REVIEW ARTICLE

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Heparin Resistance — Clinical Perspectives and Management Strategies

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Drug resistance is defined as the lack of expected response to a standard therapeutic dose of a drug or as resistance resulting from biologic changes in the target, as occurs in antibiotic resistance. Heparin resistance, the failure to achieve a specified anticoagulation level despite the use of what is considered to be an adequate dose of heparin, is neither well understood nor well defined. Heparin resistance usually refers to an effect of unfractionated heparin, for which doses are measured and adjusted, rather than low-molecular-weight heparin, which is not routinely monitored with laboratory testing. Although it is infrequently invoked in inpatient settings, heparin resistance has been reported in critically ill patients with coronavirus disease 2019 (Covid-19) who are at high risk for thrombosis.[1-3] This review provides a clinical summary of heparin resistance and potential management strategies.

Inhibition of Coagulation

Heparin is a negatively charged, sulfated glycosaminoglycan polysaccharide polymer isolated from porcine intestine, where it is stored in mast-cell granules.[4] Unfractionated heparin is a mixture of polymers with chain lengths ranging from 3000 to 30,000 daltons (mean, 15,000), whereas low-molecular-weight heparin, purified from unfractionated heparin, has a more uniform polymer size and a molecular weight of 3500 to 5000 daltons.[5] Heparin polymers bind to antithrombin and thereby accelerate the interaction between antithrombin and thrombin or antithrombin and factor Xa, either of which results in the inhibition of prothrombotic activity. A specific pentasaccharide sequence of unfractionated heparin and low-molecular-weight heparin binds to antithrombin and can inhibit factor Xa, but longer, unfractionated heparin polymers containing 18 or more polysaccharide units are required to inhibit thrombin.[5] Although low-molecular-weight heparin can inhibit thrombin, it preferentially inhibits factor Xa. Unfractionated heparin also inhibits factor Xa, but its overwhelming effect is on thrombin. The difference in size between low-molecular-weight heparin and unfractionated heparin affects the molecular mechanisms of each and accounts for differences in effect and possibly in resistance to their effects (Fig. 1). Although unfractionated heparin has greater interindividual variation in pharmacodynamic effects than low-molecular-weight heparin, its short half-life and rapid reversibility with the administration of protamine make it the anticoagulant of choice when careful control of anticoagulation is needed, such as in critically ill patients or in conjunction with the extracorporeal circuits used in patients undergoing cardiopulmonary bypass or extracorporeal membrane oxygenation (ECMO).

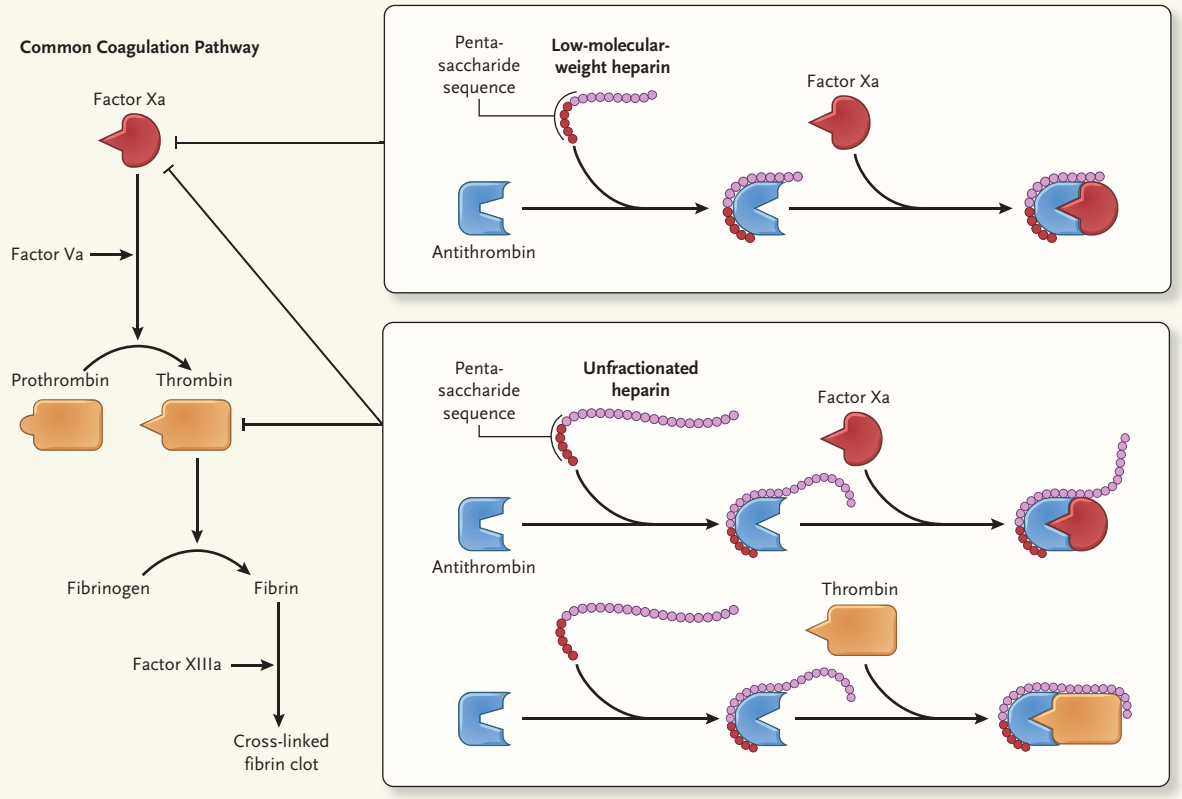

Figure 1. Location of Anticoagulant Targets in Coagulation Pathways.

A specific five-sugar sequence (pentasaccharide) is required for any type of heparin to bind to antithrombin. Low-molecular-weight heparin first binds antithrombin, enhancing its activity. When it forms a complex with antithrombin, both unfractionated heparin and low-molecular-weight heparin can inhibit factor Xa. However, the longer polysaccharide chains found in unfractionated preparations are required for the inhibition of thrombin; the long heparin chain must bind both antithrombin and thrombin in order to inhibit thrombin activity. Low-molecular-weight heparin primarily inhibits factor Xa in a ratio that ranges from 2:1 to 4:1, depending on the composition of the chain lengths in a given preparation; some of the longer chains present in preparations of low-molecular-weight heparin can bind to both antithrombin and thrombin, thereby inhibiting thrombin. Unfractionated heparin has some inhibitory effects on factor Xa activity, but its main role involves the inhibition of thrombin. Fondaparinux is a synthetic molecule that contains the specific pentasacchride sequence; it works through antithrombin as well but its long half-life of 17 to 20 hours and its dependence on renal clearance make it difficult to use in critically ill hospitalized patients. Parenteral direct thrombin inhibitors, which directly inhibit thrombin independent of antithrombin, include argatroban and bivalirudin.

IDENTIFICATION OF HEPARIN RESISTANCE

Heparin resistance is often defined as the need for high heparin doses to achieve a targeted level of anticoagulation, yet the threshold dose is not well defined. Identifying heparin resistance is further complicated by the lack of consensus on the appropriate target level and the best way to measure the effects of heparin. One reported definition suggests that the need for more than 35,000 U per day to achieve anticoagulation constitutes heparin resistance, but the targeted level of anticoagulation is not specified.[6,7] In patients undergoing cardiopulmonary bypass, the definition of heparin resistance often used is the need for a dose of more than 500 U per kilogram of body weight to achieve an activated clotting time of 400 to 480 seconds.[8]

The identification of heparin resistance depends on the laboratory test used, the degree of anticoagulation targeted, and the definition

Table 1. Parenteral Anticoagulant Therapy.*

Characteristic	Unfractionated Heparin	Low-Molecular-Weight Heparin	Argatroban	Bivalirudin
Structure	Glycosaminoglycan	Glycosaminoglycan	Chemical	Polypeptide
Molecular weight — daltons	3000–30,000	3500–5000	508	2180
Target inhibition	Factor Xa, factor IIa (thrombin)	Factor Xa	Factor IIa (thrombin)	Factor IIa (thrombin)
Cofactor	Antithrombin	Antithrombin	None	None
Half-life	Approximately 1 hr; may increase at higher doses	Approximately 3–6 hr with normal renal function	45 min	25 min
Monitoring	aPTT, anti–factor Xa level, ACT	Anti–factor Xa level	aPTT, dilute thrombin time, ACT	aPTT, dilute thrombin time, ACT
Metabolism	Reticuloendothelial	Renal	Hepatic	Renal
Route of administration	IV or subcutaneous	IV or subcutaneous	IV	IV

* Caution is advised when using low-molecular-weight heparin or bivalirudin in patients with renal failure and when using argatroban in patients with severe liver disease, since the main metabolic pathways of elimination are impaired. See institutional guidelines or guidance in package inserts for information on dosing and monitoring. ACT denotes activated clotting time, aPTT activated partial-thromboplastin time, and IV intravenous.

of resistance used. The two main types of functional laboratory tests used to monitor anticoagulation with unfractionated heparin are clot-based assays and chromogenic assays (Table 1).

DIAGNOSTIC TESTS

FUNCTIONAL ASSAYS

The functional assays used to monitor heparin anticoagulation measure how quickly clot formation occurs in vitro. The most commonly used test is the plasma-based activated partial-thromboplastin time (aPTT). Another functional assay, the whole-blood–based activated clotting time, is widely used for point-of-care monitoring in interventional procedures, such as percutaneous coronary interventions and extracorporeal circulation. Most automated clot-based assays evolved out of mechanical detection of the formed clot with different determination methods, especially point-of-care tests.

ACTIVATED PARTIAL-THROMBOPLASTIN TIME

The aPTT is used to monitor unfractionated heparin anticoagulation when heparin is administered intravenously to achieve a target therapeutic range of 0.2 to 0.8 IU per milliliter for the treatment or prevention of thrombosis. There are different therapeutic ranges for patients with acute coronary syndromes and those with venous thromboembolism. Citrated patient plasma is recalcified, phospholipid is added, and the sample is then incubated with a contact-factor activator (kaolin, micronized silica, or ellagic acid). The time from recalcification to clot formation is measured in seconds.[6] Most aPTT assays used today rely on optical density to detect fibrin clot formation.[9] Results from different laboratories may vary owing to differences in the reagents used to determine the aPTT, including whether or not phospholipid components are added. The aPTT plateaus at high heparin levels, responding in a nonlinear or log-linear fashion to the high heparin levels used during invasive procedures.[10] In clinical practice, substantial changes in the aPTT can be associated with only minor changes in heparin level, especially when there is variation in the patient's levels of procoagulant proteins, such as factor VIII and fibrinogen, as can be found during acute inflammatory illness. A shorter aPTT in a patient with increased levels of factor VIII does not necessarily correspond to a loss of the effect of anticoagulation in response to unfractionated heparin.[11]

ACTIVATED CLOTTING TIME

The activated clotting time, a modification of the Lee–White clotting time, adds an activator, such as diatomaceous earth, kaolin, or glass beads, to whole blood to accelerate in vitro clotting by

activating the contact system. Unlike the aPTT, the activated clotting time has a range of sensitivity to high heparin levels — 1 to 5 IU per milliliter — that is linear and can therefore be used for patient monitoring during cardiopulmonary bypass and other interventional procedures in which high doses of heparin are used.[12] Several patient-related variables (e.g., the presence of acquired or congenital deficiency states and the use of inhibitors such as antiphospholipid antibodies) and several procedure-related variables (e.g., hypothermia after cardiopulmonary bypass and the practice of hemodilution) can prolong the activated clotting time independent of the effects of heparin.[13-15]

CHROMOGENIC ASSAYS

Chromogenic assays use synthetic chemical substrates that are cleaved by the activated factor. In chromogenic anti–factor Xa assays, citrated patient plasma is added to an excess of factor Xa; the presence of an anticoagulant that inhibits factor Xa will decrease its activity, producing a result that is inversely proportional to the anticoagulant level. Chromogenic anti–factor Xa assays are increasingly used to monitor unfractionated heparin, since these assays reflect only the plasma heparin level and are not influenced by variables that affect the aPTT, such as elevated factor VIII levels.[16,17] The anti–factor Xa is a quantitative assay used to monitor unfractionated heparin activity within the clinical range for which the aPTT is used.[18] Several chromogenic assays for heparin add an excess of exogenous antithrombin, which may prevent the identification of heparin resistance in patients with a low antithrombin level. Anti–factor Xa assays are often used to monitor heparin when standard functional assays of aPTT are inaccurate or misleading, as they would be in patients with congenital or acquired factor-deficiency states, disseminated intravascular coagulopathy, or antiphospholipid antibodies.[19]

MECHANISMS OF RESISTANCE

Identification of the cause of heparin resistance is based on both laboratory and clinical data. Multiple mechanisms are responsible for resistance and are related to the combination of the distinct properties of unfractionated heparin and patient-specific factors.

Biologic Molecules that Bind Heparin.

- Coagulation factors: antithrombin, factor VIII, factor Xa, fibrinogen, tissue-factor pathway inhibitor, von Willebrand factor
- Cell-adhesion proteins: integrins, L-selectin, P-selectin
- Chemokines: interleukin-8, platelet factor 4, tumor necrosis factor-α
- Extracellular matrix proteins: collagen, fibrinogen, laminin
- Glycoproteins: histidine-rich glycoprotein
- Lipoproteins: apolipoprotein E, lipoprotein lipase
- Microbial proteins
- Nuclear proteins: histones, transcription factors
- Viral proteins

NONSPECIFIC BINDING

Strong negatively charged heparin molecules bind to many proteins, including platelet factor 4, histidine-rich glycoprotein, lipoproteins, von Willebrand factor, factor VIII, and fibrinogen, as well as to monocytes, endothelial cells, growth factors, and nonendothelial surfaces, including intravenous tubing and extracorporeal circuit components (see box).[20,21] The longer polymers of unfractionated heparin facilitate binding to these substances and are responsible for the wide variability in patient response and dose requirements not seen with the shorter low-molecular-weight chains of heparin.[5]

ANTITHROMBIN DEFICIENCY

Deficiency of antithrombin (formerly referred to as antithrombin III) resulting from acquired causes is a commonly implicated cause of heparin resistance. Many disease states — or their treatments — are associated with reduced antithrombin levels, including liver disease, sepsis, acute disseminated intravascular coagulation, asparaginase use in patients with acute leukemia, and the use of extracorporeal circuits in cardiopulmonary bypass or ECMO.[22] Replacement recommendations are based on expert consensus, since to date no studies are known to have assessed the minimum level of antithrombin required for anticoagulant activity with heparin. Heparin use itself can result in decreased antithrombin activity, an effect that is seen primarily with unfractionated heparin and not with low-molecular-weight heparin.[23] Among patients undergoing cardiopulmonary bypass in whom high doses of heparin are used, antithrombin supplementation with purified or recombinant antithrombin has been effective in

restoring responsiveness to heparin in several clinical trials.[24,25] Antithrombin supplementation also improves results on anticoagulation assays, particularly the activated clotting time, and often makes it possible to decrease heparin doses, effects that have made supplementation a commonly used practice in cardiac surgery.[26,27] Patients with hereditary antithrombin deficiency may also be at risk for heparin resistance, but similar evaluation of the effects of antithrombin supplementation in these patients has not been performed.

PLATELET INTERACTIONS

Heparin can bind to platelets to transiently decrease platelet counts after platelet transfusions.[28] The administration of unfractionated heparin can also activate platelets and release platelet factor 4, a known heparin-binding protein. It can also trigger antibody formation and cause heparin-induced thrombocytopenia, which is itself a known explanation for heparin resistance.[29]

The use of antiplatelet agents can affect whole-blood clotting tests, including the activated clotting time, resulting in increased responsiveness to heparin, whereas agents or conditions that lead to rapid platelet activation can decrease the test's response to heparin, especially in patients who have undergone cardiopulmonary bypass. Platelet activity does not affect the aPTT or anti–factor Xa levels.[30]

ELEVATED LEVELS OF COAGULATION FACTORS

In patients with Covid-19 and other acute inflammatory states, increased levels of factor VIII and fibrinogen shorten the aPTT and are associated with the need for increased doses of unfractionated heparin to achieve target aPTTs, which suggests heparin resistance.[31] The increased levels of coagulation factors do not affect anti–factor Xa assays.

ANDEXANET ALFA

As a decoy factor, andexanet alfa reverses the anticoagulant effects of direct factor Xa inhibitors and the indirect anticoagulants fondaparinux, low-molecular-weight heparin, and unfractionated heparin.[32] A number of reports have noted that patients undergoing cardiac surgery who are treated with andexanet alfa to reverse the effects of apixaban or rivaroxaban have required excessive doses of unfractionated heparin to achieve targeted anticoagulation levels, which reveals a new potential cause of heparin resistance.[33,34]

COVID-19

The hypercoagulable state associated with Covid-19 has increased the use of unfractionated heparin in an overwhelming number of hospitalized patients, especially those in the intensive care unit, to prevent and treat thrombotic events, including the clotting that occurs in dialysis and in ECMO circuits.[3] The dose of heparin needed to prevent thrombosis and adverse outcomes in patients in various stages of illness due to Covid-19 is not known and is being actively investigated in randomized trials. This increase in heparin use has prompted a reexamination of the problem of heparin resistance. Multiple factors contribute to the thrombotic complications associated with Covid-19 and may result in heparin resistance, as has occurred with other types of infection, such as H1N1 influenza, in the past; these factors include elevated levels of factor VIII, fibrinogen, von Willebrand factor, and possibly antiphospholipid antibodies in the presence of endothelial injury.[35]

TESTING AND TREATMENT

COAGULATION TESTING

If heparin resistance is a concern, anti–factor Xa can be used to measure the heparin level. If the anti–factor Xa level is low, then the dose of unfractionated heparin should be increased to achieve the standard target of 0.3 to 0.7 IU per milliliter.[36] Although there is controversy regarding the question of whether the aPTT or the anti–factor Xa level provides the best information for monitoring the level of unfractionated heparin, in patients with Covid-19, the anti–factor Xa level may more accurately reflect unfractionated heparin activity, especially in those with substantial inflammation and elevated levels of fibrinogen and factor VIII, those whose baseline aPTT is elevated owing to the presence of antiphospholipid antibodies, or those in whom disseminated intravascular coagulation develops.[37,38]

ANTITHROMBIN SUPPLEMENTATION

Low antithrombin levels may cause heparin resistance, and preexisting heparin administration

can decrease circulating levels. However, data supporting indications of clinical benefit with antithrombin supplementation outside of cardiac surgery are lacking. In one small study involving patients with Covid-19, low antithrombin levels were not observed.[2]

DIRECT THROMBIN INHIBITORS

The direct thrombin inhibitors argatroban and bivalirudin are administered intravenously primarily in patients with heparin-induced thrombocytopenia, especially when percutaneous intervention or ECMO is needed.[39,40] These agents directly inhibit thrombin without requiring antithrombin and are frequently administered in critically ill patients, including those with Covid-19. The two agents are traditionally monitored with the use of aPTT or activated clotting time and are increasingly used in the ICU in patients with Covid-19. Although direct thrombin inhibitors act downstream of factor VIII to inhibit thrombosis, it is possible that elevated fibrinogen levels affect the use of aPTT in monitoring direct thrombin inhibitors, as occurs with its use in monitoring unfractionated heparin; unfortunately, no other assays for the monitoring of direct thrombin inhibitors administered intravenously have been approved for clinical use.

SUMMARY

Heparin resistance is often invoked when the aPTT does not increase as expected in response to a given dose of heparin. In patients with Covid-19 and those with other acute infections, substantial discordance is often noted in the results of functional clot-based assays and chromogenic-based, anti–factor Xa assays and is caused by the elevated levels of factor VIII and fibrinogen, which shorten the aPTT. However, unfractionated heparin can also bind to other acute-phase biologic molecules released in inflammatory states, which neutralizes its effects and results in the need to increase the heparin dose to achieve anticoagulation. With the use of both functional and quantitative tests, the clinical response to unfractionated heparin can be assessed to confirm circulating levels of heparin as part of a management strategy for situations in which heparin resistance is a concern.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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