

Richard B. Weiskopf, M.D., Editor

Anesthesiology 2004; 100:722-30

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Current Concepts of Hemostasis

Implications for Therapy

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AS early as 1964, it was proposed that coagulation reactions leading to hemostasis occurred in sequential steps in which a zymogen clotting factor, when activated, was capable of activating subsequent clotting factors in a waterfall or cascade mechanism.¹ Factor XII was activated by a surface, such as collagen, leading to factor XIIa, which then was capable of activating factor XI to XIa and thereafter to sequential activation of the other clotting factors, finally leading to the rapid conversion of prothrombin to thrombin. Later, this concept was modified when it was found that clotting factors previously thought to be enzymes were in fact cofactors. For example, factor VIII was found to be a cofactor for factor IX, and factor V was found to be a cofactor for factor X (fig. 1). Those who accepted this concept of coagulation envisioned intrinsic and extrinsic pathways of coagulation. The intrinsic system was composed entirely of factors in the circulating blood, whereas the extrinsic pathway included tissue factor (TF), thought to be extrinsic to the circulation and which acted as a receptor for factor VII. This concept held that factor X could be activated by both the intrinsic and extrinsic pathways. However, it was realized early on that the extrinsic and intrinsic systems were not independent of one another. It was known that deficiency of factor XII, prekallikrein, and high-molecular-weight kininogen were not associated with bleeding. Furthermore, deficiencies of factors VIII and IX were not compensated for by an intact extrinsic system, neither was a deficiency of factor VII alleviated by an intact intrinsic pathway. Ultimately, it

was realized that the TF/VIIa complex could activate both factors IX and X, suggesting that the extrinsic and intrinsic pathway concept was not applicable to *in vivo* hemostasis, though the concept was a valuable scheme for diagnostic purposes.

Although not shown in figure 1, it is now known that factor VIII circulates in complex with von Willebrand factor, the latter acting as a carrier molecule that serves to transport factor VIII from circulation to the platelet surface by virtue of the binding of von Willebrand factor. von Willebrand factor also plays a role in the adhesion of platelets to components of the vessel wall.

Newer Concept of the Coagulation Reactions

Recently, the work of several investigators has indicated that the initiating event leading to the hemostatic plug is the exposure of TF and the formation of a TF/VIIa complex. This TF/VIIa complex is anchored to a TF-bearing cell, where the TF has a cytoplasmic domain, a transmembrane domain, and an intracytoplasmic domain.²

Role of the Tissue Factor-bearing Cell

Cells expressing TF are found in extravascular cells surrounding blood vessels as well as other tissues. TF is also present in circulating leukocytes, but it is usually encrypted, *i.e.*, not active except under certain circumstances.³

A cell-based *in vitro* assay system using monocytes as a source of TF and unactivated platelets as the ultimate surface for thrombin generation has been developed. Using this cell-based system, we have found that the TF/VIIa complex on the TF-bearing cell has two main functions as shown in figure 2 (top panel).⁴ *In vitro* experiments suggest that the TF/VIIa complex activates (1) factor X to Xa and (2) factor IX to IXa. The factor Xa remains in the vicinity of the TF-bearing cell and activates factor V to Va, leading to a factor Xa/Va complex on the TF cell, which is capable of converting small amounts of prothrombin to thrombin, again in the vicinity of the TF-bearing cell. This small amount of thrombin serves as a priming mechanism for subsequent hemostatic events as shown in figure 2 (top panel). As can be seen, this small amount of thrombin is capable of activating platelets, factor VIII, factor V, and factor XI and separating factor

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Received from the Division of Hematology/Oncology, Carolina Cardiovascular Biology Center, University of North Carolina School of Medicine, Chapel Hill, North Carolina. Submitted for publication April 12, 2002. Accepted for publication October 22, 2003. Supported by grants No. HL06350 and No. HL48320 from the National Institutes of Health, Bethesda, Maryland.

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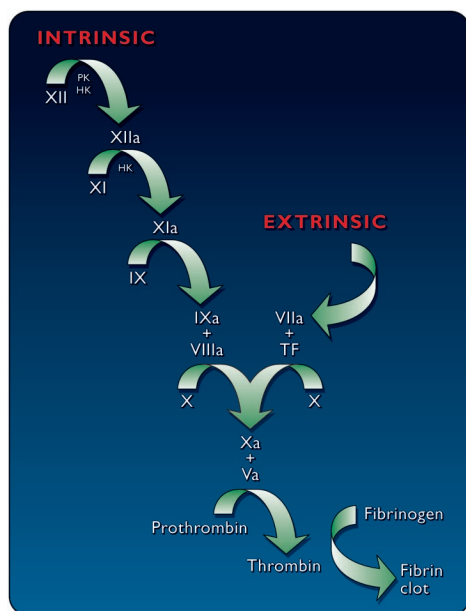


Fig. 1. Intrinsic system represents the clotting factors in the circulating blood. Extrinsic system represents tissue factor (TF) in complex with factor VII. Activation of factor XII was thought to be due to exposure of surface collagen and required cofactors prekallikrein (PK) and high-molecular-weight kininogen (HK). a = activated; roman numerals = clotting factors.

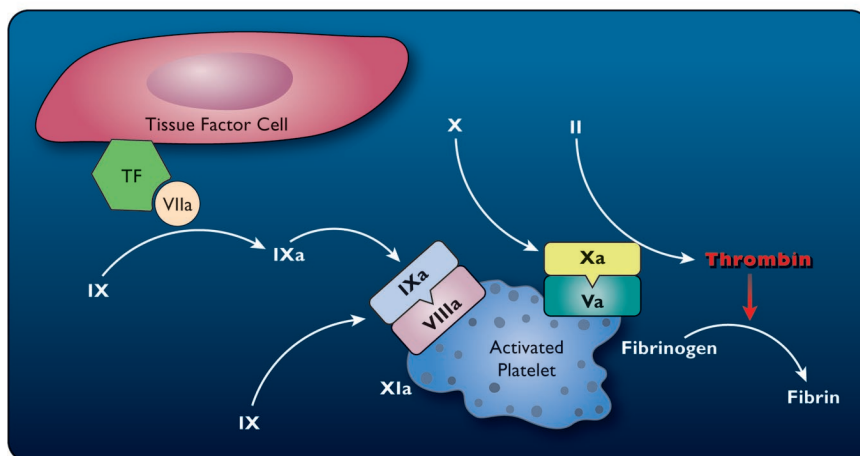
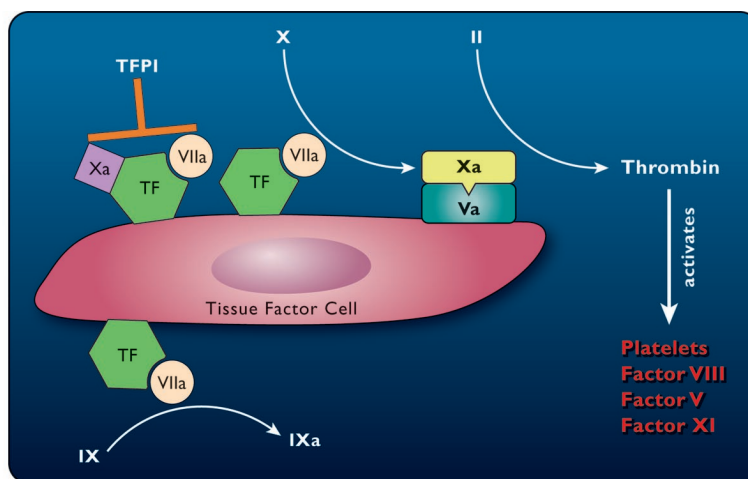
VIII from von Willebrand factor. After the priming amount of thrombin is formed, the factor Xa/VIIa/TF complex is inhibited by TF pathway inhibitor as shown in figure 2 (top panel). It is assumed that the TF cell is extravascular, though there is evidence suggesting that encrypted blood TF can be “decrypted” and discharged from leukocytes as microparticles that associate with platelets.³

The factor IXa formed by the TF-bearing cell does not remain in the vicinity of the cell but rather occupies a binding site, probably a specific binding protein, on the activated platelet surface adjacent to its cofactor, factor VIIIa. Subsequent events leading to thrombin generation take place on the surface of activated platelets.

Role of the Activated Platelet

As shown in figure 2 (bottom panel), activated platelets serve to bind the cofactors VIIIa and Va first and subsequently their respective enzymes, factors IXa and Xa. Factor IXa on the activated platelet surface and in the presence of its cofactor VIIIa then recruits more factor X from solution and activates factor X to Xa. Factor Xa then occupies a binding protein on the platelet surface adjacent to its cofactor, factor Va, to form the prothrombinase complex.⁴ This prothrombinase complex is capable

Fig. 2. (Top panel) The two main functions of tissue factor (TF) are shown: (1) to activate factor X and (2) to activate factor IX. Factor Xa remains in the vicinity of the TF cell and activates factor V. The complex of factors Xa/Va can convert a small amount of prothrombin (factor II) to thrombin with the results shown in the figure. Tissue factor pathway inhibitor (TFPI) then inhibits the complex of TF/VIIa/Xa as a control mechanism. (Bottom panel) The activated platelet derived from unactivated circulating platelets resulting from the thrombin generation on the TF cell shown in the top panel. Activated cofactors Va and VIIIa occupy sites on the activated platelet before binding of the respective enzymes, factors IXa and Xa. Factor Xa on the activated platelets is recruited from circulating factor X and is different from the factor X on the TF cell. The burst of thrombin generation takes place on the platelet surface. Thrombin generation can be boosted by further activation of factor IX by factor XIa. The burst of thrombin is sufficient to convert fibrinogen to fibrin.



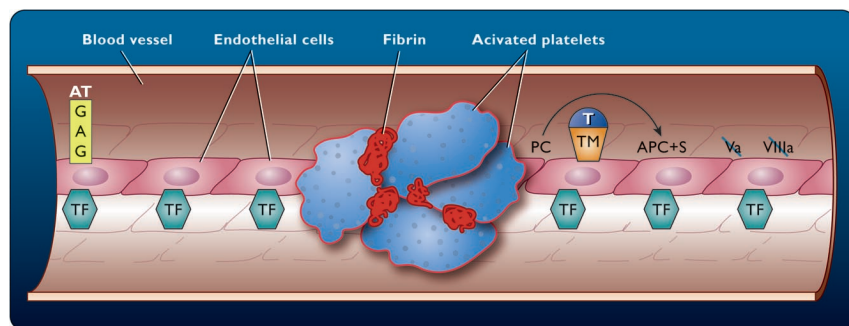


Fig. 3. APC = activated protein C; AT = antithrombin; GAG = glycosaminoglycans with antithrombin inhibit excess thrombin; PC = protein C; S = protein S, the cofactor of protein C; T = thrombin; TF = tissue factor; TM = thrombomodulin. Va and VIIIa with slashes indicate Va and VIIIa inactivated by activated protein C. Activated platelets and fibrin form a hemostatic plug.

of converting large amounts of prothrombin to thrombin in amounts sufficient to clot fibrinogen (fig. 2, bottom panel). In addition, thrombin generation can be boosted by factor XIa, which can convert more IX to IXa, ultimately leading to an increase in thrombin generation. This concept explains why factor XI deficiency is always mild. Even if there were no factor XI, individuals would still have tenase and prothrombinase complexes present so that some thrombin would be formed.

Role of Endothelial Cells

With the injury to the vessel wall, there is exposure of TF in the extravascular space leading to the events noted in figure 2. Thus, an injury in the vessel wall results in the formation of a hemostatic plug consisting of a mass of activated platelets interspersed with fibrin. Thrombin generation would then need to be limited precisely to the site of the vessel wall injury. This is accomplished by control mechanisms as indicated in figure 3. The excess thrombin that would gain access to the circulation would be inhibited by antithrombin. It would also be inhibited on adjacent normal endothelium because the thrombin escaping from the initial hemostatic plug would occupy thrombomodulin on the endothelial cell to form a thrombin/thrombomodulin complex. The thrombin/thrombomodulin complex would activate protein C, which, in the presence of its cofactor (protein S), would be capable of inactivating both Va and VIIIa escaping from the endothelial cell surface (fig. 3). In this way, thrombin formation would be localized to the site of the vessel wall injury and would prevent a clot from extending to the normal endothelial cell surface or occluding the vessel lumen.

Control Mechanisms

Several control mechanisms exist for localizing fibrin formation to the site of injury, including TF pathway inhibitor, the protein C system, antithrombin, and glycosaminoglycans on the vessel wall, all of which are depicted schematically in figure 3. Disturbance in these mechanisms can lead to thrombotic disorders.⁵

Implications for Therapy

A careful history with specific questions about excessive bleeding or bruising is the best way to identify patients likely to experience excessive hemorrhage during or after surgery.

Congenital and Acquired Factor Deficiencies

In preparation for a surgical procedure, a clinician should be able to assess the risk of bleeding based on a patient's history and medication use. Congenital factor deficiencies, e.g., the hemophilias, von Willebrand's disease, and platelet disorders, usually present with symptoms in early life with a family history of abnormal bleeding. The characteristics of the clotting factors are listed in table 1. Patients with a congenital deficiency of any of the factors need treatment before, during, and after the surgical procedure. Many of these factors are

Table 1.

Characteristics of Coagulation Factors		
Factors	Plasma half life (hour)	Plasma Concentration (microgram/ml)
Fibrinogen	72-120	2,000-4,000
Prothrombin	60-70	100-150
V	12-16	5-10
VII	3-6	0.5
VIII	8-12	0.1
IX	18-24	4-5
X	30-40	8-10
XI	52	5
XII	60	30
Protein C	6	4-5
Protein S (total)	42	25
Tissue Factor	---	---
Thrombomodulin	---	---
Antithrombin	72	150-400
Tissue Factor Pathway Inhibitor	---	0.1

Table 2.

Sources of Blood Clotting Factors		
Fresh (frozen) plasma [§] Cryoprecipitate [§]	Contains all clotting factors Fibrinogen, FVIII, vWF	
Plasma-derived FVIII	Purity	Manufacturer
Humate P [†]	Intermediate (FVIII & vWF)	Aventis ¹
Profilate [*]	Intermediate (FVIII & vWF)	Alpha ²
Alphanate	high purity	Alpha ²
Koate	high purity	Bayer ³
Hemofil M	high purity	Baxter-Bioscience ⁴
Monoclate	high purity	Aventis ¹
Monarc M	high purity	Red Cross ⁵
Hyate-C (derived from porcine plasma)	intermediate	Ipsen ⁶
Recombinant FVIII		
Advate	high purity	Baxter-Bioscience ⁴
Kogenate FS (Helixate FS)	high purity	Bayer ³
Recombinate	high purity	Baxter-Bioscience ⁴
Refacto	high purity	Wyeth ⁷
Plasma-derived Factors II, VII, IX, X (Prothrombin complex concentrates (PCCs))		
Konyne	low purity	Bayer ³
Profilnine	low purity	Alpha ²
Proplex	low purity	Baxter-Bioscience ⁴
Bebulin	low purity	Baxter-Bioscience ⁴
Plasma-derived Factor IX		
Mononine	high purity	Aventis ¹
Alphanine	high purity	Alpha ²
Recombinant Factor IX		
BeneFix	high purity	Wyeth ⁷
Recombinant VIIa		
NovoSeven	high purity	Novo Nordisk ⁸
Activated Prothrombin Concentrates		
FEIBA [‡] AUTOPLEX [‡]	low purity low purity	Baxter-Bioscience ⁴ Nabi-Novartis ⁹
[§] All plasma and plasma products should be carefully screened for hepatitis, HIV and other known transmissible agents. vWF is von Willebrand factor. [†] In addition to intermediate purity factor VIII, these products contain von Willebrand factor (vWF). It should be noted that high purity factor VIII products are devoid of von Willebrand factor. [‡] Activated prothrombin concentrates containing prothrombin and variable amounts of factors VII, IX, and X. These agents are used for patients who have inhibitors to factors VIII and IX. ¹ Aventis Pharmaceuticals, Parsippany, NJ ² Alpha Therapeutic Corp., Los Angeles, CA ³ Bayer Corporation, Pharmaceuticals Division, Biological Products, West Haven, CT ⁴ Baxter International, Deerfield, IL ⁵ American Red Cross, Arlington, VA ⁶ Ipsen Ltd, Slough, Berkshire, UK ⁷ Wyeth Pharmaceuticals, Collegeville, PA ⁸ Novo Nordisk A/S, Bagsvaerd, Denmark ⁹ Nabi Biopharmaceuticals, Boca Raton, FL		

now available as highly purified plasma-derived or recombinant products. There are currently purified forms of fibrinogen, factor VIII, factor IX, factor VII, and the vitamin K-dependent factors in so-called prothrombin complex concentrates. Purified concentrates of the clotting factors have been treated to effectively eliminate or eradicate transmissible agents capable of causing infectious diseases (table 2).⁶ Where specific factor concentrates are indicated for congenital deficiencies, they can be used as noted in table 2. Consultation with a hematologist may be beneficial in patients who need replacement therapy with specific agents.

There are acquired disorders in which variable deficiencies of factors occur. For example, multifactor deficiency may occur in patients with hepatic disease, renal insufficiency, disseminated intravascular coagulation, and other conditions. Before surgery, acquired bleeding

disorders should be well characterized to define the specific clotting factor deficiencies that can be replaced by one or more of the agents listed in table 2. Acquired thrombocytopenia or qualitative platelet defects may be found in certain patients and pose a problem for anesthesiologists and surgeons. Such patients may need platelet transfusions before operative procedures.

Anticoagulants

Medications that alter hemostasis such as antiplatelet agents and anticoagulants that affect primary platelet plug formation or fibrin plug formation, respectively, should be assessed before surgery or anesthesia to prevent bleeding. Reversal of the effect of these agents can frequently be accomplished by simple discontinuation of the drug. Because discontinuation of anticoagulant agents can be deleterious in some clinical conditions, it

Table 3.

Medications that Affect Platelet Aggregation								
Drug	Site of Action	Route	Plasma Half-life	Metabolism	Antidote	Stop Before Procedure	Prolongation of PT/PTT	Indication
Aspirin	COX 1-2	Oral	20 min	Hepatic	None	7 days	No/No	Treatment and secondary prevention of AMI and stroke
Dipyridamole	Adenosine	Oral	40 min	Hepatic	None	24 hours	No/No	PVD
Clopidogrel	ADP	Oral	7 hrs	Hepatic	None	5 days	No/No	CAD/PVD
Ticlopidine	ADP	Oral	4 days	Hepatic	None	10 days	No/No	CAD/PVD
Abciximab	GPIIb-IIIa	IV	30 min	Renal	None	72 hours	No/No	ACS/PCI
Eptifibatide	GPIIb-IIIa	IV	2.5 hrs	Renal	None	24 hours	No/No	ACS/PCI
Tirofiban	GPIIb-IIIa	IV	2 hrs	Renal	Hemodialysis	24 hours	No/No	ACS
COX = cyclooxygenase ADP = adenosine diphosphate GP = glycoprotein			IV = intravenous AMI = acute myocardial infarction PVD = peripheral vascular disease			CAD = coronary artery disease PCI = percutaneous coronary intervention ACS = acute coronary syndromes		

is helpful to know not only how to reverse the drug but when to restart the medication. In the paragraphs below, strategies for management of surgical patients on a variety of anticoagulant agents are described.

Antiplatelet Agents

Antiplatelet agents are mainly used for the prevention of arterial thrombosis in different clinical settings and generally affect platelet plug formation by different mechanisms (table 3). Aspirin is the most commonly used antiplatelet agent. It is a direct inhibitor of cyclooxygenase 1 and 2. Aspirin inhibits platelet aggregation even at low doses, and the effect lasts for the life span of the platelets (7–10 days) because of irreversible blockade of the thromboxane A₂ pathway by acetylation of cyclooxygenase. Other nonsteroidal antiinflammatory drugs, such as those depicted in table 4, inhibit platelet aggregation anywhere from 2 h to several days.

Although the risk of bleeding from anesthesia and surgery in patients taking nonsteroidal antiinflammatory drugs is low, the safest approach is to discontinue these agents before the procedure (table 4). After the nonsteroidal antiinflammatory drugs are discontinued, platelet function returns to normal in 12–48 h.

In case of excessive bleeding during surgery, platelet transfusions may be indicated. The same applies for the thienopyridines (ticlopidine and clopidogrel), which inhibit adenosine diphosphate receptors with peak activity at days 3–5 and an antiplatelet effect that can last for 7–10 days.

Newer antiplatelet agents that have a profound and sustained effect on platelet function are the GPIIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban) (table 3). These medications are given intravenously and usually in combination with heparin. Anesthesia and surgery in patients using these agents may result in excessive

Table 4.

Non-steroidal Anti-inflammatory Medications							
Drug	Site of Action	Route	Plasma Half-life	Metabolism	Antidote	Stop Before Procedure	Prolongation of PT/PTT
Piroxicam	COX 1-2	Oral	50 hours	Hepatic	None	10 days	No/No
Indomethacin	COX 1-2	Oral/Supp	5 hours	Hepatic	None	48 hours	No/No
Ketorolac	COX 1-2	Oral/IV	5-7 hours	Hepatic	None	48 hours	No/No
Ibuprofen	COX 1-2	Oral	2 hours	Hepatic	None	24 hours	No/No
Naproxen	COX 1-2	Oral	13 hours	Hepatic	None	48 hours	No/No
Diclofenac	COX 1-2	Oral	2 hours	Hepatic	None	24 hours	No/No
Rofecoxib Celecoxib	COX 2	Oral	10-17 hours*	Hepatic	None	None	No/No
COX = cyclooxygenase; COX 1-2 inhibitors affect platelet aggregation Supp = suppositories IV = intravenous *half-life is dose dependent with larger doses having a longer half-life							

Table 5.

Anticoagulants and Thrombolytics								
Drug	Site of Action	Route	Plasma Half-life	Excretion	Antidote	Stop Before Procedure	Prolongation of PT/PTT	Indication
Unfractionated Heparin	IIa/Xa	IV/SC	1.5 hours	Hepatic	Protamine	6 hr	No/Yes	Thromboembolism Thromboprophylaxis
LMWHs	Xa ?IIa	SC	4.5 hours	Renal	Protamine (partially)	12-24 hrs	No/No	Thromboembolism Thromboprophylaxis
Streptokinase	Plg	IV	23 min	Hepatic	Antifibrinolytics	3 hr	Yes/Yes	AMI, PE
t-PA	Plg	IV	< 5 min	Hepatic	Antifibrinolytics	1 hr	Yes/Yes	AMI, PE
Oral anticoagulants	Vitamin K dependent factors	Oral	2-4 days	Hepatic	Vitamin K rFVIIa PCCs Plasma	2-4 days	Yes/No	Thromboembolism Thromboprophylaxis
t-PA = tissue plasminogen activator IV = intravenous SC = subcutaneous LMWH = low molecular weight heparin rFVIIa = recombinant factor-VIIa PCCs = prothrombin complex concentrates AMI = acute myocardial infarction PE = pulmonary embolism Plg = plasminogen								

bleeding or hematoma formation. As a general rule, surgery or anesthesia in these patients should be delayed until the effect of the drug dissipates or is reversed. Given the short half-life, cessation of the drug⁷ is usually sufficient; however, thrombocytopenia due to GPIIb/IIIa inhibitors, although usually transient, can occasionally persist for several weeks. Therefore, monitoring of platelet counts in patients receiving these agents is suggested, particularly in patients experiencing excessive bleeding. In some patients, administration of freshly prepared platelets may be indicated to counter hemorrhage. Such drugs should be avoided in patients with renal insufficiency.

Oral Anticoagulants

Oral anticoagulants, such as warfarin, inhibit synthesis of the vitamin K-dependent coagulation factors, including factors II, VII, IX, X and proteins C and S. Warfarin and warfarin-like drugs have a relatively long plasma half-life. The anticoagulant effect of these drugs can be reversed by stopping the medication and waiting approximately 4 days for normalization of the prothrombin time (PT). Warfarin can also be reversed by administration of small doses of vitamin K orally or parenterally, usually 1–2 mg. Immediate reversal can be accomplished by means of administration of recombinant factor VIIa⁸ or, if this is not available, administration of 1–2 units fresh frozen plasma or a prothrombin complex concentrate (table 2).⁹ It is prudent to check the PT and international normalized ratio (INR) before anesthesia or surgery in these patients.

Unfractionated Heparin

The use of low-dose or “minidose” unfractionated heparin for thromboprophylaxis (5,000 U every 12 h) seems to pose a low risk for hemorrhage during anesthesia or surgery (table 5). However, there is a risk of central nervous system bleeding in these patients, so neurosur-

gery or spinal anesthesia should be avoided until at least 6 h after the last heparin dose.

Patients who receive therapeutic anticoagulation with regular doses of standard heparin are at high risk of bleeding during and after surgery. As a general rule, standard heparin should be stopped at least 6 h before surgery. When needed, heparin can be restarted approximately 12 h postoperatively, but close monitoring of heparin concentrations and close observation of the patient for excessive hemorrhage is warranted. For immediate reversal of anticoagulation, protamine sulfate can be used.

Low-molecular-weight Heparin

When therapeutic low-molecular-weight heparin is administered, peak plasma concentrations occur approximately 4 h after the initial dose, but activity persists up to 24 h (table 5). The PT and activated partial thromboplastin time are usually not affected by therapeutic doses, so monitoring requires measurement of anti-factor Xa levels.¹⁰ This is especially important in patients with renal insufficiency, obesity, and pregnancy.

The risk of bleeding from therapeutic doses of low-molecular-weight heparin approaches that of standard heparin. Therefore, care should be taken to delay surgery until 12 h after the last dose of low-molecular-weight heparin. Should emergency reversal of anticoagulation be needed, protamine sulfate completely neutralizes anti-IIa activity and neutralizes approximately 65% of anti-Xa activity of low-molecular-weight heparin.¹¹ There are conflicting reports as to whether rFVIIa is effective in the reversal of low-molecular-weight heparin.^{12,13} Therefore, the use of recombinant VIIa as an antidote for low-molecular-weight heparin or derivatives is not entirely clear.

Thrombolytic Agents

In general, surgical procedures should be delayed in patients receiving thrombolytic agents until clotting test

Table 6.

Other Anticoagulants								
Drug	Site of Action	Route	Plasma Half-life	Metabolism	Antidote	Stop Before Procedure	Prolongation of PT/PTT	Indication
Pentasaccharide	Xa	SC	14-17 hr	Renal	rFVIIa?	4 days	No/No	Thromboprophylaxis
Bivalirudin	Ila	IV	25 min	Hepatic	None	2-3 hrs	Yes/Yes	Coronary interventions
Argatroban	Ila	IV	45 min	Hepatic	None	4-6 hrs	*Yes/Yes	HIT
Hirudin	Ila	IV	1.5 hours	Renal	PMMA Dialysis	8 hrs	*Yes/Yes	HIT
APC	Va/VIIa	IV	2 hrs	Hepatic	None	12 hrs	No/Yes	Severe sepsis
Ximelagatran	Ila	Oral	3 hours	Renal	None	24 hrs	Yes/Yes	Thromboprophylaxis Treatment of DVT
Ila = thrombin APC = activated protein C IV = intravenous SC = subcutaneous HIT = heparin-induced thrombocytopenia PMMA = polymethyl-methyl acrylate *Argatroban and Lepirudin may increase the normal PT 4-5 seconds								

results return to normal (table 5). Fortunately, active thrombolytic agents, such as tissue plasminogen activator, are short lived.

Other Anticoagulant Agents

Before anesthesia or surgery, the effects of less commonly used anticoagulants, such as hirudin and argatroban (table 6), should be taken into consideration. There are no specific antidotes for most of these agents. However, most have short half-lives of 1–2 h, so, before anesthesia, the agent should be stopped several hours before surgery. There is a special situation with pentasaccharide. There is no specific antidote for this agent, and the half-life is around 17 h, with activity lasting 48 h or longer. However, a recent publication suggests that recombinant FVIIa can normalize thrombin generation in healthy volunteers after the administration of subcutaneous pentasaccharide.¹³

Use of Recombinant Factor VIIa in Special Circumstances

Hemophilia

Factor VIIa (NovoSeven; Novo Nordisk A/S, Bagsværd, Denmark) is a recombinant product.¹⁴ It has been approved by the U. S. Food and Drug Administration for use in patients with hemophilia and inhibitors. Although the mechanism of action of factor VIIa in bypassing the need for factors VIII and IX is debated, some believe that factor VIIa, in addition to enhancing the TF pathway, can also bind loosely to platelets and directly activate factor X to factor Xa, which, in the presence of factor Va, leads to an increase in thrombin generation.¹⁵ Although thrombin generation is never completely normalized, it is sufficient to enhance hemostasis.

Several hundred thousand standard doses of rFVIIa have been given to patients with hemophilia in different clinical situations. It has been used successfully in major surgical procedures, including joint replacements, nephrectomy,

amputations, and insertion and removal of central catheters, among others, with success rates of around 90%. In these studies, doses of 90–120 $\mu\text{g/kg}$ body weight were given every 2 h for the first 24 h, depending on the type of surgery and clinical response. Some of the patients also received antifibrinolytic therapy.^{16,17}

There seem to be a subset of patients with hemophilia and inhibitors that do not respond clinically to the standard doses of rFVIIa (90–120 $\mu\text{g/kg}$ body weight). Preliminary studies show that there is variable individual thrombin-generating capacity. In these individuals, administration of “megadoses” of rFVIIa (150–300 $\mu\text{g/kg}$) may be sufficient to achieve hemostasis.¹⁸ In some cases, even a single high dose of rFVIIa (approximately 200 $\mu\text{g/kg}$) may be sufficient to treat mild to moderate bleeding.¹⁹

“Off-label” Use

The off-label, *i.e.*, non-Food and Drug Administration-approved, use of recombinant factor VIIa in the United States is widely reported and increasing. Case reports, pilot studies, and controlled trials have shown the apparent efficacy of this drug in serious bleeding disorders, including liver disease, liver transplantation, severe trauma, surgical procedures, quantitative and qualitative platelet disorders, and intracerebral hemorrhage, among others. In many of these cases, transfusion of large quantities of erythrocytes, plasma, cryoprecipitate, and platelets were ineffective, and the use of one to two doses of rFVIIa was enough to substantially decrease or stop the bleeding.²⁰ Again, in all these circumstances, the most likely common denominator is defective thrombin generation caused by a number of hemostatic changes, such as thrombocytopenia, decreased plasma concentration of coagulation proteins, hyperfibrinolysis, hypothermia, and, in some cases, dilutional coagulopathy due to massive blood transfusions.

The prophylactic use of rFVIIa also has been reported

in individuals with normal coagulation profiles who undergo surgical procedures that are known to be associated with increases in perioperative blood loss, such as retropubic prostatectomy. In a double-blind, placebo-controlled study of patients undergoing prostatectomy, 8 patients received 20 μg FVIIa/kg body weight, 16 received 40 μg FVIIa/kg, and 12 were assigned to the placebo arm. Recombinant factor VIIa was administered as a single dose in the early operative phase. The median perioperative blood loss was 1,235 ml in the 20- μg /kg group and 1,089 ml in the 40- μg /kg group, compared with 2,688 ml in the placebo group. None of the patients in the 40- μg /kg group needed a transfusion, compared with 7 of 12 patients in the placebo group. There were no adverse events reported in the 36 patients.²¹

In another randomized, double-blind, placebo-controlled trial, 204 patients without coagulopathy received 20 or 80 μg /kg rFVIIa or placebo before undergoing hepatectomy. Patients who received the higher dose of rFVIIa needed 30% less transfusion of erythrocytes compared with the placebo group. There was no difference in the 20- μg /kg group and no serious adverse events reported.²² Therefore, a low dose of rFVIIa (40–80 μg /kg) may be sufficient to improve or reinforce the formation of a tighter hemostatic plug in individuals with normal coagulation who undergo certain surgical procedures decreasing or avoiding the use of blood products. Also, by using a recombinant product, the risk of transmitting blood-borne pathogens is avoided.

Recombinant factor VIIa may also be useful in situations in which transfusion of blood products is unacceptable, *i.e.*, Jehovah's Witnesses who undergo major surgical procedures or are in a life-threatening bleeding situation.^{23,24}

Gastrointestinal Bleeding and Liver Disease

Liver disease can be associated with multiple hemostatic abnormalities, the most pronounced deficiency being factor VII. These patients also carry some degree of thrombocytopenia and, on occasion, hyperfibrinolysis, which puts them at an increased risk of upper and lower gastrointestinal hemorrhages as well as bleeding from routine procedures and major surgical interventions.

A well-known *in vitro* effect of rFVIIa is shortening of the PT. Its effect has also been evaluated in individuals taking vitamin K antagonists and in liver disease. In a randomized, placebo-controlled study, 28 healthy volunteers received acenocoumarol twice daily to increase the INR above 2, and doses of rFVIIa between 3 and 320 μg /kg were administered. All dosages normalized the INR in a dose-dependent manner. No evidence of activation of the coagulation system was seen in these healthy individuals.²⁵ Deveras and Kessler⁸ treated 13 patients with rFVIIa who presented with excessive anticoagulation from the use of warfarin. A single dose of rFVIIa that ranged between 12 and 90 μg /kg body weight immedi-

ately reversed the prolonged PT in all of the patients. Four of the patients who had clinically significant hemorrhage with INRs between 5.8 and 13.9 had immediate cessation of bleeding after administration of rFVIIa. Five patients needed rapid reversal before invasive procedures, and the remaining four patients were at increased risk of bleeding, with INRs from 6.2 to greater than 20. No adverse events or bleeding during or after the interventions were reported in this study.

In a single-center, open-label study, 10 patients with prolonged PTs due to alcoholic cirrhosis and acute variceal bleeding were treated with a single dose of 80 μg rFVIIa/kg body weight and evaluated for a period of 12 h. All patients received routine standard treatment. Recombinant FVIIa normalized the PT in all patients within 30 min after administration. Its effect lasted for more than 4 h in seven patients and for around 2 h in the remaining three patients. Immediate bleeding control was obtained in all patients after administration of rFVIIa, with no reported adverse events.²⁶

The use of different doses of rFVIIa has also been evaluated in patients with liver disease. In an initial study, 10 nonbleeding patients with cirrhosis and prolonged PTs received 5, 20, or 80 μg rFVIIa/kg body weight during a 3-week study period. Normalization of the PT was dose dependent, lasting up to 12 h with the 80- μg /kg dose.²⁷ In a more recent study, 65 individuals with prolonged PTs and advanced liver disease received 5, 20, 80, or 120 μg /kg rFVIIa before undergoing laparoscopic liver biopsy. The PT was corrected in the majority of the patients, and again, a dose-dependent effect was seen. None of the 65 patients needed transfusion of blood products or surgical intervention; however, 13 individuals needed an additional dose of 80 μg /kg rFVIIa. One thrombotic event and one case of disseminated intravascular coagulation were reported, but both events were considered by the investigator as unlikely to be related to the use of rFVIIa.²⁸

On the basis of these data and personal experience, FVIIa is considered to be safe and effective for the reversal of anticoagulation of vitamin K antagonists and when used in patients with liver disease during acute bleeding episodes or surgical procedures.²⁹ Doses between 20 and 80 μg /kg should be sufficient to achieve hemostasis. The response to rFVIIa is based on a subjective clinical evaluation because no currently available laboratory test can accurately monitor the clinical effectiveness of this agent.

Other

Surgical conditions often necessitating special attention with respect to hemostasis are cardiopulmonary bypass surgery, liver transplantation surgery, and severe trauma. In patients who need surgery after undergoing severe trauma associated with severe bleeding, factor VIIa has been used successfully to effect hemostasis.³⁰

The use of FVIIa in these conditions constitutes off-label use, not approved by the Food and Drug Administration. The administration of rFVIIa at doses ranging from approximately 60 to more than 100 $\mu\text{g/kg}$ body weight has resulted in remarkable diminution of generalized bleeding after surgery, which ceased after subsequent doses of rFVIIa. Further experience with and clinical trials of this off-label use are needed before it can be generally recommended.

Summary

The revised model of coagulation has implications for therapy of both hemorrhagic and thrombotic disorders. Of particular interest to anesthesiologists is the management of clotting abnormalities before, during, and after surgery. Most hereditary and acquired coagulation factor deficiencies can be managed by specific replacement therapy using clotting factor concentrates.

Specific guidelines have also been developed for perioperative management of patients using anticoagulant agents that inhibit platelet or coagulation factor functions. Finally, recombinant factor VIIa has been used off-label as a hemostatic agent in some surgical situations associated with excessive bleeding that is not responsive to conventional therapy.

References

1. Davie EW, Ratnoff OD: Waterfall sequence for intrinsic blood clotting. *Science* 1964; 164:1310-2
2. Giesen PL, Nemerson Y: Tissue factor on the loose. *Semin Thromb Hemost* 2000; 26:379-84
3. Rauch U, Nemerson Y: Circulating tissue factor and thrombosis. *Curr Opin Hematol* 2000; 7:273-7
4. Roberts HR, Monroe DM, Oliver JA, Chang JY, Hoffman M: Newer concepts of blood coagulation. *Haemophilia* 1998; 4:331-4
5. Roberts HR, Monroe DM, Hoffman M: Molecular biology and biochemistry of the coagulation factors and pathways of hemostasis, Williams Hematology, 6th edition. Edited by Beutler E, Lichtman MA, Coller BS, Kipps TJ, Seligsohn U. New York, McGraw Hill, 2001, pp 1409-34
6. Kasper CK: Hereditary clotting factor disorders and their management. *Haemophilia* 2000; 6(suppl 1):13-27
7. Horlocker TT, Wedel DJ, Schroeder DR, Rose SH, Elliott BA, McGregor DG, Wong GY: Preoperative antiplatelet therapy does not increase the risk of spinal hematoma associated with regional anesthesia. *Anesth Analg* 1995; 80:303-9
8. Deveras RA, Kessler CM: Reversal of warfarin-induced excessive anticoagulation with recombinant human factor VIIa concentrate. *Ann Intern Med* 2002; 137:884-8
9. Preston FE, Laidlaw ST, Sampson B, Kitchen S: Rapid reversal of oral anticoagulation with warfarin by a prothrombin complex concentrate (Beriplex): Efficacy and safety in 42 patients. *Br J Haematol* 2002; 116:619-24
10. Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R, Granger C, Ohman EM, Dalen JE: Heparin and low-molecular-weight heparin: Mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest* 2001; 119(suppl):64S-94S
11. Holst J, Lindblad B, Bergqvist D, Garre K, Nielsen H, Hedner U, Ostergaard PB: Protamine neutralization of intravenous and subcutaneous low-molecular-weight heparin (tinzaparin, Logiparin): An experimental investigation in healthy volunteers. *Blood Coagul Fibrinolysis* 1994; 5:795-803
12. Chan S, Kong M, Minning DM, Hedner U, Marder VJ: Assessment of recombinant factor VIIa as an antidote for bleeding induced in the rabbit by low molecular weight heparin. *J Thromb Haemost* 2003; 1:760-5
13. Bijsterveld NR, Moons AH, Boekholdt SM, van Aken BE, Fennema H, Peters RJ, Meijers JC, Buller HR, Levi M: Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation* 2002; 106:2550-4
14. Hedner U: Recombinant factor VIIa (NovoSeven) as a hemostatic agent. *Semin Hematol* 2001; 38(suppl 12):43-7
15. Hoffman M, Monroe DM, and Roberts HR: Activated factor VII activates factors IX and X on the surface of activated platelets: Thoughts on the mechanism of action of high-dose activated factor VII. *Blood Coagul Fibrinolysis* 1998; 9(suppl 1):S61-5
16. Shapiro AD, Gilchrist GS, Hoots WK, Cooper HA, Gastineau DA: Prospective, randomised trial of two doses of rFVIIa (NovoSeven) in haemophilia patients with inhibitors undergoing surgery. *Thromb Haemost* 1998; 80:773-8
17. Ingerslev J: Efficacy and safety of recombinant factor VIIa in the prophylaxis of bleeding in various surgical procedures in hemophilic patients with factor VIII and factor IX inhibitors. *Semin Thromb Hemost* 2000; 26:425-32
18. Kenet G, Lubetsky A, Luboshitz J, Martinowitz U: A new approach to treatment of bleeding episodes in young hemophilia patients: A single bolus megadose of recombinant activated factor VII (NovoSeven). *J Thromb Haemost* 2003; 1:450-5
19. Cooper HA, Jones CP, Campion E, Roberts HR, Hedner UE: Rationale for the use of high dose rFVIIa in a high-titre inhibitor patient with haemophilia B during major orthopaedic procedures. *Haemophilia* 2001; 7:517-22
20. Hedner U, Erhardtsen E: Potential role of recombinant factor VIIa as a hemostatic agent. *Clin Adv Hematol Oncol* 2003; 1:112-9
21. Friederich PW, Henny CP, Messelink EJ, Geerdink MG, Keller T, Kurth KH, Buller HR, Levi M: Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: A double-blind placebo-controlled randomised trial. *Lancet* 2003; 18:201-5
22. Lodge P, Jaeck D, Jonas S, Fridberg MJ: Recombinant factor VIIa (NovoSeven) in partial hepatectomy: A randomized placebo-controlled, double-blind clinical trial. *Hepatology* 2003; 36(pt 2):211a
23. Tanaka KA, Waly AA, Cooper WA, Levy JH: Treatment of excessive bleeding in Jehovah's Witness patients after cardiac surgery with recombinant factor VIIa (NovoSeven). *ANESTHESIOLOGY* 2003; 98:1513-5
24. Papatheodoridis GV, Chung S, Keshav S, Pasi J, Burroughs AK: Correction of both prothrombin time and primary haemostasis by recombinant factor VII during therapeutic alcohol injection of hepatocellular cancer in liver cirrhosis. *J Hepatol* 1999; 31:747-50
25. Erhardtsen E, Nony P, Dechavanne M, French P, Boissel JP, Hedner U: The effect of recombinant factor VIIa (NovoSeven) in healthy volunteers receiving acenocoumarol to an international normalized ratio above 2.0. *Blood Coagul Fibrinolysis* 1998; 9:741-8
26. Ejlersen E, Melsen T, Ingerslev J, Andreasen RB, Vilstrup H: Recombinant activated factor VII (rFVIIa) acutely normalizes prothrombin time in patients with cirrhosis during bleeding from esophageal varices. *Scand J Gastroenterol* 2001; 36:1081-5
27. Bernstein DE, Jeffers L, Erhardtsen E, Reddy KR, Glazer S, Squiban P, Bech R, Hedner U, Schiff ER: Recombinant factor VIIa corrects prothrombin time in cirrhotic patients: A preliminary study. *Gastroenterology* 1997; 113:1930-7
28. Jeffers L, Chalasani N, Balart L, Pyrsopoulos N, Erhardtsen E: Safety and efficacy of recombinant factor VIIa in patients with liver disease undergoing laparoscopic liver biopsy. *Gastroenterology* 2002; 123:118-26
29. Escobar M, Harvey RD: Experience with the use of recombinant factor VIIa in a university hospital. *Blood* 2001; 98:a3902
30. Martinowitz U, Kenet G, Segal E, Luboshitz J, Lubetsky A, Ingerslev J, Lynn M: Recombinant activated factor VII for adjunctive hemorrhage control in trauma. *J Trauma* 2001; 51:431-8