J. McCarthy, M.D.

THROMBOSIS IN CARDIOVASCULAR MEDICINE: A REVIEW OF PATHOPHYSIOLOGY, MECHANISMS OF DRUG ACTION, AND THE "ALPHABET" OF ESTABLISHED AND EMERGING THERAPIES

John McCarthy, M.D.; Jocelyn Szeto, M.D.

Methodist DeBakey Heart & Vascular Center, The Methodist Hospital, Houston, Texas

Abstract

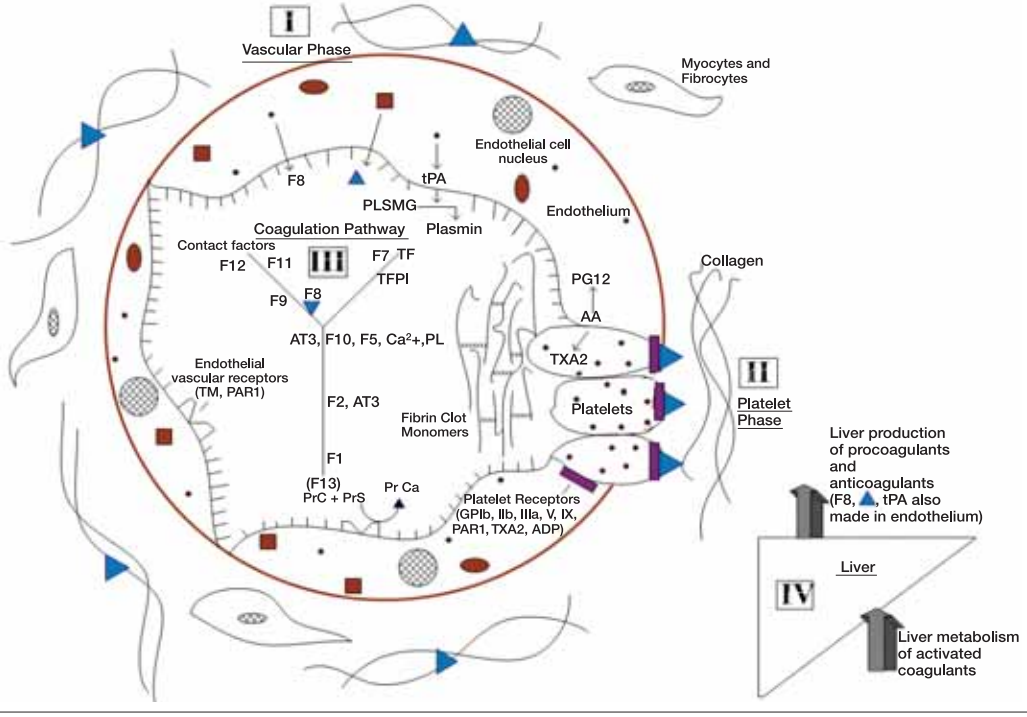
Thrombosis is a physiologic hemostatic response to vascular injury. Thrombus generation has evolved as a complex event involving multiphasic biologic inputs and regulation. Pathologic thrombosis in cardiovascular medicine afflicts millions of U.S. citizens per year, exacting a death total in the hundreds of thousands of people. These morbid events are particularly common in the settings of trauma, major surgery, and high-risk medical patients both inside and outside of the hospital. The frequency of all of these risks increases as our population grows and ages. The discussion that follows sketches the roots of our understanding of pathologic thrombosis through a clinical case example, a highlight of the historically key concepts involved, identification of the phasic inputs into thrombus formation and regulation, and a listing of the therapeutics and agents used in treating the thrombosis "epidemic."

A Patient Example and Pathophysiology of Thrombosis

A 60-year-old woman reported chest pain and shortness of breath at 72 hours after coronary artery bypass surgery for symptomatic angina and 3-vessel coronary artery atherosclerosis. On physical examination, a regular heart rate, clear pulmonary auscultation, and normal lower limb examination were observed. However, an indurated and tender left internal jugular vein catheter site was palpated, and a noncyanotic left upper extremity swelling was seen. Doppler-ultrasound and chest computed tomography confirmed thrombosis of the left internal jugular-subclavian-axillary veins and a right pulmonary embolus. The screening platelet count and heparin-induced antiplatelet antibody test were normal. The D-dimer was marginally elevated. The jugular vein catheter was removed, and the patient was placed on a heparin drip "bridge" while warfarin oral dosing was becoming therapeutic. All symptoms and signs resolved within days, and the warfarin treatment was discontinued after 12 weeks. This case is a common occurrence and one of a myriad of settings in which thrombosis occurs in cardiovascular diseases.

The 19th-century German cytopathologist Rudolf Virchow identified the core triad of elements that precipitate vascular thrombosis: vascular trauma and pathology, blood flow stasis, and hypercoagulable hemostasis.[1] These principles remain at the center of our thinking about pathophysiology, diagnosis, and therapeutics

Figure 1. Phases of coagulation in small vessels.



Legend

□ Coagulation phase; ▲ Von Willebrand Protein; Heparan; F: Coagulation factor protein; TF: Tissue factor; GP:Glycoprotein; ADP: Adenosine diphosphate; AT3: Antithrombin 3; Pr C: Protein C; Pr S: Protein S; Pr Ca: Activated Protein C; PLSMG: Plasminogen; TFPI: Tissue factor pathway inhibitor; AA: Membrane arachadonic acid; PGI2: Prostacyclin I2; TM: Thrombomodulin receptor; PAR 1: Protease-activated receptor 1; TXA2: Thromboxane A2; tPA: Tissue plasminogen activator; PL: Phospholipid; Ca^{2+}: Calcium ion; UFH: Unfractionated heparin; LMWH: Low molecular weight heparin; D: Direct; I: Indirect; P: Parenteral; O: Oral

of thrombosis in the 21st century. Vascular thrombosis remains an epidemic, especially given that the elements of Virchow's triad increase in prevalence with the age of the population. Current antithrombotic therapeutics are designed to manipulate thrombosis pathophysiology, including particular aspects of vascular pathobiology, platelet function, hemostatic protein cascade, physiologic liver coagulation protein production and metabolism, and the naturally occurring anticoagulation system (see Figure 1). As a corollary to our understanding of pharmacologic therapeutics, it should be remembered that virtually all antithrombotic drug therapies display increased bleeding as a prime side effect.

Vascular Therapies (Phase I)

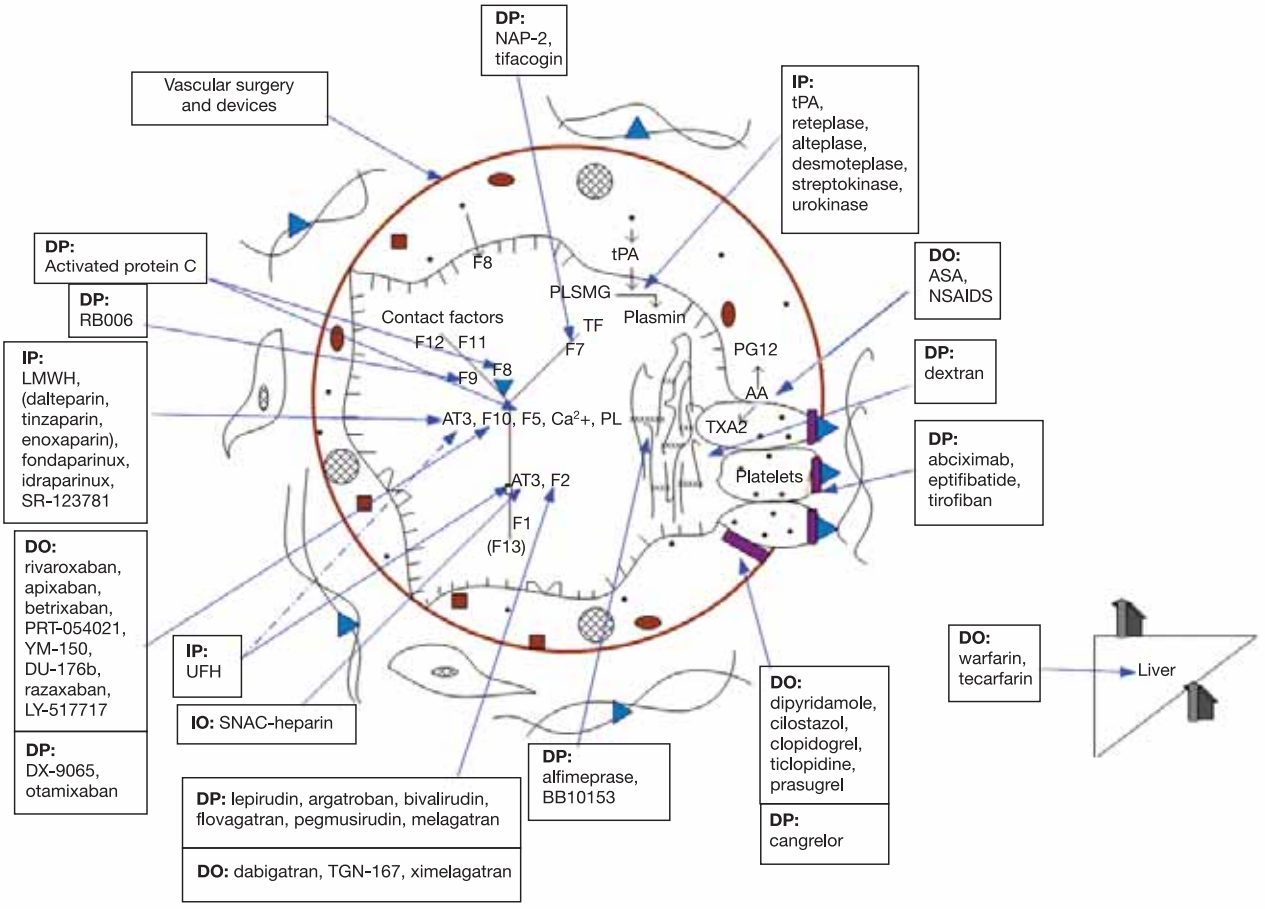
Therapies of blood vessel pathologies may be prophylactic or interventional. Included here are vascular reconstruction surgeries, decompression maneuvers, revascularization and bypass procedures, angioplasty, thrombectomy, vascular grafting, and vascular devices (i.e., prosthetic valves, stents, venous filters, and external venous compressors). These are used to correct prothrombotic vascular anomalies, outlet obstructions, stenoses, vasculopathies such as ASCVD and vasculitis, and intravascular occlusions. Manipulation of blood rheology-vessel interface (ex-pentoxifylline, plasmapheresis of antibodies and pathologic substances) has been of marginal or temporizing use only. Stem cell applications to repair regional end-organ and endovascular injury remain investigational.[2] Some of these therapies are touched upon elsewhere in this journal but otherwise remain beyond the scope of this discussion.

Antiplatelet Therapies (Phase II)

Agents that inhibit the platelet phase of coagulation are designed to interrupt platelet attachment to injured vascular surfaces or to thwart metabolic secretion and shape change by platelets. In general, these agents are employed more often against arterial thrombosis. Arteries are where higher blood flow produces higher sheer forces at the blood-vascular interface. In turn, these forces allow initial platelet attachment physiology to play a more important role in arterial clot generation than in thrombosis of the lower-flow venous system. Clinical settings of arterial occlusion include stroke, transient ischemic attack, coronary artery disease, acute coronary syndrome, and peripheral arterial ischemia. Intravenous dextran, a polymer of glucose, is a vascular volume expander that also inhibits platelet aggregation and some fibrin polymerization (see Figure 2). Dextran is now seldom used due to its weak antithrombotic interaction with platelets, associated fluid overload, more frequent anaphylactic reactions, and slow metabolism profile.

Drugs that inhibit the integrin-like platelet receptors (IIb/IIIa directly, and indirectly other glycophorins) that are responsible for fibrinogen and von Willebrand protein attachment include abciximab, eptifibatide, and tirofiban. These potent intravenous agents are most commonly used in the setting of percutaneous

Figure 2. Anticoagulants and sites of action.



intravascular interventions. One must be vigilant to recognize the occasional severe thrombocytopenia that can be caused by these medications.[3]

Drugs that are designed to inhibit adenosine diphosphate (ADP)-mediated platelet secretion and aggregation are the orally administered adenosine-reducing agent dipyridamole, phosphodiesterase inhibitor cilostazol, and ADP-receptor antagonists such as oral clopidogrel, ticlopidine, and prasugrel. Intravenous cangrelor also blocks the ADP receptor. These drugs are of modest potency. Of note, cilostazol and ticlopidine have had limited use due to exacerbation in congestive heart failure and the occasional precipitation of thrombotic thrombocytopenic purpura, respectively.

Aspirin remains a modestly effective oral agent used in irreversibly inhibiting the arachidonic acid-cyclooxygenase pathway of platelet aggregation. Other oral nonsteroidal anti-inflammatory agents (NSAIDS) also can act through this mechanism to a variable and lesser degree. Other agents that inhibit platelet membrane receptors such as the ADP receptor, the protease activated receptor-1 (PAR-1) that generates platelet-associated thrombin, and the thromboxane-A2 receptor are currently being investigated.[4, 5] Oral anagrelide and intravenous prostacyclin (PGI2) are seldom used for their platelet aggregation inhibiting properties because of frequent side effects, such as thrombocytopenia and worsening of left heart failure, respectively.

Coagulation Protein Inhibition (Phase III)

There has been a proliferation of studies of existing and prospective coagulation protein inhibitors in the variable settings of vascular thrombosis, especially in venous thromboembolic (VTE) disease and atrial fibrillation (AF). All of these drugs interact with the coagulation protein "cascade" to retard or inhibit fibrin monomer clot deposition. These agents include some that act directly against coagulation proteins and others that act indirectly through intercessor mechanisms (i.e., antithrombin 3). Many of these drugs are parenteral while some are orally absorbed (see Figure 2). Intravenous or subcutaneous unfractionated heparin (UFH) indirectly inhibits thrombin (F2) activity, factor 10, and, to a lesser extent, other upstream coagulation factors. It is relatively less expensive, has a short half-life, and is effective at reducing the frequency of thrombotic events by up to 90%. Some 3% of patients may develop the "paradoxical" antibody-mediated heparin-induced thrombocytopenia and thrombosis syndrome (HITT), which has a high morbidity (limb loss, stroke, myocardial infarction) and mortality.[6] Because of UFH reversibility with protamine, it remains the mainstay anticoagulant in pump-oxygenator assisted cardiovascular surgeries.

More expensive direct thrombin inhibitor alternatives (for treating HITT) include intravenous lepirudin (renally excreted), argatroban (hepatic clearance), and bivalirudin (75% nonrenally metabolized). However, these alternatives seem to cause more bleeding during cardiovascular surgery than UFH. Intravenous flovagatran and pegmusirudin are additional direct F2 inhibitors in development, while oral ximelagatran and its intravenous metabolite melagatran have ceased development due to unacceptable liver toxicity profiles.[7] Dabigatran is a recently approved, twice-daily oral F2 inhibitor for nonvalvular AF and for VTE prophylaxis. Its successful use in treating VTE in studies nationally and abroad undoubtedly will result in a wider use of dabigatran. The drug TGN-167 is another oral F2 inhibitor under investigation.[8] Because of poor patient compliance in trials, the modified heparin polymer/SNAC-heparin is no longer being developed.

F10 inhibition has also proved to be equal or superior to F2 inhibition in the treatment of VTE and other types of thrombosis. The parenteral forms of low-molecular-weight heparin (LMWH) include dalteparin, enoxaparin, and tinzaparin. These, and the noncross-reactive subcutaneous pentasaccharide fondaparinux, are all effective indirect F10 inhibitors and are renally excreted. They also have lower risks of osteoporosis side effect than UFH. Other indirect, parenteral F10 inhibitors under investigation include a biotinylated idraparinux (reversible via avidin application) and SR-123781 (a pentasaccharide analogue with long half-life).[9]

Oral direct F10 inhibitors have become a major interest because of their potential effectiveness, ease of administration, and lesser need for laboratory monitoring. Rivaroxaban and apixaban are furthest along in development and have shown repeated noninferiority to heparin and warfarin control group regimens.[10] Betrixaban (PRT-054021), YM-150, and DU-176b are other oral direct F10 inhibitors in earlier stages of development, as are parenteral direct F10 inhibitors DX-9065a and otamixaban.[11] Razaxaban and LY517717 are oral small-molecule F10 inhibitors whose development stalled due to increased bleeding manifestations and lack of demonstrated efficacy, respectively.

Tissue factor-F7a complex inhibitors (e.g., nematode anticoagulant protein-2, recombinant tissue factor pathway inhibitor) and factor 9a inhibitor (e.g., RNA aptamer) are parenteral agents in early development.[12] Intravenous activated protein C application is known to decrease clot formation via catabolism of factor 5a and factor 8a. However, this agent is primarily used to dampen inflammatory response to bacteremic sepsis, so that its efficacy as an anticoagulant is undefined.

Decreasing Liver Coagulation Protein Production (Phase IV)

The liver generates most of the procoagulant proteins and catabolizes downstream activated coagulation factors. The agents used for the longest time in clinical anticoagulation are parenteral UFH, which is derived from the intestines of domesticated mammals, and oral warfarin-like compounds that were first found in northern prairie vegetation. These drugs were isolated in the first third of the 20th century. Heparin is discussed with other clotting factor inhibitors (see above). Warfarin is unique in that it effectively decreases vitamin K-dependent liver coagulation protein production (factors 2, 7, 9, 10, protein C, protein S, and others). In this way, warfarin decreases blood clotability overall. Warfarin is an oral competitive inhibitor of vitamin K's cofactor function in gamma-carboxylation of glutamic acid residues. These residues are in key coagulation factor protein domains that interact with the calcium and the phospholipid bilayer "platform." This platform is integral to the efficient assembly line processing of the coagulation cascade that results in fibrin clot formation.

Warfarin is easy for patients to take orally, relatively inexpensive, and virtually the only drug in its class produced for use in humans in the United States. However, warfarin use suffers from frequent laboratory monitoring due to its low therapeutic index, frequent patient variations in genetic metabolism profile and in intestinal absorption, frequent interactions with other drugs, and a 3% yearly major hemorrhage incidence. Though intravenous vitamin K can reverse warfarin's effect in 6 to 12 hours, the 4–5 day oral time-to-action and time-to-dissipation generally makes warfarin more cumbersome to use in urgent settings.

There is considerable interest among clinicians in the development of effective oral warfarin replacement agents that are easier to use. One such candidate is the oral warfarin analog, tecarfarin.[13] It is not metabolized by the CYP450 system and thus has fewer drug-drug interactions. It was noninferior to warfarin in one human clinical thrombosis study. Other oral warfarin replacement drugs were mentioned earlier in the section on coagulation protein inhibitors.

Clot Lysis Strategies

While coagulation protein inhibitors retard intravascular thrombus formation and propagation, thrombolytic agents actually lyse and degrade thrombi, especially those that are newly formed or only days old. Exploitation of thrombolytics has been effective in venous, arterial, and even intravascular device thrombosis. This has been at the expense of increased bleeding complications, especially at areas of pre-existing lesions, surgical wounds, and vascular punctures. These latter circumstances remain relative contraindications for the use of thrombolytic drugs.

Plasminogen is made in the liver and lyses fibrin clots when converted to active plasmin. The early plasminogen activator agents were streptokinase and urokinase, derived from bacteria and uroepithelium, respectively. The endothelium-derived protein, tissue plasminogen activator (tPA), has replaced the earlier agents and has greater fibrin clot specificity. Truncated and recombinant analogues of tPA (e.g., alteplase, reteplase, tenecteplase) have longer half-lives and higher fibrin specificity. Fibrinolytics in development stage include a direct proteolysis mechanism via a snake venom derivative (alfimeprase), a tPA-like agent (desmoteplase), and a modified plasminogen-like drug (BB10153).[7] All thrombolytics are parenterally applied and often catheter-directed at the thrombus site. Another thrombolysis-promoting class of drugs, plasminogen-activator-inhibitor-I blockers, remains in pre-clinical development.

Summary

The elements of vascular thrombosis (Virchow's triad) were identified in the 19th century and still characterize the pathophysiology of the clinical thrombosis epidemic we face today. This article has been a review and update on the mechanisms and agents used to target and manipulate the phases of hemostasis (vascular, platelet, liver function, coagulation protein, and thrombus counter-regulation). Anticoagulation procedures and drugs remain the cornerstone of treatment of vascular thrombosis. Always to be balanced with bleeding risks and other toxicities, these approaches to thrombosis require familiarity and expertise that draw on both the science and art of medicine in their application to our patients' individual circumstances.

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