged both *in vitro*[218] and *ex vivo*[88] when routine doses of heparin and aprotinin are used. Prolongation of celite ACT values by aprotinin may relate to inhibition of kallikrein,[206] Hageman factor (Factor XII),[207] and Factor IX activation[208] by aprotinin. Because recent evidence indicates that aprotinin inhibits the tissue factor pathway by binding the Factor VIIa tissue factor complex,[211] celite ACT measurements might therefore also be prolonged *via* reduced tissue factor–mediated activation of Factor IX.[219] This interaction is important because significant tissue factor pathway–mediated activation of the extrinsic pathway has been identified during CPB.[9] Prolongation of celite ACT may also reflect aprotinin's intrinsic anticoagulant properties.[209,210] When compared to an aprotinin concentration of 200 KIU/ml, the equipotent dose of heparin required to inhibit whole blood clotting time is 0.69 U/ml.[210] In summary, the prolongation of celite ACT[218] may reflect aprotinin's anticoagulant properties,[209,210] inhibition of contact activation,[207] or ability to preferentially inhibit celite-mediated activation *in vitro.*[89]

Patients receive smaller heparin doses and have lesser blood heparin concentrations when heparin dosing is guided by celite ACT protocols during aprotinin administration.[220] Although some researchers have suggested that aprotinin is a heparin-sparing agent,[221] Hunt *et al.*[222] suggested that heparin doses be administered to maintain celite ACT values greater than 750 s when aprotinin is used. Because of the potential risks of subtherapeutic heparin anticoagulation,[203,223] the package insert recommends that adequate heparin anticoagulation be maintained by using clotting assays that are unaffected by aprotinin (Aprotinin package insert; Bayer Inc.). Aprotinin generally does not affect kaolin ACT,[88,218] most likely because kaolin more potently activates coagulation than celite[89] and because aprotinin binds kaolin.[224] However, data from a recent study[210] indicate that kaolin ACT values are slightly prolonged in the presence or absence of heparin after aprotinin doses of 400 KIU/ml, which supports previous findings that aprotinin prolongs kaolin-activated aPTT measurements.[225] Alternative possibilities for monitoring heparin anticoagulation in the presence of aprotinin include the HiTT, the HMT, and the HiPT. Although the HiTT is unaffected by aprotinin,[107,108] recent evidence reveals only a modest correlation ($r = 0.52$) with heparin levels during CPB.[91] Although HMT measurements were unaffected by apro-

Table 5. Studies That Have Examined the Effect of Heparin-coated Circuits on Blood Loss, Transfusion, Thromboembolic Complications, or Markers of Hemostatic System Activation

Reference	No. of Patients	Heparin Protocol*		CPBT (min)	Design	Blood Loss (ml/24 h)†		Transfusion‡ (NC *vs.* C)	Thromboembolic Complications, % (NC *vs.* C)	Activation Markers
		NC	C			NC	C			
Kutenen, 1997[192]	30	300 U/kg > 480 s	100 U/kg > 200 s	84	P,R	991 (600–1420)	880 (410–1,600)	ND 47% *vs.* 40%	MI, CVA, D: 7 *vs.* 20	↑F1.2, DD, FPA in coated
Aldea, 1996[187]	234	HDR > 480 s	HDR > 280 s	88	P,R	651 ± 403	561 ± 257§	↓32% *vs.* 48% ↓2.0 U *vs.* 4.3 U	MI, CVA, D§: 9 *vs.* 2	NA
Shapira, 1996[188]	C = 120, NC = 232	300 U/kg > 480 s	100 U/kg > 280 s	118	Ret	1054 ± 911	558 ± 466§	↓64% *vs.* 86% ↓18.6 U *vs.* 6.9 U	MI, CVA, D: 10 *vs.* 7	NA
Ovrum, 1996[185]	C = 17, NC = 16	400 U/kg > 480 s	100 U/kg > 250 s	49	P,R	628 (420–1360)	615 (265–1,035)	2 U *vs.* 0 U	MI, D: 3 *vs.* 0	↑F1.2, ↓BTG in coated
Ovrum, 1995[179]	C = 17, NC = 18	400 U/kg > 480 s	100 U/kg > 250 s	47	P,R	675 (355–1305)	620 (405–830)	ND	ND	NA
Aldea, 1996[326]	C = 9, NC = 455	300 U/kg > 480 s	100 U/kg > 280 s	88	P	984 ± 616	323 ± 67§	↓0% *vs.* 68%	MI, CVA, D: 4 *vs.* 0	NA
von Segressor, 1994[190]	104	300 U/kg > 480 s	100 U/kg > 180 s	69	P,R	1039 ± 732	790 ± 393§	↓46% *vs.* 86% ↓300 *vs.* 957 ml	MI, VGP, D: 6 *vs.* 6	NA
Fosse, 1994[182]	20	400 U/kg > 480 s	150 U/kg > 150 s	90	P,R	662 (550–805)	660 (480–700)	ND	NA	NA
Sellevoid, 1994[178]	20	300 U/kg > 480 s	150 U/kg > 240 s	79	P,R	638 ± 213	646 ± 313	ND, autotransfusion	NA	NA
von Segresser, 1993[190]	15	300 U/kg > 480 s	100 U/kg > 180 s	72	P,R	432 ± 162	311 ± 111	↓143 *vs.* 416	NA	NA
Borowiec, 1992[196]	14	300 U/kg > 400 s	225 U/kg > 300 s	94	P,	10 ml/kg	8.7 ml/kg	390 *vs.* 600 RC 840 *vs.* 380 FFP	NA	NA
Borowiec, 1992[191]	20	300 U/kg 400 s	150 U/kg > 250 s	85	P,R	559 ± 24	786 ± 65§	10 *vs.* 9.1 RC 8.9 *vs.* 10.8 FFP	NA	↓FDPs in coated
Fukutomi, 1996[180]	20	250 U/kg	> 400 s	168	P,R	1350 ± 125	600 ± 250§	40% *vs.* 30%	NA	↓BTG in coated
Boonstra, 1994[193]	30	300 U/kg	400–800 s	94	P,R	931 ± 136	709 ± 101	ND	NA	ND
Wagner, 1994[194]	20	300 U/kg	> 480 s	140	P,R	1226 ± 180	1064 ± 153	ND, 2/10 *vs.* 3/10	NA	ND
Gorman, 1996[195]	20	300 U/kg	> 400 s	117	P,R	555 ± 83	780 ± 213§	↑35 U *vs.* 92 U§	NA	↑Plt Agg in coated

C = heparin-coated; NC = not coated; CPBT = mean times for cardiopulmonary bypass; P = prospective; Ret = retrospective; R = randomized; ND = no difference; MI = myocardial infarction; CVA = cardiovascular accident; VGP = vein graft patency; D = death; NA = not assessed; F1.2 = prothrombin fragment 1.2; BTG = β thromboglobulin; FPA = fibrinopeptide A; Plt Agg = platelet aggregation; HDR = heparin dose response; DD = D-dimers; RC = red cells; FFP = fresh frozen plasma.

* Protocols for initial and subsequent (*i.e.,* during CPB) administration of heparin for patients treated with heparin-coated *vs.* not-coated circuits.

† Values are mean ± SD or mean (95% confidence intervals) of chest tube drainage in the first 24 h in the intensive care unit with the exception of Kutenan *et al.*[192] (16 h).

‡ Summarized as either the percentage of patients requiring transfusion, mean units required, or volume of red blood cells required; decreased/increased requirements are displayed as arrows.

§ $P < 0.05$.

tinin in one evaluation,[105] data from another study suggest that they are.[106] The HiPT, which evaluates the antithrombotic properties of heparin *via* extrinsic pathway activation, also is unaffected by aprotinin[108]; however, more clinical trials are needed to characterize its potential usefulness.

Finally, methods that measure heparin concentration can be used to monitor heparin during CPB in patients receiving aprotinin. However, only the HepTest and the automated protamine titration assay have been evaluated for potential interactions with aprotinin. Although aprotinin also does not affect these two measurement systems,[92,100] either one should be accompanied by an assay that accurately evaluates the anticoagulant properties of heparin, such as the kaolin ACT, despite the presence of aprotinin. Although use of heparin concentration methods will result in administration of greater doses of heparin, this is not necessarily disadvantageous because aprotinin attenuates the inhibition of platelet function by heparin[226] and reduces heparin-related bleeding when higher doses of heparin are administered.[144] Other promising broad-spectrum protease inhibitors, such as nafamostat, are undergoing investigation during extracorporeal circulation,[227] but very little information is available about the impact of these agents on heparin monitoring systems. Because these studies reveal that celite ACT values increase markedly with the presence of heparin and aprotinin, alternative possibilities (*e.g.*, kaolin ACT, whole blood heparin concentration, HiTT, HMT, and HiPT) for monitoring heparin anticoagulation in the presence of aprotinin should be used.

Antithrombin III. Enhancement of heparin's antithrombotic properties by ATIII supplementation can potentially preserve the hemostatic system during CPB, especially in patients who have acquired ATIII deficiency related to preoperative heparin infusions,[65–68] excessive CPB-related hemodilution (or both), or consumption.[25,65,66] The initial findings of decreased thrombin (*e.g.*, fibrinopeptide A) activity observed by Hashimoto *et al.*[64] in pediatric patients supplemented with pooled ATIII concentrates was recently confirmed by Levy *et al.*[228] using recombinant (*i.e.*, transgenic) ATIII. Inverse relations were observed between ATIII concentration and markers of thrombin (*e.g.*, fibrin monomer) and fibrinolytic (D-dimer) activity in this latter study.[228] As previously addressed, available methods, such as the HDR and HRT tests, can potentially identify patients with heparin resistance from ATIII deficiency.[61]

Platelet Inhibitors. Infusion of the antiplatelet agent dipyridamole decreases platelet activation and depletion during extracorporeal circulation. In a prospective, randomized trial comparing dipyridamole to placebo, postoperative blood loss and transfusion requirements decreased significantly, but the magnitude of change was small.[229] Fish *et al.*[230] found significant platelet-sparing properties with prostacyclin, whereas DiSesa *et al.*[231] found none. These inconsistent findings, combined with the occurrence of hypotension, explain why prostacyclin has never gained popularity for routine use during CPB. Other reports have detailed the variable effectiveness of preoperative antiplatelet agents, such as aspirin and dipyridamole,[232–234] or the effectiveness of intraoperative administration of nonspecific platelet inhibitors, such as prostacyclin,[157] or prostaglandin E_1,[235] as supplements to heparin in patients with heparin-induced thrombocytopenia (HIT). Newly developed specific platelet glycoprotein receptor blockers, such as abciximab (Reopro; Eli Lilly, Indianapolis, IN),[236] have been shown to reduce thrombotic complications related to coronary angioplasty procedures. Platelet inhibitors may be useful in patients with HIT if they are reversible or have short pharmacokinetic half-lives similar to agents such as eptifibatide (Integrelin; COR Therapeutics, San Francisco, CA) or tirofiban (Aggrastat; Merck & Co., Inc., West Point, PA). These agents also may be useful as a heparin adjunct to preserve platelets during CPB.[237,238]

Synergistic prolongation of clot times by heparin and abciximab has been previously reported[87,239,240] and may lead to marked prolongations of ACT values during CPB. This synergistic prolongation may relate in part to inhibition by abciximab of thrombin generation,[241] greater preferential inhibition of platelet-mediated prothrombin activation by heparin, or both.[242] Although platelets may be preserved during CPB by agents such as eptifibatide[238] or bistatin,[237] heparin doses should not be decreased in cardiac surgical patients who have received these new Gp IIb/IIIa inhibitors until safety data regarding the use of lower heparin doses have accumulated. New point-of-care platelet function tests potentially can be used to assess the degree of platelet inhibition during CPB and guide therapy in patients with excessive bleeding after CPB. These tests include the following: *in vitro* bleeding time[243,244]; platelet-mediated clot retraction[245,246]; tests of clot viscoelastic properties, such as thromboelastography or sonoclot analysis[247–249]; agglutination of fibrinogen-coated beads[250]; platelet activating factor-mediated clot acceleration[239,251,252]; point-of-care adaptations of glass bead re-

tention[253]; hemostatometry[17,226]; or whole blood impedance aggregometry (Chronolog Corp., Havertown, PA).[254]

LMWH, Heparinoids, and Defibrinogenating Agents. Newly developed antithrombotic agents may decrease consumption of coagulation factors and platelets by overcoming heparin's inability to completely inhibit clot-bound thrombin[47] and platelet-bound Va/Xa activity.[255,256] Heparin analogues or derivatives, such as dermatan sulfate,[257] LMWH (*e.g.*, dalteparin),[258] or the heparinoid Orgaran (Org 10172; Organon Teknika, Oss, The Netherlands) that consist of heparan, chondroitin, and dermatan sulfate[259–263] can decrease activation of the hemostatic system by inhibiting thrombin, Factor Xa, or both. Dermatan sulfate predominately inhibits thrombin. LMW heparin preferentially inhibits Factor Xa but also inhibits thrombin to a lesser extent, whereas Orgaran inhibits thrombin and Factor Xa to the same extent. LMW heparin and Orgaran both are neutralized incompletely by protamine, which limits the clinical usefulness of these agents. In fact, the lack of reversibility has led to excessive blood loss after CPB in patients who received these agents.[262–265] However, new agents such as heparinase,[21,160] recombinant platelet factor 4,[158,159] and protamine derivatives[266] have been shown to reverse LMWH. Monitoring the antithrombotic properties of LMWH and Orgaran during CPB can be difficult; however, assays such as the Heptest that directly assess anti-Xa and anti-IIa activity may be useful.

Defibrinogenating agents such as ancrod (Knoll Pharmaceuticals, Mt Olive, NJ)[267,268] have been used instead of heparin in patients with HIT, but blood loss has been excessive because fibrinogen must be replaced before clotting can resume.[267] New whole blood fibrinogen assays may potentially be useful when defibrinogenating agents, such as Ancrod, are used to confirm therapeutic hypofibrinogenemia during CPB and restoration of levels after CPB.[269]

Direct Thrombin Inhibitors and Other New Anticoagulants. Newly developed direct thrombin inhibitors, such as hirulog,[270] recombinant hirudin,[271,272] argatroban,[273] thrombin inhibitor peptide,[274] or polypeptide aptamer,[275] that do not require ATIII or HCII to inhibit even clot-bound thrombin (fig. 3) can circumvent some of the limitations of heparin and may be useful in patients with HIT. Although bleeding complications potentially can result from their potent binding of thrombin and the lack of reversal agents, recombinant hirudin or lepirudin (Refludan; Hoechst Marion, Roussel, Kansas City, MO) has been used in a few patients without major bleeding complications.[271,272,276] Concurrent use of a platelet inhibitor may be necessary for patients whose anticoagulation regimen during CPB involves the use of direct thrombin inhibitors because these agents do not directly inhibit platelets. This is shown by the marked decrease in platelet function during CPB in two patients who received hirudin.[271,272] Although aPTT values have been used to monitor patients who received hirudin,[271,272] a poor correlation between hirudin concentration and ACT or aPTT values was observed in one recent study.[277] The ecarin clotting assay, a clot-based method that uses a prothrombin-activating snake venom derivative, can be measured using the TAS instrument and may be a reasonable alternative monitoring method. A good correlation ($r^2 = 0.63$) was observed between recombinant hirudin levels and ecarin clotting-time values in eight patients during CPB.[277] However, ecarin clotting-time values can be substantially prolonged by hemodilution (*i.e.*, $> 30\%$),[277] which may necessitate use of a modified version (*e.g.,* using platelet-poor plasma) of the test. Finally, assays such as the Heptest that directly assess anti-Xa and anti-IIa activity also may be useful; however, little information is available regarding the use of this assay to monitor anticoagulation during CPB with hirudin.

Another new agent, pentosanpolysulfate, recently was used as a heparin alternative during CPB.[278,279] In two preliminary reports, ACT was used for monitoring when pentosanpolysulfate was used as a heparin alternative during CPB.[278,279]

New inhibitors of other factors within the intrinsic (*e.g.*, Factor VIII–Factor IX complex inhibitor, tick anticoagulant peptide)[280,281] and tissue factor[282] pathways are being developed and may be useful in decreasing activation of the hemostatic system during CPB (fig. 5). Unfortunately, there is very little information available about monitoring anticoagulation with new inhibitors of other factors within the intrinsic[280,281] and tissue factor[282] pathways. The authors of this review claim that available point-of-care anticoagulation monitors will be inadequate for a number of these new agents. Ideal point-of-care monitoring systems should accurately reflect thrombin activity, and possibly also fibrinolytic activity and platelet activation or function, and should only be influenced by hypothermia and hemodilution if these variables affect the endpoints that are being assessed (*e.g., in vivo* thrombin activity).

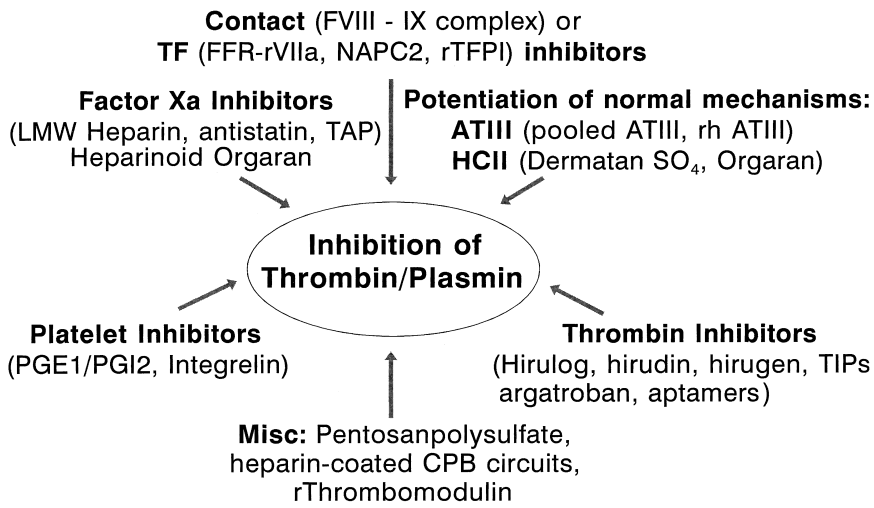

Fig. 5. Emerging heparin adjuncts and alternatives that inhibit hemostatic system activation or, more specifically, that inhibit thrombin and fibrinolysis. Newer antithrombotic agents include inhibitors of the contact and tissue factor paths, Factor Xa inhibitors, direct thrombin inhibitors, indirect thrombin inhibitors, or miscellaneous agents, such as pentosanpolysulfate, heparin-coated cardiopulmonary bypass (CPB) circuits, or recombinant thrombomodulin. LMW = low-molecular-weight heparin; TAP = tick anticoagulant peptide; PGE_1 = prostaglandin E_1; PGI_2 = prostaglandin I_2; rh ATIII = recombinant human antithrombin III; HC II = heparin cofactor II; pooled ATIII = pooled plasma–derived antithrombin III concentrates; FVIII–IX complex = Factor VIII–IX complex assembly inhibitor; FFR-rVIIa = FFR-ck-active-site–inhibited recombinant Factor VIIa; rTFPI = recombinant tissue factor pathway inhibitor; TIP = thrombin inhibitor peptide.

Summary

The literature does not consistently support the importance of anticoagulation monitoring techniques during CPB. This is best reflected by studies that have evaluated the impact of the ACT method on blood loss and transfusion outcomes. Inconsistent findings from studies that evaluated the impact of ACT monitoring may be related to either suboptimal study design (*i.e.*, retrospective, unblinded, nonrandomized) or possibly the diagnostic inprecision of the ACT method used in these studies. There are a small number of well-controlled studies, some of which suggest that bleeding and transfusion outcomes can be improved by refining heparin monitoring techniques, either by sustaining better anticoagulation during CPB or by optimizing protamine doses (*i.e.*, when empiric protocols result in excessive protamine doses). More well-controlled studies are needed to better define the importance of anticoagulation management during CPB.

The authors thank Robert Baugh, Ph.D., for his technical assistance with the survey within this manuscript and Rao Saleem, M.D., and Tina Tapas for their assistance with the preparation of this manuscript.

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Appendix

Summary of a 1993 Survey.

In 1993, 1,665 members of the Society of Cardiovascular Anesthesiologists (SCA) and American Society of Extracorporeal Technology (AmSECT) received a questionnaire designed to characterize their current clinical practices of heparin anticoagulation and reversal and monitoring for cardiac surgical procedures involving cardiopulmonary bypbass (CPB). Of the 1,665 questionnaires sent, responses were received from 63% (n = 1,049) of SCA or AmSECT members; of these 1,049 responses, 967 (92%) were selected to eliminate duplicate responses within the same institutions: The survey results must be evaluated with caution. The lack of fully completed questionnaires and the age of the survey constitute significant limitations. Because not all respondents answered all questions, the total numbers reported are sometimes much lower than expected because they represent the numbers of responses to each individual question.

Body weight was the method used by 95% of respondents to determine the initial heparin dose, which was 300 U/kg for 67% of respondents and 400 U/kg for 16% of respondents. Bovine lung heparin was used in 67% of centers, whereas 19% used porcine mucosal heparin, and the remaining 14% used both preparations. Heparin management was monitored by 99.5% of the respondents, and the most common tests used were activated clotting time (ACT; 99%) and blood heparin concentration values (16%). However, 34 of 967 (3.5%) respondents did not measure the ACT before initiation of CPB. Celite ACT (Hemochron instrument) was used in 70% of centers surveyed, whereas kaolin ACT (either ACT or Hepcon instruments) was used in the remaining 30%. The target ACT and the trigger for additional heparin administration during CPB was between 400–480 s in most centers (81%); trigger ACT values of 400 and 480 s represented 41% and 32%, respectively, whereas an additional 8% used a value between 400 and 480 s. The median acceptable ACT value was 400 s, but this included values ranging from 240 s to 1,000 s. For 153 of 967 respondents, heparin concentrations (levels) were monitored during CPB, and most (92%) respondents who monitored heparin concentrations maintained levels between 3 and 4 U/ml (IU), with 64% at 3 U/ml and 19% at 3.5 U/ml. Using data from the 721 replies to this question, 85% of clinicians routinely added heparin to the CPB circuit priming solution. Of the sites that added heparin to the CPB circuit, 74% added between a median value of 5,000 U (30%), but the dose varied from 100 U to 50,000 U. Of 777 responses, the median and mode CPB priming volume value was 2,000 ml, with a 95% confidence interval of 1,400–2,500 ml.

The technique used to determine protamine dose varied between institutions. Of 474 respondents, 47% (223) determined the protamine dose based on a fixed ratio (*e.g.,* milligrams protamine per milligrams heparin, with 1 mg heparin = 100 U heparin) to the total dose of heparin administered. An additional 44% used one of the following four methods to estimate residual heparin concentration: (1) 40% used whole blood protamine titration heparin concentration, (2) 3% used manual protamine titration dose–response, (3) 1% used the protamine response test, and (4) 0.2% used Sonoclot. Of the centers that used a fixed ratio of protamine-to-heparin dose (n = 225), 77% used a ratio between 1 and 1.5 to 1, the most common ratios being either 1.3:1 (31%) or 1.5:1 (23%). Using 891 responses, protamine was administered over a 5-min period in 35% of centers and over a 10-min period in 43% (both mode and median) of centers, and 91% of respondents infused protamine over a 15-min period or less.