Chapter 24

Transfusion Medicine and Coagulation Disorders

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Coagulation and bleeding assume particular importance when operations are performed on the heart using extracorporeal circulation. This chapter begins with a discussion of the depth and breadth of hemostasis relating to cardiac procedures, beginning with coagulation pathophysiology. The pharmacology of heparin and protamine is described next. This background is then applied to treatment of the bleeding patient.

OVERVIEW OF HEMOSTASIS

Proper hemostasis requires the participation of innumerable biological elements (Box 24-1). They can be divided into four topics to facilitate understanding: coagulation factors, platelet function, the endothelium, and fibrinolysis. The reader must realize this is for simplicity of learning and that in biology the activation creates many reactions and control mechanisms, all interacting simultaneously. The interaction of the platelets, endothelial cells, and proteins to either activate or deactivate coagulation is a highly buffered and controlled process. It is perhaps easiest to think of coagulation as a wave of biological activity occurring at the site of tissue injury (Fig. 24-1). Although there are subcomponents to coagulation itself the injury/control leading to hemostasis is a four-part event: initiation, acceleration, control, and lysis (recanalization/fibrinolysis). The initiation phase begins with tissue damage, which is really begun with endothelial cell destruction or dysfunction. This initiation

BOX 24-1 *Components of Hemostasis*

- Coagulation factor activation
- Platelet function
- Vascular endothelium
- Fibrinolysis and modulators of coagulation

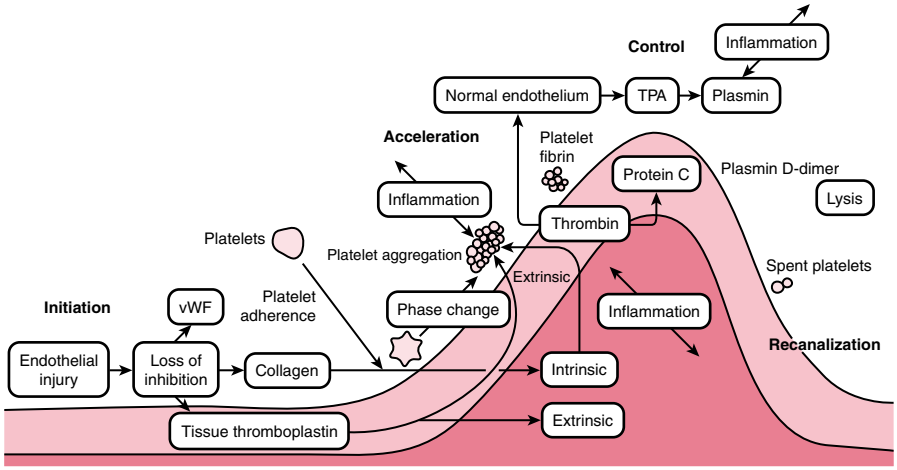

Figure 24-1 Coagulation is a sine wave of activity at the site of tissue injury. It goes through four stages: initiation, acceleration, control, and lysis/recanalization. (Redrawn with permission from Spiess BD: Coagulation function and monitoring. In Lichtor JL [ed]: Atlas of Clinical Anesthesia. Philadelphia, Current Medicine, 1996.)

phase leads to binding of platelets, as well as protein activations; both happen nearly simultaneously and each has feedbacks into the other. Platelets adhere and create an activation or acceleration phase that gathers many cells to the site of injury and creates a large number of biochemical protein cascade events. As the activation phase ramps up into an explosive set of reactions, counter-reactions are spun off, leading to control proteins damping the reactions. The surrounding normal endothelium exerts control over the reactions. Eventually the control reactions overpower the acceleration reactions and lysis comes into play.

The other key concept is that hemostasis is part of a larger body system—inflammation. Most of the protein reactions of coagulation control have importance in signaling inflammation and other healing mechanisms. It is no wonder that cardiopulmonary bypass (CPB) has such profound inflammatory effects when it is considered that each of the activated coagulation proteins and cell lines then feeds into upregulation of inflammation.

Protein Coagulation Activations

Coagulation Pathways

The coagulation factors participate in a series of activating and feedback inhibition reactions, ending with the formation of an insoluble clot. A *clot* is the total of platelet-to-platelet interactions leading to the formation of a platelet plug and then the

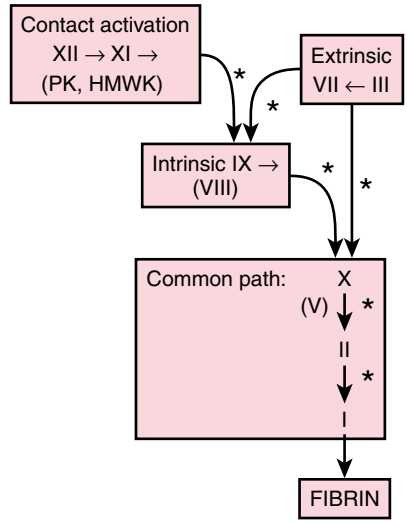

Figure 24-2 Depiction of coagulation protein activation sequence. Asterisks denote participation of calcium ion. PK = prekallikrein; HMWK = high-molecular-weight kininogen.

cross-linking of platelets to each other by way of the final insoluble fibrin that leads to a stable clot. Clotting is not simply the activation of proteins leading to more protein deposition.

With few exceptions, the coagulation factors are glycoproteins synthesized in the liver, which circulate as inactive molecules termed *zymogens.* Factor activation proceeds sequentially, with each factor serving as substrate in an enzymatic reaction catalyzed by the previous factor in the sequence. Hence, this has classically been called a "cascade" or "waterfall" sequence. Cleavage of a polypeptide fragment changes an inactive zymogen to an active enzyme. The active form is termed a *serine protease* because the active site for its protein-splitting activity is a serine amino acid residue. Many reactions require the presence of calcium ion (Ca^{2+}) and a phospholipid surface (platelet phosphatidylserine). The phospholipids occur most often either on the surface of an activated platelet or endothelial cell and occasionally on the surface of white cells. So anchored, their proximity to one another permits reaction rates profoundly accelerated (up to 300,000-fold) from those measured when the enzymes remain in solution. The factors form four interrelated arbitrary groups (Fig. 24-2): the contact activation and the intrinsic, extrinsic, and common pathways.

CONTACT ACTIVATION

Factor XII, high-molecular-weight kininogen (HMWK), prekallikrein (PK), and factor XI form the contact, or surface, activation group. Because factor XII autoactivates by undergoing a shape change in the presence of a negative charge, in vitro coagulation tests use glass, silica, kaolin, and other compounds with negative surface charge. One potential in vivo mechanism for factor XII activation is disruption of the endothelial cell layer, which exposes the underlying negatively charged collagen matrix. Activated platelets also provide negative charges on their membrane surfaces. HMWK anchors the other surface activation molecules, PK and factor XI, to damaged endothelium or activated platelets. Factor XIIa cleaves both factor XI, to form factor XIa, and PK, to form kallikrein.

INTRINSIC SYSTEM

Intrinsic activation forms factor XIa from the products of surface activation. Factor XIa splits factor IX to form factor IXa, with Ca^{2+} required for this process. Then factor IXa activates factor X with help from Ca^{2+}, a phospholipid surface (platelet), and a glycoprotein cofactor, factor VIIIa.

EXTRINSIC SYSTEM

Activation of factor X can proceed independently of factor XII by substances classically thought to be extrinsic to the vasculature. Any number of endothelial cell insults can lead to the production of tissue factor by the endothelial cell. At rest, the endothelial cell is very antithrombotic. However, with ischemia, reperfusion, sepsis, or cytokines, the endothelial cell will stimulate its production of intracellular NFκb and send messages for the production of messenger RNA for tissue factor production. This can happen quickly, and the resting endothelial cell can turn out large amounts of tissue factor. It is widely held today that the activation of tissue factor is what drives many of the abnormalities of coagulation after cardiac surgery, rather than contact activation.[1] Thromboplastin, also known as tissue factor, released from tissues into the vasculature, acts as a cofactor for initial activation of factor X by factor VII. Factors VII and X then activate one another with the help of platelet phospholipid and Ca^{2+}, thus rapidly generating factor Xa. Factor VIIa also activates factor IX, thus linking the extrinsic and intrinsic paths.

COMMON PATHWAY

Factor Xa splits prothrombin (factor II) to thrombin (factor IIa). The combination of factors Xa, Va, and Ca^{2+} is termed the *prothrombinase complex.* Factor Xa anchors to the membrane surface (of platelets) via Ca^{2+}. Factor Va, assembling next to it, initiates a rearrangement of the complex, vastly accelerating binding of the substrate, prothrombin. Most likely, the factor Xa formed from the previous reaction is channeled along the membrane to this next reaction step without detaching from the membrane.

Thrombin cleaves the fibrinogen molecule to form soluble fibrin monomer and polypeptide fragments termed *fibrinopeptides A* and *B*. Fibrin monomers associate to form a soluble fibrin matrix. Factor XIII, activated by thrombin, cross-links these fibrin strands to form an insoluble clot. Patients with lower levels of factor XIII have been found to have more bleeding after cardiac surgery.

VITAMIN K

Those factors that require calcium (II, VII, IX, X) depend on vitamin K to add between 9 and 12 γ-carboxyl groups to glutamic acid residues near their amino termini. Calcium tethers the negatively charged carboxyl groups to the phospholipid surface (platelets), thus facilitating molecular interactions. Some inhibitory proteins also depend on vitamin K (proteins C and S).

Modulators of the Coagulation Pathway

Thrombin, the most important coagulation modulator, exerts a pervasive influence throughout the coagulation factor pathways. It activates factors V, VIII, and XIII; cleaves fibrinogen to fibrin; stimulates platelet recruitment and chemotaxis of leukocytes and monocytes; releases tissue plasminogen activator (t-PA), prostacyclin, and nitric oxide from endothelial cells; releases interleukin-1 from macrophages; and with thrombomodulin, activates protein C, a substance that then inactivates factors Va and VIIIa. Note the negative feedback aspect of this last action. The latest thinking on coagulation function centers around the effects of thrombin. The platelets, tissue

factor, and contact activation all are interactive and are activated by a rent in the surface of the endothelium or through the loss of endothelial coagulation control. Platelets adhere to a site of injury and in turn are activated, leading to sequestration of other platelets. It is the interaction of all of those factors together that eventually creates a critical mass. Once enough platelets are interacting together, with their attached surface concomitant serine protease reactions, then a thrombin burst is created. Only when enough thrombin activation has been encountered in a critical time point, then a threshold is exceeded, and the reactions become massive and much larger than the sum of the whole. It is thought that the concentration and ability of platelets to react fully affect the ability to have a critical thrombin burst. CPB may affect the ability to get that full thrombin burst due to its effects on platelet number, platelet-to-platelet interactions, and the decreased amounts of protein substrates.

The many serine proteases that compose the coagulation pathways are balanced by serine protease inhibitors, termed *serpins.* This biological yin and yang leads to an excellent buffering capacity. It is only when the platelet-driven thrombin burst so overwhelms the body's localized anticoagulation or inhibitors that clot proceeds forward. Serpins include α_1-antitrypsin, α_2-macroglobulin, heparin cofactor II, α_2-antiplasmin, antithrombin (also termed antithrombin III), and others.

Antithrombin (ATIII) constitutes the most important inhibitor of blood coagulation. It binds to the active site (serine) of thrombin, thus inhibiting thrombin's action. It also inhibits, to a much lesser extent, the activity of factors XIIa, XIa, IXa, and Xa; kallikrein; and the fibrinolytic molecule plasmin. Thrombin bound to fibrin is protected from the action of antithrombin, thus explaining the poor efficacy of heparin in treating established thrombosis. ATIII is a relatively inactive zymogen. To be most effective antithrombin must bind to a unique pentasaccharide sequence contained on the wall of endothelial cells in the glycosaminoglycan surface known as heparan; the same active sequence is present in the drug heparin. An important note is that activated ATIII is active only against free thrombin. Most thrombin in its active form is either bound to glycoprotein-binding sites of platelets or in fibrin matrices. When blood is put into a test tube and clot begins to form (e.g., in an activated coagulation time [ACT]), 96% of thrombin production is yet to come. The vast majority of thrombin generation is on the surface of platelets and on clot-held fibrinogen. Platelets through their glycoprotein-binding sites and phospholipid folds protect activated thrombin from attack by ATIII. Therefore, the biological role of ATIII is to create an anticoagulant surface on endothelial cells. It is not present biologically to sit and wait for a dose of heparin before CPB.

Another serpin, *protein C,* degrades factors Va and VIIIa. Like other vitamin K–dependent factors, it requires Ca^{2+} to bind to phospholipid. Its cofactor, termed *protein S,* also exhibits vitamin K dependence. Genetic variants of protein C are less active and lead to increased risk for deep vein thrombosis and pulmonary embolism. When endothelial cells release thrombomodulin, thrombin then accelerates by 20,000-fold its activation of protein C. Activated protein C also promotes fibrinolysis.

Regulation of the extrinsic limb of the coagulation pathway occurs via tissue factor pathway inhibitor (TFPI), a glycosylated protein that associates with lipoproteins in plasma.[2] TFPI is not a serpin. It impairs the catalytic properties of the factor VIIa/tissue factor complex on factor X activation. Both vascular endothelium and platelets appear to produce TFPI. Heparin releases TFPI from endothelium, increasing TFPI plasma concentrations by as much as sixfold.[2]

von Willebrand factor (vWF), a massive molecule composed of disulfide-linked glycosylated peptides, associates with factor VIII in plasma, protecting it from proteolytic enzymes. It circulates in the plasma in its coiled inactive form. Disruption of the endothelium either allows for binding of vWF from the plasma or allows for

expression of vWF from tissue and from endothelial cells. Once bound, vWF uncoils to its full length and exposes a hitherto cryptic domain in the molecule. This A-1 domain has a very high affinity for platelet glycoproteins. Initially, vWF attaches to the GPIα platelet receptor, which slows platelet shear forces. This is not enough to bind the platelet, but it creates a membrane signal that allows for early shape change and expression of other glycoproteins, GPIb and GPIIb/IIIa. Then, secondary GPIb binding connects to other vWF nearby, binding the platelet and beginning the activation sequence. It bridges normal platelets to damaged subendothelium by attaching to the GPIb platelet receptor. An ensuing platelet shape change then releases thromboxane, β-thromboglobulin, and serotonin and exposes GPIIb/IIIa, which binds fibrinogen.

Platelet Function

Most clinicians think first of the coagulation proteins when considering hemostasis. Although no one element of the many that participate in hemostasis assumes dominance, platelets may be the most complex. Without platelets, there is no coagulation and no hemostasis. Without the proteins, there is hemostasis, but it lasts only 10 to 15 minutes as the platelet plug is inherently unstable and breaks apart under the shear stress of the vasculature. Platelets provide phospholipid for coagulation factor reactions; contain their own microskeletal system and coagulation factors; secrete active substances affecting themselves, other platelets, the endothelium, and other coagulation factors; and alter shape to expose membrane glycoproteins essential to hemostasis. Platelets have perhaps as many as 30 to 50 different types of cell receptors. The initial response to vascular injury is formation of a platelet plug. Good hemostatic response depends on proper functioning of platelet adhesion, activation, and aggregation (Fig. 24-3).

Platelet Adhesion

Capillary blood exhibits laminar flow, which maximizes the likelihood of interaction of platelets with the vessel wall. Red cells and white cells stream near the center of the vessels and marginate platelets. However, turbulence causes reactions in endothelium that leads to the secretion of vWF, adhesive molecules, and tissue factor. Shear stress is high as fast-moving platelets interact with the endothelium. When the vascular endothelium becomes denuded or injured, the platelet has the opportunity to contact vWF, which is bound to the exposed collagen of the subendothelium. A platelet membrane component, glycoprotein (GP)Ib, attaches to vWF, thus anchoring the platelet to the vessel wall. Independently, platelet membrane GPIa and GPIIa and IX may attach directly to exposed collagen, furthering the adhesion stage.

The integrin glycoproteins form diverse types of membrane receptors from combinations of 20 α and 8 β subunits. One such combination is GPIIb/IIIa, a platelet membrane component that initially participates in platelet adhesion. Platelet activation causes a conformational change in GPIIb/IIIa, which results in its aggregator activity.

Platelet adhesion begins rapidly—within 1 minute of endothelial injury—and completely covers exposed subendothelium within 20 minutes. It begins with decreased platelet velocity when GPIb/IX and vWF mediate adhesion, followed by platelet activation, GPIIb/IIIa conformational change, and then vWF binding and platelet arrest on the endothelium at these vWF ligand sites.[3]

Platelet Activation and Aggregation

Platelet activation results after contact with collagen, when adenosine diphosphate (ADP), thrombin, or thromboxane A_2 binds to membrane receptors, or from certain platelet-to-platelet interactions. Platelets then release the contents of their dense (δ)

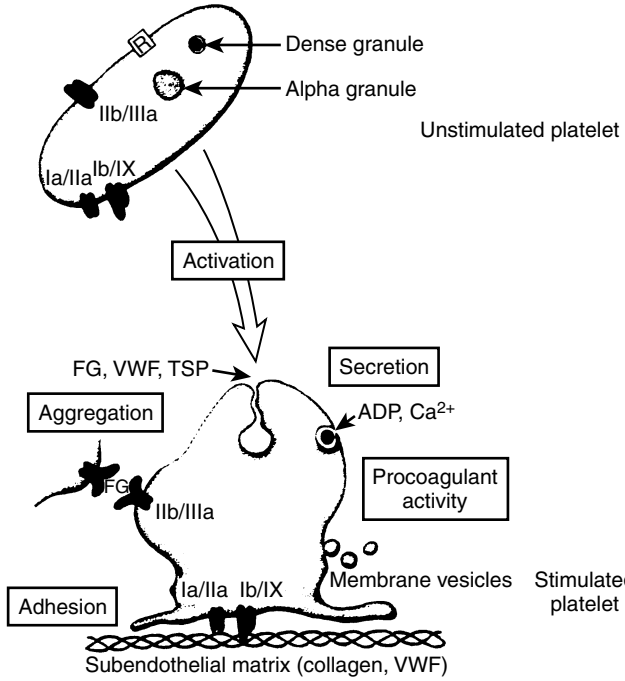

Figure 24-3 Platelet function in hemostasis. Glycoproteins Ib and IX and von Willebrand factor (vWF) mediate adhesion to the vessel wall. Glycoproteins IIb and IIIa and integrin molecules fibrinogen (FG) and thrombospondin (TSP) mediate platelet aggregation. (From George J, Shattil SJ: The clinical importance of acquired abnormalities of platelet function. N Engl J Med 324:27, 1991.)

granules and α granules. Dense granules contain serotonin, ADP, and Ca^{2+}; α granules contain platelet factor V (previously termed platelet factor 1), β-thromboglobulin, platelet factor 4, P-selectin, and various integrin proteins (vWF, fibrinogen, vitronectin, and fibronectin). Simultaneously, platelets employ their microskeletal system to change shape from a disk to a sphere, which changes platelet membrane GPIIb/IIIa exposure. Released ADP recruits additional platelets to the site of injury and stimulates platelet G protein, which in turn activates membrane phospholipase. This results in the formation of arachidonate, which platelet cyclooxygenase converts to thromboxane A_2. Other platelet agonists besides ADP and collagen include serotonin, a weak agonist, and thrombin and thromboxane A_2, both potent agonists. Thrombin is by far the most potent platelet agonist, and it can overcome all other platelet antagonists as well as inhibitors. In total, there are more than 70 agonists that can produce platelet activation and aggregation.

Agonists induce a shape change, increase platelet intracellular Ca^{2+} concentration, and stimulate platelet G protein. In addition, serotonin and thromboxane A_2 are potent vasoconstrictors. The presence of sufficient agonist material results in platelet aggregation. Aggregation occurs when the integrin proteins (mostly fibrinogen) released from α granules form molecular bridges between the GPIIb/IIIa receptors of adjacent platelets (the final common platelet pathway).

Prostaglandins and Aspirin

Endothelial cell cyclooxygenase synthesizes prostacyclin, which inhibits aggregation and dilates vessels. Platelet cyclooxygenase forms thromboxane A_2, a potent aggregating agent and vasoconstrictor. Aspirin irreversibly acetylates cyclooxygenase,

rendering it inactive. Low doses of aspirin, 80 to 100 mg, easily overcome the finite amount of cyclooxygenase available in the nucleus-free platelets. However, endothelial cells can synthesize new cyclooxygenase. Thus, with low doses of aspirin, prostacyclin synthesis continues while thromboxane synthesis ceases, decreasing platelet activation and aggregation. High doses of aspirin inhibit the enzyme at both cyclooxygenase sites.

Reversible platelet aggregation is blocked by aspirin, as the platelet cyclooxygenase is inhibited. However, the more powerful agonists that yield the calcium release response can still aggregate and activate platelets, because cyclooxygenase is not required for those pathways.

Drug-Induced Platelet Abnormalities

Many other agents inhibit platelet function.[4] β-Lactam antibiotics coat the platelet membrane, whereas the cephalosporins are rather profound but short-term platelet inhibitors. Many cardiac surgeons may not realize that their standard drug regimen for antibiotics may be far more of a bleeding risk than aspirin. Hundreds of drugs can inhibit platelet function. Calcium channel blockers, nitrates, and β-blockers are ones commonly utilized in cardiac surgery. Nitrates are effective antiplatelet agents and that may be part of why they are of such benefit in angina, not just for their vasorelaxing effect on large blood vessels. Nonsteroidal anti-inflammatory drugs (NSAIDs) reversibly inhibit both endothelial cell and platelet cyclooxygenase.

In addition to the partial inhibitory effects of aspirin and the other drugs just mentioned, new therapies have been developed that inhibit platelet function in a more specific manner. These drugs include platelet adhesion inhibitor agents, platelet-ADP-receptor antagonists, and GPIIb/IIIa receptor inhibitors (Table 24-1).

ADHESION INHIBITORS

Dipyridamole (Persantine) and cilostazol (Pletal) alter platelet adhesion by various mechanisms, including cyclic adenosine monophosphate (cAMP), phosphodiesterase III, and thromboxane A_2 inhibition. Dipyridamole has been used with warfarin in some patients with artificial valves and with aspirin in patients with peripheral vascular disease.

ADP RECEPTOR ANTAGONISTS

Clopidogrel (Plavix) and ticlopidine (Ticlid) are thienopyridine derivatives that inhibit the ADP receptor pathway to platelet activation. They have a slow onset of action because they must be converted to active drugs, and their potent effects last the lifetime of the platelets affected (5 to 10 days). Clopidogrel is the preferred drug because it has a better safety record than ticlopidine. It is administered orally once daily to inhibit platelet function and is quite effective in decreasing myocardial infarctions after percutaneous coronary interventions (PCIs). The combination of aspirin and clopidogrel has led to increased bleeding, but it is sometimes used in an effort to keep vessels and stents open. The thromboelastogram (TEG) with ADP added can be used to determine the degree of inhibition due to these drugs.

GPIIB/IIIA RECEPTOR INHIBITORS

These are the most potent (>90% platelet inhibition) and important platelet inhibitors because they act at the final common pathway of platelet aggregation with fibrinogen, no matter which agonist began the process. All of the drugs mentioned earlier work at earlier phases of activation of platelet function. These drugs are all administered by intravenous infusion, and they do not work orally. The GPIIb/IIIa inhibitors are often used in patients taking aspirin because they do not block thromboxane A_2 production.

Table 24-1 Antiplatelet Therapy

Drug Type	Composition	Mechanism	Indications	Route	Half-life	Metabolism
Aspirin	Acetylsalicylic acid	Irreversible COX inhibition	CAD, AMI, PVD, PCI, ACS	Oral	10 days	Liver, kidney
NSAIDs	Multiple	Reversible COX inhibition	Pain	Oral	2 days	Liver, kidney
Adhesion inhibitors (e.g., dipyridamole)	Multiple	Block adhesion to vessels	VHD, PVD	Oral	12 hr	Liver
ADP receptor antagonists (e.g., clopidogrel)	Thienopyridines	Irreversible inhibition of ADP binding	AMI, CVA, PVD, ACS, PCI	Oral	5 days	Liver
GPIIb/IIIa receptor inhibitors						
Abciximab (ReoPro)	Monoclonal antibody	Nonspecific—binds to other receptors	PCI, ACS	IV	12-18 hr	Plasma proteinase
Eptifibatide (Integrilin)	Peptide	Reversible—specific to GPIIb/IIIa	PCI, ACS	IV	2-4 hr	Kidney
Tirofiban (Aggrastat)	Nonpeptide-tyrosine derivative	Reversible—specific to GPIIb/IIIa	PCI, ACS	IV	2-4 hr	Kidney

COX = cyclooxygenase; CAD = coronary artery disease; AMI = acute myocardial infarction; PVD = peripheral vascular disease; PCI = percutaneous coronary intervention; ACS = acute coronary syndrome; VHD = valvular heart disease; CVA = cerebrovascular disease; IV = intravenous; ADP = adenosine diphosphate; GP = glycoprotein.

The dose of heparin is usually reduced when used with these drugs. Platelet activity can be monitored to determine the extent of blockade. Excessive bleeding requires allowing the short-acting drugs to wear off, while possibly administering platelets to patients receiving the long-acting drug abciximab. Most studies have found increased bleeding in patients receiving these drugs who required emergency CABG.

Vascular Endothelium

The cells that form the intima of vessels provide an excellent nonthrombogenic surface. Characteristics of this surface, which may account for its nonthrombogenicity, include negative charge; incorporation of heparan sulfate in the grid substance; the release of prostacyclin, nitric oxide, adenosine, and protease inhibitors by endothelial cells; binding and clearance of activated coagulation factors both directly, as occurs with thrombin, and indirectly, as evidenced by the action of thrombomodulin to inactivate factors Va and VIIIa via protein C; and stimulation of fibrinolysis.

Nitric oxide vasodilates blood vessels and inhibits platelets. Its mechanism involves activation of guanylate cyclase with eventual uptake of calcium into intracellular storage sites. Prostacyclin (PGI_2) possesses powerful vasodilator and antiplatelet properties. Endothelium-derived prostacyclin opposes the vasoconstrictor effects of platelet-produced thromboxane A_2. Prostacyclin also inhibits platelet aggregation, disaggregates clumped platelets, and, at high concentrations, inhibits platelet adhesion. Prostacyclin increases intracellular concentrations of cAMP, which inhibits aggregation. Thromboxane acts in an opposite manner. The mechanism of prostacyclin action is stimulation of adenylyl cyclase, leading to reduced intracellular calcium concentrations. Some vascular beds (e.g., lung) and atherosclerotic vessels secrete thromboxane, endothelins, and angiotensin, all vasoconstrictors, as well as prostacyclin. Activation of platelets releases endoperoxides and arachidonate. These substances, utilized by nearby damaged endothelial cells, provide substrate for prostacyclin production.

Fibrinolysis

Fibrin breakdown, a normal hematologic activity, is localized to the vicinity of a clot. It remodels formed clot and removes thrombus when endothelium heals. Like clot formation, clot breakdown may occur by intrinsic and extrinsic pathways. As with clot formation, the extrinsic pathway plays the dominant role in clot breakdown. Each pathway activates plasminogen, a serine protease synthesized by the liver, which circulates in zymogen form. Cleavage of plasminogen by the proper serine protease forms plasmin. Plasmin splits fibrinogen or fibrin at specific sites. Plasmin is the principal enzyme of fibrinolysis, just as thrombin is principal to clot formation. Plasma normally contains no circulating plasmin, because a scavenging protein, α_2-antiplasmin, quickly consumes any plasmin formed from localized fibrinolysis. Thus, localized fibrinolysis, not systemic fibrinogenolysis, accompanies normal hemostasis.

Extrinsic Fibrinolysis

Endothelial cells synthesize and release t-PA. Both t-PA and a related substance, urokinase plasminogen activator (u-PA), are serine proteases that split plasminogen to form plasmin. The activity of t-PA magnifies on binding to fibrin. In this manner also, plasmin formation remains localized to sites of clot formation. Epinephrine, bradykinin, thrombin, and factor Xa cause endothelium to release t-PA, as do venous occlusion and CPB.

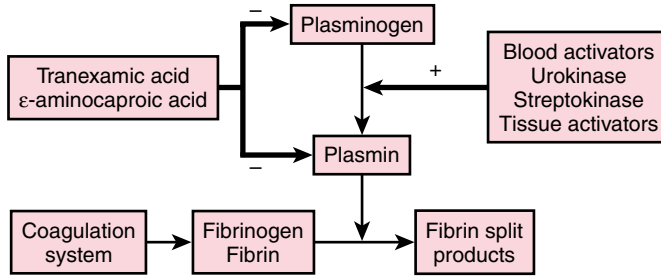

Figure 24-4 The fibrinolytic pathway. Antifibrinolytic drugs inhibit fibrinolysis by binding to both plasminogen and plasmin. Intrinsic blood activators (factor XIIa), extrinsic tissue activators (t-PA, u-PA), and exogenous activators (streptokinase, ASPAC) split plasminogen to form plasmin. (From Horrow JC, Hlavacek J, Strong MD, et al: Prophylactic tranexamic acid decreases bleeding after cardiac operations. J Thorac Cardiovasc Surg 99:70, 1990.)

Intrinsic Fibrinolysis

Factor XIIa, formed during the contact phase of coagulation, cleaves plasminogen to plasmin. The plasmin so formed then facilitates additional cleavage of plasminogen by factor XIIa, forming a positive feedback loop.

Exogenous Activators

Streptokinase (made by bacteria) and urokinase (found in human urine) both cleave plasminogen to plasmin, but do so with low fibrin affinity. Thus, systemic plasminemia and fibrinogenolysis as well as fibrinolysis ensue. Acetylated streptokinase plasminogen activator complex (ASPAC) provides an active site, which is not available until deacetylation occurs in blood. Its systemic lytic activity lies intermediate to those of t-PA and streptokinase. Recombinant t-PA (rt-PA; Alteplase) is a second-generation agent that is made by recombinant DNA technology and is relatively fibrin specific.

Clinical Applications

Figure 24-4 illustrates the fibrinolytic pathway, with activators and inhibitors. Streptokinase, ASPAC, and t-PA find application in the lysis of thrombi associated with myocardial infarction. These intravenous agents "dissolve" clots that form on atheromatous plaque. Clinically significant bleeding may result from administration of any of these exogenous activators or streptokinase.

Fibrinolysis also accompanies CPB. This undesirable breakdown of clot after surgery may contribute to postoperative hemorrhage and the need to administer allogeneic blood products. Regardless of how they are formed, the breakdown products of fibrin intercalate into sheets of normally forming fibrin monomers, thus preventing cross-linking. In this way, extensive fibrinolysis exerts an antihemostatic action.

HEPARIN

Pharmacology

Chemical Structure

The *N*-sulfated-D-glucosamine and L-iduronic acid residues of heparin alternate in copolymer fashion to form chains of varying length (Fig. 24-5). As a linear anionic polyelectrolyte, with the negative charges being supplied by sulfate groups, heparin demonstrates a wide spectrum of activity with enzymes, hormones, biogenic amines,

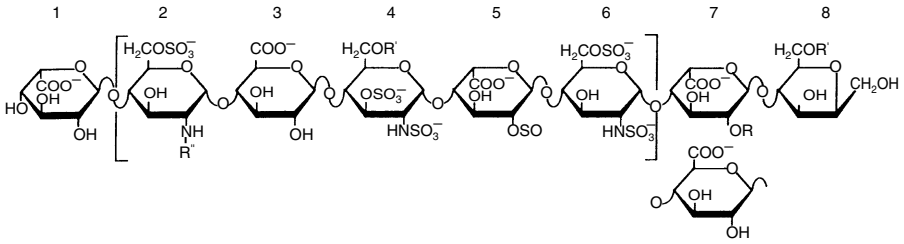

Figure 24-5 An octasaccharide fragment of heparin, a substituted alternating copolymer of iduronic acid and glucosamine. The leftmost sugar is iduronic acid. Note the numerous sulfate groups and the acetyl substitution on the second sugar. Variations in sugar substitutions and in chain length produce molecular heterogeneity. Brackets indicate the pentasaccharide sequence that binds to antithrombin. (From Rodén L: Highlights in the history of heparin. In Lane DA, Lindahl U [eds]: Heparin. Boca Raton, FL, CRC Press, 1989.)

and plasma proteins. A pentasaccharide segment binds to antithrombin. Heparin is a heterogeneous compound: the carbohydrates vary in both length and side chain composition, yielding a range of molecular weights from 5000 to 30,000, with most chains between 12,000 and 19,000. Today, the standard heparin is called unfractionated heparin (UFH).

Source and Biological Role

Heparin is found mostly in the lungs, intestines, and liver of mammals, with skin, lymph nodes, and thymus providing less plentiful sources. Abundance of heparin in tissues rich in mast cells suggests these as the source of the compound. Its presence in tissues with environmental contact suggests a biological role relating to immune function. Heparin may assist white blood cell movements in the interstitium after an immunologic response has been triggered.

Most commercial preparations of heparin now use pig intestine, 40,000 pounds of which yield 5 kg of heparin. Prevention of postoperative thrombosis constituted the initial clinical use of heparin in 1935.

Potency

Heparin potency is determined by comparing the test specimen against a known standard's ability to prolong coagulation. Current United States Pharmacopeia (USP) and British Pharmacopoeia (BP) assays use a PT-like method on pooled sheep's plasma obtained from slaughterhouses.

UFH dose should not be specified by weight (milligrams) because of the diversity of anticoagulant activity expected from so heterogeneous a compound. One USP unit of heparin activity is the quantity that prevents 1.0 mL of citrated sheep's plasma from clotting for 1 hour after addition of calcium. Units cannot be cross-compared among heparins of different sources, such as mucosal versus lung or low-molecular-weight heparin (LMWH) versus UFH or even lot to lot, because the assay used may or may not reflect actual differences in biological activity. None of these measures has anything to do with the effect of a unit on anticoagulation effect for human cardiac surgery.

Pharmacokinetics and Pharmacodynamics

The heterogeneity of UFH molecules produces variability in the relationship of dose administered to plasma level of drug. In addition, the relationship of plasma level to biological effect varies with the test system. A three-compartment model describes

heparin kinetics in healthy humans: rapid initial disappearance, saturable clearance observed in the lower dose range, and exponential first-order decay at higher doses. The rapid initial disappearance may arise from endothelial cell uptake. The reticuloendothelial system, with its endoglycosidases and endosulfatases, and uptake into monocytes, may represent the saturable phase of heparin kinetics. Finally, renal clearance via active tubular secretion of heparin, much of it desulfated, explains heparin's exponential clearance.

Male gender and cigarette smoking are associated with more rapid heparin clearance. The resistance of patients with deep vein thrombosis or pulmonary embolism to heparin therapy may be due to the release from thrombi of platelet factor 4 (PF4), a known heparin antagonist. Chronic renal failure prolongs elimination of high, but not low, heparin doses. Chronic liver disease does not change elimination.

Loading doses for CPB (200 to 400 units/kg) are substantially higher than those used to treat venous thrombosis (70 to 150 units/kg). Plasma heparin levels, determined fluorometrically, vary widely (2 to 4 units/mL) after doses of heparin administered to patients about to undergo CPB. The ACT response to these doses of heparin displays even greater dispersion. However, the clinical response to heparin administered to various patients is more consistent than suggested by in vitro measurements.

Actions and Interactions

Heparin exerts its anticoagulant activity via ATIII, one of the many circulating serine protein inhibitors (serpins), which counter the effects of circulating proteases. The major inhibitor of thrombin and factors IXa and Xa is ATIII; that of the contact activation factors XIIa and XIa is α_1-proteinase inhibitor; kallikrein inhibition arises mostly from C1 inhibitor. Antithrombin activity is greatly decreased at a site of vascular damage, underscoring its primary role as a scavenger for clotting enzymes that escape into the general circulation.

Antithrombin inhibits serine proteases even without heparin. The extent to which heparin accelerates antithrombin inhibition depends on the substrate enzyme: UFH accelerates the formation of the thrombin-antithrombin complex by 2000-fold but accelerates formation of the factor Xa-antithrombin complex by only 1200-fold. In contrast, LMWH fragments preferentially inhibit factor Xa. Enzyme inhibition proceeds by formation of a ternary complex consisting of heparin, antithrombin, and the proteinase to be inhibited (e.g., thrombin, factor Xa). For UFH, inhibition of thrombin occurs only on simultaneous binding to both antithrombin and thrombin. This condition requires a heparin fragment of at least 18 residues. A pentasaccharide sequence binds to antithrombin. LMWHs, consisting of chains 8 to 16 units long, preferentially inhibit factor Xa. In this case, the heparin fragment activates antithrombin, which then sequentially inactivates factor Xa; heparin and factor Xa do not directly interact (Fig. 24-6).

Several investigators have demonstrated continued formation of fibrinopeptides A and B, and prothrombin fragment F1.2 and thrombin-antithrombin complexes, despite clearly acceptable anticoagulation for CPB by many criteria. These substances indicate thrombin activity. The clinical significance of this ongoing thrombin activity has had limited study. The ACT must be more prolonged to prevent fibrin formation during cardiac surgery compared with during extracorporeal circulation without surgery, because surgery itself incites coagulation. UFH in conjunction with antithrombin appears to work in plasma only on free thrombin. When considering what is known today about thrombin burst and thrombin activity, heparin appears to be relatively inefficient, because there is not much free thrombin. Thrombin is held on the surface of activated platelets at various glycoprotein binding sites including the GPIIb/IIIa site. Most thrombin

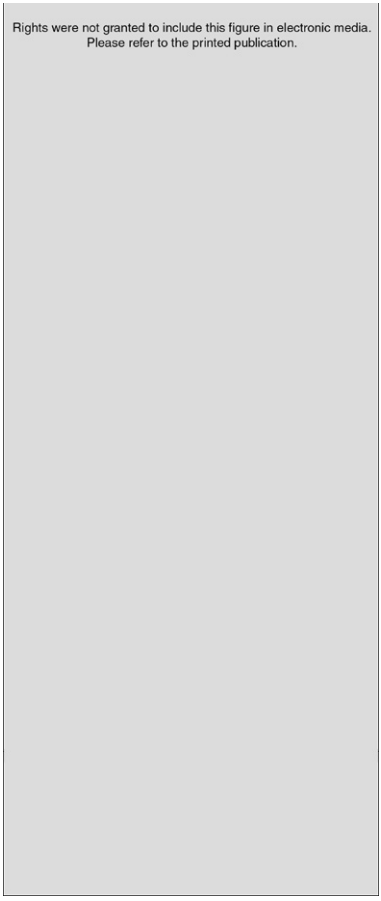

Figure 24-6 Antithrombin interaction (AT) with factor Xa may occur with either low-molecular-weight heparin (H) (**A**) or standard unfractionated heparin (**B**). Inhibition of thrombin (factor IIa), however, requires simultaneous binding of the heparin molecule to both antithrombin and thrombin (**C**). (From Holmer E, Soderberg K, Bergqvist D, Lindahl U: Heparin and its low-molecular-weight derivatives: Anticoagulant and antithrombotic properties. Haemostasis 16[suppl 2]:1, 1986.)

is fibrin bound, and heparin-antithrombin complexes do not bind at all to this thrombin unless the level of heparin is pushed far above what is used routinely for CPB. The idea behind using heparin for CPB is that by creating a large circulating concentration of activated antithrombin, whenever a thrombin molecule is produced, an available antithrombin molecule will be there to immediately bind to it before it can have any further activating effect. Clearly, that is unrealistic with the knowledge that thrombin exerts its main activity by binding to the surface of platelets.

Heparin Resistance

Patients receiving UFH infusions exhibit a much diminished ACT response to full anticoagulating doses of UFH for CPB (200 to 400 units/kg). With widespread use of heparin infusions to treat myocardial ischemia and infarction, heparin resistance or,

BOX 24-2 *Problems with Heparin as an Anticoagulant for Cardiopulmonary Bypass*

- Heparin resistance
- Heparin-induced thrombocytopenia
- Heparin rebound
- Heparin's heterogeneity and variable potency

more appropriately, "altered heparin responsiveness" has become more problematic during cardiac surgery (Box 24-2).[5]

Mechanism

Hemodilution accompanying CPB decreases antithrombin levels to about half of normal levels. There are, however, outlier patients who have profoundly low antithrombin levels. It is possible to see ATIII levels as low as 20% of normal, and these levels correspond to levels seen in septic shock and diffuse intravascular coagulation. However, supplemental antithrombin may not prolong the ACT, which means that the heparin available has been bound to sufficient or available antithrombin. The only way that the ACT would be prolonged is if there is excess heparin beyond available antithrombin. Reports of heparin resistance for CPB ascribe its occurrence variously to the use of autotransfusion, previous heparin therapy, infection, and ventricular aneurysm with thrombus.

The individual anticoagulant response to heparin varies tremendously. Some presumed cases of heparin resistance may represent nothing more than this normal variation. Regardless of cause, measurement of each individual's anticoagulant response to heparin therapy for CPB is warranted. Heparin resistance helps focus the debate regarding whether anticoagulation monitoring should measure heparin concentrations or heparin effect: the goal of anticoagulation is not to achieve heparin presence in plasma but to inhibit the action of thrombin on fibrinogen, platelets, and endothelial cells. Therefore, heparin effect is usually measured.

Treatment

Most commonly, additional heparin prolongs the ACT sufficiently for the conduct of CPB. Amounts up to 800 units/kg may be necessary to obtain an ACT of 400 to 480 seconds or longer. Whereas administration of fresh frozen plasma (FFP), which contains antithrombin, should correct antithrombin depletion and suitably prolong the ACT, such exposure to transfusion-borne infectious diseases should be avoided whenever possible. This modality is reserved for the rare refractory case. Rather than administer FFP, centers normally accepting only ACTs of 480 seconds or longer for CPB might consider accepting 400 seconds or less, or administering ATIII concentrate.

Antithrombin concentrate specifically addresses antithrombin deficiency. It is a solvent detergent-treated and heat-inactivated product providing greater protection against infectious disease transmission than that provided by FFP. The literature supports its success in treating heparin resistance during cardiac surgery. A multicenter study on the efficacy of using a recombinant human antithrombin (rhAT) in heparin-resistant patients undergoing CPB was published.[6] The patients received 75 units/kg of rhAT, which was effective in restoring heparin responsiveness in most patients. However, some patients still required FFP and the patients bled more than did a control group postoperatively.

BOX 24-3 ***Considerations in Determining the Proper Dose of Protamine to Reverse Heparin***

- The proper dose is very broad and difficult to know exactly.
- The dose should be determined by a measurement of coagulation.
- The dose should be administered over at least 10 minutes.

Heparin Rebound

Several hours after protamine neutralization for cardiac surgery, some patients develop clinical bleeding associated with prolongation of coagulation times. This phenomenon is often attributed to reappearance of circulating heparin. Theories accounting for "heparin rebound" include late release of heparin sequestered in tissues, delayed return of heparin to the circulation from the extracellular space via lymphatics, clearance of an unrecognized endogenous heparin antagonist, and more rapid clearance of protamine in relation to heparin. Studies demonstrating uptake of heparin into endothelial cells suggest that these cells may slowly release the drug into the circulation once plasma levels decline with protamine neutralization. It is doubtful how much heparin rebound contributes to actual bleeding. This phenomenon may be caused by TFPI release from the surface of endothelial cells or other causes of bleeding.

Treatment and Prevention

Although still debated by a few, most clinicians accept heparin rebound as a real phenomenon. However, clinical bleeding does not always accompany heparin rebound. When it does, administration of supplemental protamine will neutralize the remaining heparin (Box 24-3).

Heparin Effects other Than Anticoagulation

Unfractionated heparin was never biologically intended to circulate freely in plasma.[7] As such it has a number of underappreciated and untoward effects. All too often the effects of CPB have been asserted as causing a coagulopathy; however, the effect of heparin contributing to this has not been widely studied. That is because there has not been an alternative anticoagulant to compare with heparin until now. In the future, there may be better anticoagulants to use during cardiac surgery.

Heparin exerts its anticoagulant activity by activating a binding site on ATIII; and without antithrombin, heparin has no intrinsic anticoagulation effect. Antithrombin does have anticoagulant effects of its own, but its ability to bind to thrombin is increased 100- to 2000-fold by the presence of the pentasaccharide sequence of heparin. Less than one third of all mucopolysaccharides present in a dose of heparin contain the active pentasaccharide sequence. The other molecules may have a number of adverse properties.

UFH chelates calcium. When a large bolus dose of heparin is given, there is a slow and steady decline in blood pressure, probably due to decreased vascular resistance and decreased preload. Both arterial and venous vessels are dilated by the decrease in the calcium level. The heparin is given while patients are being prepared for CPB, and there are numerous mechanical events (i.e., catheters being inserted into the right atrium and vena cava and arrhythmias) that can be blamed for the hypotension, rather than the heparin itself.

Heparin is important for a number of angiogenesis and repair activities of tissue, and these effects may have something to do with its antineoplastic effect. Heparin also affects lipid, sodium and potassium, and acid-base metabolism. These effects are not usually seen acutely but come into play when patients have been on heparin infusions for days in the intensive care unit.

The immunologic effects of heparin are profound: 30% to 50% of cardiac surgery patients have heparin antibodies present in their blood by the time of hospital discharge. The clinical implications of these prevalent antibodies remain unknown.

Heparin-Induced Thrombocytopenia

Heparin normally binds to platelet membranes at GPIb and other sites and aggregates normal platelets by releasing ADP. A moderate, reversible, heparin-induced thrombocytopenia (HIT), now termed *type I,* has been known for half a century. The fact that heparin actually triggers an acute drop in platelet count should be considered a biological event, because heparin, even in trace amounts, triggers the expression of many different platelet glycoproteins. Some have termed this *activation* of platelets, but it is not total activation. Heparin's prolongation of the bleeding time is probably related to both activation of the platelets as well as heparin binding to the GPIb surface.

In contrast to these predictable effects of heparin, occasional patients develop progressive and severe thrombocytopenia (<100,000/mm^3), sometimes accompanied by a debilitating or fatal thrombosis. This syndrome is termed *type II heparin-induced thrombocytopenia* (HIT II). A platelet count in excess of 100,000/mm^3 does not mean that HIT II is not present. A drop in platelet count in excess of 30% to 50% over several days in a patient who is receiving or who has just finished receiving heparin is probably HIT II.

Mechanism

These patients demonstrate a heparin-dependent antibody, usually IgG, although others are described, which aggregates platelets in the presence of heparin.[8] During heparin therapy, measured antibody titers remain low, owing to antibody binding to platelets. Titers rise after heparin therapy ceases; but paradoxically, antibody may be undetectable a few months later. Two other features are unexpected: first, the antibody does not aggregate platelets in the presence of excess heparin; and, second, not all reexposed patients develop thrombocytopenia.

The platelet surface contains complexes of heparin and PF4. Affected patients have antibody to this complex. Antibody binding activates platelets via their FcγII receptors and activates endothelium (Fig. 24-7). The activation of the platelet surface triggers a secondary thrombin release. Platelets can attach to each other creating what is known as a white clot syndrome. But if secondary thrombin generation is created through antibody activation of the platelets then a fibrin clot can be the result. In the absence of heparin, the heparin-PF4 antigen cannot form.

In the absence of an endothelial defect, the only responses to the antibody-antigen interaction are platelet consumption and thrombocytopenia. Atheroma rupture, endovascular interventions such as balloon angioplasty, vascular surgery, and other procedures that disrupt endothelium can provide a nidus for platelet adhesion and subsequent activation. PF4, released with platelet activation, binds to heparin locally, thus not only removing the inhibition of coagulation but also generating additional antigenic material (Fig. 24-8). Clumps of aggregated platelets thrombose vessels, resulting in organ and limb infarction. Amputation and/or death often occurs with established HIT with thrombosis (HITT). The presence of heparin-PF4 antibodies

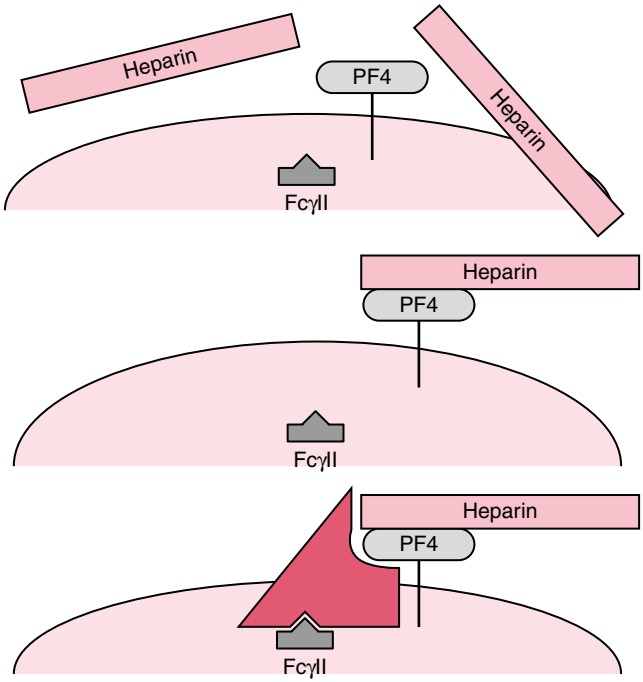

Figure 24-7 Presumed mechanism of the interaction among heparin, platelets, and antibody in heparin-induced thrombocytopenia. **Top,** Platelet factor 4 (PF4) released from platelet granules is bound to the platelet surface. **Middle,** Heparin and PF4 complexes form. **Bottom,** The antibody binds to the PF4-heparin complex and activates platelet FcγII receptors.

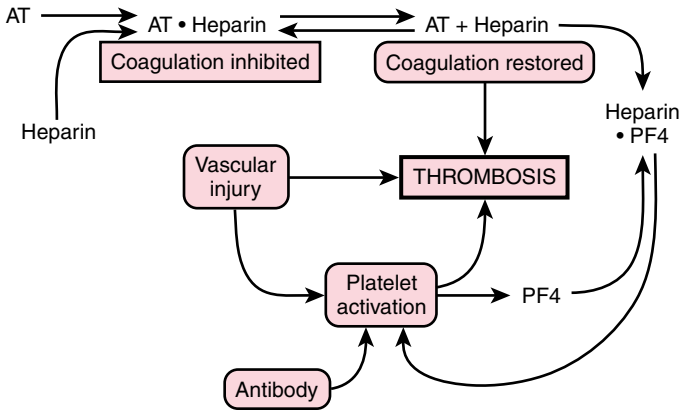

Figure 24-8 Mechanism of thrombosis accompanying heparin-induced thrombocytopenia. Normally, heparin and antithrombin (AT) form a complex that inhibits coagulation. Platelet factor 4 (PF4), released from platelets upon activation, binds heparin and drives the dissociation reaction of the antithrombin-heparin complex to the right, restoring coagulation locally. Restored coagulation mechanisms and activated platelets form thrombus in the presence of vascular injury. (Adapted from Parmet JL, Horrow JC: Hematologic diseases. In Benumof J [ed]: Anesthesia and Uncommon Diseases, 3rd ed. Philadelphia, WB Saunders, 1997.)

has recently been associated with other adverse effects. It appears that if a patient undergoes cardiac surgery with positive antibodies, the risk of mortality and/or myocardial infarction may at least double.

Incidence and Diagnosis

Estimates of the true incidence of this syndrome are confounded by different diagnostic thresholds for platelet count, varying efforts to detect other causes, and incomplete reports. After 7 days of therapy with UFH, probably 1% of patients develop HIT; after 14 days of therapy the prevalence is 3%. Using a platelet count of 100,000/mm^3, multiple reports comprising more than 1200 patients revealed an overall incidence of HIT of 5.5% with bovine heparin and 1.0% with porcine heparin. Other recent research has found the preoperative incidence of ELISA-positive patients to be between 6.5% to 10%. This means that antibodies are present and that may not mean that thrombocytopenia is occurring. Of great interest is that many more patients develop positive tests for ELISA antibodies by days 7 to 30 after cardiac surgery. Somewhere between 25% and 50% of patients develop these antibodies.

Heparin-induced thrombocytopenia can occur not only during therapeutic heparin administration but also with low prophylactic doses, although the incidence is dose related. Even heparin flush solution or heparin-bonded intravascular catheters can incite HIT. Cases of platelet-to-platelet adhesion creating a "white clot" in otherwise normal patients have been observed in the oxygenator and the reservoir of CPB machines. The fact that such events have been reported even when all other tests appeared normal signals the unpredictable nature of the heparin-PF4 antibody as well as the biological activity of UFH.

Although HIT usually begins 3 to 15 days (median, 10 days) after heparin infusions commence, it can occur within hours in a patient previously exposed to heparin. Platelet count steadily decreases to a nadir between 20,000 and 150,000/mm^3. Absolute thrombocytopenia is not necessary; only a significant decrease in platelet count matters, as witnessed by patients with thrombocytosis who develop thrombosis with normal platelet counts after prolonged exposure to heparin. Occasionally, thrombocytopenia resolves spontaneously despite continuation of heparin infusion.

Clinical diagnosis of HIT requires a new decrease in platelet count during heparin infusion. Laboratory confirmation is obtained from several available tests. In the serotonin release assay, patient plasma, donor platelets, and heparin are combined. The donor platelets contain radiolabeled serotonin, which is released when donor platelets are activated by the antigen-antibody complex. Measurement of serotonin release during platelet aggregation at both low and high heparin concentrations provides excellent sensitivity and specificity.

A second assay measures more traditional markers of platelet degranulation in a mixture of heparin, patient plasma, and donor platelets. The most specific test is an enzyme-linked immunosorbent assay for antibodies to the heparin-PF4 complex.

Measurement of platelet-associated IgG is poorly specific for HIT, because of numerous other causes of antiplatelet IgG. This test should not be used in the diagnosis of HIT.

Heparin-Induced Thrombocytopenia with Thrombosis

The incidence of HITT is 1.7% with bovine heparin and 0.3% with porcine heparin; thus, thrombosis accompanies more than one in five cases of HIT. It is clear that the longer patients are on heparin the more likely it is that they will develop antibody; and with

the knowledge that today close to 50% of cardiac patients develop antibodies, it is possible that a significant number of long-term or early mortalities might be due to undiagnosed HITT. In several studies in the catheterization laboratory, it has been shown that if HITT antibodies are present before the performance of angioplasty, the mortality and combined morbidity are greatly increased, perhaps double or more. One study has been carried out in almost 500 patients undergoing CABG surgery looking for the presence of antibodies and outcome. The incidence of antibody-positive patients was approximately 15%, and their length of stay in the hospital and mortality were more than doubled. Occasional rare situations in which the CPB circuit suddenly clots or when there is early graft thrombosis or whole-body clotting may all be variants of HITT, but none of these cases can be readily studied because they are so rare. If such an occurrence does happen, HITT should be in the differential diagnosis. The occurrence of thrombosis at first seems paradoxical. However, HITT has as its hallmark a huge thrombin burst that can occur all over the body. With such massive thrombin generation the triggering of thrombosis is natural. Thrombosis may then activate the fibrinolytic system to produce a picture of consumptive coagulopathy.

From 15% to 30% of patients who develop HIT with thrombosis will develop severe neurologic complications, require amputation of a limb, or die. Lower limb ischemia constitutes the most frequent presentation. Venous clots occur probably as frequently as arterial ones but are not detected as often. Unfortunately, no test predicts the thrombosis component of HIT; thrombosis should be anticipated in the presence of vascular injury, such as puncture sites for catheterization.

Treatment and Prevention

In the absence of surgery, bleeding from thrombocytopenia with HIT is rare. In contrast to other drug-induced thrombocytopenias, in which severe thrombocytopenia commonly occurs, more moderate platelet count nadirs characterize HIT. Platelet transfusions are not indicated and may incite or worsen thrombosis. Heparin infusions must be discontinued, and an alternative anticoagulant should be instituted. LMWHs can be tested in the laboratory using serotonin release before patient administration. Although thrombosis may be treated with fibrinolytic therapy, surgery is often indicated. No heparin should be given for vascular surgery. Monitoring catheters should be purged of heparin flush, and heparin-bonded catheters should not be placed. Antiplatelet agents, such as aspirin, ticlopidine, or dipyridamole, which block adhesion and activation and, thus, PF4 release, provide ancillary help.

The patient presenting for cardiac surgery who has sustained HIT in the past presents a therapeutic dilemma. Antibodies may have regressed; if so, a negative serotonin release assay using the heparin planned for surgery will predict that transient exposure during surgery will be harmless. However, no heparin should be given at catheterization or in flush solutions after surgery.

Patients with HIT who require urgent surgery may receive heparin once platelet activation has been blocked with aspirin and dipyridamole or, in the past, the prostacyclin analog iloprost. Unfortunately, iloprost is no longer available. The problem with this strategy is obtaining sufficient blockade of platelet activity.

Another alternative, delaying surgery to wait for antibodies to regress, may fail because of the variable offset of antibody presence and the unpredictable nature of platelet response to heparin rechallenge. Plasmapheresis may successfully eliminate antibodies and allow benign heparin administration. Finally, methods of instituting anticoagulation without heparin may be chosen.

Table 24-2 Therapeutic Options for Anticoagulation for Bypass in Patients with Heparin-Induced Thrombocytopenia*

1. Ancrod
2. Low-molecular-weight heparin or heparinoid (test first!)
3. Alternative thrombin inhibitor (hirudin, bivalirudin, argatroban)
4. Use a single dose of heparin, promptly neutralize with protamine, *and*
   a. Delay surgery so antibodies can regress; *or*
   b. Employ plasmapheresis to decrease antibody levels; *or*
   c. Inhibit platelets with iloprost, aspirin and dipyridamole (Persantine), abciximab, or RGD blockers

In all cases
1. No heparin in flush solutions
2. No heparin-bonded catheters
3. No heparin lock intravenous ports

*No agent is indicated for anticoagulation in CPB at this time.

BOX 24-4 *Potential Replacements as an Anticoagulant for Cardiopulmonary Bypass*

- Ancrod
- Low-molecular-weight heparins
- Factor Xa inhibitors
- Bivalirudin or other direct thrombin inhibitors
- Platelet receptor inhibitors

LMWH heparin, as an alternative to UFH, has been used for urgent surgery. While LMWHs can also induce thrombocytopenia, by displaying different antigenic determinants, they may prove acceptable alternatives for patients who develop HIT from UFH. Table 24-2 summarizes the therapeutic options available for urgent cardiac surgery in patients with HIT.

New Modes of Anticoagulation

The hemostatic goal during CPB is complete inhibition of the coagulation system. Unfortunately, even large doses of heparin do not provide this, as evidenced by formation of fibrinopeptides during surgery. Despite being far from the ideal anticoagulant, heparin still performs better than its alternatives. Current substitutes for heparin include ancrod, a proteinase obtained from snake venom that destroys fibrinogen; heparin fragments, which provide less thrombin inhibition than the parent, unfractionated molecule; direct factor Xa inhibitors; and direct thrombin inhibitors (Box 24-4).

Ancrod

Ancrod abnormally cleaves fibrinogen, resulting in its rapid clearance by the reticuloendothelial system. Thrombin, thus, has no substrate on which to act. Proper patient preparation for CPB (plasma fibrinogen, 0.4 to 0.8 g/L) requires more than 12 hours. Replenishment of fibrinogen via hepatic synthesis is slow; cryoprecipitate and/or FFP administration will speed restoration of coagulation. Patients

anticoagulated in this fashion bleed more and require more cryoprecipitate and FFP compared with heparin-anticoagulated patients. Ancrod is not commercially available in the United States.

Direct Thrombin Inhibitors

Hirudin, a single-chain polypeptide containing 65 amino acids with a molecular weight of 7000 and produced by the medicinal leech *Hirudo medicinalis,* binds directly to thrombin without need of a cofactor or enzyme, inhibiting all the proteolytic functions of thrombin. This inhibition includes actions on fibrinogen; factors V, VIII, and XIII; and platelets.

Modifications of hirudin include hirugen, a synthetic peptide containing residues 53-64 of the native hirudin, and hirulog, formed by attaching the amino acid sequence d-phe-pro-arg-pro-(gly) to the amino-terminal end of hirugen. Hirugen inhibits thrombin's action on fibrinogen, but not on factor V. Hirulog has full inhibitory properties but is slowly cleaved by thrombin itself to a hirugen-like molecule.

Hirudin depends on renal excretion; renal failure prolongs its elimination half-life of 0.6 to 2.0 hours. Although there are no known direct neutralizing agents for these drugs, administration of prothrombin complex may partially restore coagulation by enhancing thrombin generation. Clinical trials of hirudin compounds have yielded mixed results. It has been used for patients with HITT but the longer half-life of approximately 90 minutes means that many of these patients bleed after cardiac surgery. Hirudin is highly antigenic and will lead to immune complexes being created to itself in about 40% of patients. If it is used a second time, the overall incidence of anaphylaxis may be as high as 10% of all patients who have received it before.

New direct thrombin inhibitors are now available (Fig. 24-9).[9] These include argatroban and bivalirudin. Argatroban is a derivative of arginine and is a relatively small molecule. It binds at the active cleavage site of thrombin and stops thrombin's action on serine proteases. It is completely hepatically cleared and has a half-life of 45 to 55 minutes with prolongation when liver function is depressed or liver blood flow is decreased. There is no reversal agent for argatroban. It has been approved by the U.S. Food and Drug Administration (FDA) for anticoagulation in the face of HITT, but there has not been, to date, a large-scale prospective randomized trial for cardiac surgery or any type of comparison to heparin/protamine. Some case reports do exist of successful usage of argatroban in HITT patients with acceptable amounts of postoperative bleeding. It has been more commonly utilized in the ICU for patients with hypercoagulable syndromes and HITT.

Bivalirudin is a synthetic peptide based on the structure of hirudin (previously called hirulog). Pharmacologists have taken the active amino acids at either end of the hirudin molecule and biosynthesized them. One active site competitively binds to the fibrinogen-binding site of thrombin, and the other 20-amino-acid sequence binds to the active serine cleavage site of thrombin. The two sequences of amino acids are connected together by a tetraglycine spacer. This fully manufactured molecule is highly specific for thrombin and has the unique property that it binds to both clot-bound and free thrombin. Heparin binds only to free plasma thrombin. Bivalirudin has a shorter half-life than argatroban and hirudin; the half-life is approximately 20 to 25 minutes. Like the other direct thrombin inhibitors, it also has no reversal agent analogous to protamine. So when it is used, it must wear off. Bivalirudin undergoes destruction by the molecule to which it binds and deactivates, thrombin; it spontaneously is destroyed by thrombin (proteolytic cleavage). The more thrombin activation that is present (i.e., the less bivalirudin that is present), the shorter is the half-life. Only about 20% of the molecular activity is eliminated by renal clearance. In mild to moderate renal failure, the effect on bivalirudin clearance is fairly small.

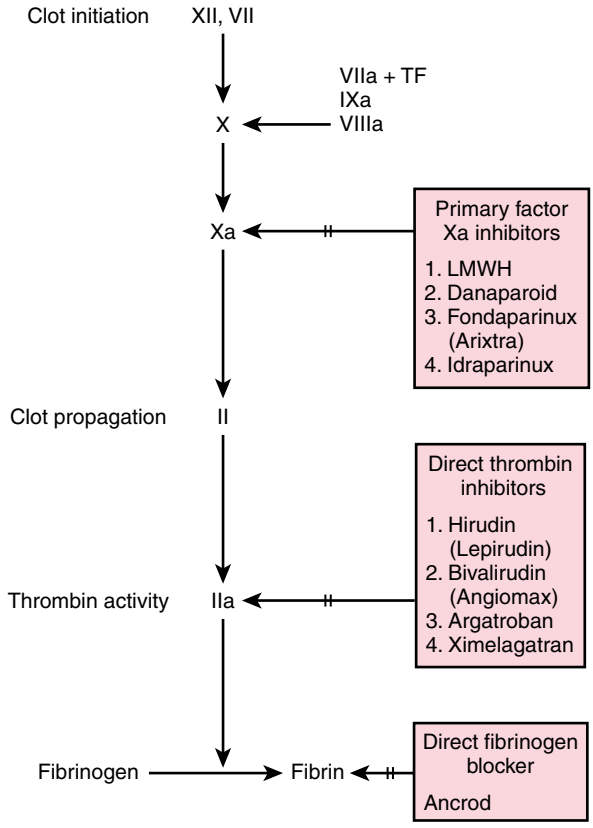

Figure 24-9 Alternatives to heparin. New modes of anticoagulation are shown in the boxes on the right side of the figure where they inhibit either factor Xa, thrombin, or fibrinogen. LMWH = low-molecular-weight heparin.

Several clinical trials of bivalirudin for cardiology procedures or cardiac surgery have been completed and published. Other ongoing and pivotal trials aiming for FDA approval are under way comparing bivalirudin to heparin/protamine for both on- and off-pump CABG cases as well as for patients with HITT. Bivalirudin has been FDA approved as a primary anticoagulant for angioplasty. In trials comparing bivalirudin to either heparin/protamine alone or heparin plus the use of a IIb/IIIa inhibitor, bivalirudin was found to have at least equal or better safety and less bleeding than either of the other therapies. When compared with heparin/protamine alone in PCI, bivalirudin was found to be superior, not just in bleeding, but also in terms of morbidity and mortality (as a combined endpoint). In a trial of 100 off-pump CABG patients randomized to receive either bivalirudin or heparin/protamine, bleeding and outcome were equal between the groups.[10] These patients underwent recatheterization at 3 months, and it was found that the bivalirudin patients had overall better flow down their grafts than did the patients who had received heparin/protamine. A phase I/II safety trial of bivalirudin in 30 on-pump CABG patients has also shown good safety, but no comparison was carried out to look at advantages against heparin/protamine. At this time, considerable research is ongoing and whether bivalirudin will prove superior to heparin/protamine for routine CABG is yet to be seen.[11] When used, the doses for CPB have been a 0.75-mg/kg bolus followed by an infusion

at 1.75 mg/kg/hr titrated to the ACT (target, 2.5 times baseline). The CPB system is also primed with 50 mg, and no stasis can be allowed in the CPB circuit due to metabolism of bivalirudin during CPB. The infusion is stopped 15 to 30 minutes before CPB is discontinued, and patients bleed for up to 4 to 6 hours. In off-pump coronary artery bypass grafting similar doses to ACT targets of 350 to 450 seconds have been used.

In the face of HITT syndrome, case reports continue to show effectiveness and utility of bivalirudin. This is an off-label use of the drug because it has not been FDA approved.

PROTAMINE

Pharmacology

Protamine neutralizes heparin-induced anticoagulation. It is a nitrogenous alkaline substance from sperm heads of salmon. Composed of nearly two-thirds arginine, protamines contain many positive charges. Their biological role is to associate with the negatively charged phosphate groups of nucleic acids.

Neutralization of heparin-induced anticoagulation is the primary use of protamine. Formation of complexes with the sulfate groups of heparin forms the basis for this "antidote" effect. Protamine neutralizes the antithrombin effect of heparin far better than its anti–factor Xa effect. This distinction may arise from the need for thrombin, but not factor Xa, to remain complexed to heparin for antithrombin to exert its inhibitory effect. Because porcine mucosal heparin has more potent anti–factor Xa activity than bovine lung heparin, today's available heparin may prove to be more difficult to neutralize with protamine. Protamine's poor efficacy in neutralizing anti–factor Xa activity limits the utility of LMWH compounds as anticoagulants for CPB.

In the presence of circulating heparin, protamine forms large complexes with heparin. Excess protamine creates larger complexes. The reticuloendothelial system may then dispose of these particles by endocytosis. Although this action has not been proved, macrophages in the lung may constitute the site for elimination of these complexes, because intravenous administration of protamine permits formation of heparin/protamine complexes in the pulmonary circulation first. Proteolytic degradation of the protamine complexed to heparin conceivably results in free heparin. Protamine degradation in vivo proceeds by the action of circulating proteases, among them carboxypeptidase N, an enzyme that also clears anaphylatoxins and kinin pathway products. The time course of protamine disappearance from plasma in patients remains poorly investigated.

The recommended dose of protamine to neutralize heparin varies widely. This variability has been accounted for by differences in timing, temperature, and other environmental factors; choices for coagulation tests and outcome variables; and speculation and unproven assumptions. Protamine titration tests at the conclusion of CPB can determine the amount of heparin remaining in the patient. With automated versions of this test and simple assumptions regarding the volume of distribution of heparin, the amount needed to neutralize the heparin detected in the patient's vasculature can easily be calculated.

An alternative scheme splits a calculated dose of protamine of 1 mg/100 units into two separate doses: an initial dose (75% of the total) after CPB, with the remainder after reinfusion of blood from the bypass circuit. This scheme prevented increased plasma heparin levels and prolongation of the activated partial thromboplastin time (aPTT), compared with a control group. The ACT remained unchanged, perhaps a reflection of its insensitivity to small amounts of circulating heparin.

Adverse Reactions

The potential for a deleterious response to protamine administration raises serious questions and difficult choices in clinical care before, during, and after cardiac operations.

Rapid Administration

PERIPHERAL CARDIOVASCULAR CHANGES

Systemic hypotension from protamine occurs with rapid injection.[12] Decreased systemic vascular resistance (SVR) accompanies the systemic hypotension, whereas venous return and cardiac filling pressures decrease.

What constitutes slow administration? A neutralizing dose given over 5 minutes or longer will rarely engender cardiovascular changes. Systemic hypotension from rapid injection in humans has been ascribed to pharmacologic displacement of histamine from mast cells by the highly alkaline protamine, similar to the mechanism by which curare, morphine, and alkaline antibiotics (e.g., vancomycin and clindamycin) cause hypotension.

EFFECTS ON CARDIAC INOTROPY

Cardiac output (CO) predictably decreases after rapid administration when preload is allowed to decrease. Initial reports indicated a myocardial depressant effect. Patients with established ventricular compromise might suffer further degradation of contractile performance upon exposure to unbound protamine.

Platelet Reactions

The most underappreciated reaction to protamine is thrombocytopenia. When protamine is administered, it binds heparin wherever it comes into contact with it. It may find heparin attached to the surface of platelets and then coat the surface of the platelets with heparin/protamine complexes. It is also possible that heparin and protamine could form cross-links between platelets because the protamine is polycationic and can bind a number of heparin molecules. The end result is a decrease in platelet count within 10 to 15 minutes of administration of protamine. The usual is roughly a 10% drop in platelet count, but it can be larger, when normalization of coagulation is expected. It appears that the platelets are sequestered by the reticuloendothelium and particularly the pulmonary vasculature. It is unclear if those patients with the largest drop in platelets develop the worst bleeding or if they are at the highest risk of pulmonary vasoconstriction and pulmonary hypertension secondary to thromboxane release. The sequestered platelets come back into the circulation over the next few hours, and by 1 to 4 hours the platelet count returns toward normal.

Anaphylactoid Reaction

ALLERGY, ANAPHYLAXIS, AND ADVERSE RESPONSES

Not all adverse responses to protamine are allergic reactions. Hypersensitivity allergic reactions involve release of vasoactive mediators resulting from antigen-antibody interaction. The broader term *anaphylactoid reaction* includes not only severe immediate hypersensitivity allergy, termed *anaphylaxis,* but also other life-threatening idiosyncratic responses of nonimmunologic origin.[13]

DIABETES MELLITUS

Patients receiving protamine-containing insulin develop antibodies to protamine. Between 38% and 91% of these patients demonstrate an antiprotamine IgG; far fewer patients develop an antiprotamine IgE. Do these antibodies cause adverse responses

to protamine administration? Few patients with diabetes actually develop hemodynamic compromise from protamine.

PRIOR EXPOSURE TO PROTAMINE

Previous protamine exposure may occur at catheterization, at prior vascular surgery, or at dialysis. Multiple exposures at intervals of about 2 weeks maximize the chance of an allergic response.

A single intravenous exposure to protamine will engender an IgG or IgE antibody response in 28% of patients. Nevertheless, many thousands of patients each year receive protamine at both catheterization and then later at surgery without sequelae. They offer evidence of the safety of this sequence and the rarity of intravenous exposure to protamine generating clinically significant antibodies.

FISH ALLERGY

Salmon is a vertebrate, or true fish (also known as "fin" fish), as opposed to shellfish, which are invertebrates. Patients allergic to fin fish can respond to protamine with anaphylaxis. No data link shellfish and protamine allergies.

VASECTOMY

Within 1 year of vasectomy, 22% of men develop cytotoxic (IgG) antibody to human protamine, which may cross-react with salmon protamine due to similarity among protamines. These autoantibodies exist in weak titers, however. Prospective studies demonstrate that patients with prior vasectomy receive protamine during cardiac surgery without adverse response.

Pulmonary Vasoconstriction

Several years after pulmonary artery catheters achieved common usage and case reports sensitized clinicians to adverse responses to protamine, Lowenstein and associates reported a series of cases in which protamine caused systemic hypotension, decreased left atrial pressure, elevated rather than decreased pulmonary artery pressure, and right ventricular distention and failure.[14] Unlike in anaphylaxis, plasma histamine levels do not change during this idiosyncratic, catastrophic pulmonary vasoconstriction, thus justifying a separate classification for this unusual response.The duration of pulmonary hypertension may vary substantially from brief episodes to those requiring reinstitution of CPB.

Animal models of type III protamine responses demonstrate that heparin must precede the protamine, that heparin/protamine complexes activate the complement pathway, and that blockade of complement activation attenuates pulmonary damage. Furthermore, leukocytes respond to complement activation by forming free radicals, which stimulate the arachidonate pathway. Blockade of this pathway mitigates the pulmonary response, whereas antihistamines do not. Figure 24-10 summarizes the speculative mechanisms of various adverse responses to protamine.

Theoretically, slow administration should limit type III reactions, because large heparin/protamine complexes would less likely form. Slow dilute infusion (see later) has decreased this adverse response to protamine.

On detection of sudden pulmonary hypertension and systemic hypotension, protamine infusion should cease, as should administration of any cardiovascular depressant. Administration of a heparin bolus should be considered in an attempt to reduce heparin/protamine complex size. Excess heparin would theoretically attract protamine away from large complexes to yield a larger number of smaller size particles. If hemodynamics have not deteriorated sufficiently to warrant immediate reinstitution of CPB, 70 units/kg of heparin should be tried first, then 300 units/kg

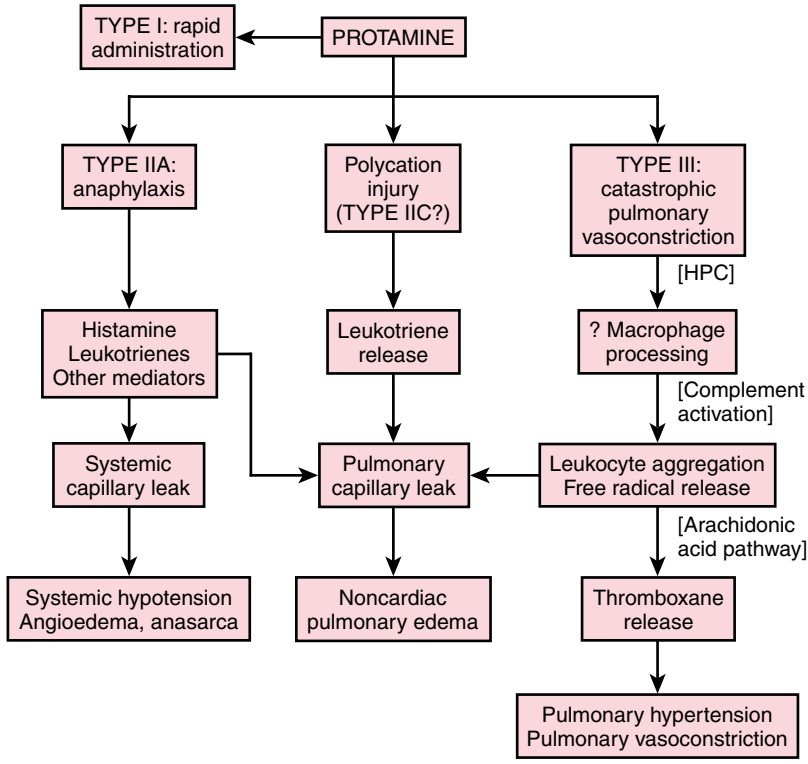

Figure 24-10 Speculative mechanisms of some protamine reactions. HPC = heparin-protamine complex. (From Horrow JC: Heparin reversal of protamine toxicity: Have we come full circle? J Cardiothorac Vasc Anesth 4:539, 1990.)

if that fails. Inotropic support should be selected so as not to worsen the pulmonary hypertension; isoproterenol (0.1 to 0.2 μg/kg bolus followed by 0.1 to 0.3 μg/kg/min) or milrinone appear best suited for this purpose. Milder cases may revert without intervention, merely by halting protamine administration, a highly desirable outcome insofar as the treatments outlined above all extract a price, whether it be arrhythmias from inotropes or bleeding from heparin. Rechallenge with protamine should be avoided.

Guidelines for Clinical Use

The most important principle in avoiding adverse responses to protamine is to administer the drug slowly. Dilution aids this goal by limiting the impact of an undetected rapid administration. A neutralizing dose (3 mg/kg, or 21 mL on average of a 10-mg/mL solution) can be added to 50 mL of clear fluid; then the diluted drug can be administered into a central vein by infusion over 10 to 15 minutes. It is important to provide a carrier flow when administering by peripheral vein, so that the long tubing does not slowly fill with drug rather than the drug enter the patient. Additional doses of undiluted protamine are given from small syringes (5 mL) at a maximum rate of 20 mg/min to adults. Proper choice of materials (small syringes, small drop administration sets, and use of diluent) helps protect against too-rapid drug delivery.

Slow administration should decrease the likelihood of a type I and a type III adverse response. However, anaphylactic response (type IIA) may occur at any delivery rate.

Alternatives to Protamine

This section discusses techniques for neutralizing heparin other than administration of protamine.

Hexadimethrine

This synthetic polycation is 1.1 to 2.0 times more potent than protamine. Hexadimethrine (Polybrene) engenders the same biological responses as protamine when administered rapidly: systemic hypotension, decreased SVR, and rapid disappearance from plasma. Pulmonary hypertension occurs after hexadimethrine neutralization of UFH. Patients allergic to protamine have received hexadimethrine without adverse effects. After reports of renal toxicity, hexadimethrine was withdrawn from clinical use in the United States. Animal studies confirm glomerular injury from hexadimethrine.

Heparinase

The enzyme heparinase, bonded to an exit filter of an experimental bypass circuit and interposed at the conclusion of CPB, decreased blood heparin levels within two passes. Current filters achieve 90% heparin removal with a single pass.

Systemic administration of the enzyme heparinase I, produced by *Flavobacterium,* results in a return of the ACT to normal in an ex vivo model, animal models of CPB, and human volunteers. Initial investigation in patients undergoing elective coronary artery bypass grafting operations confirms the utility of heparinase in neutralizing heparin-induced anticoagulation.[15]

Because the enzyme remains in the vasculature for some time after administration (the half-life is 12 minutes in healthy subjects), should an immediate need arise to reinstitute CPB, patients would require not only repeat doses of heparin, but also an infusion of heparin to counter the lingering effects of the enzyme.

BLEEDING PATIENT

After cardiac surgery, some patients bleed excessively. Chest tube drainage of more than 10 mL/kg in the first hour after operation or a total of more than 20 mL/kg over the first 3 hours after operation for patients weighing more than 10 kg is considered significant. Also, any sudden increase of 300 mL/hr or more after minimal initial drainage in an adult usually indicates anatomic disruption warranting surgical intervention.

The TEG has been extensively tested both alone and in conjunction with a number of other tests including prothrombin time (PT), platelet count, and fibrinogen. The TEG has been shown to have the best predictive accuracy for postoperative bleeding.[16] Using an algorithm based on the TEG and other tests, blood product utilization was cut considerably. Chest tube bleeding was not different, but the TEG did predict which patients might bleed abnormally. Work with TEG monitoring has shown that it can detect both hypocoagulable states as well as hypercoagulable states. New additives to the testing make it sensitive to the ADP receptor platelet antagonists as well as the GPIIb/IIIa inhibitors.

Insult of Cardiopulmonary Bypass

More so than patient factors, CPB itself acts to impair hemostasis. Bypass activates fibrinolysis, impairs platelets, and affects coagulation factors. Hypothermia, employed in most centers during CPB, adversely affects hemostasis as well.

Fibrinolysis

Numerous investigations support the notion that CPB activates the fibrinolytic pathway. Despite clinically adequate doses and blood concentrations of heparin, coagulation pathway activity persists. Formation of prothrombin and fibrinopeptide fragments and thrombin/antithrombin complexes document continued thrombin activity in this setting. The site of thrombin activity probably resides in the extracorporeal circuit, which contains a large surface of thrombogenic material. Thrombin activation results in fibrinolytic activity. Activation of fibrinolysis may be localized to those external sites of fibrin formation. Plasminogen activator concentrations rise during CPB, whereas levels of its inhibitor PAI-1 remain unchanged. This scenario is consistent with activation of fibrinolysis during CPB. Neither of the labels "primary" or "secondary" applies to the fibrinolysis peculiar to bypass.

Previous generations of oxygenators may have engendered systemic fibrinogenolysis more easily due to their more thrombogenic designs. In these (now more uncommon) instances of fibrinolysis, the TEG may demonstrate clot lysis. Even when fibrinolysis remains limited to the sites of extravascular fibrin formation, the fibrin degradation products so formed might impair hemostasis. In many cases, the mild fibrinolytic state engendered during CPB resolves spontaneously with little clinical impact.

Platelet Dysfunction

Thrombocytopenia occurs during CPB as a result of hemodilution, heparin, hypothermia-induced splenic sequestration of platelets, and platelet destruction from the blood-gas and blood-tissue interfaces created by cardiotomy suction, filters, and bubble oxygenators. Platelet count rarely dips below 50,000/mm^3, however.

Not only does the number of platelets decrease during CPB, but remaining platelets become impaired by partial activation. Fibrinogen and fibrin, which adhere to artificial surfaces of the extracorporeal circuit, form a nidus for platelet adhesion and aggregation. A reduced content of platelet α granules constitutes the evidence for partial activation. Nearly one third of circulating platelets undergo α-granule release during CPB. Bypass also depletes platelet glycoprotein receptors Ib and IIb/IIIa. These platelets cannot respond fully when subsequent hemostatic stimuli call for release of granule contents. Use of frequent cardiotomy suction and bubble oxygenators aggravates the extent of platelet activation.

Activation of the fibrinolytic system may contribute to platelet dysfunction. Local formation of plasmin affects platelet membrane receptors. Antifibrinolytic medications preserve platelet function and prevent some platelet abnormalities that occur during bypass.

Clotting Factors

Denaturation of plasma proteins, including the coagulation factors, occurs at blood-air interfaces. Liberal use of cardiotomy suction and prolonged use of oxygenators potentially impair coagulation by decreasing coagulation factor availability. Hemodilution also decreases factor concentrations. However, rarely do coagulation factor levels fall below the thresholds for adequate formation of fibrin in adult surgery.

Hypothermia

Hypothermia potentially affects hemostasis in many ways. First, the splanchnic circulation responds to hypothermia with sequestration of platelets. After warming, the accompanying thrombocytopenia reverses over 1 hour. Second, transient platelet

BOX 24-5 ***Useful Drugs to Reduce Bleeding during Cardiac Surgery***

- Aprotinin
- Tranexamic acid or ε-aminocaproic acid
- Recombinant factor VIIa
- Desmopressin

dysfunction occurs, evidenced by a platelet shape change, increased adhesiveness, inhibition of ADP-induced aggregation, and decreased synthesis of both thromboxane and prostacyclin. Third, a specific heparin-like inhibitor of factor Xa becomes more active. Protamine cannot neutralize this factor, which might be heparan.

Fourth, hypothermia slows the enzymatic cleavage on which activation of coagulation factors depends. Many biological phenomena display a 7% attenuation of activity for each decrease of 1°C in temperature. While coagulation factor structure remains unaltered, formation of fibrin may be sluggish when the patient is cold. Fifth, hypothermia accentuates fibrinolysis. The fibrin degradation products so formed then impair subsequent fibrin polymerization. Cold-induced injury of vascular endothelium can release thromboplastin, which then incites fibrin formation and activates fibrinolysis.

Prevention of Bleeding

The possible transmission of serious viral illness during transfusion of blood products and impairment of immune function generate concern among clinicians and patients. Many techniques attempt to limit viral exposure, including donation of autologous blood or directed blood, blood scavenging during and after surgery, and efforts to limit perioperative hemorrhage.

Pharmacologic Factors

HEPARIN AND PROTAMINE

The prudent clinician's admonition to administer no drug to excess applies well to this pair of essential drugs. Too little heparin invites active fibrin formation during CPB with consumption of clotting factors and platelets and excessive activation of the fibrinolytic system. Too much heparin risks postoperative heparin rebound. With too little protamine, the remaining unneutralized heparin impairs hemostasis by its anticoagulant action. Doses of protamine excessive enough to overwhelm the endogenous proteases may exert an anticoagulant effect, as well as invite polycation-induced lung injury and pulmonary vasoconstriction. The optimal approach utilizes coagulation testing to estimate the appropriate heparin and protamine doses and confirms both adequate anticoagulation and its neutralization.

Desmopressin

This analog of vasopressin provides more potent and longer lasting antidiuretic activity than vasopressin, with little vasoconstriction (Box 24-5). Like the parent compound and like epinephrine and insulin, desmopressin releases coagulation system mediators from vascular endothelium. Factor VIII coagulant activity increases 2- to 20-fold and is maximal 30 to 90 minutes after injection. Factor XII levels also increase. In response to desmopressin, endothelium releases the larger multimers of vWF, as well as t-PA and prostacyclin. Nevertheless, the overall effect of desmopressin is procoagulant, perhaps because of the impact of factor VIII and vWF.

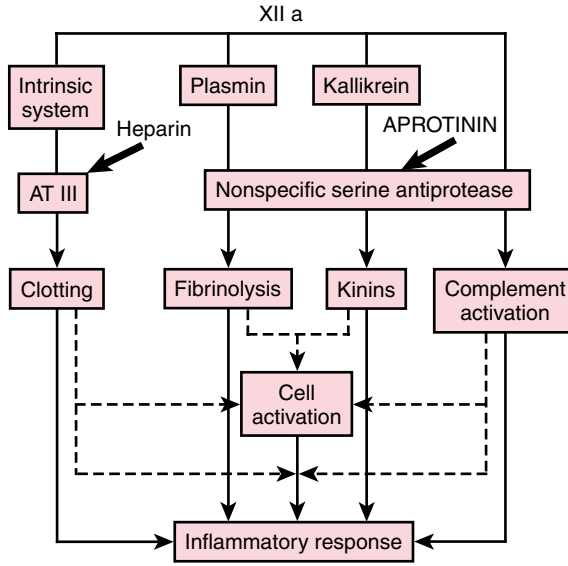

Figure 24-11 Actions of aprotinin on the contact coagulation system, fibrinolytic pathway, and complement activation. (From Royston D: The serine antiprotease aprotinin [Trasylol]: A novel approach to reducing postoperative bleeding. Blood Coag Fibrin 1:55, 1990.)

The optimal dose of desmopressin is 0.3 μg/kg. Intravenous, subcutaneous, and intranasal routes are all acceptable. After plasma redistribution with an 8-minute half-life, metabolism in liver and kidney and urinary excretion yield a plasma half-life of 2.5 to 4 hours. Levels of factor VIII persist in plasma long after desmopressin excretion due to the release of vWF. Rapid intravenous administration decreases systemic blood pressure and SVR, possibly by prostacyclin release or stimulation of extrarenal vasopressin V_2 receptors. The drug's antidiuretic action poses no problem in the absence of excessive free water administration.

SYNTHETIC ANTIFIBRINOLYTICS

Effective fibrinolysis inhibition requires an intravenous loading dose of 10 mg/kg for tranexamic acid followed by 1 mg/kg/hr or 50 mg/kg of ε-aminocaproic acid followed by infusions of 25 mg/kg/hr. Infusion rates require downward adjustment when serum creatinine is elevated.

Several investigations, using prophylactic antifibrinolytics, document a savings in blood loss, as well as in blood transfused in a general population of cardiac surgery patients. By commencing administration of tranexamic acid before CPB, chest tube drainage in the first 12 hours after operation decreased by 30% and the likelihood of receiving banked blood within 5 days of operation decreased from 41% to 22%. Prophylactic antifibrinolytics may spare platelet function by inhibiting the deleterious effects of plasmin. Administration of very large doses of antifibrinolytics appears to offer no greater savings. Cardiac surgery patients undergoing repeat operation may benefit particularly from prophylactic antifibrinolytic administration.[17]

APROTININ

Bovine lung provides the source of this 58-residue polypeptide serine protease inhibitor. Aprotinin inhibits a host of proteases, including trypsin, plasmin, kallikrein, and factor XIIa activation of complement (Fig. 24-11). The adult intravenous dose for

surgical hemostasis is 2 million kallikrein inhibitor units (KIU) for both patient and bypass pump, followed by 600,000 KIU/hr. The elimination half-life of aprotinin, 7 hours, is considerably longer than that of the synthetic antifibrinolytics; after 6 days, aprotinin continues to be excreted in the urine.

Royston and coworkers documented more than a fourfold reduction in blood loss during repeat cardiac surgery. Subsequent studies using high-dose aprotinin confirmed conservation of blood products and a reduction in bleeding, ranging from 29% to 50%. Studies clearly demonstrate decreased fibrinolysis in aprotinin-treated patient groups; preservation of platelet GPIb, or blockade of a plasmin-mediated platelet defect may also explain the hemostatic mechanism of aprotinin.

High-dose aprotinin alone prolongs the celite ACT. Most investigators simply avoid the celite ACT and use kaolin ACT. The kaolin ACT adsorbs about 98% of aprotinin and any intrinsic antithrombin effect that aprotinin has is therefore mitigated. It is recommended to use the kaolin ACT and keep the length of ACT time the same as if aprotinin was not being used. An animal protein, aprotinin can cause anaphylaxis, although this is uncommon (<1 in 1000). Aprotinin costs significantly more than equivalent doses of synthetic antifibrinolytic drugs. The discussion and argument about cost effectiveness of aprotinin versus other antifibrinolytics has continued for more than 10 years. The major concerns today with aprotinin are its adverse effects on renal function and overall cardiovascular outcome; These concerns led to its removal from the market in 2007.[18]

Determine the Cause

The complexity of human hemostasis, augmented by unexpected behavior of coagulation tests, can lead to confusion in the diagnosis of bleeding after cardiac surgery. *Anatomic sources* of bleeding frequently present once systemic blood pressure achieves sufficient magnitude. Some clinicians prefer to identify these sources before chest closure with a provocative test (i.e., allowing brief periods of hypertension). Generous chest tube drainage early after operation suggests an anatomic source. Retained mediastinal clot may engender a consumptive coagulopathy. A widened mediastinum on chest radiograph suggests the need for surgical drainage.

Nonsurgical causes of bleeding (platelets, coagulation factors, and fibrinolysis) usually manifest as a generalized ooze. Inspection of vascular access puncture sites aids in this diagnosis. Bleeding from other areas not manipulated during surgery (stomach, bladder) may also occur.

Coagulation tests aid diagnosis. Because the PT and aPTT are usually prolonged by several seconds after CPB, only values more than 1.5 times control suggest factor deficiency. Elevation of the ACT should first suggest unneutralized heparin, then factor deficiency.

A decreased platelet count, usually denoting hemodilution or consumption, requires correction with exogenous platelets in any bleeding patient. However, bleeding patients with insufficient functional platelets may demonstrate normal platelet counts early after operation. For this reason, clinicians have sought rapid diagnostic tests of platelet function and attempted correlation with bleeding after CPB.

Low plasma fibrinogen occurs from excessive hemodilution or factor consumption and is corrected with cryoprecipitate or FFP. The thrombin time is useful here. Most clinical laboratories can perform this test with rapid turnaround. A prolonged thrombin time denotes unneutralized heparin, insufficient fibrinogen, or high concentrations of fibrin degradation products. Finally, direct measurement of fibrin degradation products denotes fibrinolytic activity. In the absence of a cause for a consumptive coagulopathy, antifibrinolytic therapy may be useful.

Table 24-3 A Treatment Plan for Excessive Bleeding after Cardiac Surgery

Action	Amount	Indication
Rule out surgical cause	—	No oozing at puncture sites; chest radiograph
More protamine	0.5 to 1 mg/kg	ACT > 150 s or aPTT > 1.5 times control
Warm the patient	—	"Core" temperature < 35°C
Apply PEEP*	5 to 10 cm H_2O	—
Desmopressin	0.3 μg/kg IV	Prolonged bleeding time
Aminocaproic acid	50 mg/kg, then 25 mg/kg/hr	Elevated D-dimer or teardrop-shaped TEG tracing
Tranexamic acid	10 mg/kg, then 1 mg/kg/hr	Elevated D-dimer or teardrop-shaped TEG tracing
Platelet transfusion	1 U/10 kg	Platelet count < 100,000/mm^3
Fresh frozen plasma	15 mL/kg	PT or aPTT > 1.5 times control
Cryoprecipitate	1 U/4 kg	Fibrinogen < 1 g/L or 100 mg/dL

*Positive end-expiratory pressure (PEEP) is contraindicated in hypovolemia.
ACT = activated coagulation time; PT = prothrombin time; aPTT = activated partial thromboplastin time; TEG = thromboelastographic.

Table 24-3 lists a treatment plan for excessive bleeding after cardiac surgery. Interventions appear not in order of likelihood but rather by priority of consideration. Thus, surgical causes should be ruled out before seizing on the diagnosis of a consumptive coagulopathy. The priority will also vary among institutions, depending on the availability and cost of resources. This table provides a simple algorithm for treating postoperative bleeding. More complete schemes present a daunting level of complexity that deter implementation (Fig. 24-12).

Adjunctive Therapy

WARMING

Bleeding patients with core or intermediate zone temperatures below 35°C will benefit from warming efforts, both passive (warm ambient temperature, adequate body coverings, low ventilator fresh gas flows, airway heat and humidity exchangers) and active (heated humidifiers, warmed intravenous fluids, forced air convective warming blankets). All too often, in the effort to maintain intravascular volume, intensive care unit personnel administer liters of room-temperature (≤20°C) or refrigerated (0° to 4°C) fluids, which render patients hypothermic.

POSITIVE END-EXPIRATORY PRESSURE

One popular method to limit bleeding after cardiac surgery is application of positive end-expiratory pressure (PEEP) (5 to 10 cm H_2O). A tamponade effect in the mediastinum may explain this salutary effect.

BLOOD PRESSURE

Maintenance of systemic blood pressure in the low-normal range promotes tissue perfusion while limiting leakage around suture lines. Adequate depth of anesthesia during surgery and sufficient postoperative analgesia and sedation should be verified before initiating vasodilator therapy.

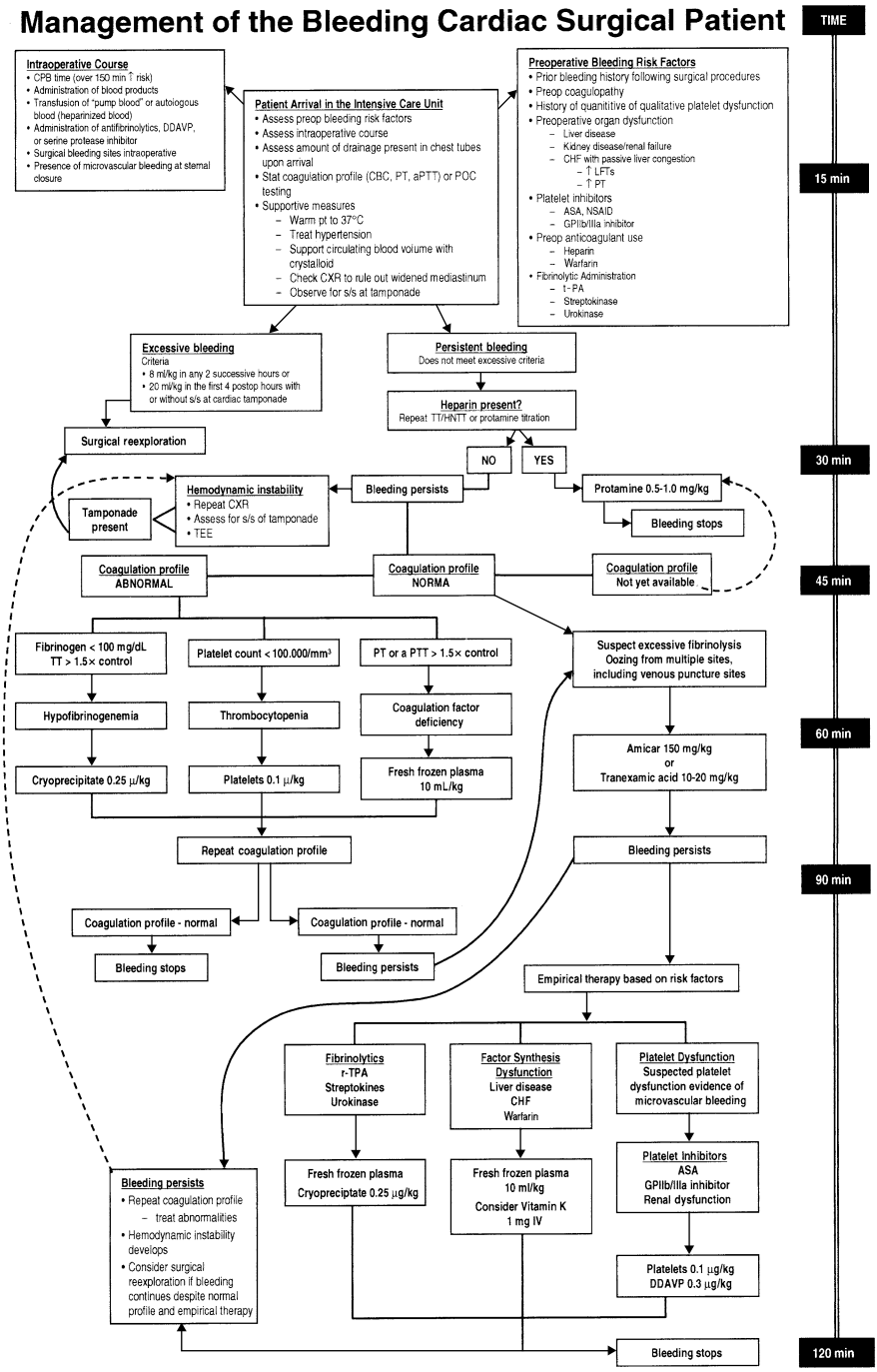

Figure 24-12 Algorithm for treating excessive bleeding. (From Milas B, Johes D, Gorman R: Management of bleeding and coagulopathy after heart surgery. Semin Thorac Cardiovasc Surg 12:326, 2000.)

Blood Products

The bleeding patient becomes subject to additional hemostatic derangements. The need to maintain intravascular blood volume arises in nearly all cases before identification of the cause of bleeding. Clear fluid or colloid will replenish intravascular volume. However, red blood cells, platelets, and coagulation factors become diluted when continued bleeding is treated with such replacement. Also, packed red blood cells and banked whole blood do not provide platelets or sufficient factor V or factor VIII to maintain hemostasis. Although routine prophylactic administration of FFP or platelets plays no role in modern cardiac surgical care, demonstration of a platelet count below 100,000/mm^3 or prolongation of the PT or aPTT despite adequate heparin neutralization *in a patient actively bleeding* is an indication for platelet or plasma replacement.

Banked blood should be infused to maintain a hemoglobin concentration that allows appropriate oxygen delivery to tissues. Because patients undergoing cardiac surgery also experience the hemodiluting and antihemostatic effects of CPB, the prudent clinician will commence platelet and factor replenishment earlier in the course of hemorrhage while awaiting laboratory confirmation. Each unit of platelet concentrate supplies about 10^{11} platelets, which increases the platelet count by about 20,000/mm^3 in the adult. Enough plasma accompanies platelet concentrates to supply the equivalent of 1.0 to 1.5 units of plasma for each 6 units of platelets.

Shed mediastinal blood can be collected and given back to patients using a closed drainage system. The drainage fluid, often collected in citrate, contains little fibrinogen. Presence of tissue and other debris in this fluid suggests the need for filtration before reinfusion. Shed mediastinal fluid supplies red blood cells without risk of viral transmission via allogeneic blood products.

Drugs

Recombinant factor VIIa (rFVIIa NovoSeven) has been approved for use in hemophiliacs who are resistant to factor VIII concentrates. When rFVIIa is administered, it binds to tissue factor and activates factor X leading to thrombin and fibrin formation. These then activate platelets. Thrombin generation and clotting take place on the surface of platelets and at sites of injury.[19,20] Numerous reports have been published of the off-label use of this "rescue agent" to stop bleeding in surgical patients, including cardiac surgical patients after CPB.

In hemophiliacs, the recommended dose is 90 μg/kg. However, reports in cardiac surgical patients have suggested doses of 30 μg/kg, while continuing ongoing component therapy and monitoring the PT/international normalized ratio. The half-life is about 2 hours and the dose may have to be repeated if bleeding continues. Most of the anecdotal reports have been positive, with a marked decrease in bleeding taking place.

SUMMARY

- It is easiest to think of coagulation as a wave of biological activity occurring at the site of tissue injury consisting of initiation, acceleration, control, and lysis.
- Hemostasis is part of a larger body system—inflammation. The protein reactions in coagulation have important roles in signaling inflammation.
- Thrombin is the most important coagulation modulator, interacting with multiple coagulation factors, platelets, tissue plasminogen activator, prostacyclin, nitric oxide, and various white blood cells.

- The serine proteases that compose the coagulation pathway are balanced by serine protease inhibitors, termed *serpins.* Antithrombin is the most important inhibitor of blood coagulation.
- Platelets are the most complex part of the coagulation process, and antiplatelet drugs are important therapeutic agents.
- Heparin requires antithrombin to anticoagulate blood and is not an ideal anticoagulant for cardiopulmonary bypass. Newer anticoagulants are actively being sought to replace heparin.
- Protamine can have many adverse effects. Ideally, a new anticoagulant will not require reversal with a toxic substance like protamine.
- Antifibrinolytic drugs are often given during cardiac surgery; these drugs include ε-aminocaproic acid and tranexamic acid.
- Recombinant factor VIIa is the latest drug to be studied as a "rescue agent" to stop bleeding during cardiac surgery. It appears to be very effective but has not yet been studied adequately.
- Every effort should be made to avoid transfusion of banked blood products during routine cardiac surgery. In fact, bloodless surgery is a reality in many cases.

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