CHAPTER 142

Principles of Anticoagulation in Extracorporeal Circuits

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ANTICOAGULATION INTERMITTENT HEMODIALYSIS HEPARIN CLOTTING MEMBRANE

There is a fine balance between hemostasis and hemorrhage in the human body, managed by a complex system of plasma, cellular, and endothelial factors.[1] *Coagulation* is the normal process occurring when vascular injury results in the formation of a fibrin clot; *thrombosis* refers to the pathologic formation of clot in response to injury, stasis, and hypercoagulability.[1] Intermittent and continuous dialysis therapies depend on adequate anticoagulation in their extracorporeal circuit (ECC) to maximize circuit and filter longevity, which will increase clearance and lessen costs and nurse time requirements. Insufficient anticoagulation results in decreased filter performance, clotting, and blood loss. Excessive anticoagulation leads to bleeding complications, which occur in 5% to 26% of treatments. Patients with acute kidney injury (AKI) are at risk for hemorrhagic and thrombotic complications. Bleeding can be caused by uremic platelet dysfunction or by the anticoagulants used for dialysis. The activation of coagulation during dialysis can lead to blood loss, estimated to 300 to 750 mL/yr in patients undergoing chronic hemodialysis.[2] This chapter deals with the principles of anticoagulation in the ECC, the disturbances that occur in critically ill patients with AKI, and the importance of the intrinsic pathway, platelet activation, and the fibrinolytic system in affecting ECC patency. This chapter addresses the circuit design, contributions of membrane/blood interaction, and how these factors may be modified, in addition to the anticoagulation techniques for intermittent hemodialysis.

Coagulation in Critically Ill Patients

Prevention of blood coagulation depends on a complex interaction of endothelial cells, blood cells, and plasma factors.[3] The balance between procoagulant and anticoagulant activity is a delicate one. This equilibrium is disturbed when blood is forced through an ECC, because the endothelial component is removed temporarily from the mix. As a result, the balance is shifted toward coagulation. There are numerous routes through which activation can occur, with the end result being platelet aggregation and formation of a clot. Shifting back the balance requires addition of an anticoagulant to the ECC, which then can favor bleeding. In critically ill patients with sepsis and multiorgan failure, the imbalance in the normal clotting mechanisms can be extreme, with activation of multiple inflammatory pathways and downregulation of anticoagulant pathways.[3,4] Activated monocytes and polymorphonuclear cells add to the coagulation cascade via increased expression of tissue factor and production of reactive oxygen species.

The processes of hemostasis and coagulation involve many functional areas, including platelet function, coagulation enzyme cascades, contact activation, natural anticoagulants, the endothelium, and fibrinolysis.[3] When blood is exposed to the foreign surface of an ECC, two principal mechanisms of thrombus formation traditionally have been considered important: the intrinsic pathway of blood coagulation and platelet adhesion and activation. The traditional theory postulates that the intrinsic pathway in ECC can begin with the "contact activation factors," such as factor XII, high-molecular-weight kallikrein, and prekallikrein, which occur more readily on a negatively charged surface. However, a recent study looking at blood

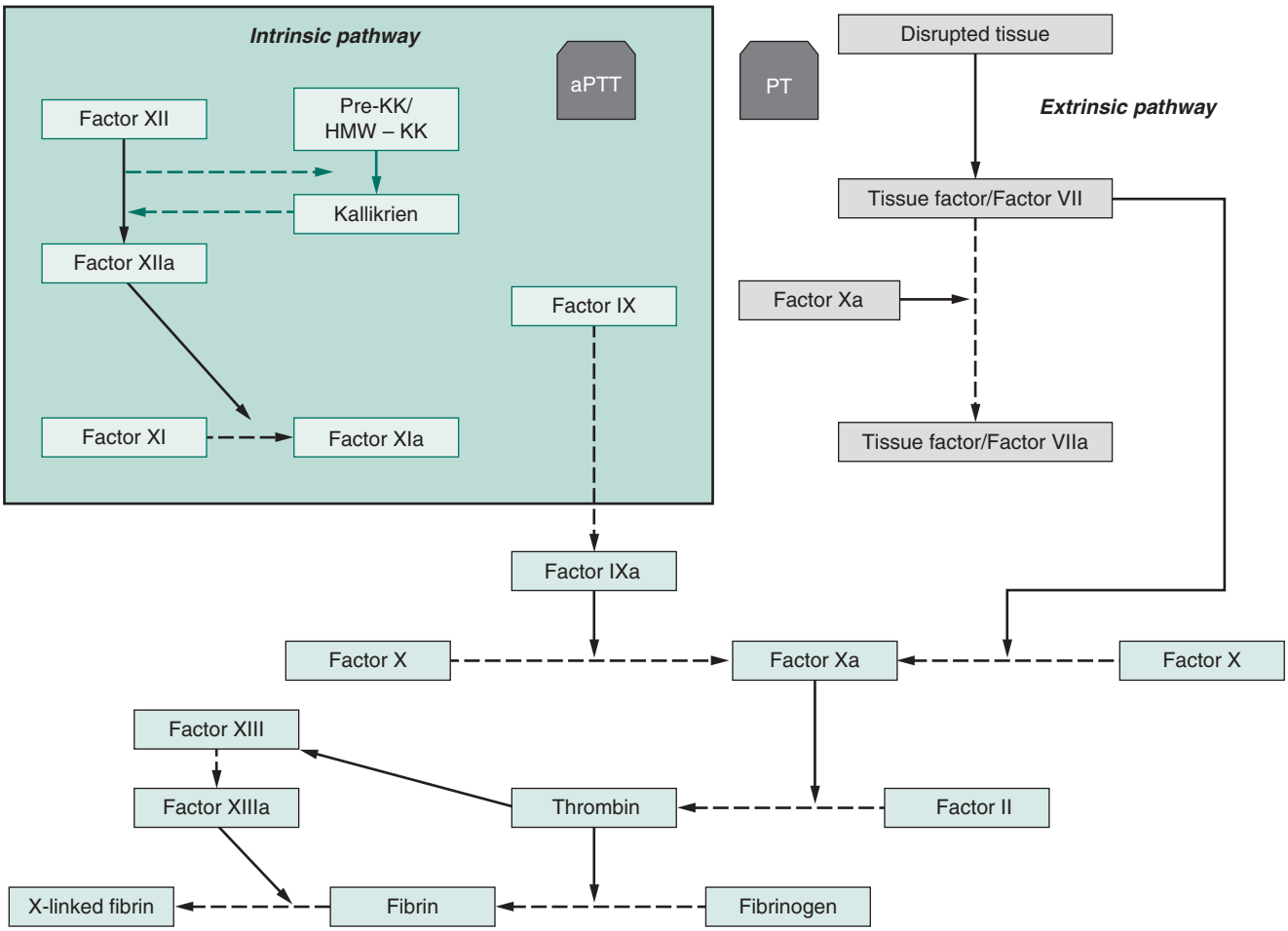

FIGURE 142.1 Schematic showing coagulation pathway the coagulation system is divided in three pathways: (1) the extrinsic pathway activated by tissue factor resulting from release from activated endothelial cells, macrophages, leukocytes, and platelets; (2) the contact activation pathway (intrinsic pathway) triggered by activation of factor XII and kallikreins; (3) and the final common pathway. *aPTT,* Activated partial thromboplastin time; *HMW,* high molecular weight; *KK,* kallikrein; *PT,* prothrombin time.

parameters in continuous venovenous hemodialysis (CVVH) circuits without heparin did not demonstrate any change in plasma levels of factor XIIa-C1 inhibitor complex or the kallikrein-C1 inhibitor complex, findings that would argue against significant involvement of contact activation of the intrinsic pathway in clotting in CVVH.[5] These results were in keeping with those of a previous study, which did not find an increase in contact activation factors in a system using polyacrylonitrile membranes and systemic heparinization.[6] The generation of thrombin can also start with the activation of factor X, either on the surface of activated platelets or by the integrin receptor membrane attack complex 1 (MAC-1) on leukocytes.[7] However it is initiated, it then proceeds through an amplifying series of enzyme reactions, is moderated by multiple negative and positive feedback loops, and culminates in the production of thrombin and the formation of a stable, cross-linked fibrin clot (Fig. 142.1).

Platelet Dysfunction

Many abnormalities have been described in uremic platelets, including decreased thromboxane A_2, abnormal intracellular calcium mobilization, increased intracellular cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), and abnormal aggregability.[8,9] Platelets undergo transient morphologic changes secondary to circulating through the ECC. These changes are consistent with primary, reversible aggregation and activation.[3] Platelet activation can occur because of interaction with the activated clotting cascade (e.g., thrombin) or from contact with the ECC. Platelet activation and adhesion in the ECC and on dialysis membranes do not require von Willebrand factor (vWF). The reaction either occurs directly on the foreign surface or is promoted by various adsorbed plasma proteins, including fibrinogen.[10]

Once platelet adhesion occurs, the platelet activation sequence follows, which also can be initiated by thrombin. The important stages in this sequence include shape change, aggregation, secretion of thromboxane B_2 (which is involved in activating other platelets), elaboration of contents of alpha granules and dense granules, platelet surface membrane modification, and, ultimately, platelet contraction and fusion. The platelet membrane modification provides a surface on which procoagulant reactions are facilitated. Platelets contribute substantially to thrombus formation in the ECC, and increased levels of thromboxane B2 and factor III thromboglobulin can demonstrate their activation during dialysis.[11] The increase in thromboxane B_2 is higher in heparin-free dialysis compared with heparin dialysis.[12] Adherence can occur quickly when platelets are exposed to the ECC foreign surface. Multiple studies have shown that patients with a higher baseline platelet count

require more heparin to achieve comparable filter life and that lower platelet counts are associated with a decreased risk of filter clotting.[13–15]

Fibrinolytic System

The fibrinolytic system has as its main enzyme plasmin, an active fibrin protease that is produced from plasminogen. There is an increase in fibrinolytic activity during dialysis, secondary to an increase in the endothelial release of tissue plasminogen activator (tPA). It is believed that the blood contact with the dialysis membrane provides the stimulus for this reaction. There is no evidence that this response limits clotting in the ECC. However, in the study by Bouman already mentioned, baseline levels of factor XIIa-C1 inhibitors and kallikrein-C1 inhibitor complexes were lower in the subgroup of patients with early increased thrombin generation, which would be consistent with decreased fibrinolysis. Confusing these results was the presence of a trend toward increased levels of plasmin-antiplasmin complex (normally associated with increased fibrinolysis) in the patients with early clotting. The authors hypothesized that these levels of plasmin-antiplasmin complexes may have been more a marker of coagulation than of fibrinolytic activity. Alternatively, it was speculated that these same elevated complex levels may have reflected a higher baseline thrombin generation, which then could have activated endogenous anticoagulant protein C and resulted in less coagulation in the CVVH circuit.[5] Factor XIIa and kallikrein are believed to be important in the activation of fibrinolysis. Factor XII can activate fibrinolysis by activating prekallikrein (and with subsequent urokinase-type plasminogen activator), causing the prekallikrein-driven generation of kallikrein (leading to increased tPA), and by directly activating plasminogen. Activated protein C also promotes fibrinolysis because of its inhibitory effect on plasminogen activator inhibitor. Thus decreased levels of activated protein C with sepsis may tip the balance toward coagulation; however, this effect may be offset by the consumption of coagulation factors associated with disseminated intravascular coagulation (DIC), which would favor bleeding.[3]

Extrinsic Pathway

The extrinsic pathway begins with factor VII, which depends on the release of the tissue factor thromboplastin to have an effect on its natural targets, factors IX and X. Thromboplastin is released from injured vessel walls and is expressed by activated monocytes, usually in response to endotoxins, cytokines, hypoxia, advanced glycation end products, growth factors, and oxidative stress.[16] However, the extrinsic pathway and its mechanisms have not been found to be important in the formation of ECC thrombi (see Fig. 142.1).

Natural Anticoagulants

Natural anticoagulant systems are in place and include antithrombin III (ATIII), a serine protease inhibitor. Its actions, which are potentiated by heparin and heparin sulfate (located in vessel walls), include inhibition of thrombin; factors Xa, IXa, XIa, and XIIa; and kallikrein. Multiple studies have shown subnormal levels of ATIII in critically ill patients, and low levels have been associated with filter failure.[17] A retrospective study of septic, ATIII-deficient patients undergoing continuous renal replacement therapy (CRRT) showed reduced filter clotting when heparin anticoagulation was supplemented with ATIII.[18] Protein C, in reactions catalyzed by protein S, inactivates factors Va and VIIIa, thus limiting thrombin generation. Protein C is activated by the binding of thrombin to vascular endothelial-associated thrombomodulin.[3] Decreased levels of activated protein C with sepsis may tip the balance toward coagulation (however, as mentioned previously, this coexists with DIC-associated consumption of coagulation factors, which favors bleeding). In a study of patients with severe sepsis undergoing CVVH, treatment with continuous intravenous recombinant human activated protein C removed the need for additional anticoagulation. Filter life compared favorably with that observed with the use of unfractionated heparin.[19]

Hypercoagulable State

A hypercoagulable state exists to some extent secondary to uremia. Patients with end-stage renal disease and those who are critically ill with acute kidney injury/uremia have intrinsic clotting system activation. They have increased levels of procoagulant factors VII and VIII, decreased levels of coagulation inhibitors such as ATIII and proteins C and S, and impaired fibrinolysis. Dialysis can be associated with the release from endothelial cells of other procoagulant substances such as vWF, 6-keto-prostaglandin F_{1a}, and tPA.[11] There is also a large dialysis-associated increase in the levels of prothrombin and thrombin-antithrombin complexes (TAT), even more so when anticoagulation is suboptimal or withheld.[20]

Contributions to Clotting

Catheter

The length and internal diameter of dialysis catheters, as well as any kinks, can affect blood flow, promoting clotting. Position-related changes in blood flow rates can lead to clotting. Femoral lines have been shown in some studies to increase chances of clotting.[18] Large-bore, small-length catheters are preferable for arteriovenous, non-pumped systems, to allow a high blood flow rate. In pumped systems, the size of the catheter depends on the site of insertion (internal jugular, femoral, or subclavian), and choosing an appropriate length is key to maintain circuit patency and reduce recirculation. For example, femoral catheters shorter than 20 cm had significantly greater recirculation (26.3%) than those longer than 20 cm (8.3%) as shown by Little et al.[21,22] Strategies for preventing intraluminal thrombosis include saline flushing of catheter lumens at the beginning and at the end of each session, anticoagulant interdialytic locking using heparin or sodium citrate, and carefully closing the clamp after the anticoagulant lock has been placed.[23] There seems to be no difference between coated (GamCath Dolphin Protect 1320 coated catheter, Gambro, Hechingen, Germany) and standard temporal catheters in terms of mean circuit life, but a lower dose of heparin was required when a coated catheter was used.[24]

Circuit, Tubing, and Membrane

Improving the laminar flow configuration, minimizing stagnant areas in dialyzer headers, keeping tubing lengths short, avoiding dependent loops, minimizing reservoir

volumes, and decreasing air-blood interface in traps all can help prevent clotting.[3] The air-blood interface in the bubble trap can be the initial site for clotting. However, direct heparin injection into the air trap was not found to improve circuit life, although the dose used may have been insufficient.[25] Recently, an experimental model was developed to test biochemical markers of coagulation activation at various times and sites in a dialysis circuit. The authors measured TAT complexes and found that the blood lines alone, without a dialyzer attached, did not activate significantly coagulation during the first 20 minutes of circulation; in contrast, when a dialyzer was included in the system, only 5 minutes of circulation was needed to activate coagulation.[26]

Pumped ECC systems have the advantage of ensuring more consistent blood flows, regardless of the patient's blood pressure, which can contribute to circuit life. In non-pumped systems such as continuous arteriovenous hemofiltration (CAVH), membrane geometry may be important, because parallel-plate dialyzers result in greater urea clearance than hollow-fiber configurations in this setting. Parallel plates have less flow resistance, which may result in less unstirred layers at the membrane-blood interface and potentially less clotting. However, in pumped systems such as CVVH, flat-plate dialyzers were not shown to have an advantage over hollow-fiber designs in terms of prolonging circuit longevity, and there was an insignificant trend favoring the latter.[25]

The membrane represents approximately 95% of the blood contact area in the circuit. The perfect nonthrombogenic membrane material remains elusive. Membrane failure occurs secondary to red blood cell, platelet, and protein coating of the membrane. The filter can represent the point in the ECC at which the flow is the slowest, creating an environment favorable to red blood cell aggregation, especially if macromolecules such as fibrinogen and artificial plasma substitutes are present and facilitate the creation of molecular bridges.[3,27] However, when experiments using membranes with larger surface areas were carried out, with the idea that the larger the membrane, the longer the period of time before saturation and failure, no difference was observed in circuit life between membranes of 0.75 versus 1.3 m^2.[25]

The degree of biocompatibility may affect the thrombotic potential of a membrane. Cellulosic and synthetic polymer membranes activate the complement system, but synthetic membranes adsorb the activated products more readily, leading to less overall stimulation of the system.[28] It has been difficult to determine whether thrombogenicity differs between cellulose and synthetic membranes; the results have been contradictory, possibly because of the variety of anticoagulation methods chosen. Polyacrylonitrile (PAN) membranes have been found to be associated with a higher clotting frequency than polyamide membranes in a number of studies.[14,29] This may have to do with the high negative charge of a PAN membrane, which has been shown to correlate with the degree of activation of Hageman's factor, kallikrein, and bradykinin. In keeping with this hypothesis, a study comparing polyamide and PAN membranes showed that the latter was associated with a greater effect on the levels of TAT.[30] Membranes with higher porosity may lead to removal of the anticoagulant (e.g., r-hirudin), whereas an unmodified cellulosic membrane may result in its accumulation.

Some membranes can be precoated with heparin (e.g., AN69-ST [Hospal, Lyon, France], Hemophan [Akzo, Wuppertal, Germany]), which allows circuits to remain patent longer with either no anticoagulant or with reduced anticoagulant.[31] Grafting of polyethyleneimine onto an AN69 PAN membrane decreases surface electronegativity, and the surface then repels cationic plasma molecules, including high-molecular-weight kininogen. Conversely, strongly anionic heparin is bound tightly to the modified membrane and is included in the blood-derived membrane coating the synthetic polymer.[31] Multiple studies have looked at the increased biocompatibility of heparin-coated surfaces and have found a decreased adsorption of fibrinogen, diminished platelet activation and aggregation, decreased complement activation, and less formation of platelet-leukocyte aggregates.[32–34] In a recent retrospective study, the combination of a heparin-grafted AN69ST dialyzer with a citrate-enriched dialysate found no differences in the amount of ultrafiltation and the prescribed treatment time between dialysis sessions using this strategy and sessions were anticoagulation was employed. The effective blood flow was significantly higher in patients with no anticoagulation.[35] A single-center, prospective, randomized, double-blind controlled trial with crossover design comparing filter survival with the AN69ST membrane and the original AN69 membrane in 39 patients treated with CVVH without additional heparin found no differences in terms of filter survival.[36] Similar results were found in a more recent study with similar design.[37]

Low-molecular-weight heparin (LMWH)–coated circuits also were shown to be effective, without additional anticoagulation, in intermittent hemodialysis patients with normal coagulation parameters.[34] This study confirmed the increased biocompatibility of heparin-coated surfaces, although TAT levels rose after the fourth hour of dialysis if no additional dalteparin was given. There remains some controversy as to the relative importance, in regard to hemocompatibility, of the interaction of surface-bound heparin with ATIII (and subsequent inactivation of key coagulation factors), compared with the adsorption and cleavage of plasma proteins with these coated membranes.[32] Studies have shown that, to produce valid results, in vitro experiments evaluating the thrombogenic potential of membranes using platelet adhesion and protein adsorption measurements always should use nonanticoagulated blood.[33]

The optimal life requirement of a filter used for CRRT remains controversial. Some studies show that high-flux membranes become maximally coated with proinflammatory molecules by 24 hours, and if attempts are made to extend the life beyond that point, these molecules are released back into the circulation.[38] A low dialysate pH can contribute to dialyzer clotting, although data are scarce since the initial mention of this problem in 1977.[39]

Blood Flow

In pumped systems, the pump speed setting does not necessarily reflect actual delivered blood flow. A recent study using a customized miniature Doppler flow probe (mounted on the tubing before the filter) coupled to a computer allowed for flow wave analysis during CRRT.[40] The results showed a high frequency of flow reductions in the medium range (34% to 67% reduction) in the diastolic phase (the trough period after the forward stroke of the roller cam), which were not detected by the machine's alarms. The authors found a strong inverse correlation between the frequencies of these medium-level flow reductions and filter life. The correlation was even stronger than the correlation with standard anticoagulation variables. The reductions in flow were associated with backward flow of blood and stasis, which, in the setting of continued ultrafiltration, would result in further hemoconcentration across the filter, contributing to clotting. In addition, shear stress could be increased, and stasis could increase the duration of the

interaction between blood and membrane, leading to prolonged exposure to the activated coagulation cascade. The authors speculated that possible triggers to these flow reductions may include catheter kinking or dysfunction and changes in patient position, such as sitting up with subsequent underfilling of neck veins. Any degree of catheter dysfunction would contribute to these low blood flows.

Effects of Ultrafiltration

Low blood flow rates and excessive ultrafiltration can lead to detrimental increases in filtration fraction, resulting in local increases in the hematocrit at the level of the dialyzer membrane, which leads to increased clotting. These result from not only the alterations in flow characteristics (rheologic effects) but also the effect of convective mass transfer. In an experiment using polysulfone dialyzers, this variable was higher with hemofiltration/hemodiafiltration than with high-flux hemodialysis because of the greater total ultrafiltration volume, and resulted in increased procoagulatory activity, as measured by TAT (associated with intravascular thrombin formation) and D-dimer levels.[41] Although this finding was not associated with increased filter clotting risk, the increased procoagulatory profile was believed to be secondary to the fluid shear stress generated by the filtration of large amounts of fluid from the blood, with the platelets at the periphery being more affected, and subsequent activation of the coagulation system.[42] Maintenance of filtration fractions of 20% or less is optimal. This can be accomplished through the use of prefilter dilution and adjustments in blood flow rates.[43]

Predilution Versus Postdilution

Predilution reduces the viscosity of the blood, which can help prevent buildup of cellular sludge at the level of the membrane. Several studies have demonstrated increased circuit life with predilution versus postdilution.[44] One such study showed a median circuit life of 18 versus 13 hours, and another, more recent, study achieved durations of 45.7 versus 16.1 hours with predilution versus postdilution, respectively.[45,46] A recent crossover study did not demonstrate such a difference, but it was limited by small sample size.[9] However, the study did demonstrate that postdilution resulted in a higher number of filters clotting within the first hour—two to seven, as opposed to none when predilution was used.

Use of Erythropoietin

Erythropoietin has been found to decrease bleeding time, to increase the levels of vWF and fibrinogen, and to reduce the levels of ATIII and protein C.[47–50] It has been blamed for contributing to increased thrombosis. A direct effect on platelets, in terms of increased adhesion and aggregability, also has been demonstrated in hemodialysis patients after 20 weeks of therapy.[51] It is possible that the effect is dosage related, because higher doses were found to be associated with lower prothrombin fragment concentrations.[20]

Hematocrit

Hematocrit is the most important determinant of viscosity, and a higher hematocrit can increase the chances of thrombosis. Exogenous erythropoietin can add to this risk, apart from its effects on platelets. Blood transfusion into the circuit proximal to the filter can lead to clotting and should be avoided, especially if no anticoagulant is being used. The advantages of the better flow that mild anemia may provide must be balanced against the risks of decreased oxygen delivery to the tissues.

ANTICOAGULATION TECHNIQUES FOR INTERMITTENT HEMODIALYSIS

In this section we review some of the anticoagulation strategies used in patients treated with intermittent hemodialysis (IHD) and with CRRT, the use of citrate is discussed in Section 25.

Unfractionated Heparin

Unfractionated heparin (UFH) is a member of the glycosaminoglycan family (molecular weight 5–100 kDa); it is the most widely used systemic anticoagulant for renal replacement therapies. It is composed of repeating units of sulfated D-glucosamine and D-glucuronic acid.[52] UFH works primarily by biding to ATIII and inactivating the serine protease cascade (predominantly IIa, and also IXa, Xa). Some smaller UFH molecules are cleared renally so that they have an increased half-life and can result in anticoagulant effect but with a normal aPTT.[53,54]

UFH has a short action time of approximately 3 to 5 minutes with a normal half-life of 30 to 120 minutes, which can increase up to 180 minutes in AKI patients.[55] UFH is a highly charged large molecule that can be absorbed onto plasmatics; thus it is important to dilute UFH to minimize adsorption and to improve mixing with the blood before entry into dialyzer. For IHD, a loading dose of 10 to 20 U/kg followed by a maintenance infusion of 10 to 20 U/kg/hr, then terminating approximately half an hour before the end of the dialysis session is recommended.[56] Prolonged filter life without increased risk of bleeding has been described when the systemic aPTT was between 35 to 45 seconds, whereas the dosage of UFH was not a predictor of circuit survival.[29] UFH can be monitored using the activated partial thromboplastin time ratio (aPTTr) with a target of 1.5 to 2.5; for patients at risk of bleeding loading dose must be reduced by 50%. An additional small bolus could be given if clots are noted in the circuit aiming for an aPTT of 80 seconds. An alternative regime is to omit the loading dose and start with a low-dose infusion of 15 UI/kg/hr.[57] UFH could be neutralized with protamine sulphate in case of active bleeding at a dose of 1 mg/1000 UI of heparin.[58]

Regional Unfractionated Heparin

This anticoagulation strategy was designed to maximize circuit life while minimizing systemic heparin exposure in patients with high risk of bleeding. Patients received a constant infusion of UFH prefilter along with a constant infusion of protamine postfilter. A proposed regime consists of a loading dose of 10 to 20 UI/kg followed by an infusion of 3 to 20 UI/kg/hr as a maintenance dose prefilter and protamine infused at 1 mg/100 UI postfilter.[59] The aPTT should be monitored pre- and post-UFH infusion and then postprotamine to allow adjustment to the infusions, and

as such it has been difficult to develop a standard protocol.[60] Accumulation of protamine can cause anaphylactoid reactions and precipitate hemorrhage. The Kidney Disease: Improving Global Outcomes (KDIGO) group reviewed the evidence for regional UFH and advised not using it for patients at high risk of bleeding because of the longer half-life of UFH and the risk of rebound and accumulation of heparin.[21]

Low-Molecular-Weight Heparins

There are several different low-molecular-weight heparins (LMWH) in clinical use (e.g., enoxaparin, nadroparin, dalteparin, reviparin), and each is different with varying half-lives, molecular weight, and pharmacokinetics. LMWH have a longer half-lives, less nonspecific biding to endothelium, plasma proteins, and platelets as compared with UFH. LMWH cause less platelet and leukocyte aggregation and fibrin deposit within the filter.[61]

For IHD a single loading dose administered as a bolus may provide adequate anticoagulation because LMWH are excreted renally at a 50% reduction of the bolus administration. This dose is advised for patients at high risk of bleeding: for example, reducing the dose of enoxaparin from 0.8 to 1 mg/kg to 0.4 to 0.5 mg/kg (aiming for anti-Xa activity of 0.4 IU/mL). It is recommended not to use longer half-life heparins because they may increase the risk of bleeding as a result of accumulation. LMWH with shorter half-lives, such as tinzaparin (half-life of 5 hours), are preferred for IHD.[62]

Heparinoids

Danaparoid acts predominantly on anti-Xa via ATIII but also has some inhibitory effect on factor IIa. This additional action inhibits platelet factor 4 (PF4) binding to platelets and therefore prevents immune complex-PF4 formation, preventing platelet destruction by heparin-induced thrombocytopenia (HIT) antibodies. Because half-life of danaparoid is prolonged in patients with AKI (30 hours), a single bolus dose can provide effective anticoagulation for IHD (2500 U or 35 U/kg, then adjusting the dose according to anti-Xa activity monitoring).[63]

A natural heparinoid (dermatan-sulphate) that binds to heparin cofactor II and acts predominantly by inactivating factor IIa has been used for IHD as either as a single dose of 6 mg/kg followed by an infusion of 0.65 mg/kg/hr.[64] However, as some filters adsorb dermatan-sulphate, a greater dose may be required with polyacrylonitrile filters.

Synthetic heparinoid (fondaparinux and idraparinux) is now available. Because the half-life is 17 to 21 hours they can be given as a single dose before IHD from 1.5 to 5.0 mg, aiming for a target anti-Xa activity between 0.2 and 0.4 U/mL postdialysis.[65]

Direct Thrombin Inhibitors

First-generation recombinant hirudin (r-hirudin) and second-generation argatroban are the preferred anticoagulants for patients with HIT.[66] They act by directly inhibiting free and clot-bound thrombin without cross-reaction to heparin factor 4 antibodies.[67] R-hirudin has a prolonged half-life from 1 to 2 hours and up to 50 hours in anephric patients. Argatroban, on the other hand, which is metabolized hepatically, has a shorter half-life of approximately 35 minutes and is cleared insignificantly by high-flux hemodialysis of hemodiafiltration.[68,69] The recommended dose for r-hirudin is a bolus of 0.03 to 0.4 mg/kg, depending on the filter used and for argatroban either a single loading dose of 250 μg/kg followed by an infusion of 2 μg/kg/min, then stopping 1 hour before the end of dialysis or repeated boluses of 250 μg/kg.[69,70] One advantage of argatroban is that it can be monitored using aPTT, aiming for an aPTT of 1.5 to 2.5 times the baseline (reduced dosages are required for liver failure patients).

Prostanoids

Prostacyclin (PGI_2) and other prostanoids are natural anticoagulant and antiplatelet agents; they reduce platelet aggregation and adherence to vessels walls. Prostanoids have a short half-life (2 minutes) as vasodilators, but the antiplatelet effects could last 2 hours.[71] Prostanoids could be used alone or in combination with UFH. The usual standard infusion dosage is 2.5 to 10 mg/kg/min, titrating the rate up from 0.5 ng/kg/min before starting IHD to avoid hypotension.[72] Prostanoids are cleared during renal replacement therapies (about 40%). Because they do not act directly on the anticoagulation system they cannot be monitored with a standard laboratory test.

Side Effects of Anticoagulants

Heparin binds to PF4 and forms an epitope. This site can trigger the formation of antibodies in 20% to 30% of patients, with 1% to 3% of patients developing clinical thrombocytopenia and heparin-induced thrombocytopenia.[73] Two thirds of these patients will develop thromboembolic manifestations. Heparin does block thrombin generation, interactions of platelets, leukocytes, and factor XII with foreign surfaces; indeed, it can facilitate these interactions.[3] Heparin also can lead to consumption of ATIII. Other adverse reactions to heparin include allergic reactions, pseudopulmonary embolism syndrome resulting from heparin-associated antibody, and profound hypotension secondary to bradykinin and C5a generation.[56]

The LMWH enoxaparin does not cause endothelial cell activation and release of cell adhesion molecules.[41,74] It is believed to reduce monocyte adhesion to vascular endothelial cells by inhibiting lipopolysaccharide-induced E-selectin expression as well as intercellular adhesion molecule 1 (ICAM-1) expression induced by tumor necrosis factor.[74] LMWH has a reduced incidence of thrombocytopenia. In cases of hemorrhage, fresh frozen plasma and activated factor VII may be required, because protamine may not be effective.

The major drawback with PGI_2 is systemic hypotension requiring fluid or vasopressor resuscitation in approximately 15% of cases.[72]

Endothelium

Normally, the vascular endothelium performs anticoagulant and antithrombotic functions. Endothelial cells produce heparin sulfate, which binds ATIII and potentiates its protease inhibitor activity. This results in excellent local control of thrombin generation. The various factors produced by or associated with the endothelium are numerous. Those with procoagulant activity include plasminogen activator inhibitor, tissue factor, and vWF. The endothelium contributes

anticoagulant activity through ATIII, glucose aminoglycans, nitric oxide, prostacyclin, protein S, thrombomodulin, tissue factor pathway inhibitor, and tPA. Disruption of normal endothelial cell function, such as occurs in sepsis and inflammatory disorders, can decrease the anticoagulant and fibrinolytic activity and shift the balance toward clotting.[3]

CONCLUSION

Patients with renal dysfunction are at risk for thrombosis secondary to being in a hypercoagulable state. If they require dialysis, the risk is increased because of blood and circuit interactions. On the other hand, they are at risk for hemorrhage secondary to the effects of uremia on platelet function, as well as the effects of any anticoagulant used during their treatments. Whether and when circuit clotting ultimately occurs depends on a balance among these factors and other contributing factors from the patient's clinical situation, such as the presence of sepsis or DIC. The goal of the nephrologist remains prolongation of ECC life in the safest manner possible for the patient. Precoating of membranes with UFH or LMWH seems to render them more biocompatible. The use of these membranes, as well as the smart use of activated protein C in certain situations, may allow for less clotting with reduced doses of systemic heparin. Use of replacement fluids in prefilter mode and avoidance of excessive ultrafiltration and blood flow reductions also can lead to improved circuit patency. Although UFH remains the most commonly used anticoagulant, there are now an increasing number of other options; these include LMWH, heparinoids, direct thrombin inhibitors, prostanoids, and serine protease inhibitors. When choosing the type of anticoagulation for renal replacement therapies in AKI, the clinician must consider several aspects, such as the half-life, how to monitor, how to reverse the effect in case of severe bleeding, if the anticoagulant is dialyzable or not, and how to balance the benefits and risk of each drug.

Key Points

1. Intermittent and continuous dialysis therapies depend on adequate anticoagulation in their extracorporeal circuit to increase circuit and filter life.
2. Insufficient anticoagulation results in decreased filter performance, clotting, and blood loss; on the other hand, excessive anticoagulation leads to bleeding complications, which occur in 5% to 26% of treatments.
3. There are several factors that must be considered and assess to improve circuit patency, such as type of catheter and membranes use, pre- versus post-dilution techniques, and blood flow.
4. Use of replacement fluids in prefilter mode and avoidance of excessive ultrafiltration and blood flow reductions also can lead to improved circuit patency.
5. Anticoagulants can delay or prevent circuit clotting; their use should be based on a careful assessment of the likely risk and benefits in a given patient.

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