■■ REVIEW ARTICLE

CME

Heparin Sensitivity and Resistance: Management During Cardiopulmonary Bypass

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Heparin resistance during cardiac surgery is defined as the inability of an adequate heparin dose to increase the activated clotting time (ACT) to the desired level. Failure to attain the target ACT raises concerns that the patient is not fully anticoagulated and initiating cardiopulmonary bypass may result in excessive activation of the hemostatic system. Although antithrombin deficiency has generally been thought to be the primary mechanism of heparin resistance, the reasons for heparin resistance are both complex and multifactorial. Furthermore, the ACT is not specific to heparin's anticoagulant effect and is affected by multiple variables that are commonly present during cardiac surgery. Due to these many variables, it remains unclear whether decreased heparin responsiveness as measured by the ACT represents inadequate anticoagulation. Nevertheless, many clinicians choose a target ACT to assess anticoagulation, and interventions aimed at achieving the target ACT are routinely performed in the setting of heparin resistance. Treatments for heparin resistance/alterations in heparin responsiveness include additional heparin or antithrombin supplementation. In this review, we discuss the variability of heparin potency, heparin responsiveness as measured by the ACT, and the current management of heparin resistance.   (Anesth Analg 2013;116:1210–22)

A major challenge to the advancement of cardiac surgery is establishing a way to prevent thrombosis within the cardiopulmonary bypass (CPB) circuit. Since the discovery of heparin by McLean in 1916 and the subsequent discovery of its antidote, protamine, heparin has been effectively used as the primary method of anticoagulation during cardiac surgery.[1] Hattersley[2] introduced the activated clotting time (ACT) in 1966 as a bioassay for monitoring heparin's anticoagulant effect. When the ACT fails to reach target levels after heparin administration, the concern is raised that anticoagulation is subtherapeutic. At best, subtherapeutic anticoagulation leads to low levels of activation of the coagulation system on CPB and may potentially result in a consumptive coagulopathy that can manifest as excessive bleeding after heparin neutralization. At worst, subtherapeutic anticoagulation can result in the formation of thrombi within the CPB circuit or the patient's end organs. Therefore, a target ACT is chosen that is believed to be sufficiently more than the minimal ACT, below which subtherapeutic anticoagulation occurs. Unfortunately, both the minimal ACT and the ideal target ACT remain unknown. This fact is highlighted in a recent survey that demonstrated wide variations among institutions in regards to what ACT is targeted.[3]

Heparin resistance during cardiac surgery is defined as the failure of unusually high doses of heparin to achieve a target ACT. Alternatively, heparin resistance can be better defined by a decreased heparin dose response (HDR) curve. Depending on the specific definition used, the reported incidence of heparin resistance during cardiac surgery ranges from 4% to 26% (Table 1).[4–8,10] Heparin resistance is a multifactorial disorder that is complicated by the variability in heparin's anticoagulant effect and the fact that the ACT is not specific to heparin. The diagnosis of heparin resistance often leads to interventions aimed at achieving the target ACT and providing an adequate margin of safety in regards to anticoagulation. The aim of this review is to discuss the variability of heparin potency, heparin responsiveness as measured by the ACT, and the current management of heparin resistance.

HEPARIN

Unfractionated heparin (UFH) has long been the anticoagulant of choice for initiation and maintenance of CPB because it is effective, inexpensive, and easily reversed. However, a major drawback of UFH is its variable anticoagulant effect among patients. A multitude of factors contribute to this variability, and clinicians must understand the pharmacology of UFH to appreciate its limitations.

UFH is a heterogeneous mixture of polysaccharides with molecular weights ranging from 5,000 to 30,000 Da (5–35 polysaccharide units) with a mean molecular weight of 15,000 Da.[12] Heparin is a naturally occurring compound isolated from either a bovine or porcine source and, because it is not homogenous, requires purification. Heparin's primary mechanism of action is indirectly mediated through catalyzing the anticoagulant effect of antithrombin (AT), an endogenous

Table 1. Definition and Incidence of Heparin Resistance

Reference	Heparin-loading dose	Target ACT	Incidence of heparin resistance
Avidan et al.[4]	400 U/kg	480 s	66/193 (18%)
Avidan et al.[5]	400 U/kg	480 s	54/296 (13%)
Ranucci et al.[6]	300 U/kg	480 s	104/500 (21%)
Ranucci et al.[7]	Not stated	One or more ACT <400 s after heparinization, or the need for AT administration	53/200 (26%)
Staples et al.[8]	500 U/kg	480 s	949/4280 (22%)
Koster et al.[9]	500 U/kg	480 s	Not reported
Williams et al.[10]	450 U/kg	480 s (or 600 s if using aprotinin)	85/2270 (4%)
Lemmer et al.[11]	600 U/kg	600 s (patients aprotinin treated)	Not reported

ACT = activated clotting time; AT = antithrombin.

Figure 1. Binding of heparin and antithrombin (AT) is dependent on heparin possessing a critical penta-saccharide sequence (dark green), which is present in only one-third of heparin molecules. A, A minimum of 18 saccharides are required to form a heparin/AT/thrombin ternary complex and act as a template for which both AT and thrombin can interact. Heparin molecules of shorter chain length do not inhibit thrombin. B, Inhibition of factor Xa by AT can occur at chain lengths <18 saccharides and only requires that heparin contain the critical pentasaccharide sequence.
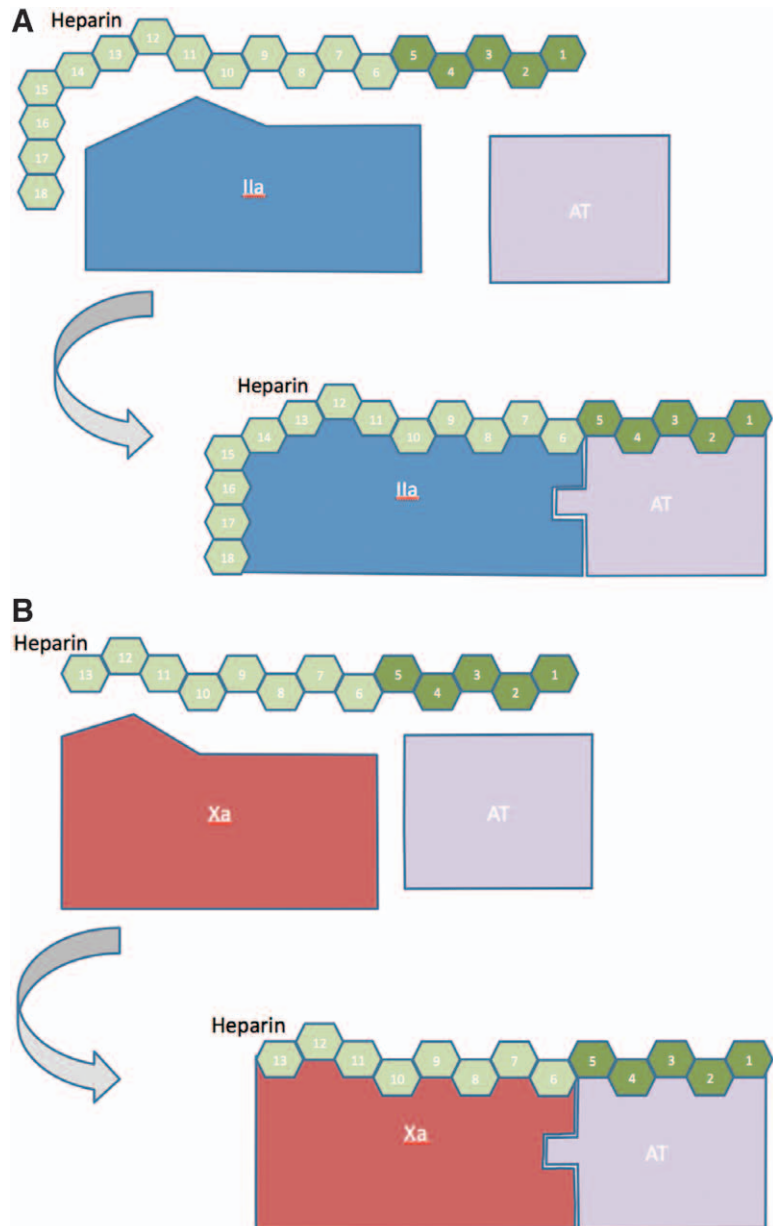
inhibitor of thrombin (factor IIa), factor Xa, and other factors (Fig. 1). A secondary mechanism of action includes catalyzing the anticoagulant properties of heparin cofactor II (HC II).

The variability of heparin response among patients has a biochemical and pharmacokinetic basis. Biochemically,

binding of heparin and AT is dependent on heparin possessing a critical pentasaccharide sequence, which is present in only one-third of heparin molecules.[13–21] The heparin molecules lacking this critical sequence may possess alternative anticoagulant activity as well as contribute to a variety
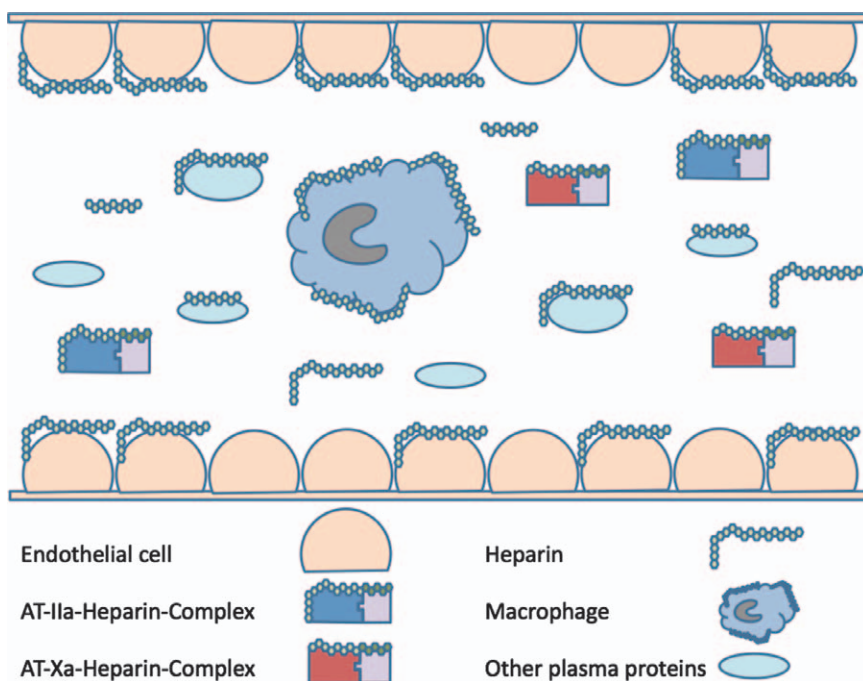
Figure 2. After IV administration, heparin nonspecifically binds to endothelial cells, macrophages, and various plasma proteins. Additionally, heparin binds to antithrombin (AT) and ultimately forms a complex with factors IIa or Xa. The remaining heparin circulates in the blood unbound.

Endothelial cell

AT-IIa-Heparin-Complex

AT-Xa-Heparin-Complex

Heparin

Macrophage

Other plasma proteins

of other untoward effects.[22,23] Furthermore, the heparin chain length must contain a minimum of 18 saccharides to form a heparin/AT/thrombin ternary complex and act as a template for which both AT and thrombin can interact.[24] When this complex forms, the inhibition of fluid-phase thrombin is accelerated 4,000-fold.[25] However, fibrin-bound thrombin is protected from the heparin/AT complex and is not inhibited.[26] Alternatively, inhibition of factor Xa by AT can occur at chain lengths <18 saccharides and only requires that heparin contain the critical pentasaccharide sequence. Acceleration of factor Xa inhibition is 1200-fold.[25]

A second AT-independent anticoagulant effect is mediated via HC II.[27] As this effect is AT independent, it does not require a specific saccharide sequence to be present. At heparin concentrations >1.0 units/mL, heparin interacts with HC II in a charge-dependent fashion and results in thrombin inactivation.[27] This mechanism is also dependent on the chain length of heparin and functions optimally at chain lengths >24 saccharide units. Additionally, heparin concentrations >2.0 U/mL have been shown to inhibit fibrin-bound thrombin in an AT-independent fashion.[26] At the present time, the clinical relevance of this mechanism during cardiac surgery remains unclear. Nonetheless, Intimatan, a HC II agonist, is a possible alternative to heparin in low AT states.[28]

The pharmacokinetics of heparin are both complex and variable before even considering the effects of hemodilution, hypothermia, CPB, and organ dysfunction during cardiac surgery. After IV administration, heparin immediately binds to various plasma proteins, macrophages, and endothelial cells (Fig. 2).[29–35] Clearance of heparin is by both a rapid-saturable and a slower nonsaturable mechanism.[36–38] The rapid-saturable phase consists of internalization and metabolism of heparin in both endothelial cells and macrophages. Subsequent clearance is slower and largely from renal elimination. Because of this pharmacokinetic profile, higher doses result in both an increase in the intensity and duration of the anticoagulant effect. The biologic half-life of heparin increases from 30 minutes with an IV bolus of 25 units/kg, to 60 minutes with an IV bolus of 100 units/kg, to 150 minutes with an IV bolus of 400 units/kg.[36,37,39] Alternatively, the elimination half-life of low molecular weight heparin (3–6 hours) is mainly removed by nonsaturable renal elimination, which results in a significantly prolonged elimination half-life in the setting of renal insufficiency.

UFH is, by nature, a very heterogeneous molecule. It is because of this heterogeneity that heparin's potency is standardized to ensure equivalent potency among batches. Before 2008, the United States Pharmacopoeia (USP) standard and the World Health Organization (WHO) standard (i.e., international standard) for heparin potency were not equivalent. The discrepancy resulted in the USP standard potency being 10% greater than the WHO standard.[a] Since 2008, the USP has revamped its potency unit assignments to harmonize the USP standard with the WHO standard. The conversion of potency standardization in the United States may have resulted in a decrease in ACT values and a higher incidence of heparin resistance.[40] Additionally, the heterogeneity of heparin molecules may lead to variability in potency within lots of UFH. However, the variability in potency of the finished product should only be ±10%. Despite the attempt at standardization, monitoring of the anticoagulant effect of heparin is recommended to ensure an adequate anticoagulant response and prevent overdosing with this complicated drug.

ANTICOAGULATION MONITORING
Activated Clotting Time
The ACT is a relatively simple test that works by mixing fresh, whole blood with a contact activator (e.g., kaolin,

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[a] Available at: www.usp.org/hottopics/heparin.html. Accessed March 27, 2012.
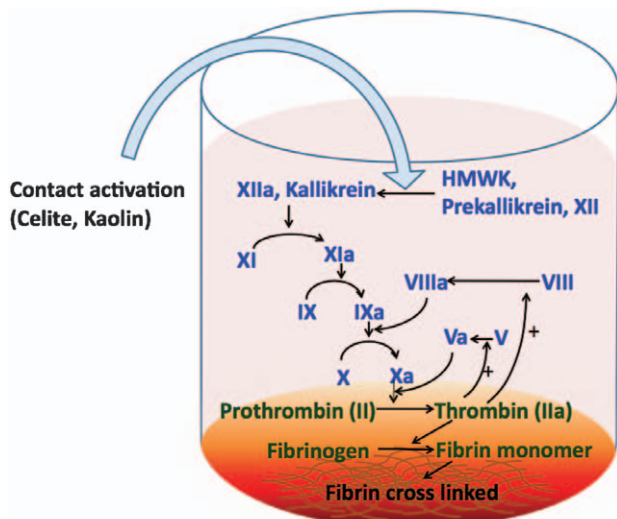
Figure 3. The activated clotting time (ACT) is initiated by adding a contact activator (i.e., celite, kaolin) to whole blood. The contact activator subsequently activates the intrinsic coagulation cascade. The end point of the ACT is the formation of fibrin clot. As demonstrated, there are multiple factors other than heparin and antithrombin (AT) that impact the ACT. The factors in the intrinsic pathway are represented in blue and the factors in the common pathway are represented in green. HMWK = high molecular weight kininogen.

Table 2. Factors Affecting Activated Clotting Time

- Hypothermia
- Hemodilution
- Medications
  ◦ Heparin
  ◦ Warfarin
  ◦ Aprotinin (celite more likely than kaolin)
  ◦ Platelet inhibitors (therapeutic medications like cyclooxygenase inhibitors, IIb/IIIa or adenosine diphosphate inhibitors, or antiplatelet antibodies)
  ◦ Direct thrombin inhibitors (e.g., hirudin derivatives, argatroban)
  ◦ Protamine
- Platelet count
- Factor deficiencies (any contact or common pathway coagulation factor)
  ◦ Contact factors (factor XII/factor XI, kallikrein) or intrinsic (factor VIII)
  ◦ Antithrombin
  ◦ Common pathway (factor V, II)
  ◦ Fibrinogen
- Disease states: anticardiolipin/antiphospholipid antibodies

celite). The contact activator mimics the negatively charged surface of the CPB circuit by initiating the intrinsic pathway of the coagulation cascade (factor XII, prekallikrein, and high molecular weight kininogen [HMWK]). Multiple steps occur within the test tube, and the test end point occurs when a measurable fibrin clot is detected (Fig. 3). The ACT is then measured as the time required to transform blood from a liquid to a gel, which is detected with one of several different detection methodologies (e.g., decrease rate of gravity-dependent descent of a plunger system or the movement of a metal chip as detected by a magnetic sensor). Unlike the activated partial thromboplastin time, which becomes unclottable at heparin concentrations commonly used during cardiac surgery (2–10 units/mL), the ACT can still be used to detect the effects of heparin.

The ACT is affected by multiple variables, many of which are commonly seen during cardiac surgery (Table 2). The first step in addition of a contact activator is activation of factor XII to factor XIIa and prekallikrein to kallikrein. These activated factors form a complex with HMWK. Although patients with deficiencies of factor XII, prekallikrein, or HMWK do not bleed excessively, they will have a baseline prolongation of the in vitro ACT.[41–47] Therefore, monitoring heparin's in vivo anticoagulant effect with the ACT in patients with a deficiency in any of these factors is problematic. In patients with a factor XII deficiency, increasing in vivo factor XII levels with fresh frozen plasma (FFP) has been successful in returning the ACT to baseline levels, but it introduces the risks of transfusions to the patient.[41,47–49] Alternatively, a mixing study (e.g., plasma-modified ACT) can be used to correct the factor XII deficiency in vitro and has been useful in monitoring heparin's anticoagulant effect.[43] A final approach for heparin management in patients with deficiencies of contact activators is titration of heparin to either a whole blood heparin concentration or

anti-Xa level. Although this approach has been used successfully, it fails to monitor heparin responsiveness.[45,46,50,51]

Aprotinin administration prolongs the ACT in the presence or absence of heparin.[52,53] The mechanism for this prolongation is believed to be aprotinin's ability to inhibit contact activation and is present only when celite is used as the activator.[52–60] The in vitro difference in the kaolin and celite-activated ACT can be explained by the fact that the positively charged aprotinin binds to the negatively charged kaolin, thus negating the anticoagulant effect of aprotinin.[57] Thus, in the presence of aprotinin and heparin, the prolongation of the celite ACT is a reflection of both aprotinin's and heparin's anticoagulant effect whereas prolongation of the kaolin-activated ACT is a reflection of only heparin. Therefore, to avoid under-heparinization, the kaolin-activated ACT is recommended as it excludes aprotinin's anticoagulation effect.[57]

The activation of factor XII leads to the initiation of the intrinsic pathway, which includes sequential activation of factors XI, IX, VIII, and X. Single factor deficiencies (e.g., hemophilia A or B), global deficiencies (e.g., hemodilution) and acquired coagulation factor deficiencies (e.g., vitamin K antagonists) will all result in a prolongation of the ACT.[61–67] Furthermore, each step in the intrinsic pathway is regulated by enzymatic activity, which is slowed in the setting of hypothermia and will prolong the ACT.[62,68] However, this effect is only seen when the ACT is run with a device that requires more than 1 mL of whole blood.[69] Devices requiring less volume are not affected, because the blood is easier to warm to normothermia in a timely fashion.

On completion of the intrinsic pathway, the common pathway begins with factor Xa catalyzing the conversion of prothrombin to thrombin. Thrombin has many actions that include activation of factors XI, VIII and V. Subsequently, the formation of factor VIII-IX complex (tenase) and factor V-X complex (prothrombinase) results in an exponential increase in thrombin generation. Thus, medications that inhibit thrombin (e.g., heparin, direct thrombin inhibitors) will prolong the ACT. Thrombin also catalyzes the conversion of fibrinogen to fibrin and, consequently, low fibrinogen levels are associated with a prolonged ACT.[70] Last,

many of these reactions occur on the platelet surface, hence, both platelet count and activity will affect the ACT.[71–76]

Hypercoagulable states, such as lupus anticoagulant, will also have an effect on the ACT. The presence of lupus anticoagulant results in a prolongation of the ACT in the absence of heparin. Contrary to its prolongation of the ACT in vitro, which is secondary to the binding of the in vitro activator (e.g., kaolin) by a pathologic antibody, the presence of lupus anticoagulant in vivo results in a pro-thrombotic state.[77] Different approaches have been used to overcome this limitation, including doubling of the target ACT or creating a patient-specific ACT titration curve.[78,79] As with contact activator deficiencies, an alternative approach for heparin monitoring in hypercoagulable disease states is whole blood heparin concentrations or anti-Xa levels.[77] However, the optimal heparin level is unknown in this patient population.

Protamine has been reported to prolong the ACT via inhibition of both serine proteases and platelets.[73,80–87] Thus, a high ACT after an initial protamine dose is not specific for inadequate heparin reversal and may be a reflection of protamine excess.

Further complicating anticoagulation monitoring with the ACT is the fact that the many different ACT machines used clinically vary in the activator, blood volume, temperature, and measurement techniques. The lack of standardization in ACT machines yields results that are not interchangeable.[88–92]

Heparin Dose Response

Recognizing the large variability in the ACT response to heparin and heparin decay curves, Bull et al.[93] attempted to develop a protocol that considers the individual variability in heparin responsiveness. The goal of this methodology is to determine an optimal heparin dose based on the individual response to a modest heparin dose. To make a HDR curve, a minimum of 2 ACTs must be performed (a baseline without heparin and one either after an in vivo dose or an in vitro sample with a known concentration of heparin). Additional ACTs will generate more points along the curve and ultimately result in a better HDR curve. Once a HDR curve has been established, a personalized dosing regimen can be created. For example, if the initial dose does not reach the desired ACT, the additional dose of heparin required to reach the goal ACT can be extrapolated. If adding a known heparin concentration in vitro, the heparin concentration to obtain the goal ACT can then be extrapolated (Fig. 4). Heparin responsiveness can be quantified by calculating the heparin sensitivity or heparin sensitivity index with the slope values from the following linear equations:

$$\text{Heparin Sensitivity (seconds/unit/mL)} = \frac{\text{ACT After heparin} - \text{Baseline ACT}}{\text{Heparin Concentration}} \quad (1)$$

or

$$\text{Heparin Sensitivity Index (seconds/unit/kg)} = \frac{\text{ACT After heparin} - \text{Baseline ACT}}{\text{Heparin Bolus Dose}} \quad (2)$$
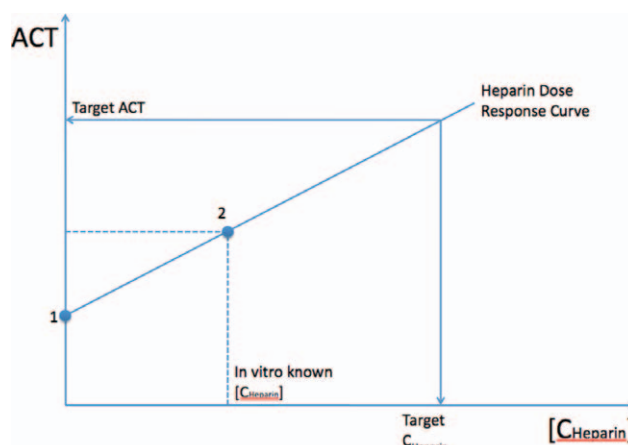

Figure 4. A heparin dose response curve can be generated to estimate the initial heparin-loading dose. A baseline blood sample is drawn and 2 activated clotting time (ACT) are run (1 without heparin [point 1] and 1 with a known concentration of in vitro heparin [point 2]). From these 2 points, a heparin dose response curve can be extrapolated and used to determine the in vivo heparin concentration that is required to achieve the target ACT. A heparin-loading dose can then be calculated using the patient's estimated blood volume.

This methodology is the basis by which the automated HDR tests (e.g., Hemochron RxDx system [International Technidyne Corp., Edison, NJ], Hepcon HMS system [Medtronic Perfusion Services, Minneapolis, MN]) determine a heparin-loading dose. Garvin et al.[94] demonstrated that the HDR fails to consistently predict the heparin bolus dose as demonstrated by the poor correlation between the calculated HDR and postbolus heparin level. However, the heparin bolus dose calculated using the HDR achieved a target ACT of 300 seconds 92.5% of the time and 350 seconds 83% of the time.[94] Potential explanations for this discrepancy include the method by which the patient's blood volume was calculated and a failure of the in vitro calculated HDR to measure heparin's true in vivo effects. Although this methodology has many limitations, attainment of a heparin level of 2.0 units/mL will result in 95% of patients having an ACT within the "safe zone" which Bull et al. described.[93,95] Also, of note is the curve may not be linear at higher concentrations.[96]

Minimum ACT

Despite high doses of heparin, the ability of blood to be activated is not completely abolished. Therefore, contact activation from the CPB circuit will result in the formation of a thrombus if the contact time is sufficient and the activator strong enough. Using an ACT with manual visualization of clot as the end point of the test, Bull et al.[97] reported a minimum ACT of 300 seconds based on visualizing thrombus in the CPB circuit. Furthermore, they described a "safe zone" between 180 and 300 seconds where CPB could be successfully completed despite activation of the coagulation system. Below 180 seconds, catastrophic thrombus formation occurred and prohibited safe completion of CPB.[97]

Bull et al.[93] failed to determine the ACT level that not only prevents thrombus formation but also minimizes coagulation activation. As demonstrated by subsequent

studies, coagulation activation continues to occur with ACTs in excess of 400 seconds.[98,99] The optimal ACT for safe conduct of CPB can then be defined as the period of time that blood can remain in contact with the CPB circuit with minimal coagulation activation. Because heparin does not inhibit fibrin-bound thrombin at levels <2.0 units/mL, it is reasonable to advocate for a minimal heparin level of at least 2.0 units/mL to achieve this goal.[26] Although there is no evidence to determine the true minimum ACT or heparin level, many institutions are safely using an ACT target ≥350 seconds and a heparin level ≥2.0 units/mL without reported complications.[3,94,95,100]

HEPARIN RESISTANCE
Mechanisms Related to AT Deficiency

AT deficiency has long been thought to be the primary mechanism of heparin resistance as heparin's anticoagulant effect is mediated indirectly via an AT pathway. Thus, a deficiency of AT decreases the ability of heparin to inhibit thrombin. AT deficiency can be either congenital or acquired in etiology. Congenital AT deficiency has a prevalence of 1 in 3,000 individuals, and these patients have AT levels approximately 40% to 60% of normal.[101] Acquired AT deficiency is associated with a variety of clinical conditions including liver disease, malnutrition, nephrotic syndrome, and heparin treatment.[102]

AT levels can be measured by both an activity test (i.e., functional assay) and an antigen level test.[103] Both are commonly expressed as a percentage with normal values ranging from 80% to 120%. The functional assay measures the ability of AT to inhibit thrombin or factor Xa in the presence of heparin. The amount of thrombin or factor Xa remaining uninhibited is inversely proportional to the AT level.[103] The antigen level only measures the amount of protein in the blood. Of the 2, the functional assay is the most appropriate one to be ordered first as it detects both quantitative and qualitative defects in AT whereas the antigen level only detects the quantitative defects.

Because heparin exerts its anticoagulant effect indirectly via AT, AT levels should correlate with measures of heparin responsiveness such as the heparin sensitivity index. This correlation holds true in vitro, especially when levels decrease to ≤60%.[104] Conversely, preoperative AT levels do not correlate well with heparin responsiveness in patients undergoing cardiac surgery.[11,104,105] Despite the poor correlation, the incidence of heparin resistance is higher in patients with low AT levels.[7,11,106] Thus, the concern still remains that low AT levels decrease heparin's anticoagulant effects. However, supplementation with AT fails to increase the ACT to target levels in all patients.[4,5] Therefore, an alternative, AT-independent mechanism must also be present for heparin resistance.

Acquired AT Deficiency
Heparin Pretreatment

The use of heparin preoperatively (24–48 hours) is commonly thought to contribute to heparin resistance.[8,63,107,108] Preoperative enoxaparin treatment has also been shown to increase the incidence of heparin resistance.[109,110] On heparin administration, the heparin-AT complex binds to thrombin and is followed by dissociation of heparin from the thrombin/AT complex. The thrombin/AT complex is then rapidly

consumed and cleared via the reticuloendothelial system resulting in an AT level decline of approximately 5% to 7% per day.[111] This decline in AT levels is thought to be the mechanism by which heparin pretreatment increases the incidence of heparin resistance.[7,8,96,108,112] Linden et al.[112] demonstrated lower AT levels in a preoperative period (80.9% vs 92.6% activity). However, the mean AT level in the heparin-pretreated group remained within the normal range, and although the preoperative AT levels were statistically different, it is unlikely that the small reduction (11.7%) is clinically significant. Additionally, Nicholson et al.[113] found no difference in AT levels between heparin-resistant and heparin-responsive patients in heparin-pretreated patients.

Although the exact mechanism has not been definitively linked to AT deficiency, the fact still remains that the heparin responsiveness, as measured by the ACT, in patients receiving heparin preoperatively is decreased. Despite the routine use of ACT in cardiac surgery, the validity of using the ACT in this patient population has been called into question. Use of the high-dose thrombin time, a more specific measure of thrombin inhibition than the ACT, demonstrated no increase in heparin requirements in heparin-pretreated patients despite the ACT demonstrating an increased incidence of heparin resistance.[114] Findings from this study suggest that heparin resistance in this patient population may, in fact, be a function of the ACT.

Other Conditions Associated with Acquired AT Deficiency

There are other causes of an acquired AT deficiency (Table 3). Decreased synthesis can occur in patients with liver disease

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Table 3. Mechanisms for Heparin Resistance

Antithrombin (AT) mediated
- Reduced synthesis (hereditary versus reduced global hepatic function)
- Accelerated clearance
  ◦ Nephropathy: renal losses leading to renal vein thrombosis
  ◦ Accelerated consumption
    ▪ Preoperative use of either unfractionated or low molecular weight heparin
    ▪ Upregulated hemostatic system: disseminated intravascular coagulation, endocarditis, deep venous thrombosis/pulmonary embolism
    ▪ Mechanical: CPB, ventricular assist device, intra-aortic balloon pump, extracorporeal membrane oxygenation

Non-AT mediated
- Increased heparin-binding
  ◦ Proteins
    ▪ Chemokines (PF4, interleukins like NAP 1, NAP 2, ENA-78, I-309, macrophage proteins like MIP, RANTES, monocyte proteins)
    ▪ Extracellular matrix proteins (laminin/collagens, thrombospondin, fibronectin/vitronectin)
    ▪ Growth factors (fibroblast, platelet-derived, vascular/hepatocyte)
    ▪ Enzymes (superoxide dismutase, cathepsin G, elastase)
    ▪ Miscellaneous (factor VIII/von Willebrand factor, Lactoferrin, Histidine-rich glycoprotein, lipoproteins/albumin)
  ◦ Platelets
    ▪ Variable, nonspecific binding
    ▪ Thrombophilia
    ▪ Platelet activation/release
    ▪ Medications—nitroglycerin

CPB = cardiopulmonary bypass; NAP = neutrophil-activating protein; MIP = macrophage inflammatory protein.

(i.e., cirrhosis) and malnutrition.[115–117] Nephrotic disease might result in ongoing loss of AT in the urine.[118,119] An upregulated hemostatic system, as seen in sepsis, disseminated intravascular coagulation and patients with a deep vein thrombosis/pulmonary embolism, can lead to greater levels of AT consumption.[116,120–122] Also, mechanical support devices such as the intra-aortic balloon pump, ventricular assist device, or extracorporeal membrane oxygenation are associated with a decline in AT levels.[8,123,124]

AT-Independent Mechanisms for Heparin Resistance

In addition to AT deficiency, there are multiple other potential mechanisms that can lead to heparin resistance that are both poorly defined and nonspecific. Becker et al.[125] concluded that IV nitroglycerin resulted in a qualitative AT defect. Brack et al.[126] observed a reduction in heparin levels with concomitant nitroglycerin infusion. Regardless of the potential mechanism, the effect of IV nitroglycerin on heparin responsiveness remains uncertain as demonstrated by several studies yielding conflicting results.[76,125–131]

After IV administration, heparin can bind to many molecules and platelets that can result in reduced biologic availability. The number of heparin-binding proteins is extensive and includes chemokines, extracellular matrix proteins, growth factors, enzymes, and many other miscellaneous proteins (Table 3). A full review of these proteins and the specific clinical scenarios during which they are increased is beyond the scope of this review.

Increased factor VIII activity augments the propagation phase of clotting and has been shown to reduce the HDR.[104] Factor VIII is an acute phase reactant that increases in the setting of inflammation. Furthermore, increased factor VIII is associated with endothelial dysfunction and has been associated with cardiovascular disease.[132–135] Therefore, one can speculate that elevated factor VIII levels are seen in the cardiac surgical population. Case reports are emerging describing increased factor VIII as a risk factor for heparin resistance.[136–141] However, the extent to which this contributes to the phenomena of heparin resistance in the cardiac surgical population requires further investigation.

TREATMENT OF HEPARIN RESISTANCE

When faced with the clinical scenario of heparin resistance, therapeutic approaches include administering additional heparin, supplement AT with FFP, supplement AT with an AT concentrate or accept the ACT and proceed with CPB without any additional treatment. Conventionally, additional heparin has been administered until the ACT reaches target levels. Case reports in the literature have documented heparin doses as high as 1200 units/kg to achieve a target ACT.[142,143] Such high doses of heparin are not without consequences as the total heparin dose is correlated with the degree of heparin rebound and a potential increase in postoperative chest tube drainage.[144,145] Moreover, there appears to be a ceiling effect in regards to anticoagulation with escalating doses of heparin.[9,96] Levy et al.[96] demonstrated that whole blood heparin concentrations >4 units/mL failed to further increase the ACT.

Successful treatment of heparin resistance with AT supplementation via FFP was first reported by Sabbagh et al.[146]

FFP is a medically accepted method of AT supplementation and contains approximately 1 IU of AT per 1 mL of FFP.[147] Thus, 2 units of FFP (approximately 500 mL) results in a dose of 500 IU of AT. However, the subsequent literature supporting FFP as an effective treatment for heparin resistance is limited, with only 1 in vitro study and several case reports published.[143,148–151] Furthermore, there are no studies showing that administration of FFP for heparin resistance improves clinical outcomes (i.e., postoperative bleeding). Although not directly looking at the efficacy of FFP, Avidan et al.[4] demonstrated that 2 units of FFP were insufficient to improve heparin responsiveness in the majority of patients. Despite the lack of evidence in the literature supporting its use, FFP has been widely used for heparin resistance and may improve heparin responsiveness in a small percentage of patients. However, safety concerns with transfusions and the time delay to thaw FFP makes this a less appealing therapy.[152] Additionally, the United States Food and Drug Administration only recommends patients with a single coagulation factor deficiency (i.e., AT) receive FFP when no specific coagulation factor concentrate is available.[b]

AT concentrates have emerged as an alternative method of AT supplementation. Although their use for heparin resistance is off label, they have been shown to be effective at improving heparin responsiveness. AT concentrate is available in both purified human and recombinant forms. Both are supplied in vials as a sterile, lyophilized powder, and the potency is standardized to the WHO international standard. The source for human purified AT is human plasma that has been pasteurized to inactivate viruses and has no known contraindications. The source for recombinant AT is genetically engineered goats, which express grams per liter quantities of AT in their milk. Thus, recombinant AT should not be given to patients with a known hypersensitivity to goat milk proteins. Although both forms of AT concentrate will increase AT levels, differences in the clinical pharmacology impact the dosing. The half-life for recombinant AT is much shorter than human purified (11.6 hours vs 3.8 days) and requires a maintenance infusion if supplementation is needed for an extended period of time. Recombinant AT also has a 4-fold higher affinity for heparin, but the clinical significance of this difference is unknown.[153] Lastly, the two are supplied in vials with different doses (1750 IU vials for recombinant AT vs 500 IU vials for human purified AT). Before a cost comparison between the 2 concentrates can be performed, consideration must be given to the differences in pharmacokinetics, the difference in amount supplied in each vial, and the expected duration of therapy.

Multiple studies have demonstrated that AT supplementation will improve heparin responsiveness as measured by the ACT.[4,5,9–11,96,154–156] Despite the improvement in the ACT, only 2 studies have shown a reduction in hemostatic activation with AT supplementation for heparin resistance during CPB and none have demonstrated a reduction in bleeding complications after CPB.[5,9] One potential explanation for the reduction in hemostatic activation is the larger doses of AT

(≥50 IU/kg or ≥3500 IU of AT concentrate for a 70 kg patient) used in these studies, which resulted in normalizing AT levels throughout the entire CPB time.[5,9] However, Levy et al.[157] demonstrated large doses of AT maintain normal AT levels throughout CPB and may enhance anticoagulation activity even in nonheparin-resistant patients. Conversely, AT levels decrease below baseline soon after commencing CPB with the standard dose (500–1000 IU) commonly given for heparin resistance. Lastly, cost should be considered before AT administration. At our institution, the acquisition cost of human purified AT is $2.71 per IU, which would translate to a cost of approximately $1355 to $2710 for the standard dose of 500 to 1000 IU.

Clearly, AT concentrate is superior to FFP in increasing the ACT, but questions remain about the overall cost of AT administration and the lack of data demonstrating an improvement in clinical outcomes. Furthermore, not all patients with AT deficiency have heparin resistance and supplementation with AT fails to raise the ACT to target levels in all patients.[4,5,7] Therefore, many patients with heparin resistance have an AT-independent mechanism, and increasing the AT levels to supraphysiological levels provides no further increase in heparin responsiveness.[104,158] Therefore, empirically treating all patients with heparin resistance with AT supplementation will lead to a therapeutic intervention for a subset of patients that not only has potential side effects (e.g., increases in heparin rebound and

related postoperative bleeding) and is costly, but also lacks efficacy.

The last therapeutic option, accepting an ACT below target and proceeding with CPB, is often not chosen for fear that anticoagulation is subtherapeutic. Historically, anticoagulation was accomplished without an ACT using a heparin-loading dose based on the patient's weight and redosing was based on the time interval since heparin was last dosed. Multiple studies comparing this method with ACT monitoring failed to demonstrate a consistent benefit in postoperative hemostasis.[159–168] In 1 study, Metz and Keats[164] had 24 of 193 patients fail to reach an ACT of 400 seconds with a heparin-loading dose of 300 units/kg. They subsequently commenced CPB without additional treatment and noted no clotting in the CPB circuit or increase in chest tube output.

Treatment Algorithm

Despite the many limitations in our current understanding of heparin resistance, a rational approach to management of heparin resistance should be undertaken (Fig. 5). Recent guidelines have recommended AT supplementation only for AT-mediated heparin resistance, but many clinicians treat patients with heparin resistance with AT concentrates without knowledge of the mechanism.[169] Preoperatively, a thorough review of the patient's clinical history will reveal patients at higher risk of heparin resistance. In these patient

Figure 5. A proposed approach to patients with heparin resistance. AT = antithrombin; ACT = activated clotting time; CPB = cardiopulmonary bypass; DIC = disseminated intravascular coagulation; PE = pulmonary embolism; ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon pump; VAD = ventricular assist device; HDR = heparin dose response; FFP = fresh frozen plasma.
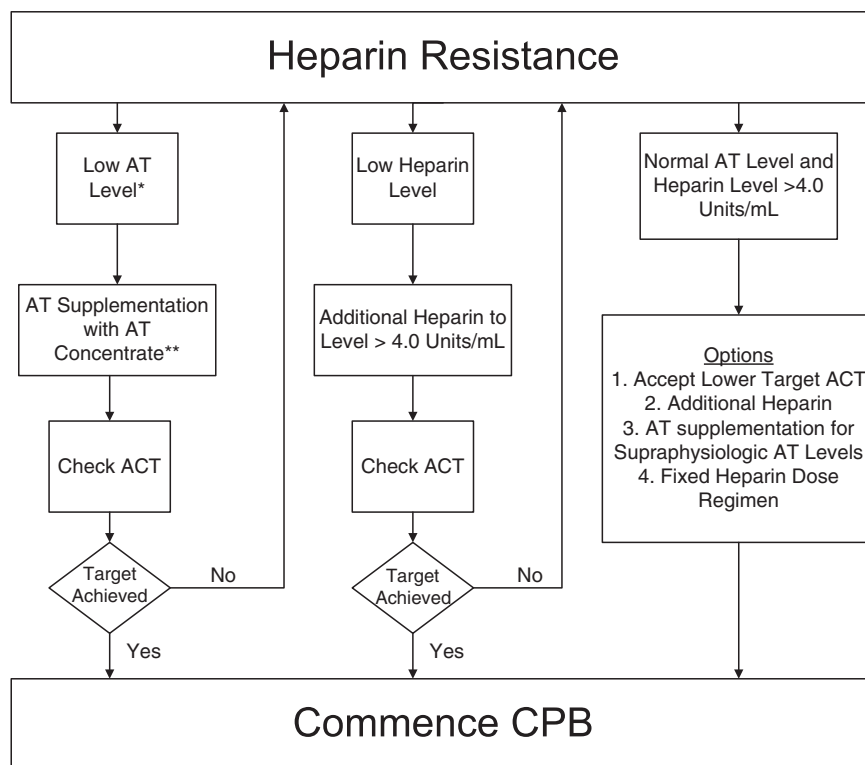
*Draw Preoperative AT Level
1. Decreased Synthesis –Liver Disease, Malnutrition
2. Increased Consumption –DIC, Sepsis, DVT/PE
3. Increased Loss –Nephrotic Syndrome
4. Mechanical Support –ECMO, IABP, VAD
5. Heparin Pretreatment > 48 hrs
6. Decreased Heparin Responsiveness as determined by an in vitro HDR curve

**FFP may be used as an alternative if AT concentrate is not available

populations, a plasma-based AT concentration may be helpful in distinguishing which patients have an AT-mediated heparin resistance. Although no studies have been done to support the utility of a preoperative AT level, determination of an AT level in patients at higher risk of heparin resistance will result in limiting empiric AT supplementation.

In patients with heparin resistance and a low AT level, AT supplementation with 500 to 1000 IU is warranted. When available, AT concentrate is the preferred method of AT supplementation, with FFP being an acceptable alternative. If the ACT fails to reach therapeutic levels with this initial dose, repeat doses should be given with a goal of attaining a normal AT level. However, clinical studies are needed to confirm a benefit of AT supplementation other than an increase in the ACT.

In patients with heparin resistance and a normal AT level, it is appropriate to administer larger doses of heparin. A whole blood heparin concentration may be useful in this scenario to ensure adequate heparin levels (minimum of 4 units/mL) and exclude a higher than expected amount of nonspecific protein binding.

Infrequently, the ACT remains below the target level despite a normal AT level and a heparin level >4.0 units/mL. The appropriate next step remains unclear; however, an argument can be made for proceeding with CPB in many of these patients. First, the target ACT varies greatly among institutions, and many institutions have target ACTs that are significantly higher than levels that are successfully used by others.[3] In institutions with a high-target ACT, heparin resistance may simply be a function of choosing too high an ACT and a reasonable approach may be to accept a lower target ACT. Even in the subset of patients who continue to have an ACT below the target level, an argument for commencing CPB using a fixed heparin dose regimen (i.e., redosing heparin every 30–60 minutes) is that there is no conclusive evidence that routinely monitoring the ACT improves postoperative hemostasis. An alternative approach is achieving supraphysiologic levels of AT. However, the mechanism of heparin resistance is unlikely to be AT mediated in patients with normal AT levels and AT supplementation will not only be costly, but also lack efficacy. Additional heparin can also be administered, but there is no evidence that heparin levels >4.0 units/mL improves anticoagulation. Lastly, an alternative anticoagulant could be considered, such as direct thrombin inhibitors, but these medications have many limitations including the lack of an antidote.

This approach fails to address the situation where an AT level is unavailable. Many institutions do not have the capability to perform an AT level. Moreover, laboratory-based testing is prolonged (30–60 minutes) and makes ordering an intraoperative AT level inefficient. Unfortunately, clinicians are left to use clinical judgment without an AT level and empirically treat the patient.

CONCLUSIONS

CPB is a technology whose routine use includes many complexities. Anticoagulation with heparin is just one of the important aspects of CPB. We have reviewed the topic of heparin responsiveness and heparin resistance. Unfortunately, the minimum ACT required for safe conduct of CPB remains unknown. However, because of the multiple factors affecting ACT levels besides AT levels and heparin concentration, a diagnosis of heparin resistance may be a function of the complexities of the ACT. When faced with heparin resistance, a rational approach should be taken that minimizes empiric therapies. To this end, ACT determinations and the definition of heparin resistance need to be standardized. Moreover, more research is needed to confirm a clinical benefit of strategies aimed at treating heparin resistance. ■

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