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Review Article

Heparin Resistance During Cardiopulmonary Bypass in Adult Cardiac Surgery

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The use of heparin for anticoagulation has changed the face of cardiac surgery by allowing a bloodless and motionless surgical field throughout the introduction of cardiopulmonary bypass (CPB). However, heparin is a drug with complex pharmacologic properties that can cause significant interpatient differences in terms of responsiveness. Heparin resistance during CPB is a weighty issue due to the catastrophic consequences stemming from inadequate anticoagulation, and the treatment of it necessitates a rationalized stepwise approach due to the multifactorial contributions toward this entity. The widespread use of activated clotting time (ACT) as a measurement of anticoagulation during CPB is examined, as it may be a false indicator of heparin resistance. Heparin resistance also has been repeatedly reported in patients infected with COVID-19, which deserves further exploration in this pandemic era. This review aims to examine the variability in heparin potency, underlying mechanisms, and limitations of using ACT for monitoring, as well as provide a framework towards the current management of heparin resistance.

Key Words: albumin; anticoagulation; antithrombin; activated clotting time; COVID-19

THE USE OF cardiopulmonary bypass (CPB) in cardiac surgery has revolutionized the field and led to tremendous advancements by allowing a bloodless and motionless surgical field.[1] The technical challenge of preventing thrombosis within the extracorporeal circuit (ECC) was overcome with the use of heparin[2,3] and its effective antidote, protamine,[4,5] which allowed for safe anticoagulation to be established and subsequently reversed at the end of surgery. The adequacy of heparin anticoagulation during CPB commonly is monitored using the activated clotting time (ACT),[6] which is a point-of-care test of coagulation developed by Hattersley in 1966.[7]

However, a decreased responsiveness to heparin, also known as heparin resistance, can occur in some patients during CPB, leading to subtherapeutic ACT levels. Inadequate anticoagulation potentially may result in activation of the coagulation cascade, leading to complications such as consumptive coagulopathy, excessive postoperative bleeding, and thromboembolic phenomenon.[8] Unfortunately, the target ACT, which balances the risks of circuit thrombosis and excessive bleeding, is still unclear, resulting in a wide variation of ACT targets, ranging from 400-to-500 seconds, used for initiation and maintenance of CPB in clinical practice.[6] This has led to inconsistency in defining heparin resistance, with varying criteria used in the current literature for both the initial bolus dose of heparin and target ACT for initiating CPB.[6,9]

This review aims to examines the variability in heparin potency, underlying mechanisms, limitations of using ACT for monitoring, and the current management of heparin resistance.

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The impact of the ongoing COVID-19 pandemic on heparin responsiveness also is discussed.

Activation of the Hemostatic System During Cardiac Surgery

The function of the hemostatic system is to limit blood loss during vessel wall endothelial injury by forming a localized platelet-fibrin plug through activation of the coagulation cascade, which can occur via the extrinsic (tissue factor) or intrinsic (contact activation) pathways, though the latter has not been shown to play an important role for *in vivo* hemostasis.[10] These 2 pathways eventually merge when factor X becomes activated and catalyzes the formation of thrombin from prothrombin (factor II) with the help of activated cofactor V. Thrombin, in turn, converts fibrinogen (factor I) to fibrin, which is important for clot stabilization. In addition, thrombin also is essential for the activation of platelets, factors V, VIII, and XI, as well as limiting clot propagation by activating protein C and releasing tissue plasminogen activator and tissue factor pathway inhibitor.[11] These enzymatic reactions occur rapidly on the phospholipid surfaces of activated platelets to produce a platelet-fibrin clot, though newer *in vivo* imaging data have suggested that the activated endothelium adjacent to sites of injury may be an important biologic membrane surface as well.[12]

During CPB, both intrinsic and extrinsic pathways of the hemostatic system are activated by blood contact with foreign non-endothelial ECC surfaces, release of tissue factor from surgical manipulation, reinfusion of shed blood via cardiotomy suction, and systemic inflammatory responses.[13] Thrombin generation has been shown to persist during CPB, with marked and sustained increases in thrombin activation markers, though much of the thrombin generated is in the non-hemostatic form, which gives rise to soluble fibrin.[14] Thrombin bound to soluble and circuit-bound fibrin is resistant to antithrombin (AT) inhibition[15]; hence, adequate thrombin suppression is required to prevent thrombus formation and consumptive coagulopathy within the ECC.

Heparin

Unfractionated heparin (UFH) is the mainstay anticoagulant used for CPB during cardiac surgery today. The advantages of its use include the ease of administration, low cost, effectiveness, short half-life, and rapid antagonism by protamine.[16] However, the variability in its pharmacologic properties has led to significant interpatient differences in heparin responsiveness, which have been observed both *in vitro* and *in vivo*.[17,18]

Unfractionated heparin is a heterogeneous mixture of naturally occurring, negatively charged, and highly sulfated polysaccharides with low- and high-molecular-weight fractions ranging from 1,000-to50,000 Daltons found in mast-cell granules.[16,19] Pharmaceutical heparin is isolated and purified from either bovine or porcine mucosal tissues. Heparin exerts its anticoagulant action indirectly by binding to AT, a serine protease inhibitor, which accelerates the latter's irreversible inhibition of thrombin and activated factor X (factor Xa) and, to a lesser extent, activated factors IX, XI, and XII, plasmin,

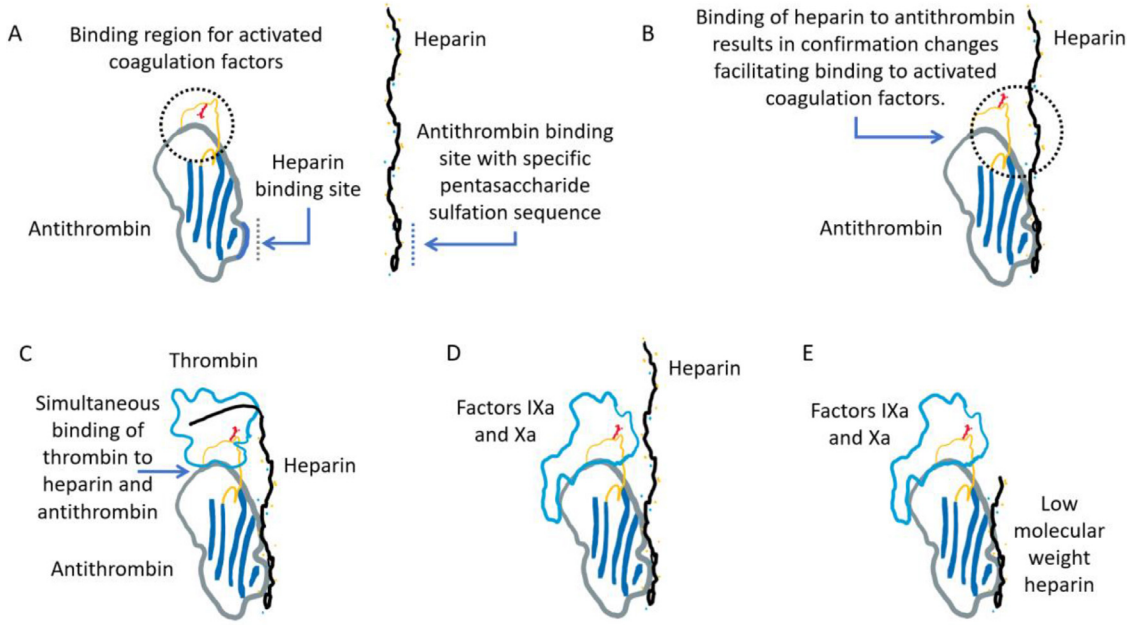

Fig 1. Interactions among antithrombin (AT), heparin, and activated coagulation factors (thrombin in C and factor IXa or Xa in D and E). (A and B) Binding of AT to a specific pentasaccharide sulfation sequence within the heparin polymer induces a conformational change in the binding sites of AT for activated coagulation factors. (C) Both AT and thrombin bind to the same heparin chain. The ability of heparin to act as a template for AT and thrombin depends on its length and, thus, on its molecular weight. Approximately 18 monosaccharide units are minimal to bridge AT to thrombin. (D) Factors IXa and Xa bind to an allosteric site on the pentasaccharide-activated AT without simultaneous binding to the same heparin chain. The inhibition of factors IXa and Xa can occur with heparin lengths <18 monosaccharide units. (E) The binding and inhibition of factors IXa or Xa by AT in the presence of low-molecular-weight heparin.

and kallikrein (Fig 1).[20] However, variability in the response to heparin occurs as only one-third of heparin molecules possess the specific pentasaccharide sequence required for AT binding.[21] In addition, AT-mediated thrombin inhibition requires long-chain heparin molecules with a minimum chain length of 18 oligosaccharide units.[22] This serves as a template for the binding of AT and thrombin simultaneously, which accelerates thrombin inhibition by up to 4,000-fold.[23]

Thrombin inhibition also occurs via an AT-independent pathway mediated by heparin cofactor II (HCII), which requires heparin molecules with chain lengths of ≥6 oligosaccharide units, though optimal inhibition of up to 10,000-fold is achieved with chain lengths of 20-to-24 oligosaccharide units.[24] The HCII-heparin complex has the added advantage of inhibiting clot-bound thrombin, which can form during CPB and is otherwise resistant to AT-heparin complex inhibition.[15,25] However, the physiologic importance of HCII as an anticoagulant remains unclear because its deficiency has not been proven to be strongly associated with prothrombotic pathologic states.[26]

All molecular weight fractions of heparin are able to mediate factor Xa inhibition via AT so long as they possess the specific pentasaccharide sequence, as this reaction does not require the simultaneous binding of factor Xa and AT.[16] Heparin also has been shown to mediate the release of tissue factor pathway inhibitors[27] and activate fibrinolysis.[28]

The pharmacokinetic properties of UFH also play a role in influencing its potency. Unfractionated heparin binds to a wide variety of positively charged plasma proteins, including platelet factor 4 (PF4), histidine-rich glycoprotein, lipoproteins, albumin, von Willebrand factor, factor VIII, and fibrinogen, as well as endothelial cells, platelets, and macrophages.[29,30] In conditions such as thromboembolic disease or sepsis, in which there can be varying concentrations of these heparin-binding proteins, the anticoagulation response to UFH often is unpredictable.[31-34] These nonspecific interactions are facilitated by the long chain lengths (ie, higher molecular weights) of heparin found in UFH, which are present in much lower concentrations in low-molecular-weight heparin (LMWH) preparations, thus explaining the more consistent and predictable pharmacokinetic profile of the latter.[35,36] Metabolism occurs primarily in the reticuloendothelial system, and ≤50% of UFH is excreted unchanged by the kidneys.[37] Elimination occurs through the following 2 mechanisms: a rapid saturable pathway via the reticuloendothelial system, and a slower nonsaturable pathway via the kidneys.[37] As a result, the biologic half-life of UFH is dependent on the dose administered, ranging from 30 minutes with an intravenous dose of 25 U/kg, 60 minutes with 100 U/kg, and up to 150 minutes with 400 U/kg.[8,38,39] Hepatic and renal clearance also are reduced during CPB due to hypothermia and decreased organ perfusion, which may further prolong heparin's elimination half-life.[40]

Activated Clotting Time for Monitoring Coagulation

The ACT is considered to be the gold standard for monitoring anticoagulation during CPB.[41] It is a modified Lee and White[42] point-of-care test of whole blood coagulation involving platelet phospholipids in the hemostatic process, as opposed to other standard tests of coagulation, which primarily are focused on plasma hemostasis. The target ACT values maintained during CPB are usually between 400 and 480 seconds.[6]

Measurement of ACT involves the use of a contact activator, such as celite, kaolin, or glass beads, which activates the intrinsic and common pathways of the clotting cascade when exposed to fresh, whole blood by mimicking the negatively charged foreign surfaces of the CPB circuit. The blood sample is collected in a plastic syringe free of anticoagulant, and the test is performed immediately, as contact activation begins in the syringe. After warming the blood sample to 37°C, the ACT measurement device measures the time taken for fibrin clot formation. Therefore, different syringe materials or delays in testing may cause variability in the results. The different ACT measurement devices incorporate different technical methods to detect end-point ACT (eg, mechanical optical, photo-optical, amperometric, or photomechanical technology).[43] Depending on the detection method used, the ACT either is derived or obtained in real time. Hence, ACT values obtained from different ACT measurement devices are not interchangeable, as different contact activators, sample volumes, and clot detection methodologies are employed.[43,44] The advantages of using ACT for monitoring include its cost, simplicity, rapid turnover, fairly linear relationship with heparin concentrations >1 U/mL, and ability to detect the effects of heparin, even at the high concentrations required for cardiac surgeries (2-10 U/mL), which otherwise would render the activated partial thromboplastin time (aPTT) test unclottable.[45]

However, there are many factors that can influence the ACT during cardiac surgery, in addition to the different technologies employed to derive the ACT (Table 1).[8,16,43,46] Studies have demonstrated a lack of correlation between ACT values and plasma heparin concentrations during CPB, and postulated that this could be due to the influence of hypothermia and hemodilution effects on the ACT assays.[47-49]

Due to the limitations of using ACT for monitoring, alternative methods have been suggested, such as measuring whole blood heparin concentrations with the Hepcon Hemostasis Management System (Medtronic, Minneapolis, MN), though results regarding its correlation with plasma anti-Xa activity, traditionally considered to be the gold standard for measuring anticoagulation effects of heparin, have been mixed.[49,50] The Hepcon HMS allows individualized heparin and protamine dosing based on each patient's responsiveness to heparin. At least 2.5 mL of non-heparinized blood are collected from the patient, and 0.4 mL are allocated by the machine to each of the 6 chambers within the heparin-dose response (HDR) cartridge. These 6 chambers contain varying concentrations of heparin—2 with no heparin, 2 with 1.5 U/mL of heparin, and 2 with 2.5 U/mL of heparin. The resulting ACT levels corresponding to the known heparin concentrations are plotted to determine the HDR curve from which a heparin loading dose can be calculated using the patient's estimated blood volume to achieve a target ACT. Heparin assay cartridges subsequently are used

Table 1
Factors Influencing Measurement of Activated Clotting Time

Patient
1. Preoperative medications
• Vitamin K epoxide reductase inhibitors (eg, warfarin)
• Platelet inhibitors (eg, cyclooxygenase inhibitors, $P2Y_{12}$ receptor inhibitors)
• Oral direct thrombin inhibitors (eg, dabigatran)
• Factor Xa inhibitors (eg, apixaban, rivaroxaban)
• Glycoprotein IIb/IIIa inhibitors (eg, abciximab, eptifibatide, tirofiban)
2. Platelet count and function
3. Factor deficiencies
• Intrinsic pathway (eg, factors XII, XI, VII, VIII and kallikrein)
• Common pathway (eg, factors V, II)
• Antithrombin
• Fibrinogen
4. Proinflammatory states (eg, antiphospholipid syndrome, vasculitis, DVT, DIVC)
Cardiopulmonary bypass
1. Hypothermia
2. Hemodilution
Method of evaluating ACT
1. Type of activator (eg, diatomaceous earth, kaolin, silica, glass)
2. Technical method for ACT measurement (eg, mechanical optical, photo-optical, amperometric, photomechanical)
3. Derived or real time ACT
Intraoperative anticoagulant
1. Source of heparin (eg, bovine, porcine)
2. Parenteral direct thrombin inhibitors (eg, bivalirudin, argatroban)

Abbreviations: ACT, activated clotting time; DIVC, disseminated; DVT, deep vein thrombosis; intravascular coagulopathy.

to measure circulating heparin concentrations during CPB using an automated heparin protamine titration method, which also can calculate the protamine dose required for heparin neutralization at the end of CPB.[44,51] High-dose thrombin time (HiTT) is another point-of-care test that is more specific for the effects of heparin because it involves only the final common pathway of the clotting cascade and is unaffected by temperature and hematocrit changes during CPB.[52]

Heparin Resistance

Due to the widespread use of heparin for anticoagulation during CPB, a frequently encountered problem is that of heparin resistance. It is defined as the inability of an adequate dose of heparin to achieve a desired ACT or a decreased slope on the HDR curve.[8] The incidence of heparin resistance is between 4% and 26%, depending on the initial heparin bolus administered and the target ACT level required for initiating CPB.[6,8] A generally accepted definition is the need for >500 U/kg of heparin to achieve an ACT of 400-to-480 seconds.[53,54]

The HDR curve was described first by Bull et al,[55] to account for the interindividual variability seen in heparin responsiveness, and may play a role in the early detection of heparin resistance.[56] As previously mentioned, it is generated using a minimum of 2 ACT values (baseline and an ACT response to a known *in vivo* or *in vitro* concentration of heparin), though additional ACT values will provide more points for a better-fitted curve.[55] Extrapolation of the HDR curve determines the optimal *in vivo* heparin concentration required to achieve a target ACT value, and the corresponding heparin loading dose can be calculated. Besides observing a decreased slope of the HDR curve, a heparin sensitivity index can be obtained using the slope values from the HDR curve to quantify heparin responsiveness. A heparin sensitivity index <1 s/U/kg usually is indicative of heparin resistance.[57]

Mechanisms of Heparin Resistance

Underlying causes of heparin resistance can be complex and usually are multifactorial, namely due to the variability of heparin potency on anticoagulation, as well as patient-specific factors (Table 2).[8,9] In addition, there are limitations of using ACT for monitoring, which are not specific for the anticoagulation effects of heparin, thus complicating the clinical picture.

Antithrombin Deficiency

Antithrombin deficiency long has been purported as the main cause of heparin resistance because heparin exerts its effects indirectly by catalyzing the anticoagulation activity of

Table 2
Mechanisms of Heparin Resistance

Antithrombin Deficiency
1. Congenital
2. Acquired
• Decreased synthesis (eg, liver disease, malnutrition)
• Increased clearance (eg, nephrotic syndrome)
• Increased consumption (eg, heparin therapy)
• Upregulated hemostatic system (eg, sepsis, infective endocarditis, DIVC, DVT, PE)
• Mechanical support devices (eg, ECMO, IABP, CPB)
• Medications (eg, asparaginase)
Non-Antithrombin Mediated
1. Increased heparin binding to other proteins, cells and non-endothelial surfaces
• Plasma proteins (eg, albumin, cell adhesion proteins, glycoproteins, lipoproteins, nuclear; proteins, microbial proteins, viral proteins)
• Extracellular matrix proteins (eg, laminin, collagens, thrombospondin, fibronectin, vitronectin)
• Chemokines (eg, PF4, interleukins, macrophage proteins, monocyte proteins)
• Cells (eg, endothelial cells, macrophages, platelets)
• Miscellaneous (eg, von Willebrand factor, factor VIII, fibrinogen)
• Nonendothelial surfaces (eg, intravenous tubings, ECMO circuits)
2. High platelet count ≥300,000 cells/mm^3 (due to the activation of PF4, a strong inhibitor of heparin)
3. Low albumin concentrations ≤35 g/dL (albumin exhibits heparin-like action)
4. Preoperative relative hypovolemia (dehydration leading to increased concentration of other compatible molecules binding to heparin)
5. Medications (eg, andexanet alfa)

Abbreviations: CPB, cardiopulmonary bypass; DIVC, disseminated intravascular coagulopathy; DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; PE, pulmonary embolism; PF4, platelet factor 4.

endogenous AT. Normal AT activity in adults ranges from 80% to 120%, and AT deficiency commonly is defined as AT activity <80%.[58]

Antithrombin deficiency can be either acquired or congenital. Several disease states or their treatments can contribute to acquired AT deficiency either by reduced synthesis or increased consumption. These conditions include heparin treatment, liver disease, malnutrition, nephrotic syndrome, sepsis, acute disseminated intravascular coagulopathy, asparaginase use in patients with acute leukemia, and the use of mechanical support devices, (eg, intra-aortic balloon pump, CPB, and extracorporeal membrane oxygenation [ECMO]).[8,9,13,53,59,60] The ECC devices cause thrombin formation and AT depletion through the exposure of blood to ECC foreign surfaces and ischemic endothelium of the heart, inadequate heparinization, direct reinfusion of shed blood from cardiotomy suction, and exposure to non-heparinized blood.[13] The mechanisms of heparin resistance are detailed in Table 2.

The preoperative use of heparin (24-48 hours) is thought to contribute to heparin resistance by depleting AT through the clearance of thrombin-AT complexes via the reticuloendothelial system,[61] though this is seen mostly with UFH compared with LMWH preparations.[8,53,54,62] This results in diminished AT reserves and subsequently reduced efficacy for heparinization prior to CPB.[63] Despite this, several studies have shown that HDR is independent of AT concentrations,[63-66] and not all of the patients who had an inadequate ACT demonstrated low AT activity, questioning the validity of using ACT in this group of patients. A more suitable measure of anticoagulation, such as HiTT or anti-Xa levels, might be more appropriate in such circumstances.[67,68]

Non-Antithrombin–Mediated Mechanisms

As previously mentioned, heparin binds to a multitude of positively-charged plasma proteins and cellular components due to its strong negative charge. It also binds to a variety of cells, such as endothelial cells, platelets, and macrophages. In addition, heparin binds to the ECC, contributing to its reduced bioavailability.[9,28,30]

High platelet counts of ≥300,000 cells/mm^3 have been found to increase heparin resistance.[54,57,69] A possible explanation for this could be due to the activation of PF4, which is a strong inhibitor of heparin that is released by activated platelets.[70] Heparin also displaces PF4 from its endothelial binding to heparinoids, increasing the plasma concentrations of PF4 and providing an additional mechanism for heparin resistance.[57]

Low albumin concentrations of ≤35 g/dL have been demonstrated to increase heparin resistance.[54] Albumin possesses some structural similarity to heparin and seems to exert a heparin-like action. The highly negatively charged albumin molecule potentially could bind to positively charged groups on AT.[71] Hence, hypoalbuminemia may act as a surrogate indicator for heparin resistance.

Relative hypovolemia also has been proposed as a possible contributor to heparin resistance.[54] This could be due to the vasoconstriction from dehydration, concentrating plasma proteins and acute phase reactants per unit volume of blood, thereby increasing the chances of heparin binding to other compatible molecules instead of AT. Therefore, a larger dose of heparin would be required to overcome the competitive binding.

Several studies have shown increased factor VIII concentrations in patients with apparent heparin resistance.[72-75] Factor VIII is an acute-phase reactant and is increased in inflammatory states. Increased factor VIII activity augments the propagation phase of clotting and has been shown to reduce HDR.[76] However, most of these studies measured heparin resistance with aPTT instead of ACT. An interesting point to note would be that, in such situations, anti-Xa activity was not influenced by increased levels of factor VIII, even though aPTT was shortened. Hence, aPTT underestimated the effects of anticoagulation with UFH, and anti-Xa activity would be a more accurate depiction of adequate heparinization in this scenario.[74] However, the question now lies in whether increased factor VIII levels potentially could be thrombogenic and if therapeutic anti-Xa levels could lead to a false sense of security with regard to adequate anticoagulation. There currently is no clear answer to this question, and further research may be warranted.

A potential new contributor toward heparin resistance would be andexanet alfa, which is a recombinant coagulation factor Xa decoy protein recently introduced for the emergency reversal of anti-Xa-targeted direct oral anticoagulants.[77] Clinical experience with andexanet alfa is limited for elective cardiac surgeries, but several case reports have documented difficulties with intraoperative heparinization after its administration.[78-80] An abstract presented at the International Society on Thrombosis and Hemostasis suggested that andexanet alfa produces heparin resistance during CPB due to its binding to UFH-AT complexes and extreme doses of UFH and, sometimes, AT supplementation may be necessary to achieve adequate anticoagulation.[81]

Management of Heparin Resistance

The management of heparin resistance during CPB follows 4 general pathways. The first is to administer additional heparin to achieve the desired ACT. Secondly, fresh frozen plasma (FFP) is administered to provide additional AT. Thirdly, AT is supplemented via AT concentrate, and the last option is to accept the subtherapeutic ACT and commence CPB without any additional treatment.[6,8,82-84]

The additional dosing of heparin to counter heparin resistance is a commonly used practice for cardiothoracic anesthesiologists.[8] Heparin usually is administered at 300-to-500 U/kg in an attempt to achieve an ACT of 400-to-480 seconds. In fact, the survey conducted by Sniecinski et al. showed that >30% of respondents (largest proportion) would administer additional heparin ≤600 U/kg, and a small percentage of respondents would administer >800 U/kg to achieve the desired ACT before commencing any alternative therapy.[6] Although it is the simplest treatment for heparin resistance,

high doses of heparin come with adverse consequences. For one, high doses of heparin may not necessarily prevent fibrin formation during CPB for patients with heparin resistance.[85] The risks of heparin rebound and postoperative bleeding are increased, as higher concentrations of heparin also bind non-specifically to multiple plasma proteins—this provides a reservoir of heparin that dissociates over time and, in turn, binds with AT even after the reversal with protamine and clearance of heparin-protamine complexes.[86] There also appears to be a ceiling dose with regard to anticoagulation for heparin, as blood concentrations of >4.1 U/mL (corresponding to 300 U/kg body weight) failed to increase ACT in an *in vitro* study conducted by Levy et al.[87]

Using FFP was one of the earliest treatments found to neutralize heparin resistance.[88,89] Fresh frozen plasma contains approximately 1 IU of AT per mL; hence, usually, 500 mL (2 units) of FFP are given to provide 500 IU of AT.[58] Despite its long history of use, there is a paucity of evidence on the treatment of heparin resistance with FFP. A systematic review by Spiess in 2008 showed that the administration of FFP may resolve heparin resistance only in some patients, and comes with added safety concerns (eg, transmission of viral infections, volume overload, and the risk of transfusion-related lung injury).[90] In centers where FFP is not immediately available, a delay to the commencement of CPB is expected due to the need for thawing and transportation of FFP to the operating room.[90] A best evidence topic review by Beattie et al. in 2014 concluded that FFP might not restore ACT to target values despite adequate heparinization in patients with heparin resistance,[91] possibly because 500 mL of FFP were inadequate to restore heparin responsiveness, and much larger volumes were required.[82] Thus far, no studies have demonstrated FFP to be beneficial in improving clinical outcomes for postoperative bleeding. Only 1 study in patients requiring ECMO support showed that early treatment with FFP in heparin-resistant patients improved survival substantially, though this result was not statistically significant, likely due to the small sample size.[92] Considering the body of evidence, the recommendation is mostly for the supplementation with AT concentrate instead of FFP should it be available.[82,84,90,91]

Antithrombin concentrate has been approved for use by the United States Food and Drug Administration since the 1980s. It is currently the treatment of choice for heparin resistance in relation to AT deficiency, and its use is highly recommended to reduce plasma transfusions in patients with AT-mediated heparin resistance immediately before CPB (Class I, Level A evidence).[93] Although the causes of reduction in plasma AT concentration mostly are acquired (in up to 23% of cardiac surgical patients) following preoperative heparin therapy, sepsis, and circulating blood through the ECC,[57,90,94] a deficiency in AT also can be inherited in an autosomal dominant pattern, with a prevalence of 1:500 to 1:5000.[95] There are 2 forms of AT concentrates available for use—purified human and recombinant forms. The human concentrate (hAT) is harvested from donated pools of plasma, which then undergoes a complex multistep extraction and purification process that includes pathogen testing before rendering it safe for use. Recombinant AT (rAT) is produced from transgenic goats and procured from milk.[83] Hence, rAT should not be given to patients with a known sensitivity to goat milk proteins.[8] Both forms of AT concentrates are similar and exhibit equivalent activity for *in vitro* thrombin and factor Xa inhibition assays. This is despite a 4-fold increase in heparin-binding affinity in rAT, as well as a shorter half-life (10.49 ± 7.19 hours for rAT compared with 56.8-68 hours for hAT), thus necessitating an infusion if rAT is to be used for extended periods.95 Antithrombin concentrate usually is dosed at 500-to-1000 IU (equivalent to 1-2 vials of hAT).[58,83,96,97] Patnik et al. recommended a formula to estimate the initial dose of AT: AT dose (IU) = (desired minus current AT level as % of normal level) X weight (kg) divided by 1.4.[95] However, this formula requires a laboratory AT level that may not be timely enough before CPB. In another study by Stammers et al, the average dose of AT concentrate required for the treatment of heparin resistance was found to be 1,029.0 ± 164.5 IU or 14.1 ± 3.4 IU/kg when normalized to body weight.[83] Each vial is reconstituted with water for injection to 10 mL of solution, which obviates the need for the large volumes required to replenish plasma AT levels seen with plasma transfusions. . Although studies have shown that AT concentrate does not necessarily improve postoperative outcomes of bleeding as compared to treatment with FFP or no treatment at all,[58,96-98] the majority of the evidence suggests that AT concentrate is a safe and effective method of restoring an adequate ACT for CPB.[58,82,83,85,87,90,91,93,96,97] One prohibitive factor would be its cost, which can be 8 times that of 2 units of FFP,[91] and another would be its lack of availability in certain institutions.[6] In the circumstances in which cost is a concern, the authors' recommendation would be to administer 1 vial (500 IU) first, followed by a second vial should the repeat ACT be inadequate for CPB.

The last option of accepting a lower ACT for CPB is seldom executed due to the fear of catastrophic consequences from inadequate anticoagulation. Clinical practice guidelines generally recommend for the ACT to be kept >480 seconds so as to provide a margin of safety.[41,99] The concept of a minimal ACT goes back to 1975 when Bull et al. demonstrated that CPB could be established safely at an ACT of 300 seconds, with no formation of small clots in the ECC, even at the conclusion of bypass.[18] This then was challenged by Young et al. in 1978, who demonstrated that the minimal ACT to avoid fibrin monomer formation during CPB was ≥400 seconds.[100] However, more recent studies have recognized that an ACT as low as 250 seconds has been accepted with no adverse consequences, especially if employing heparin-coated circuits or modern, minimally invasive ECC systems.[101-104] The studies that employed a fixed-dose regimen of heparin instead of pursuing a minimal ACT showed no increase in adverse outcomes.[105-107] In particular, Metz and Keats administered a single dose of heparin (300 U/kg) and commenced CPB without additional treatment, even when the ACT was <400 seconds. There were no reports of clot formation in the CPB circuits nor an increase in postoperative bleeding.[107] Shore-Lesserson et al. also demonstrated that adequate levels of anticoagulation are achieved despite a lower than threshold ACT when using HiTT as an alternative

monitor of anticoagulation.[67] Therefore, accepting a lower ACT for bypass in "heparin-resistant" patients might be a viable option should conventional treatments fail.

Alternatives for Anticoagulation

Direct thrombin inhibitors (DTI), such as bivalirudin and argatroban, have been established as substitutes for heparin in patients who have contraindications to heparin or protamine (eg, hypersensitivity reactions or heparin-induced thrombocytopenia).[41,99] Bivalirudin is a recombinant hirudin analog, and argatroban is a synthetic L-arginine derivative.[108] These agents directly inhibit thrombin without requiring AT, and may be alternative treatments for heparin resistance. However, the use of bivalirudin requires an avoidance of the stagnation of blood in the CPB circuit to avoid thrombosis—this requires prior modification of the ECC to allow for shunting and continuous flow of cardiotomy blood between the arterial inflow and venous circuit at the end of CPB. Bivalirudin has a relatively short half-life of 25 minutes in patients with normal renal function, which accounts for 20% of its elimination, and the remaining 80% is eliminated via proteolysis by thrombin and blood proteases.[108,109] In areas of stasis or areas isolated from the circuit, bivalirudin levels may be depleted due to metabolism by thrombin.[110] Although the decrease in bivalirudin via this mechanism may not be relevant, as bivalirudin is a reversible inhibitor of thrombin,[109] slow thrombin accumulation in a stagnant reservoir eventually may result in thrombosis, rendering the cardiotomy blood unsafe for transfusion. Also, both bivalirudin and argatroban have no specific reversal agents available. Thus, the routine use of DTI is restricted to a skilled anesthesiologist-perfusion-surgical team.[99]

Nafamostat mesilate has emerged as another possible alternative for heparin. It is a short-acting synthetic protease inhibitor, and prolongs ACT by directly inhibiting thrombin, as well as other activated coagulation factors. It also inactivates fibrinolysis and platelet aggregation, as well as suppresses blood-foreign surface reaction by blocking activated factor XII.[111-113] When administered intravenously, together with low-to-normal doses of heparin (not exceeding 500 U/kg) in cases of heparin resistance, nafamostat mesilate successfully overcame heparin resistance during the conduct of CPB without increasing the risk of perioperative ischemic stroke or death.[113,114]

Treatment Algorithm

When faced with heparin resistance, it always is prudent to take a stepwise approach toward treatment instead of administering drugs and products without understanding the mechanism behind it. An easy algorithm to follow is the one adapted from Finley and Greenberg's review paper in 2013 (Fig 2).[8]

The first step would be to obtain a detailed preoperative history on whether heparin was administered or if the patient has any risk factors for acquired AT deficiency. Should a deficiency be suspected, plasma AT concentrations can be obtained, although it is not essential. Normal plasma concentrations of AT range from 112-to-140 μg/mL. Due to the presence of interlaboratory variations, most laboratories express the AT antigen and activity levels in terms of percentages, with a normal range between 80% and 120%, where 100% of AT corresponds to 1 unit of AT in 1 mL of reference plasma.[95] If the AT activity levels are low, prebypass supplementation is possible with AT concentrate starting at 500-to-1,000 IU or with FFP should AT concentrate be unavailable,[84,93] bearing

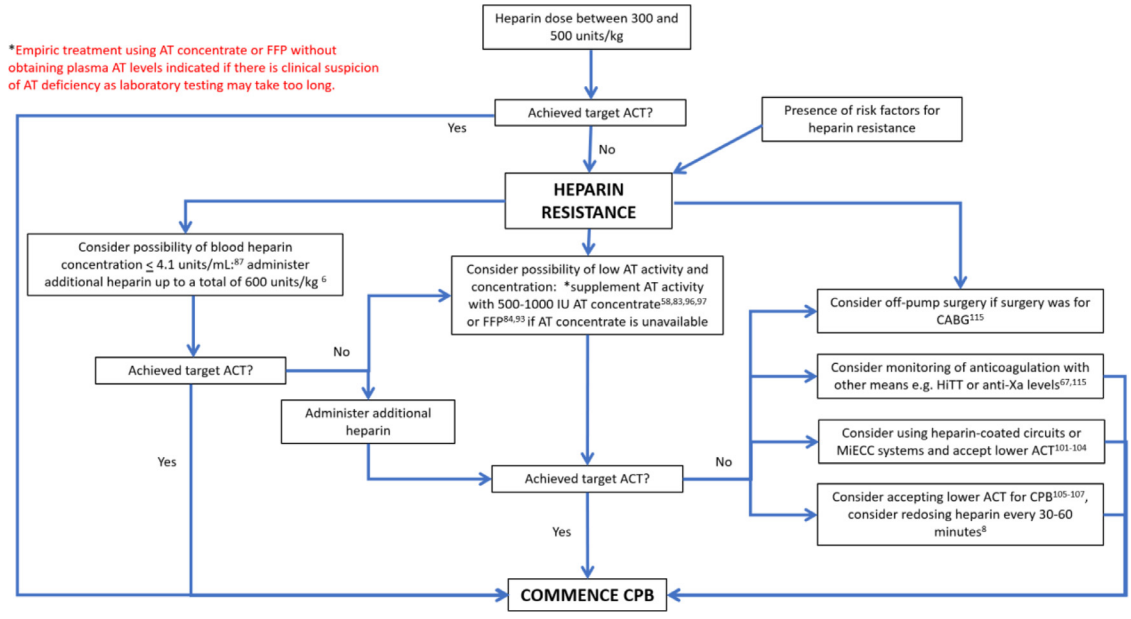

Fig 2. Algorithm for treatment of heparin resistance. Flow chart adapted from Finley and Greenberg.[8] ACT, activated clotting time; AT, antithrombin; CABG, coronary bypass graft surgery; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; HiTT, high-dose thrombin time; MiECC, minimally invasive extracorporeal circulation.

in mind that a large volume of FFP beyond 500-to-1,000 mL may be required.[82] In institutions that do not offer tests for plasma AT activity levels or where it is not practical to wait for laboratory determination of AT activity levels before the commencement of CPB, empiric treatment with AT concentrate is justified should there be a clinical suspicion of AT deficiency without laboratory testing.

For patients with normal AT activity levels, the dose of heparin can be up to 600 U/kg. If the ACT still remains persistently low, heparin concentrations can be obtained prior to increasing the dosage, as whole blood concentrations of >4.1 U/mL seem to have limited effects on ACT.[87] Furthermore, increased doses of heparin also are associated with heparin rebound and postoperative bleeding.

In patients in whom both AT activity levels and heparin concentrations are adequate, the options would be to accept a lower ACT for CPB or to consider monitoring anticoagulation with other means, such as HiTT or anti-Xa levels.[115] Cardiopulmonary bypass also can be initiated with lower than targeted ACT on a fixed-dose heparin regimen (ie, redosing heparin every 30-60 minutes).[8] Additional heparin can be administered as well, though, as previously mentioned, there is no evidence for heparin concentrations >4.1 units/mL in improving anticoagulation.[87] Alternatively, if the surgery was coronary artery bypass graft surgery, the surgeons can be engaged in a discussion as to whether the surgery can be performed without CPB as an off-pump procedure.[115] Supplementation of AT concentrate to provide supraphysiologic activity levels of AT is an option to increase the ACT. However, if AT concentrations already are sufficient, the mechanism of AT deficiency is unlikely to be AT-mediated, and supplementation would be not only pricey but also ineffive.[8,76,116]

Finally, alternative anticoagulation, such as DTIs or nafamostat mesilate, may have a role to play in the management of heparin resistance, but the pros and cons should be weighed carefully before embarking on such a route.

Heparin Resistance in the COVID-19 Era

After SARS-CoV-2 first emerged in Wuhan city, Hubei province, China, in December 2019,[117] anecdotal case reports and eventually observational studies have demonstrated a higher incidence of thromboembolic events in critically ill patients infected with COVID-19 despite anticoagulation.[118,119] The underlying hyperinflammatory and hypercoagulopathic processes provoked by the COVID-19 infection[120,121] place these patients at increased thrombotic risk, and possibly contribute to the development of heparin resistance both during CPB and in the intensive care unit.[122-124] A retrospective cohort study conducted in 15 critically ill patients with COVID-19 infection receiving therapeutic anticoagulation demonstrated heparin resistance in 80% of patients on UFH and suboptimal peak anti-Xa activity in 100% of patients on LMWH, which did not correlate with either factor VIII, fibrinogen, or AT levels.[123] Similarly, an observational study of patients with COVID-19 on continuous renal replacement therapy and ECMO noted that all of these patients conformed to the definition of heparin resistance, with no association with either AT, factor VIII, fibrinogen, thrombocytes, C-reactive protein, or ferritin.[125]

Much is not yet known about the underlying mechanisms of heparin resistance in COVID-19, and one postulated theory is that the increased concentrations of acute-phase proteins produced during the inflammatory process bind to heparin, resulting in a much lower plasma heparin concentration available for binding to AT and thrombin. In addition, elevated concentrations of factor VIII, fibrinogen, antiphospholipid antibodies, and von Willebrand factor, which commonly occur in inflammatory states and endothelial dysfunction, may contribute to heparin resistance as well.[126] Further research is, therefore, needed in this area to explore the underlying pathogenesis and determine the optimal management of anticoagulation in this high-risk patient group.

Conclusions

Heparin resistance is a complex multifactorial issue that is related to both intrinsic as well as iatrogenic factors. Apart from understanding the pharmacology of heparin, clinicians need to examine the patient's medical history, and history of drug use, as well as remain cognizant of the limitations of ACT in determining adequacy of anticoagulation for CPB before embarking on a treatment plan. Accepting a lower ACT for CPB or considering off-pump surgery also may be viable alternatives should the conventional treatment strategies fail, especially if heparin-coated circuits or minimally invasive ECC systems are used for CPB. Moreover, the COVID-19 pandemic has presented a new group of patients who are at a higher risk of heparin resistance, thus compelling the need for further research to provide optimal care for this at-risk population.

Conflict of Interest

None.

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