Anticoagulation in Patients With Acute Renal Failure Treated With Continuous Renal Replacement Therapies

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Although continuous renal replacement therapy (CRRT) provides greater cardiovascular and cerebrovascular stability compared to standard intermittent hemodialysis and/or hemofiltration, to provide adequate solute removal, the CRRT circuit must function continuously. Patients with acute renal failure are usually prothrombotic, with activation of the contact coagulation cascade and reduction in the natural anticoagulants. Thus clotting within the extracorporeal circuit can be problematic. Coagulation requires activation of the coagulation protein enzymes, calcium, platelets, and contact with phospholipid cell surface or, in the case of the CRRT circuit, plastic tubing and the dialyzer membrane. This results in a platelet plug stabilized by cross-linking strands of fibrin. Anticoagulation regimes are either directed at trying to prevent contact activation of clotting factors and platelets or the administration of agents designed to prevent coagulation by blocking the coagulation cascade or platelet activation.

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Key words

Acute renal failure, hemofiltration, coagulation cascade, anticoagulation, fibrinolysis, low molecular weight heparins, heparinoids

Introduction

Continuous renal replacement therapies (CRRTs) are increasingly used in the management of patients with acute renal failure in the intensive care and high-dependency settings. The gradual removal of plasma water and azotemic toxins during CRRT provides a major advantage over intermittent dialysis techniques. However, to achieve adequate control of azotemia, the CRRT extracorporeal circuit must function continuously, 24 hours a day, day after day (1). Anticoagulants are, therefore, routinely used to help maintain and maximize the life of the CRRT circuit by aiming to prevent coagulation primarily within the hemofilter/hemodialysis membrane. The duration of the CRRT circuit has been shown to be dependent on blood flow, platelet count, and hematocrit. Inadequate anticoagulation leads initially to reduced efficiency of the CRRT circuit in terms of both solute and fluid clearance, due to coagulation within individual membrane fibers, followed by premature hemofilter/hemodialysis membrane clotting. Continued CRRT circuit clotting leads to blood loss, loss of treatment time, and thereby inadequate treatment, and additional financial costs and nursing time in setting up a new CRRT circuit. Excessive anticoagulation, on the other hand, may result in bleeding complications, usually minor, with a reported incidence ranging from less than 5% to 26% of treatments (2,3), on occasion proving fatal (4).

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Coagulation pathways in acute renal failure

Coagulation pathways

Traditionally the clotting cascade has been divided into the intrinsic system, with activation of factor XII at the endothelial or foreign surface, and the extrinsic system, due to endothelial damage with exposure of the subendothelial matrix and the release of so-called "tissue factors" (Figure 1) (5). Apart from factor XIII, they are serine proteases, related to trypsin. Contact activation of factor XII leads to the conversion of high molecular weight kallikreins and prekallikrein to active kallikrein, which itself feeds back to increase the conversion of factor XII to active factor XII, so acting as a multiplication factor, at the start of the intrinsic, or contact, clotting cascade. Activation then proceeds down the cascade, with the activation of factors XI and IX. The activation of factor X requires not only activated factor IX, but also factor VIII, calcium ions, and phospholipids. Platelets play a key role at this stage and also in the conversion of prothrombin to thrombin, by providing calcium and their surface membranes as the predominant source of phospholipids. Activated factor X is then involved in the activation of prothrombin through to thrombin, with the reaction requiring factor V, calcium, and phospholipids. The half-life of activated thrombin in plasma is very short. However, cleaved fragments of prothrombin, known as prothrombin fragments I and II (PFI and PFII), which are stable, can be measured and used as a marker of the amount of intravascular coagulation which is occurring. Thrombin converts fibrinogen to fibrin monomers, and by activating factor XIII, the fibrin monomers become stabilized by cross linkage to form X-linked fibrin (Figure 1).

Endothelial damage results in the release of "tissue factor," which complexes with factor VII. This complex can either directly activate factor X or, following activation by activated factor X, can convert both factor IX and factor X

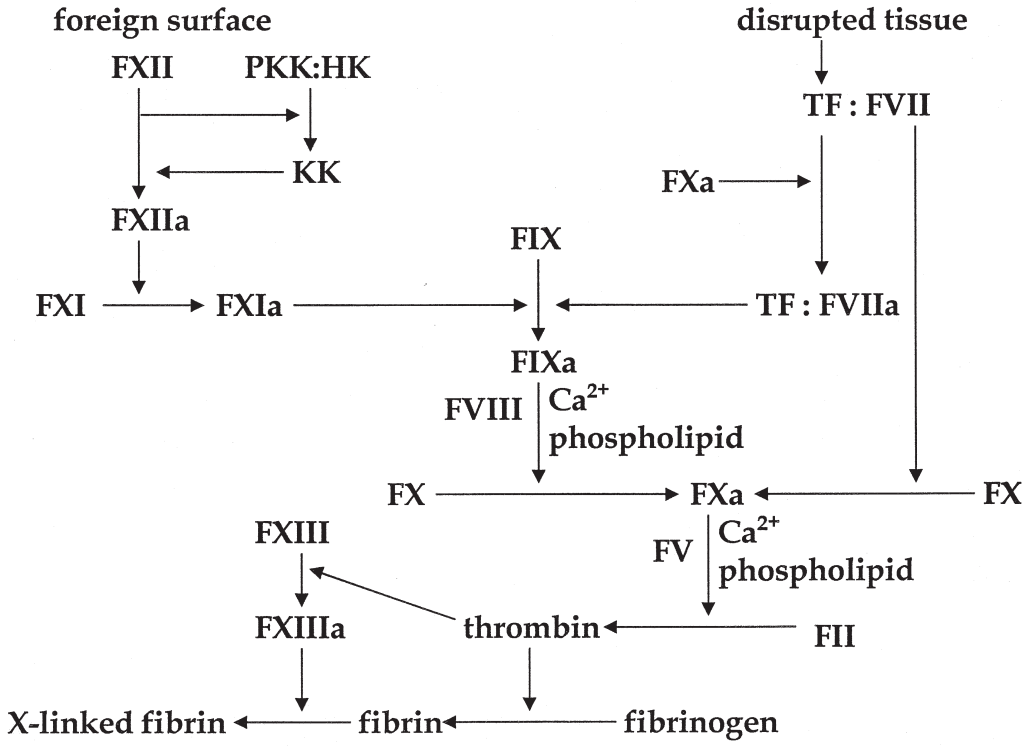

FIGURE 1 Extrinsic and intrinsic (contact) coagulation pathways. PKK = prekallikrein; HK = high molecular weight kallikrein; KK = kallikrein; TF = tissue factor.

to their active forms. This reaction with factor X acts as the extrinsic system multiplier.

Natural anticoagulants

Antithrombin III is a protease inhibitor essential for the action of heparin. It is predominantly synthesized in the liver and can bind to a variety of coagulation factors (Xa, IXa, XIa, XIIa, and kallikrein); most importantly, it binds to thrombin to form thrombin-antithrombin III complexes (TATs), so preventing the activation of fibrinogen (Figure 2). These TATs can be measured and used as a marker of intravascular coagulation. Heparin exerts its action by binding to the TAT complex. There are heparin-binding sites for both thrombin and antithrombin III on the heparin molecule. Heparin binding to antithrombin III causes a conformational change that opens up the thrombin-binding site, thus accelerating the binding of thrombin to antithrombin III, so preventing the actions of thrombin. Unfractionated heparin is a mixture of molecules of varying chain length; thus some may have both binding sites and others only the thrombin-binding site or the antithrombin III site alone. This has led to the development initially of low molecular weight heparins and more recently the synthetic heparinoids to obtain reproducible anticoagulant activity. Antithrombin III can also bind to activated factor X, which has no heparin-binding site. Other natural inhibitors of thrombin include heparin cofactor II and α_2-macroglobulin, whereas vitronectin, platelet factor 4 (PF4), histidine-rich glycoprotein, and serum amyloid P related protein can all compete with the serpins (serine protease inhibitors) to prevent heparin binding and thrombin inactivation.

Antithrombin III may also have some activity in both the intrinsic pathway, by blocking the activation of factor XII by degrading kallikrein, and also in the extrinsic pathway, by blocking the activation of factor IX (Figure 2) (5). Antithrombin III concentrations may be reduced in several conditions ranging from hepatic disease to disseminated intravascular coagulation, nephrotic syndrome, protein-losing enteropathy, following major surgery, acute thrombosis, and drugs, including heparin, estrogens, and asparaginase. The liver also produces proteins S and C. Protein C is activated by thrombin bound to endothelial thrombomodulin. Once activated, protein C can either be inactivated by binding to protein C inhibitor, a circulating plasma protein, or can bind complex with protein S on endothelial or platelet surface membrane, resulting in inactivation of activated factors V and VIII (Figure 2), thus preventing the activation of factors IX and X.

Protein C can be decreased in patients with liver disease and following orthotopic hepatic transplantation, disseminated intravascular coagulation, cardiopulmonary bypass surgery, hemodialysis, and following the administration of various drugs, including warfarin, asparaginase, and other oncologic therapeutic agents. Protein

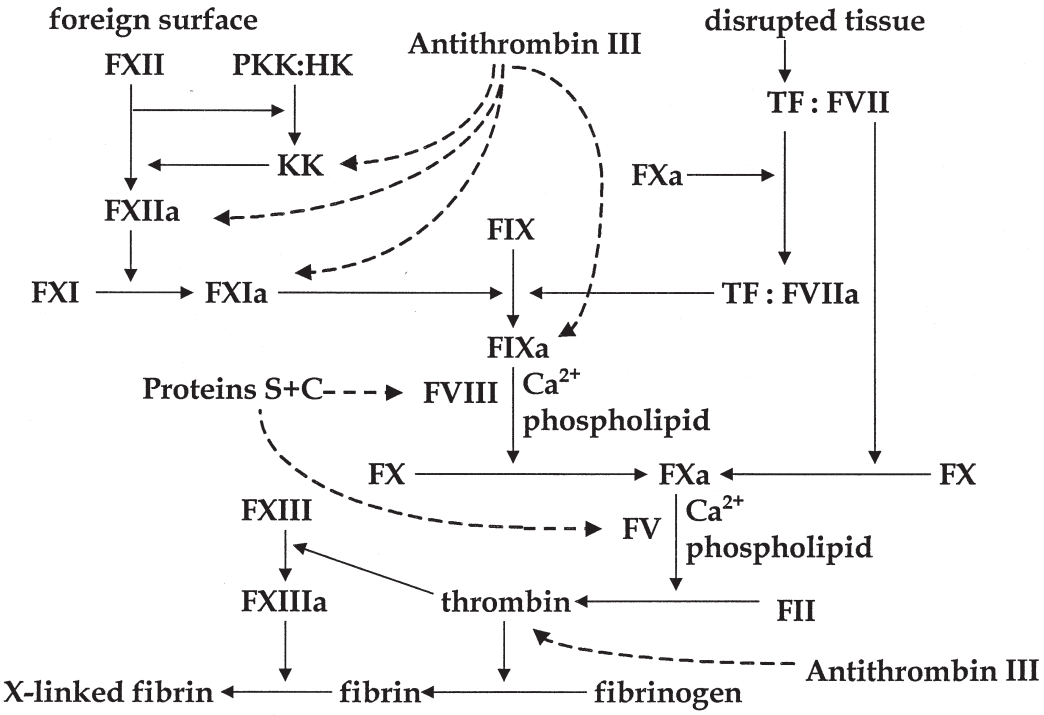

FIGURE 2 Natural inhibitors of the extrinsic and intrinsic (contact) coagulation pathways. PKK = prekallikrein; HK = high molecular weight kallikrein; KK = kallikrein; TF = tissue factor.

S is often complexed in plasma with either the binding protein of C4b (cleaved product of the fourth component of complement) or in combination with bound C4b. However, in the presence of activated protein C, protein S will dissociate from its C4b binding protein complex to form the active complex with protein C on endothelial or platelet surfaces. Protein S plasma concentrations are often reduced in patients with liver disease, disseminated intravascular anticoagulation, pregnancy, systemic lupus erythematosus, in particular, those patients with the antiphospholipid syndrome, and also following the administration of a variety of drugs, including warfarin, estrogens, and cancer chemotherapeutic agents.

The extrinsic coagulation pathway can also be blocked by the presence of tissue factor plasma inhibitor which can bind to activated factor X and also form an inactive quarternary complex with the activated forms of factors X and VII with tissue factor. Although factor VIIa is resistant to AT-III, there is an extrinsic pathway inhibitor, which is produced by the endothelium and its release is stimulated by heparin (6).

C1-esterase inhibitor and α_1-antitrypsin, other members of the serpin family, can also reduce activation of the intrinsic clotting cascade, since they target the protease factor XIIa and kallikrein and factor XIa, respectively (Figure 3).

Fibrinolysis

Cross-linked fibrin is enzymatically cleaved to fibrin degradation products by plasmin, which is formed from plasminogen (Figure 3). The conversion of plasminogen is increased by endothelial-derived tissue plasminogen activator (tPA), urokinase plasminogen activators (uPA), and kallikrein. Thus activation of the intrinsic clotting cascade also causes activation of plasminogen, so acting as a natural regulator of fibrin production. The activation of plasminogen can be blocked by fibrin monomers, plasminogen activator inhibitor (PAI), and C1-esterase inhibitor. Similarly, the action of plasmin on X-linked fibrin can be blocked by the presence of α_2-antiplasmin.

Anticoagulation pathways in acute renal failure

Several studies have shown that critically ill patients have activation of the clotting cascades with a reduction in circulating factor XII, prekallikrein, and factor VII, with an increase in fibrinogen (5). In addition, the natural anticoagulants antithrombin III, protein C, and protein S are often reduced (7). Fibrinolysis is often enhanced, as shown by increased D dimer concentrations. However, many studies have reported an increase in PAI, which would reduce plasminogen activation and so reduce fibrinolysis (5). Thus many patients with the sepsis syndrome have evidence of increased thrombotic activity with detectable circulating TATs and prothrombin breakdown products (PF1 and PF2).

Intensive care patients may have a deranged coagulation system due to underlying etiology, including multiple transfusion, liver disease, and disseminated intravascular

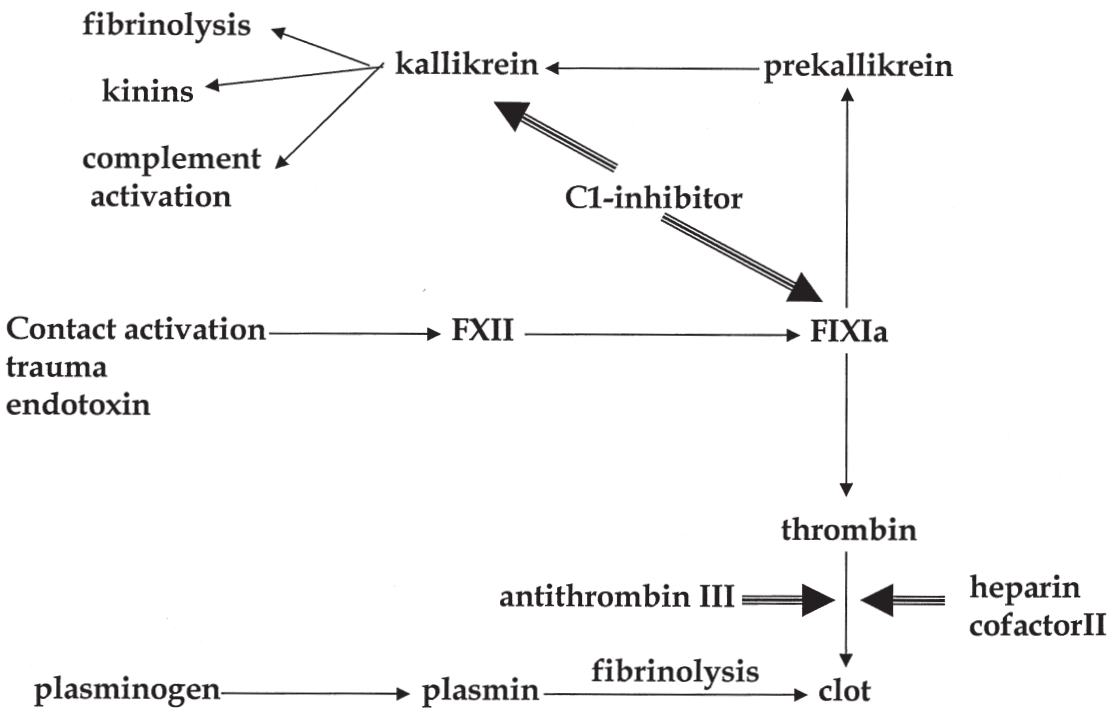

FIGURE 3 Contact pathway and inhibitors.

coagulation. Similarly, many currently used antibiotics can result in prolonged coagulation test results.

Platelets

Platelets have a series of surface receptors, which include the nonintegrin glycoprotein surface receptors and Gp Ib/factor IX and Gp IV(IIb), which bind to von Willebrand factor (vWF) and thrombospondin as their respective specific ligands. In addition, there is a series of integrin receptors, including Gp IIb/IIIa (which can bind to several ligands: fibrinogen, vWF, fibronectin, and vitronectin), the vitronectin receptor (same ligands as for Gp IIb/IIIa, but in addition thrombospondin), Gp Ia/IIa (ligand collagen), Gp Ic/IIa (ligand fibrinogen), and Gp Ic´/IIa (ligand vWF) (8).

Normal hemostasis is initiated by damage of the vessel wall resulting in exposure of subendothelial structures to flowing blood. When exposed to a foreign surface, such as the extracorporeal circuit, platelet adherence is rapid. Although the number of platelets available for hemostasis depends on the peripheral platelet count, it is more dependent on the hematocrit (5), due to red blood cell mediated transport of circulating platelets toward the vessel wall. This transport process is increased with both increasing hematocrit and blood flow and by both larger and less deformable red blood cells as well.

The effectiveness of platelet adhesion at the site of endothelial damage depends on platelet activation (Figure 4). Endothelial damage and/or loss of endothelial integrity not only reduces endothelial nitric oxide production, which normally prevents platelet activation and adhesion, but also exposes the subendothelial matrix. Platelets adhere due to interactions between glycoprotein surface receptors and their specific ligands. vWF is the main adhesive protein found in the subendothelial matrix and in the extracorporeal CRRT circuit is deposited from the circulation onto the hemofilter/hemodialyzer membrane, vascular access site, and within the venous bubble trap. Similarly, when exposed to an agonist, such as fibrinogen, platelets will aggregate to each other (Figure 4). Receptor-ligand interaction results in a conformational change of the receptor to its active form; this then leads to activation of the platelet actin binding protein and changes in the cytoskeleton. These changes result in platelet spreading and the release of platelet α-granules. In addition to providing calcium and surface membrane phospholipids for further activation of the clotting cascade, platelets also release additional factors with a procoagulant tendency, including β-thromboglobulin, PF4, platelet-derived growth factor, antiplasmin, PAI, fibrinogen, fibronectin, vWF, thrombospondin, factor V, and factor XIII (5). PF4 binding to platelets increases further platelet aggregation and secretion. It also may be involved in controlling the natural anticoagulant system, since PF4 can compete with antithrombin III, heparin cofactor II, and protein C for heparinoids. β-thromboglobulin, in

addition to its effects on fibroblasts, may also inhibit prostacyclin (PGI_2) production by endothelial cells.

Platelets in acute renal failure

Platelets can be activated by the release of vWF, thromboxane A_2, thrombin, arachidonic acid, and prostaglandins G_2 and H_2, which are synthesized by activated endothelium, as found in critically ill patients with the sepsis syndrome (9). In addition, cathepsin G and platelet activation factor, released from activated polymorphonuclear cells, can also cause platelet activation and aggregation. Adrenaline, serotonin, and vasopressin may also cause platelet activation. The majority of patients with the sepsis syndrome have a reduced peripheral platelet count and evidence of *in vitro* platelet activation (9).

Patients in the intensive care unit are a heterogeneous group of patients, some with active oozing from vascular access sites, yet with apparently normal laboratory coagulation studies and thromboelastograph, whereas others have marked thrombocytopenia coupled with abnormal coagulation studies and thromboelastograph with no evidence of hemorrhage. This may reflect that *in vivo* the major determinant in platelet-vessel wall interaction is blood flow; therefore, laboratory tests of platelet function may not necessarily reflect an *in vivo* situation (10).

Uremic patients have been shown to have an increased platelet surface expression of the integrin receptor Gp IIb/IIIa and a reduction in the nonintegrin Gp Ib (11). This is thought not to be an absolute change in the number of available receptors, but due to changes in receptor cycling between the intracytoplasmic compartment and the platelet surface. Although the binding of vWF to Gp Ib appears to be intact in uremia, at higher shear rates there may be a functional defect in the interaction between vWF and Gp IIb/IIIa (11). *In vitro* platelets from uremic patients show a reduced aggregation response to collagen, adrenaline, and adenosine diphosphate (ADP), which is due in part to a reduced production of thromboxane A_2 (TXA_2) (5). This reduction in TXA_2 can be corrected by the exogenous administration of arachidonic acid, suggesting an inhibitory factor. Thus the main clinical finding in uremia is a prolongation of the bleeding time due to ineffective platelet aggregation and activation. However, in the CRRT circuit platelets can be activated by contact within the vascular access, the plastic tubing, and the dialyzer membrane. Since hematocrit is a key determinant in the platelet-endothelial (or dialyzer membrane) interaction, by transporting platelets to the vessel wall, any reduction in hematocrit will reduce platelet adhesion and therefore activation (10).

The effect of the extracorporeal CRRT circuit on blood coagulation

Patients with acute renal failure in the intensive care setting will have evidence of intrinsic clotting cascade activity with intravascular clotting and increased fibrinolysis. Platelet function, on the other hand, is probably reduced due to the combination of anemia, thrombocytopenia, and uremia. Previous work has shown that platelets are activated, during conventional intermittent hemodialysis, by flow through the dialyzer membrane (12). Thus coagulation within the CRRT circuit would be expected.

Platelet function

Patients undergoing major cardiac surgery often return from cardiac bypass with a marked thrombocytopenia. This is due to events occurring in the extracorporeal circuit, resulting in both platelet fragmentation and functional changes (13). Platelets show a reduced *in vitro* aggregation response to ADP and collagen and were shown to have a reduction in surface membrane receptors, both Gp Ib (vWF receptor) and Gp IIb/IIIa (mainly fibrinogen receptor), and loss of the α-granules (13). Electron microscopy shows that these platelets have undergone a conformational change from resting discoid shape to the active form: elongated, thin, with many pseudopodia. These changes reflect the hypothermia of cardiac surgery coupled with mechanical stress of the pumped circuit and adhesion to the extracorporeal circuit. The latter is due to the deposition of fibrinogen on both the plastic of the extracorporeal lines and the hemofilter, which then leads to platelet adhesion through the Gp IIb/IIIa receptor (Figure 4).

The changes that occur during cardiac extracorporeal bypass are much greater than those during a standard intermittent hemodialysis treatment (14) and reflect the longer duration of circuit time during cardiac bypass, the higher blood flows achieved with an occlusive pump, and hypothermia. However, bleeding times do increase following routine hemodialysis, associated with a reduction in platelet surface Gp Ib (from 38% to 24%) and *in vitro* reduction of platelet aggregation with thrombin (from 55% to 20%) (14). Peripheral platelet counts have been reported either to remain unchanged or to decrease during prolonged treatment with CRRT (15). This reduction in platelet count appears to be greatest in those patients anticoagulated with standard unfractionated heparin and less in those given prostacyclin or no anticoagulation at all (15). *In vitro* studies of platelet function during CRRT revealed a marked decrease in maximum platelet aggregation in response to collagen (from 28% to 5%), adrenaline (from 39% to 10%), and ADP (from 44% to 16%). These changes occurred within 24 hours of starting CRRT, whereas there was no corresponding change in peripheral platelet count (16). Although there were major changes in these *in vitro* tests of platelet function, there was no associated major hemorrhage. Since hematocrit and blood flow are critical in initiating platelet aggregation, it may be that these *in vitro* tests do not accurately reflect *in vivo* activity. Our own experience is that there is no systematic change in platelet function during CRRT as assessed by serial thromboelastography. This is supported by a study with heparin anticoagulation in which there was no change in

bleeding time during the first 24 hours of CRRT, using an *in vitro* model of a damaged blood vessel to assess platelet function (15).

Coagulation factors

The exposure of blood to an extracorporeal circuit results in plasma protein adsorption. The interaction between these proteins with the artificial surface can initiate the activators of both the intrinsic and extrinsic clotting cascades. Factor XII can be directly activated by negatively charged membranes, such as polyacrylonitrile and polymethylmethacrylate, thus facilitating the conversion of high molecular weight kallikrein and prekallikrein to kallikrein (17) and initiating the intrinsic cascade (Figure 1). Kallikrein activation will result in complement activation and lead to increased conversion of plasminogen to plasmin and, therefore, increased fibrinolysis. In addition, factor XIIa inhibitor has been reported to decrease during cardiopulmonary bypass (5).

Granulocyte activation occurs during passage through the hemodialysis circuit, with release of elastase and cathepsin G. These enzymes tip the balance toward fibrinolysis by modifying plasminogen to a more active form and inactivating the inhibitors of plasmin and plasminogen activation (C1-inhibitor, a2-antiplasmin, and PAI-1). In addition, these neutrophil enzymes can degrade fibrin and inhibit coagulation by degrading several of the coagulation proteins, including factors V, VII, VIII, IX, XII, XIII. Monocyte and other mononuclear cell activation during dialysis results in the upregulation of cell adhesion molecules and integrins; the latter include the vitronectin receptor, so allowing binding to vWF, fibrinogen, and thrombospondin (12). Activation then results in the release of tissue factor, which can initiate activation of the extrinsic clotting cascade.

Despite these changes during intermittent hemodialysis, CRRT has not been reported to result in changes in the clotting cascade. Standard anticoagulation tests are either normal or unchanged by CRRT (unless patients were treated with heparin) (15). More sophisticated studies, measuring prekallikrein and factor XII, have similarly reported that CRRT does not lead to activation of the intrinsic coagulation pathway (18). Treatment with CRRT has not been observed to result in increased intravascular thrombosis, since most studies have failed to document significant changes in TATs (19). However, TATs were noted to increase prior to hemofilter clotting (18). Similarly, antithrombin III concentrations have not been shown to be affected by CRRT (20). In keeping with stable TATs, CRRT has been observed not to result in increased fibrinolysis, as shown by stable fibrinopeptide A concentrations (19).

The effect of CRRT circuit design on circuit life

Several centers have observed longer CRRT circuit duration with spontaneous continuous arteriovenous hemofiltration/continuous arteriovenous hemodialysis (CAVHF/CAVHD) when compared to pumped continuous venovenous hemofiltration/continuous venovenous hemodialysis (CVVHF/CVVHD) (20,21). Pumped and spontaneous circuits differ

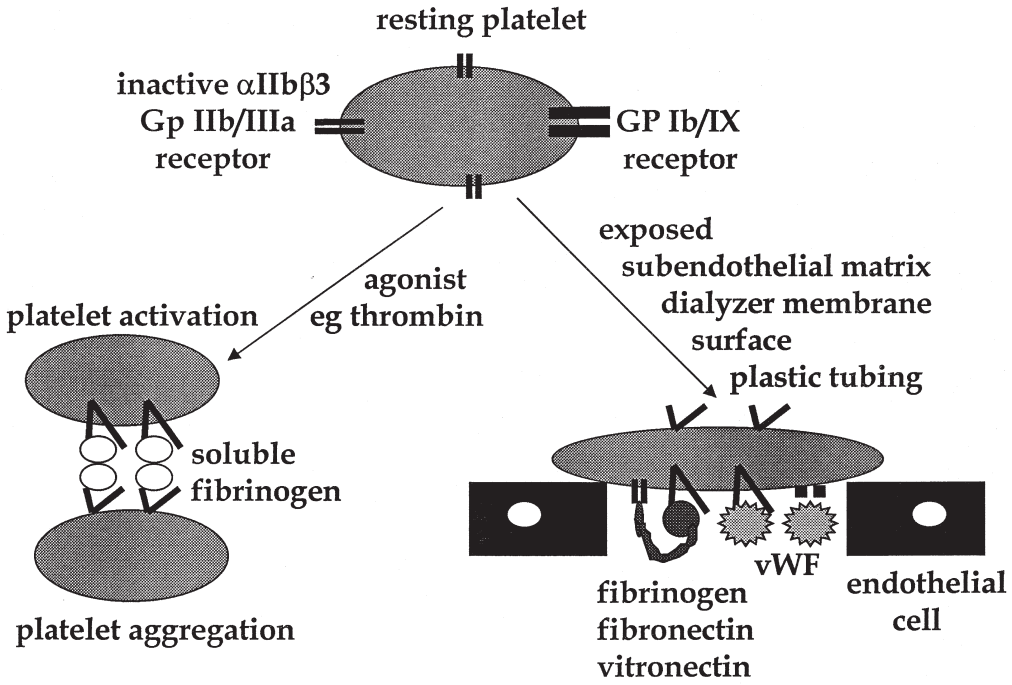

FIGURE 4 Platelet activation following exposure to circulating agonist or subendothelial matrix.

in the length of extracorporeal tubing; therefore, pumped circuits are associated with greater extracorporeal cooling. In addition, pumped circuits have a mechanical occlusive roller pump and a venous air detector, both of which may cause platelet activation (22).This suggests that the design of the extracorporeal circuit may have an effect on circuit life and is supported by Kramer's original observation that the development of a femoral arterial access catheter for CAVHF resulted in both a longer duration of the CAVHF circuit and a marked reduction in the incidence of hemorrhage, since less heparin was required to maintain the circuit (2,3). Observations on which part of the extracorporeal circuit initiates clotting have suggested that the most common site is the hemofilter/dialyzer, followed by the vascular access site and then the venous air detector (23).

Vascular access

Spontaneous CRRT circuits have traditionally employed femoral arterial and venous catheters or arteriovenous shunts. The main resistance, and therefore the greatest fall in perfusion pressure in the spontaneous circuit, is the arterial access site (24). This led to the development of specially designed femoral arterial access catheters, with a diameter of 2 mm or greater and a shortened length (8–10 cm), to provide reduced resistance to flow (24) and to maximize laminar flow within the access device (22). Using these catheters, within a mean arterial blood pressure range of 60–120 mm Hg, blood flow is greater with the femoral arterial catheter than with a radial arteriovenous shunt.

Arteriovenous fistulas and shunts result in a change in blood flow from laminar to turbulent. This has been shown to result in activation of the coagulation pathways due to endothelial activation by the turbulent blood. Reports have shown evidence of intravascular thrombosis with increased TATs, PF1, and PF2 and plasmin-α_2-antiplasmin complexes, coupled with endothelial activation, with the release of tPA and uPA. In clinical practice CAVHF circuits lasted longer and required less heparin with femoral arterial access when compared to arteriovenous (AV) shunts (21,24). Despite using shunts, the average life of the hemofilter/hemodialyzer was reported to be in excess of 48 hours (25).

Spontaneous CRRT requires arterial access, and in the elderly patient with atheromatous vessels, large bore femoral catheter insertion and AV shunt formation may be problematical. In the earlier reports of CAVHF, femoral arterial damage was noted, ranging from local hemorrhage to AV fistula formation, mycotic aneurysm formation, and arterial occlusion (2,3). In addition, spontaneous CRRT circuits depend on the patient's mean arterial blood pressure, which in critically ill patients may be labile, and a sudden decline in blood pressure can result in filter clotting (23). Thus most centers now treat patients with pumped CRRT circuits, which only require venous access. Interestingly, the reported circuit duration is less with pumped systems, ranging from less than 24 hours to 48 hours (20,21). Similarly, although circuit duration is less in the pediatric CRRT experience, AV circuits survive longer than the corresponding pumped circuit (26).Vascular access differs with a pumped circuit. Whereas single lumen catheters are used for spontaneous circuits, most centers use double lumen catheters for pumped CRRT. Although femoral catheters can be used, most centers use a subclavian or internal jugular approach. Femoral catheters may become temporarily occluded when patients are turned to prevent decubitus ulcer formation; if unnoticed this may lead to access thrombosis. In addition, femoral vein catheterization has been reported to have a 25% incidence of femoral deep vein thrombosis in intensive care unit patients.

Work studying vascular access in chronic dialysis patients has shown that the site of the tip of the double lumen venous catheter is an important factor in determining the risk of fibrin deposition at the tip and in the side holes of the catheter, so reducing effective flow and leading to catheter malfunction. Left-sided catheter placement and, more importantly, the tip of the catheter positioned in the superior vena cava, as opposed to right atrial placement, were most likely to lead to catheter occlusion (27). This is thought to be due to local turbulence in blood flow in the superior vena cava, especially when the central venous pressure is low. One of the key changes that has occurred over the past decade in the management of intensive care unit patients, with the advent of CRRT, has been the prevention of patients with the sepsis syndrome from becoming grossly edematous, with a tendency toward hypovolemia, in order to mobilize extracellular fluid. To prevent premature clotting of subclavian or jugular central venous catheters, these should be positioned within the right atrium. Because of the difficulty in positioning the tip in the right atrium, some groups have reported improved circuit life using femoral venous access (28).

Most venous access catheters are silicone rubber, dual lumen catheters designed to be inserted using a Seldinger technique. Care with insertion is required to prevent damage to the tip during insertion, since this can lead to increased blood flow turbulence and premature clotting. This results in nonlaminar blood flow and therefore increases the likelihood of platelet activation and contact cascade activation (Figure 5). In hemodialysis patients dual circular lumen catheters have been reported to provided better access than combinations of a single external circular lumen with an internal D-shaped lumen and/or two internal D-shaped lumina (29). This accords with our own clinical experience using two single circular lumen lines compared to those with a D-shaped lumen. Similarly, in the pediatric field, it can be technically difficult to insert dual lumen vascular access catheters due to the size of the veins, and some centers recommend the insertion of two single lumen catheters. More recently, heparin-bonded access lines have been introduced and reported to reduce the incidence of fibrin deposition on the catheter tip with greater patency times in children.

No CRRT circuit can function without good access. In one recent study, reduced blood pump speed, a surrogate for access malfunction, was a strong predictor for premature circuit failure (23). Further progress needs to be made in developing vascular access catheters made of nonthrombogenic material, which do not lead to the activation of platelets and coagulation pathway proteins and can be inserted atraumatically into the right atrium. It may well be that two single lumen lines, allowing nonturbulent blood flow (as used in CAVHF), are better than one double lumen catheter.

Extracorporeal lines

All CRRT circuits rely on blood lines, and these should be made with a smooth internal biocompatible surface that minimizes platelet adhesion and activation and the adsorption of coagulation pathway and prothrombogenic (e.g., vWF) proteins. Complement activation has been reported to be increased using silicone lines compared to polyvinyl chloride (Polaschegg, unpublished data), but there is a paucity of data as yet on the effect of different polymer blood lines and the risk of circuit failure due to clotting. Spontaneous CRRT lines are usually much shorter than those used with pumped circuits. This results in reduced thermal losses, which may play a role in the accelerated intrinsic coagulation system activation and platelet aggregation observed in cardiac bypass extracorporeal circuits (13).

Similarly, shorter lines result in less protein adsorption and contact activation. Pediatric patients require narrower diameter tubing, because the extracorporeal volume can be critical in neonates and critically ill infants. The initial greater flow achieved with pumped circuits often results in hemodynamic instability (30). The use of narrow diameter tubing increases the relative surface area and therefore increases contact activation. This may account for the shortened circuit life in the pediatric experience of CRRT and the persistent longer duration of spontaneous circuits, with their shorter lines, than pumped circuits (30).

Extracorporeal blood pump

Traditionally most blood pumps in pumped circuits have been roller pumps designed to be occlusive or at least partially occlusive, depending on the thickness of the blood tubing and the elasticity of the spring clips in the pump head. Thus blood is drawn out of the access device and delivered in a saw tooth flow profile to the hemofilter/hemodialyzer membrane. The actual pulsatile pressure profile will depend on both the blood pump speed and the diameter and elasticity of the tubing. In one recent study, in which the pressure in the CRRT circuit was measured between the blood pump and the dialyzer inlet, a mean maximum pressure of 202 mm Hg was recorded with an average blood pump speed of 200 mL/min, but in one-third of circuits pressures in excess of 300 mm Hg were noted (23). This is in keeping with an earlier study (31), which noted similar high prefilter pressures when a blood pump was used in the circuit (22). The variability in the saw tooth profile is greatest for the occlusive pump head. This pattern of blood flow is obviously nonlaminar, and any turbulence is likely to increase the risk of premature clotting by increasing platelet activation. In addition, the extracorporeal blood pump can lead to mechanical activation of platelets, circulating monocytes and leukocytes, and red blood cell damage, as witnessed during cardiac bypass surgery when much faster blood flows are employed (5).

More recently, a different type of blood pump has been designed (Fresenius acu-men®, Fresenius, Walnut Creek, CA, U.S.A.), which employs a bellows-like device, which sucks blood from the vascular access and then pushes it forward to the hemofilter. This system is designed to produce greater laminar flow and may be able to reduce clotting in the CRRT circuit by reducing contact activation. As yet, this system is continuing to undergo trials, and only time will tell if the change in blood pump technology will yield clinical benefits.

Hemofilter/Hemodialyzer

Clotting within the hemofilter/dialyzer membrane is the most common cause of premature clotting within the CRRT circuit, with studies reporting membrane clotting accounting for 40%–63% of all circuit losses (23). Spontaneous circuits require low pressure, high hydraulic permeability hemofilters/hemodialyzers for optimal function, since at increased resistance due to the filter/dialyzer geometry, blood flow no longer is laminar and increased clotting ensues (22). Parallel plate hemofilters/dialyzers generally have the lowest resistance to flow and provide better convective and diffusive clearances, with longer filter/dialyzer patency and lower anticoagulant requirement (24). If hollow fiber designs are used, these should be of a relatively short fiber length coupled with a larger cross-sectional area (25). In pumped CRRT circuits, high pressures can be generated (24) resulting in nonlaminar blood flow with increased turbulence recorded with flat plate designs (31) and increased premature clotting. Thus for pumped CRRT circuits hollow fiber membrane design is superior.

Ideally all membranes should have a smooth inert biocompatible and nonthrombogenic surface. The membrane composition and surface charge will determine the deposition of circulating plasma proteins, including albumin, complement, fibrinogen, and vWF onto the membrane surface. Polyacrylonitrile membranes are highly negatively charged and are known to adsorb plasma proteins and various proinflammatory cytokines and growth factors onto their surface. In one center the use of this highly negatively charged membrane was reported to result in reduced CRRT circuit patency (28), although this may have been due to circuit design, because no differences occurred when using the same membranes as dialyzers (28). When the effect of CRRT on the contact coagulation cascade using a polyacrylonitrile membrane was critically assessed, polyacrylonitrile mem-

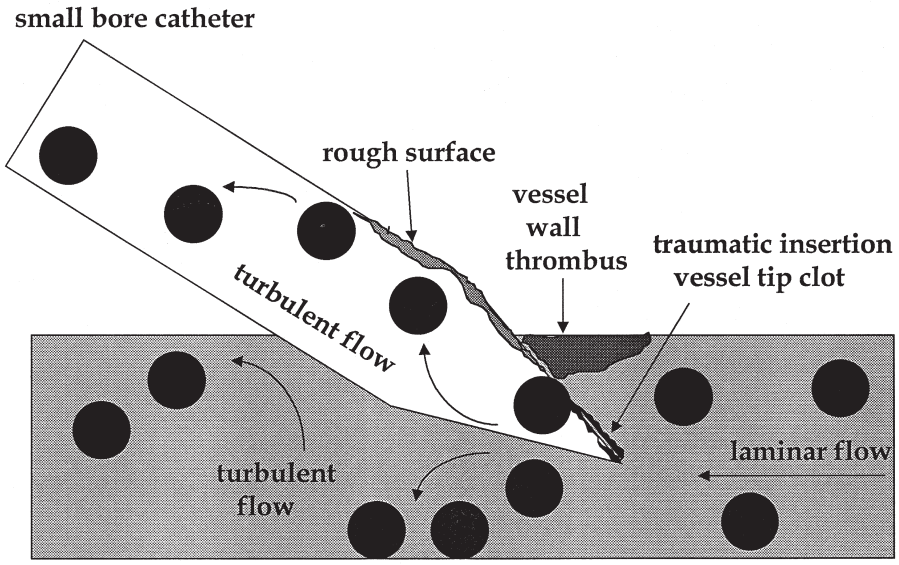

FIGURE 5 Vascular access problems resulting in turbulent blood flow following insertion of high resistance small diameter catheter, with vessel wall and catheter damage following traumatic insertion, resulting in platelet and contact cascade activation.

branes were not shown to cause any activation of the intrinsic pathway, nor was there any evidence of increased intravascular clotting (18). This latter finding is supported by other clinical studies comparing the same two membranes that did not show any membrane effect on filter/dialyzer patency rates (4). Similarly, another multicenter trial did not show any difference between polyacrylonitrile and polysulphone membranes in terms of the duration of CRRT (17). Most studies have reported that synthetic membranes require less anticoagulation than corresponding cellulosic membranes, suggesting that platelet aggregation and activation of the clotting system is yet another marker of membrane bioincompatibility.

Membrane biocompatibility varies from membrane to membrane. In general, the passage of blood across a cellulosic-based membrane results in greater activation of plasma complement proteins, more severe peripheral leukopenia and thrombocytopenia, and the generation of proinflammatory cytokines and polymorphonuclear leukocyte activation, as evidenced by elastase release, than the synthetic membranes (17). Although polysulphone and polyacrylonitrile membranes appear to be the least bioincompatible, other factors including membrane geometry, sterilization method, and dialysate composition can all affect the blood-dialyzer membrane interaction (17). Similarly, membrane bioincompatibility is greater with higher blood pump speeds due to nonlaminar turbulent blood flow through the membrane.

Predilution or postdilution fluid replacement

The design of the CRRT circuit can also predispose to increased clotting within the fibers of the hemofilter/dialyzer membrane. If a postdilutional hemofiltration circuit is used with large ultrafiltrate volumes, then this will lead to increased hemoconcentration and oncotic pressure, due to plasma water losses during the passage of blood through the membrane (32). Since platelet interactions with the membrane are dependent on red blood cell transport, increasing the hematocrit during transit along the membrane can increase platelet transport to the membrane surface. Similarly, the increased protein concentration can lead to increased protein deposition on the membrane, which could then increase activity of the contact coagulation cascade, due to deposition of factor XII.

In the development of CAVHF techniques, one group advocated the use of negative pressure applied to the ultrafiltrate channel to increase the ultrafiltrate (32). Although this may temporarily increase the ultrafiltrate rate, it also increases hematocrit and protein deposition on the membrane, leading to premature clotting and reduced membrane patency. Predilution, on the other hand, reduces the hematocrit and protein concentration entering the hemofilter/hemodialyzer. This has been clinically reported to both increase membrane patency rates (32) and reduce anticoagulant requirements (6).

Hemofiltration and/or dialysis

Most centers either use hemofiltration or hemodialysis with some ultrafiltration; therefore, there are very little data directly comparing membrane patency or circuit life between the two techniques. In the pediatric experience, although there were differences between spontaneous and pumped CRRT circuits reported by several groups, no differences have been reported between either spontaneous hemofiltration and dialysis circuits or between pumped hemofiltration and

dialysis circuits (26). On the contrary, in adult acute renal failure, spontaneous dialysis was reported to prolong membrane patency compared to filtration (28). Filter patency appears to be better maintained during pumped CRRT using a dialysis circuit than pure hemofiltration. There are two major caveats: first, some centers routinely change CRRT circuits after 72 hours; second, different intensive care units have different patient case mix and survival. The reason for the improved patency with dialysis may be due to the fact that blood pump speeds tend to be lower during dialysis, since clearances are greater and ultrafiltration volumes are modest. Thus pressure changes within the dialyzer membrane are less, resulting in more laminar flow, and the reduced ultrafiltration volumes reduce hemoconcentration and protein deposition (22). Whereas in the corresponding hemofiltration studies blood pump speeds tended to be greater, ultrafiltration volumes exceeded 1 L and fluid replacement was postdilutional, thus leading to greater turbulence within the membrane coupled with hemoconcentration and increased protein deposition.

Occasionally CRRT dialysis is performed with no ultrafiltration. When high-volume dialysis (2 L) is used with stop-go pumps (Imed, Abbingdon, Oxford, U.K.) rather than continuous flow pumps, then with high blood pump speeds saw-tooth pressure waves with peaks of 300 mm Hg or greater can be generated prior to the dialyzer (Davenport and Smye, unpublished observations). This increases nonlaminar flow within the dialyzer, resulting in reduced membrane patency and premature circuit clotting. Thus the key to preventing coagulation within the hemofilter/dialyzer membrane is to maintain laminar blood flow along the membrane, while preventing hemoconcentration and protein precipitation.

Venous air detection chamber

Gretz and colleagues demonstrated that the venous air detection chamber in the pumped CRRT circuit is another vulnerable site for clotting to develop. They showed that not only was there a combination of stagnant blood with a turbulent inflow, so predisposing to clotting, but also that the air-blood interface at the top of the chamber was important in determining premature clotting of the circuit (33). In one other study clotting starting in the venous bubble trap was the cause of premature failure in 7.5% of circuits (23). By deliberately infusing the postdilutional replacement fluid into the venous air detection chamber, to prevent an air-blood interface, they showed an increased filter patency and duration of their CRRT circuits. Venous air detection chambers are usually only a safety feature of the pumped CRRT circuit. More recently, pumped CRRT circuits have been designed without a venous bubble chamber (Prisma™, Hospal, Lyon, France). The Fresenius acu-men® (Fresenius, Walnut Creek, CA, U.S.A.) uses an air porous plastic diaphragm, which is used to pump blood through the hemofilter. Since any air within the blood compartment is extruded during passage through the bellows-like pump, no additional venous air trap is required. This system may prove of benefit in considering future designs to achieve anticoagulant-free CRRT.

Dialysate/Substitution fluid

Pre- and postdilution fluid replacement with normal saline, 5% dextrose, commercially available lactate-based substitution fluid with and without glucose, lactate-free and bicarbonate fluids have not been reported to affect filter/dialyzer clotting (5). Similarly, the same fluids and peritoneal dialysis fluid, when used as dialysate, have not been observed to have any discernible effect on membrane patency. Although in theory, the relatively high glucose concentration of peritoneal dialysis fluids could increase platelet activation and coagulation within the dialyzer.

Priming the circuit

Most centers rinse the hemofilter/dialyzer and extracorporeal lines with normal saline containing 5000 U unfractionated heparin (18,23), although the amount varies from 2500 to 20 000 U (33,34). Similarly, the priming volumes also vary from center to center, ranging from 1.0 to 4.5 L (18,23,34). Since heparin can be adsorbed to the plastic blood tubing and membrane, these differences in priming may have a clinical effect on membrane patency. The average circuit life reported was 30 hours for the group using a 1-L rinsing cycle (23), 48 hours when 2 L were used (22), and 44 hours when larger volumes were employed (18). This would suggest that a 2-L priming volume with 5000 U of heparin maximizes membrane patency.

Albumin precoating

In vitro studies showed that precoating a polyacrylonitrile dialyzer membrane with albumin (1.5 $\mu g/cm^2$) resulted in the deposition of 80 platelets/cm^2, compared to 35 800 /cm^2 when fibrinogen (2.0 $\mu g/cm^2$) was coated onto the membrane (35), thus emphasizing the importance of platelet adhesion through the Gp IIb/IIIa receptor. In clinical practice, albumin precoating of plasma exchange circuits was observed to reduce platelet accumulation and thrombus formation from 44.3% to 4.6% (36). This is supported by the experience from patients with combined liver and renal failure, where precoating the CRRT circuit with 4.5% albumin and heparin resulted in a median fall in peripheral platelet count of only 13%, compared to 23% in those anticoagulated with PGI_2 and 32% with heparin (37).

Following albumin-heparin priming, anticoagulation-free CRRT circuits then significantly outlasted those with standard heparin priming followed by either heparin or prostacyclin anticoagulation (37). This finding has not been universal and may reflect differences in albumin priming, including the duration of recirculation prior to connecting the patient to the CRRT circuit, hemofiltration compared to dialysis, and differences in patient populations (36).

Anticoagulation for CRRT

Standard unfractionated heparin

Unfractionated heparin is a mixture of glycosaminoglycan composed of alternating residues of D-glycosamine and uronic acid (molecular weight range 5–100 kD). Its major anticoagulant effect depends on a unique pentasaccharide with a high affinity binding to antithrombin (Figure 3). After its reaction with heparin, antithrombin undergoes conformational change that increases its ability to inactivate the serine proteases: thrombin, factor Xa, and factor IXa (Figure 2). Thrombin is most sensitive to this interaction, with heparin binding to both thrombin and antithrombin (Figures 3 and 6). Heparin cofactor II is also catalyzed by heparin, but the anticoagulant effect is only achieved at high levels of heparin and is specific for thrombin (5). In addition, heparin reduces the adhesion of platelets to injured arterial walls and to collagen, probably by maintaining vessel wall electronegativity (6). Standard heparins are the most commonly used anticoagulants for CRRT; however, there are great differences in methods of use. Most centers rinse the extracorporeal circuit with heparinized saline, then rinse the circuit again with normal saline prior to connecting to the patient (28), whereas others do not rinse out the heparinized saline prior to connection (18). Thus some institutions then give a bolus of heparin at the start of CRRT followed by a continuous infusion (23,34), whereas others start with a continuous infusion alone (4,38).

Since heparin is a charged molecule, it may adsorb to the plastic tubing. Thus when infused in a high concentration (e.g., 1 mL/hour of a 250 U/mL solution), not all the heparin may be infused, and that which enters the extracorporeal circuit may only mix with the blood passing closest to the anticoagulation port. Thus to achieve thorough mixing, it has been advocated that it should be infused at a low concentration but high volume (e.g., 5 U/mL or less) (32). Others have devised a "Venturi" mixing chamber to achieve thorough mixing.

Heparin may induce a state of thrombocytopenia, usually in a time- and dose-dependent manner, which may occur in patients treated by CRRT for protracted periods. This responds to a reduction in dosage and is termed "heparin-induced thrombocytopenia type I." Less commonly there may be associated agglutination of platelets and paradoxical thrombosis, which can be both arterial and venous. This syndrome occurs more commonly with bovine (up to 5%) than porcine heparin (1% or less) and is usually due to the presence of an antibody, IgG isotype, directed against a multimolecular complex of heparin and PF4. This heparin-induced thrombocytopenia type II, or heparin-associated antibody (HAT), has a peak time of onset after 5–12 days of heparin exposure. The HAT syndrome can cause both bleeding and thrombotic complications and can promote clotting in extracorporeal circuits. In most cases this is associated with a precipitous fall in the peripheral platelet count, although rarely the platelet count can be maintained. Recovery requires the avoidance of heparin. In cases of HAT associated with major thrombosis, prostacyclin or heparinoids have been used to maintain systemic anticoagulation to prevent extension of the thrombosis (39).

Heparin-dependent antibodies are routinely sought using a platelet aggregation assay, with platelets from healthy donors, the patient's plasma, and the same heparin preparation, as administered to the patient. This screening test may be falsely negative in up to 50% of cases (39), and, if suspected, a more sensitive ELISA test using PF4 complexed with heparin should then be used.

The one advantage of heparin, apart from cost, is that the dose can be adjusted according to bedside monitoring tests. The whole blood clotting time (WBCT) and the activated coagulation time (ACT) require fresh, unanticoagulated whole blood samples rapidly delivered into a glass tube at 37°C. The ACT is similar, but contains an activator of the intrinsic coagulation system. Both are prone to error, due to sampling errors, volumes tested, and test tube sizes, and require regular quality control. In addition, the results are dependent on the level of coagulation factors, platelets, and hematocrit. The activated partial thromboplastin time (APTT) is a laboratory test on plasma separated from citrated blood and should be measured in conjunction with a prothrombin time, which although little affected by heparin, provides valuable information about the levels of coagulation factors.

Centers differ not only in which monitoring tests are performed and their frequency, but also the site at which samples are taken (35,38). As discussed above, the bedside tests are affected by hemoconcentration and platelet count. Thus the results of WBCT and ACT taken from the same patient will differ, during hemofiltration with postdilutional fluid replacement, if taken prior to and postfilter, simply due to ultrafiltration increasing hematocrit and platelet concentration causing shorter times postfilter. To overcome these problems, most centers check coagulation times immediately prior to the filter/dialyzer, since if anticoagulation is required, then it must be maximum during flow through the dialyzer membrane, because this is the key site in the CRRT circuit in which clotting develops (4).

Hemorrhage is the major complication of heparin anticoagulation. One group reported an incidence of 48 hemorrhages (40 major and 8 minor) in 37 patients (38). Most studies have reported an incidence of around 25%, with some 3.5%–10% of deaths being directly attributable to problems with anticoagulation during CRRT (4,28). Although the absolute amount of heparin has not been shown to be related to the incidence of hemorrhage, this may be due to the heterogeneity of the patient populations, in terms of the levels and balance of coagulation and anticoagulant factors, but also the variability in heparin half-life (ranging from 0.66 to 4.5 hours). However, monitoring of systemic blood samples has shown that at an APTT of 15–35 sec the incidence of *de novo*

patient hemorrhage was 2.9 per 1000 hours CRRT, which increased to 7.4 at an APTT of 45–55 sec (40).

The converse, filter patency, has not been proven to be determined either by the total heparin dose, APTT, or other clotting studies (18,21,29).Very few studies have reported that either increased heparin administration resulted in increased filter patency (33) or increased APTT was associated with prolonged circuit life (41). However, several groups have noticed that lower doses of heparin can be used in patients with thrombocytopenia without any reduction in filter patency or circuit life (21,28,41).

Following heparin priming of the circuit, it is common practice to infuse standard heparin at a rate of 500–1000 U/hour (approximately 10 U/kg/hour). Most patients, therefore, receive a dose of heparin similar to that used in prophylaxis of deep venous thrombosis, compared to intermittent hemodialysis, where patients are systemically heparinized. Thus, whereas the expected WBCT for hemodialysis would be 15–20 min, the corresponding time for CRRT would be 10–15 min prior to and 6–10 min post the dialyzer/hemofilter. Similarly for the ACT: hemodialysis 200–240 sec, CRRT pre 180–240 sec, and 160–200 postfilter/dialyzer; and for the APTT: hemodialysis 120–160 sec; and for CRRT: pre 45–80 sec and 35–45 sec postfilter/dialyzer.

Whereas heparin is a very effective anticoagulant without major side effects for intermittent hemodialysis in end-stage renal failure patients, it is not the ideal anticoagulant for CRRT. In part, this is due to the intensive care patient population, the vast majority of whom have reduced antithrombin III levels, which markedly reduce the effectiveness of heparin. Thus heparin in CRRT circuits is associated with significant morbidity and mortality due to hemorrhage without providing long-lasting hemofilter/dialyzer patency. This has led to a search for alternative anticoagulants and technologies.

Regional heparinization

Regional heparinization was developed to achieve maximum anticoagulation during passage through the hemofilter/dialyzer but with minimum systemic effects, thereby reducing the risk of patient hemorrhage yet achieving prolonged membrane patency and extracorporeal life. It has been assumed that 1 mg of protamine neutralizes 100 U of standard heparin (13). Unfortunately, in clinical practice the half-life of heparin is dose-dependent and increases with prolonged administration. The heparin-protamine complex is taken up by the reticuloendothelial system and broken down, with the release of heparin back into the circulation (13). In addition, protamine has a number of potentially adverse clinical effects, including reduced cardiac output, decreased systemic vascular resistance, increased pulmonary vascular resistance, bronchospasm, and decreased platelet function (5). When given in large boluses to reverse heparin-associated hemorrhage, protamine can also cause severe anaphylactic reactions, but these are unlikely when infused during CRRT at the low doses used in clinical practice (0.6–2 mg/100 U heparin) (21).

Regional heparinization cannot be used with heparin-coated hemofilters/dialyzers, since the protamine binds to the heparin coating, so neutralizing its effect. Others have tried to reduce the incidence of heparin-associated hemorrhage by coating the hemofilter surface with protamine to prevent the systemic effects of excess heparin. Unfortunately, these membranes usually become saturated within a short period and are not suitable for CRRT.

In one study regional heparinization was compared to standard low-dose heparin (500 U/hour), during spontaneous CRRT using a dialyzer, and reported to result in a mean 33% increase in filter life, but with 9% more hemorrhagic problems and a 27% greater systemic APTT (21). When the same group compared data for a corresponding pumped CRRT circuit, again mean circuit life was 29% longer with regional heparinization, yet with 3% fewer hemorrhagic complications and similar APTTs (21). These data would favor the use of regional heparinization. However, most centers do not use this treatment due to the complexity of having to regularly monitor the APTT both pre- and postheparin infusion and postprotamine, and then adjust either the dose of heparin or protamine and/or both and then reassess. Too little protamine and the patient is at risk of hemorrhage; conversely, too much protamine and the CRRT circuit may clot or the patient adversely react to protamine.

More recently, regional heparinization has become possible due to the use of antithrombin III. Columns have now been developed containing agarose beads coated with purified antithrombin III (Clarigen Inc., Carlsbad, CA, U.S.A.), which can be inserted into the CRRT circuit postdialyzer and remove heparin (<0.1 U/mL). Although these newer developments may be useful in intermittent hemodialysis, the column is likely to be relatively quickly saturated and therefore not as yet applicable to CRRT.

In clinical practice, the variability in the amount of protamine required to neutralize 100 U heparin varies by more than threefold, making it difficult to successfully establish regional heparinization with simple standardized protocols.

Antithrombin III supplementation and heparin

Antithrombin III levels are often reduced in critically ill patients with renal failure. Studies have shown that conventional heparin anticoagulation is much less likely to prevent circuit thrombosis during CRRT in those patients with acquired antithrombin III (ATIII) deficiency (42). ATIII supplementation has been used in critically ill patients with hepatic and renal failure. In one study, using a bolus dose of 3000 U of ATIII prior to a 4-hour hemodialysis treatment, ATIII levels were well maintained during the period of hemodialysis (43). Treatment with ATIII was associated with a reduction in the total amount of standard heparin required to maintain a target whole blood clotting time, but there was no reduction in the generation of TATs, which increased significantly within the first hour of dialysis. In

addition, there was no improvement in small molecular weight solute clearance, suggesting no difference in dialyzer patency. Thus from this study repeated boluses of ATIII would be required in patients treated by CRRT, the dosage frequency depending on individual characteristics. The cost and lack of obvious benefit in terms of membrane clearance and intravascular coagulation will probably preclude the widespread use of ATIII.

Low molecular weight heparin

Low molecular weight heparins (LMWHs) are obtained by the chemical or enzymatic depolymerization of various chains of standard heparin, resulting in a molecule of around 5 kD. LMWHs, comprised of fewer than 18 saccharides, cannot bind to both ATIII and thrombin simultaneously, thus losing antithrombin activity compared to standard heparin. Since inactivation of factor Xa does not require direct heparin binding, LMWH, by activating ATIII, retains anti-Xa activity (Figure 6). Thus, when monitoring the effect of anticoagulation with LMWH, there is only a modest effect on the APTT, and special assays are required to determine the inhibition of factor Xa. Some commercial kits for testing factor Xa activity include purified ATIII. Although they are assays for heparin, or LMWHs, they are poor indicators of heparin anticoagulation, especially in critically ill patients who are usually ATIII-deficient. Thus it is important when using LMWHs to use an assay that omits exogenous ATIII, so that the LMWH dose can be titrated against anticoagulant activity; otherwise, antifactor Xa activity and the effect of LMWH on anticoagulation may not correlate. Thromboelastography can also be used to monitor anticoagulation, since the reaction time is correlated with antifactor Xa activity.

Most centers have either used a loading dose followed by a continuous infusion (44) or have given further bolus doses 6 hourly (45), although more recently continuous infusions without a loading dose have been advocated (16). Antifactor Xa activity greater than 0.25 U/mL using enoxaparin prevented clotting (45), whereas dalteparin anticoagulation (antifactor Xa activity 0.27–0.53 U/mL) was reported to result in reduced dialyzer patency and premature circuit clotting (44). Higher dalteparin doses, 35 U/kg loading dose followed by a steady infusion of 13 U/kg/hour, resulted in greater antifactor Xa activity, 0.47–0.79 U/mL (compare recommended range for standard intermittent hemodialysis, 0.2–0.4), resulted in increased dialyzer patency and decreased clotting within the extracorporeal circuit, but was associated with bleeding complications in all cases (44). More recently LMWHs have been shown to be effective when started as a continuous infusion without a loading dose (e.g., dalteparin 600 U/hour) achieving a mean antifactor Xa activity of 0.49 U/mL (therapeutic range for systemic anticoagulation 0.3–0.8 U/mL) within one hour of starting CRRT (16).

The currently available LMWHs, dalteparin, enoxaparin, and nadroparin, differ in size, half-life, and biological activity (46). The terminal half-life is much greater for the LMWHs than unfractionated heparin, with enoxaparin (Clexane) having the longest at 27.7 hours (46). Half-lives are increased in renal failure, because in the healthy subject LMWHs are degraded in the proximal tubules. Several groups have reported increased hemorrhage in patients treated with LMWHs (28,47), which may be due to the combination of difficulty in titrating the initial bolus dose and the continuous infusion rate to achieve target antifactor Xa activity, coupled with a laboratory test which included purified ATIII. If overanticoagulated, unlike standard heparin, protamine has only a partial effect, and fresh frozen plasma may therefore be required to control hemorrhage because of the prolonged half-life of the LMWHs.

When first introduced, LMWHs were tried in patients with HAT syndrome. However, it is now recognized that immune-mediated thrombocytopenia may also rarely occur with the LMWHs. Thus in patients with HAT, *in vitro* testing for cross reactivity should be determined prior to using LMWH, because in the great majority of patients with HAT, cross reactivity is the rule: dalteparin (Fragmin) 89%, nadroparin (Fraxiparin) 86%, and enoxaparin (Clexane) 83%. The therapeutic use of these drugs in HAT should be preceded by exclusion of *in vitro* cross reactivity (48).

Dermatan sulphate

Dermatan sulphate is a charged glycosaminoglycan, but with a lower charge density compared to heparin. Unlike heparin, it acts primarily through activating heparin cofactor II to inhibit thrombin formation. When used as an anticoagulant during standard intermittent hemodialysis, dermatan sulphate caused a smaller increase in APTT than heparin and also showed less platelet activity. At a loading dose of 6 mg/kg, dialyzer patency was maintained throughout dialysis without any observed hemorrhagic complications (49). The development of dermatan and chondroitin sulphate as anticoagulants has now been superseded by the synthetic heparinoids (see below).

Synthetic heparins/heparinoids

With the advent of the LMWHs, a further group of synthetic glycosaminoglycurons was developed which contained five or fewer polysaccharide residues, with a pentasaccharide. These agents are known as heparinoids because of the pentasaccharide group. Danaparoid (Orgaran) was the first to become commercially available, although others are entering clinical trials.

Heparinoids can usually be used in patients who have developed the HAT syndrome with standard and LMWHs, since there is very little cross reactivity (<10%) (48). We have recently used danaparoid in such a case complicated by iliac vein thrombosis, with no hemorrhagic problems during CRRT, and coupled with dialyzer patency and circuit life in excess of 24 hours.

The synthetic heparinoids may have an additional advantage over standard and LMWHs, in that heparin can,

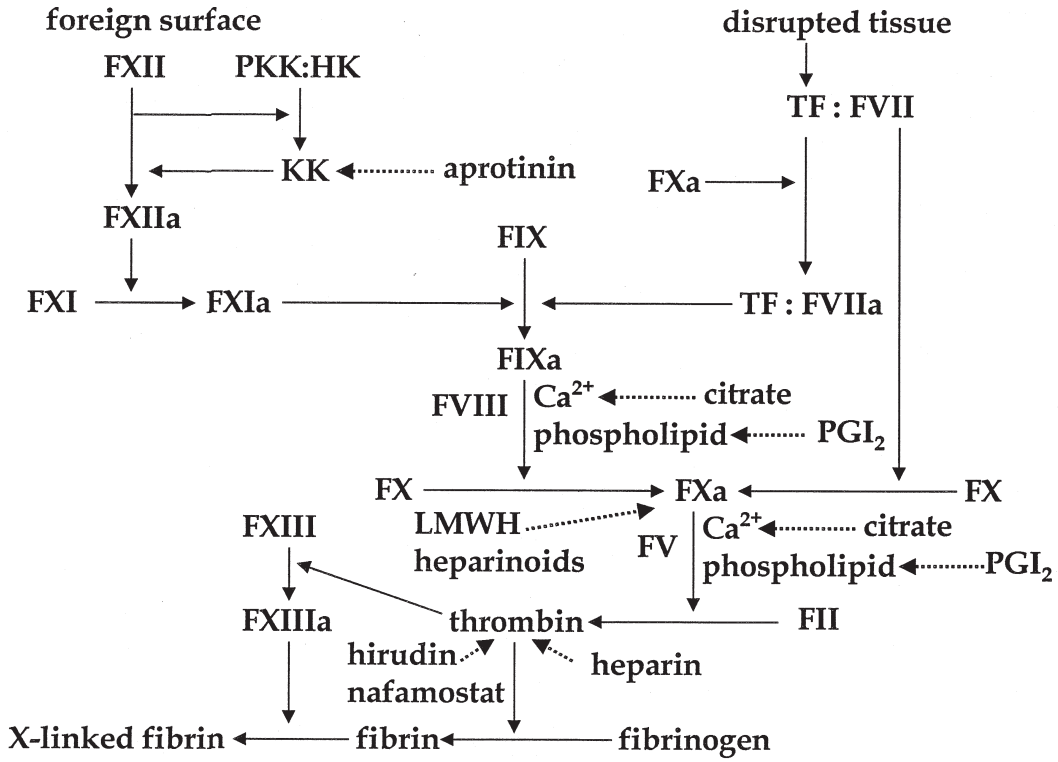

FIGURE 6 Anticoagulant mode of action on extrinsic and intrinsic (contact) coagulation pathways. PKK = prekallikrein; HK = high molecular weight kallikrein; KK = kallikrein; TF = tissue factor.

paradoxically, increase intrinsic coagulation cascade activity due to the activation of factor XI by fibrin-bound thrombin, whereas danaparoid and other synthetic pentasaccharides had little or no effect on the intrinsic clotting cascade.

Half-life activity against both factors Xa and IIa is greater for danaparoid compared to the LMWHs; yet following bolus administration, the initial effect on anti-IIa activity is least with danaparoid (46). The longer half-life of plasma anti-Xa activity, 18–25 hours, could cause problems of overanti-coagulation during CRRT when too great an infusion dose is used. We currently start with a bolus dose of 2500 U of danaparoid followed by an infusion of 400 U/hour, then adjust the rate (usually between 200 and 400 U/hour) by monitoring both antifactor Xa activity and the APTT, since there is a correlation between anti-Xa activity and the APTT.

Synthetic heparinoids have not been widely used; therefore, their safety profile in terms of bleeding risk is unknown. However, our limited clinical experience, and that of others, suggests that the risk of hemorrhage is substantially less than that with standard heparin and that filter patency and CRRT circuit life are similar to those of other anti-coagulants.

Heparin-coated extracorporeal circuits

Heparin bonding of cardiopulmonary and extracorporeal oxygenation circuits has been shown to result in a reduction in heparin requirement and risk of hemorrhage. In addition, studies assessing platelet surface glycoproteins and leukocyte activation markers showed that less activation occurred during passage through heparin-bonded circuits (50). This is in keeping with other studies that have reported reduced thrombin generation, complement activation, proinflammatory cytokines (IL-6 and IL-8), and plasticizer (di-2-ethylhexyl phthalate) release with heparin-bonded circuits (50). Electron microscopy of the hemofilters showed much less platelet and leukocyte adhesion, with less plasma protein adhesion to the heparin-coated membrane (50). However, there are conflicting data on the duration of the effectiveness of these heparin-bonded circuits, ranging from 2 hours to 5 days. Heparin bonding of CRRT circuits has been attempted by various groups, who circulated either high concentrations of heparin (33) or heparin-albumin solutions prior to commencing treatment (37). Both groups claimed improvement in filter patency and circuit life, when compared to their standard anticoagulation regimens. Phase III clinical trials with a heparin-bonded polysulphone membrane (Duraflo, Baxter, Deerfield, IL, U.S.A.) are currently in progress. Initial results again suggest less platelet activation and prolonged filter patency and circuit life (51). Despite heparin bonding of the membrane, we have found that the most common site of CRRT circuit clotting remains the hemofilter/dialyzer, although platelet activity, as assessed by βTG release, is reduced.

Heparin-bonded CRRT circuits allow the possibility of using no additional anticoagulation. Provided filter patency and circuit life exceed 48 hours, the use of heparin-bonded CRRT circuits will increase. The amount of heparin released from the membrane is very small (<1%), and we and others have not noted any change in APTT during treatment. Similarly, the frequency of hemorrhage is much lower than during standard heparin CRRT and is not significantly different from CRRT circuits with no anticoagulation.

Citrate anticoagulation

Sodium citrate chelates ionized calcium (Figure 6), which is necessary for the coagulation cascade (6). For extracorporeal use it has advantages over heparin in that it has no known antiplatelet activity, is readily removed by dialysis so reducing systemic anticoagulation, and neutralized when returned to central venous blood. Several centers have found regional citrate anticoagulation to be very effective both in terms of dialyzer membrane patency and circuit life and coupled with a marked reduction in the incidence of hemorrhagic complications (38). In one study no hemorrhagic complications were reported with citrate CRRT (34). Most centers have used trisodium citrate (4% solution), infused prior to the dialyzer at a ratio of citrate flow to blood flow of 4%. In clinical practice, using a spontaneous circuit the rate varied between 160 and 190 mL/hour to maintain a postfilter ACT of 180–220 sec (38). When regional citrate anticoagulation is used, predilutional fluid must not contain calcium or bicarbonate; therefore, 0.9% saline is often used (34). A special hyponatremic dialysate (117 mmol/L) is required containing no calcium or alkali, with a relatively high chloride content of 122.5 mmol/L (38). The hyponatremic dialysate is required because of the high sodium load prefilter due to the combination of trisodium citrate and normal saline predilution. Infusion of calcium or bicarbonate prior to or as dialysate would affect ionized calcium concentrations and therefore interfere with citrate anticoagulation. Since calcium is complexed with citrate and lost into the dialysate, calcium is infused as calcium chloride centrally, to maintain a normal ionized calcium returning to the patient (6). Most patients require 40–45 mL/hour of a 0.735% calcium chloride solution (1 mEq/10 mL) (38). Since each citrate molecule is eventually metabolized, mainly in the liver, through to three bicarbonate molecules, alkalosis may occur. To help prevent alkalosis, normal saline is given as a predilution fluid, and calcium is given as calcium chloride. Thus by giving a high chloride load, the risk of developing metabolic alkalosis is reduced (52). Although filter patency and circuit life may extend for 4–6 days, biochemical disturbances may occur, most commonly with pumped hemofiltration circuits, since the clearance of citrate is less than during dialysis, and this leads to excessive alkalosis (38). Up to 26% of patients will develop a mild metabolic alkalosis, more common in those with hepatic dysfunction and patients requiring support with large amounts of blood products (containing acid citrate dextrose anticoagulant) (53). Hypernatremia has also been reported in less than 10% of patients (53), more commonly during hemofiltration, since the prefilter sodium load cannot be removed as well as during dialysis. Occasionally, despite titrating the citrate dose according to ACT and calcium infusion according to unionized calcium concentration, patients may develop hypercitratemia, hypercalcemia, and metabolic acidosis. This is usually in the setting of acute renal failure with muscle damage and initial hypocalcemia. Despite a normal ionized plasma calcium, total plasma calciums in excess of 4 mmol/L have been observed, in association with hypercitratemia (plasma citrate >20 mmol/L, normal range 0.07–0.14 mmol/L). Such hypercitratemia suggests hepatic dysfunction, and if citrate cannot be metabolized readily through to bicarbonate, then the patient will become acidotic, due to the loss of plasma bicarbonate through the dialyzer. To prevent metabolic abnormalities, it is recommended that the WBCT be checked initially hourly, then 2 hourly, and the dose of trisodium citrate adjusted accordingly. Similarly, the ionized calcium, electrolytes, and bicarbonate should be checked twice daily and the calcium infusion adjusted (38). More recently, anticoagulation with isotonic acid citrate dextrose has been introduced, rather than trisodium citrate. This may reduce the incidence of biochemical abnormalities observed with citrate anticoagulation.

Prostacyclin

The effect of prostacyclin (PGI_2) depends on the balance with thromboxane A_2. The effects of thromboxane A_2 predominate at the damaged endothelial surface, leading to platelet activation, aggregation, and plugging of the vessel wall. When prostacyclin is infused into the extracorporeal circuit, the opposite effect on platelet function is achieved, because thromboxane A_2 concentrations are very low. Although other prostanoids, PGE_1 and PGE_2, have antiplatelet activities similar to PGI_2, they are not as potent as PGI_2. However, since they are also metabolized in the lungs, their systemic vasodilatory effects should be minimal (18). Platelet activation appears to be the key to clotting developing within the CRRT circuit (18), so PGI_2 has been successfully used as an anticoagulant in both pediatric (51) and adult acute renal failure (4). Most centers use a standard infusion of 5 ng/kg/min, with a range of 2.5–10. PGI_2 does not affect standard anticoagulation tests, apart from the bleeding time (15), and it is therefore difficult to titrate the dose to any individual patient. Thromboelastography shows the effect of PGI_2 by reducing the maximum amplitude of the trace. However, because PGI_2 is rapidly bound to platelets, changes in dosage have no discernible effect on the thromboelastograph tracing, since the platelets are saturated with PGI_2 (54). Anticoagulation with PGI_2 has been reported by many groups to significantly reduce the incidence of hemorrhage when compared to standard heparin and is used in many centers for patients at risk of hemorrhage (25,37). However, the effect of PGI_2 on filter patency and circuit life varies from center

to center. In spontaneous circuits, PGI_2, both in children and adults, has been reported to improve filter patency and circuit life when compared to standard heparin (4,30). In pumped CRRT circuits, some studies have reported an improvement in filter patency (15) and circuit life compared to heparin, whereas others found no difference (4,18). Prior to commencing CRRT, PGI_2 should be infused systemically, starting at 0.5 ng/kg/min, and the dose slowly increased to 5 ng/kg/min; then CRRT should be commenced and the infusion site switched to the CRRT circuit. This procedure minimizes the systemic vasodilatatory effects of PGI_2, which include hypotension due to reduced systemic and pulmonary vasodilatation. The half-life of PGI_2 is some 2 min, so these side effects can be readily reversed by reducing or stopping the infusion. These vasodilatatory changes can lead to an imbalance between tissue oxygen delivery and oxygen requirement, for example, in the lung-increased shunting, in the heart-reduced coronary perfusion, and in the brain cerebral hypoxia and increased intracranial pressure (37). These adverse effects can be reduced by optimizing cardiac filing pressures prior to the administration of PGI_2 and by giving albumin solutions that bind free PGI_2 (4). In addition, infusing PGI_2 prior to the filter reduces the systemic effects, because up to 40% is removed during passage through the dialyzer (22). Although PGI_2 is an effective anticoagulant, its cost has reduced its widespread use. Occasionally PGI_2 is used in patients with other complications such as pulmonary hypertension and acute liver failure, where its effects on tissue blood flow are thought to have a beneficial effect (37,47).

Serine protease inhibitors

Aprotinin

Aprotinin is a bovine serine protease inhibitor with an elimination half-life of 2 hours. The effects of aprotinin on the coagulation system depend on the circulating plasma concentration, since its affinity for plasmin is much greater than that for kallikrein (Figure 6). Thus at a plasma concentration of 125 kIU/mL (kallikrein inactivation units), aprotinin inhibits fibrinolysis and complement activation. At higher concentrations, 200 kIU/mL, kallikrein activation will be reduced (13); this may have additional benefits in the critically ill patient by improving cardiovascular stability. Reduced kallikrein activation will decrease blood coagulation activated by contact with anionic surfaces and the plastic of the extracorporeal circuit (6). In addition, by reducing neutrophil activation and, therefore, cathepsin G release, aprotinin will also reduce secondary platelet activation by neutrophils. Aprotinin was initially used to reduce excessive blood loss during cardiopulmonary bypass due to heparinization. Initial loading doses of 2×10^6 kIU were given followed by a maintenance infusion of 500 000 kIU/hour. Prevention of systemic bleeding with aprotinin does not promote coagulation within the extracorporeal circuit and may contribute to the maintenance of extracorporeal anticoagulation (6). Others have used aprotinin to maintain prolonged extracorporeal oxygenator, and recently we used aprotinin during CRRT at an infusion rate of 50 kIU/hour. When used during CRRT, we used a hemodialysis circuit with predilution and aprotinin as the only anticoagulant. Since it reduces the intrinsic coagulation cascade, this results in prolongation of the WBCT, ACT, and APTT. We aimed for a predialyzer APTT of 40–70 sec, which resulted in a membrane patency in excess of 48 hours. Unfortunately, the current costs of aprotinin will preclude its general use.

Nafamostat mesylate

Gabexate mesylate is a short-acting serine protease inhibitor (half-life 80 sec) which acts at the same sites as antithrombin-III (16). Nafamostat mesylate (6-amido-2-naphthyl p-guanidinobenzoate dimethanesulfonate) has a longer half-life of 5–8 min (55) and similar activity to gabexate. By inhibiting thrombin (Figure 6), factors Xa and XIIa, nafamostat prolongs the WBCT, ACT, and APTT, thus allowing bedside monitoring (56). A strong positive correlation has been reported between plasma nafamostat concentration and the ACT (55). Thus with a short half-life the infusion rate can be adjusted according to the bedside ACT to achieve adequate anticoagulation. Since nafamostat is readily removed during hemofiltration and dialysis (40%) (56), anticoagulation is maximum at entry to the hemofilter/dialyzer, and the concentration returning to the patient is reduced, with systemic concentrations being less than 4% of the prehemofilter concentration (55). However, nafamostat is readily adsorbed to the negatively charged polyacrylonitrile membrane, making initial dosing schedules problematic with this membrane. Nafamostat, at a starting infusion of 0.1 mg/kg/hour, has been successfully used by several Japanese centers as an extracorporeal anticoagulant for CRRT in patients with increased risk of hemorrhage (55,56). Although the incidence of reported hemorrhage (4%) was much less than that with standard heparin (67%) and LMWH (29%) (28), treatment with CRRT was shown to result in an increase in thrombin-ATIII complexes and prothrombin fragments (55,56). Thus nafamostat does not prevent the development of intravascular/extracorporeal clotting and may not result in prolonged hemofilter/dialyzer patency and circuit life (28). Currently treatment with nafamostat is around $300 per day, reducing its widespread use. Nafamostat has rarely been reported to cause eosinophilia, bone marrow suppression, and a syndrome of myalgia and arthralgia.

Hirudin

Hirudin, which comes from leaches, and the recombinant forms are direct inhibitors of thrombin (Figure 6) by direct binding and covering the active enzyme site. To date, recombinant hirudin has only been reported as an anticoagulant in intermittent hemodialysis and following cardiac angioplasty. The 4-hour half-life of the hirudin-thrombin complex is lengthened in renal failure, with significant plasma

hirudin levels being detected some 2 days after a single bolus dose given for intermittent hemodialysis (57). The activity of hirudin can be monitored by both the ACT and APTT and also functional assays of the hirudin-thrombin complex. In the cardiac field too low a dose has resulted in thrombin generation, whereas too high a dose was associated with increased risk of hemorrhage.

Platelet antibodies

Trials are currently in progress assessing the benefits of using recombinant monoclonal antibodies to platelet glycoprotein surface receptors (Gp IIb/IIIa) in patients undergoing coronary artery angioplasty and stenting. Platelets are the major factor in determining clot formation in the extracorporeal circuit (28,39), so the effectiveness of platelet antibodies, given as a bolus at the start of CRRT, on membrane patency and circuit life remains to be determined.

Combinations of anticoagulants

Heparin and prostacyclin

Although heparin interferes with the inhibitory effect of PGI_2 on platelet aggregation *in vitro*, several centers have used a combination of PGI_2 (2–6.5 ng/kg/min) and standard heparin (200–350 U/hour) (15), reporting CRRT circuit lives in excess of 48 hours. Others have added PGI_2 to heparin anticoagulation in patients, who had repeated clotting of the CRRT circuit, to good effect (47). Careful comparison of the combination of heparin and PGI_2 showed no increase in the incidence of hemorrhage in one study (15), whereas in another, although the frequency was less than that for heparin, it was greater than PGI_2 anticoagulation alone (28). Both studies reported that the combination increased hemofilter/dialyzer patency when compared either to heparin or PGI_2 alone, with filter patency maintained for up to 80 hours (28).

No anticoagulation

Ideally all CRRT circuits would be anticoagulant-free to reduce the risk of potential hemorrhage. Several groups, including pediatric centers, have tried anticoagulant-free CRRT circuits, both spontaneous and pumped, in patients judged to be at risk of hemorrhage and found that circuit life was similar to that achieved with their standard anticoagulant regimen (21,26). Others have reported that heparin requirement is related to peripheral platelet count (41) and that most patients with thrombocytopenia can be treated with no anticoagulant (28). To achieve successful anticoagulation-free CRRT, thought is required to the design of the extracorporeal circuit. The two most effective mechanical methods of maintaining the extracorporeal circuit are preventing stagnation and reducing blood viscosity. The slowest flow in the circuit is through the hemofilter/dialyzer, leading to red blood cell aggregation. This can be increased by the formation of bridges between the red cells due to the presence of fibrinogen and other plasma protein macromolecules and also synthetic colloid substitutes (13). Activation of platelets and leukocytes accelerates this cellular aggregation. Thus the anticoagulation-free CRRT circuit starts with vascular access designed to produce laminar flow with no contact activation. Then there should be a minimum of blood lines, to reduce the length of the extracorporeal circuit, with a minimum of joints or connectors to reduce unnecessary turbulent flow. The CRRT circuit should have no dependent loops, because these increase stagnation and promote coagulation. In addition, thermal losses should be minimized, since thermal losses lead to increased plasma viscosity and changes in platelet morphology, which increase the risk of coagulation. Again, shortening of the extracorporeal lines reduces thermal loss. Stasis in the venous air detector chamber should be minimized. We routinely return postfilter fluid into the air detector chamber to reduce the air-blood interface and reduce stasis (22). A biocompatible membrane is required to reduce contact activation (17). Paradoxically, high blood pump speeds are to be avoided, because they increase contact activation if occlusive roller pumps are used (22). Blood viscosity can be reduced during passage through the hemofilter/dialyzer by giving prefilter fluid dilution and by avoiding excessive blood transfusion. By careful thought to circuit design we switched to anticoagulant-free CRRT circuits as our standard circuit in 1995, following two fatalities associated with heparin anticoagulation.

Summary

To reduce the incidence of iatrogenic hemorrhage, ideally all CRRT circuits should be anticoagulant-free. This can be accomplished by design of the circuit and choice of patient: thrombocytopenic or at risk of hemorrhage. The advent of heparin-bonded membranes, lines, and vascular access catheters may help achieve the goal of no additional anticoagulant. In addition, the development of new blood pump technology will help reduce contact activation and do away with a separate venous air detector chamber. Some patients, however, will develop premature clotting of the CRRT circuit, perhaps due to inadequate vascular access or hypovolemia. Provided this is not due to inadequate vascular access, then anticoagulation is required. Of the currently available regimens, citrate, prostacyclin, and the synthetic heparinoids appear to have the greatest safety profile in terms of reducing the risk of hemorrhage.

Systemic anticoagulation may be required as part of the general management of patients in acute renal failure treated by CRRT (e.g., postcardiac surgery, major venous thrombosis). Under these circumstances anticoagulation with heparin or LMWHs appears appropriate, and if heparin-associated antibodies develop, then a synthetic heparinoid can be substituted.

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