Microvascular Thrombosis: A Serious and Deadly Pathologic Process in Multiple Diseases

Hau C. Kwaan, M.D., Ph.D.[1]

ABSTRACT

Much of our understanding of the pathogenesis of thrombosis has long been based on observations made on large blood vessels. Nevertheless, there has been a recent shift in our attention to the microvasculature and to how microcirculatory occlusion affects function of various organs in diseases. This article provides an overview of microthrombosis in small blood vessels, with discussion of the progressive stages of its development. The initial event is triggered by a variety of diseases, followed by a second phase when multiple contributory factors amplify the process with the final phase of microvascular occlusion and microvascular thrombosis. The outcome is either recovery or injury to the affected organ. If the process is generalized, it is often associated with catastrophic or fatal outcomes. Our current knowledge of the major role of contributory factors leads to a new paradigm. A therapeutic approach limited to a single target of the underlying pathogenic factor, such as the use of anticoagulants, is insufficient and too often unsuccessful. Simultaneous management of all the contributory factors should therefore be considered.

KEYWORDS: Thrombosis, disseminated intravascular coagulation, inflammation, hypercoagulable state, sepsis

Until recently, most studies on the pathogenesis of thrombosis have been centered on veins or arteries, while the microvasculature has received relatively less attention. In the past decade, however, there has been a noticeable shift from macrovascular studies to those of microvascular changes following interruption of blood flow. The resulting microvascular occlusion has a great impact on the restoration of function of affected tissues. Microvascular thrombosis can also be the result of other forms of pathology, where it may serve as the initial locus of thrombosis that results in the extension of thrombosis to larger vessels, but more often is the result of a chain of events triggered by an underlying disease. The extent of microcirculatory obstruction often reflects the severity of the underlying illness.

This article is devoted to an overview of microthrombosis in arterioles, capillaries, and venules. Several clinical disorders with common characteristic features of the pathogenesis are presented.

THE MICROVASCULATURE

The microvasculature is composed of a vast network of arterioles, capillaries, and venules. It has a much larger

capacity than that of both arteries and veins combined. Just considering the length of capillaries alone, it is 60,000 to 100,000 miles long.[1] The total volume of the capillaries is only 250 mL compared with an estimated 450 mL for arteries and 2800 mL for veins. The capillary wall is thin, comprising a layer of endothelium with pericytes and extracellular matrix. Because of their smaller diameter, the rheological characteristics of capillaries are also different than those of arteries and veins. The blood flow and the hydrostatic pressure in the capillaries are controlled by vascular tone in the arterioles and venules, and are therefore slow, but the shear rate is high due to the smaller diameter. Accordingly, the vascular wall shear stress drops sharply from arterioles to capillaries.[2] These rheological characteristics have great implications in the blood viscosity within the microvasculature. The viscosity drops sharply with increased shear rate, and is more sensitive to increases in hematocrit. Both of these features are important in the development of microthrombosis. Our knowledge in this area is limited. Because of the frequent branching of the capillaries and the constant change in vascular tone, experimental results with rigid tubes when applied to the microvasculature should be interpreted with caution.[3]

Within the microvasculature, there is a high degree of heterogeneity both in structure and function.[1,4,5] The endothelial lining may be (1) continuous with tight junction between cells (e.g., in the brain to form the blood-brain barrier, in the lymph nodes to allow lymphocyte homing, and in muscles for metabolic exchange); (2) fenestrated (e.g., in endocrine glands to allow secretion, in the gastrointestinal tract for absorption, in the choroid plexus for secretion of cerebrospinal fluid, and in the renal glomeruli for filtration); or (3) discontinuous with pores of 0.1 to 1.0 μm (e.g., in the liver sinusoids for particle exchange, in the bone marrow sinuses for passage of hematopoietic cells, and in the spleen for filtration).[6] Under physiological conditions, these functions are organ-specific with exchange and transport of proteins in the respective organs. The endothelium has also an important role in hemostasis, maintaining the balance between prothrombotic and antithrombotic factors.[7] The major prothrombotic factors are (1) for coagulation activation: tissue factor, von Willebrand factor (VWF), and the protease-activated receptors (PARs); (2) for platelet activation: thromboxane A_2, VWF, platelet activating factor; (3) for inhibition of fibrinolysis: plasminogen activator inhibitor-1 (PAI-1); and (4) for cell adhesion: various adhesive molecules such as P-selectin, E-selectin, platelet endothelial cell adhesion molecule-1, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). These factors are counteracted by (1) the anticoagulants: protein C, protein S, tissue factor pathway inhibitor (TFPI), thrombomodulin (TM),

endothelial protein C receptor, heparan and nitric oxide synthetase; (2) profibrinolytic factors: tissue plasminogen activator (tPA), urokinase-type plasminogen activator (uPA), uPA receptor, annexin A2; and (3) antiplatelet factors: prostacyclin, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) and ecto-ADPase. There is also heterogeneity in the expression of these factors. For example, the brain is poor in TM,[8] and protein C is poorly expressed in capillaries.[9] In various diseases, especially when there is an inflammatory response, the picture is altered with a predominance of prothrombotic factors, resulting in a hypercoagulable state.

PATHOGENESIS

The factors leading to the formation of microvascular thrombosis are multiple and parallel those implicated in the pathogenesis of macrovascular thrombosis.[10,11] The traditional paradigm of Virchow triad[12] is not only applicable but may be more relevant, because the smaller vessels are more susceptible to thrombosis. These factors are shown in Fig. 1. Though they appear to be similar to those found in large vessel diseases, their effects can be vastly different. Because of the size differences, both the volume and characteristics of blood flow are more sensitive to structural alterations in the microvasculature than in larger blood vessels. As discussed above, notable differences are found in their rheological properties,[2] their expression of procoagulant and anticoagulant proteins, adhesive molecules, and of proinflammatory cytokines.[7] The microvasculature is also more susceptible to the adverse effects of various abnormalities in blood. The smaller lumen is easily obstructed. There is a higher ratio of endothelial surface to luminal volume, thus providing greater exposure to the circulating blood and a higher concentration of locally released cytokines. Changes in small blood vessels rather than large vessels are the site of pathology in several disorders.

A review of recent observations on microthrombosis shows that several progressive stages can be recognized in its development. The primary occurrence can be a complication of a wide variety of disorders, including those with abnormality in the blood vessel, such as endothelial injury from severe sepsis,[13] vasculitis,[14] abnormal neovascularization in cancer tissues,[15] or radiation injury.[16] Microthrombosis can also develop as a consequence of abnormal blood flow, variably due to aggregated platelets, erythrocytes, or leukocytes. Other examples are seen in reperfusion after interruption of blood flow in organ infarction,[17] embolism, or after reconstructive or transplant surgery.[18,19] Aberrant blood flow can occur in tumor microvasculature[15] or in vascular malformations, and in the hyperviscosity syndromes.[20] The primary event can also be caused by abnormal blood components, as seen in hypercoagulable states with

Pathogenesis of microthrombosis based on Virchow's triad.

Abnormal blood vessel

e.g. Sepsis/severe trauma
Tumor microvasculature
Radiation injury

Abnormal blood flow

e.g. Aggregated platelets
Aggregated erythrocytes
Aggregated leukocytes
Reperfusion after interruption of flow in organ infarction, embolism, reconstructive surgery
Aberrant flow in vascular malformation, tumor microvasculature
Hyperviscosity

Abnormal blood components

e.g. Increased procoagulants
hereditary thrombophilia
acquired prothrombotic states
Antiphospholipid syndrome
Traumatic brain injury
Subarachnoid hemorrhage
Decreased protein C, protein S
Warfarin necrosis
Post-varicella purpura fulminans
Abnormal proteins
paraproteins (plasma cell dyscrasias)
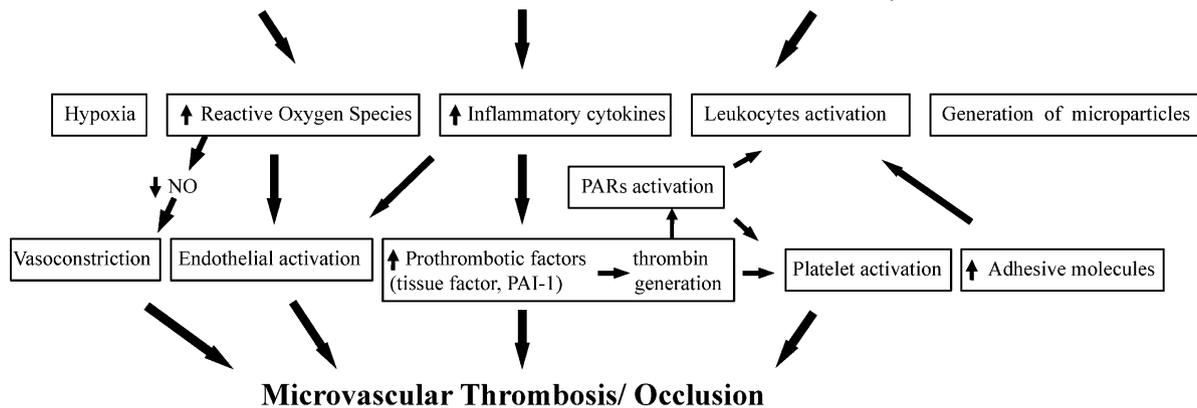abnormal fibrinogen
cryoglobulin
amyloid

| Hypoxia | ↑ Reactive Oxygen Species | ↑ Inflammatory cytokines | Leukocytes activation | Generation of microparticles |

↓ NO   PARs activation

| Vasoconstriction | Endothelial activation | ↑ Prothrombotic factors (tissue factor, PAI-1) → thrombin generation | Platelet activation | ↑ Adhesive molecules |

Microvascular Thrombosis/ Occlusion

Figure 1 Pathogenesis of microthrombosis based on Virchow triad. NO, nitric oxide; PAI-1, plasminogen activator type 1; PARs, protease activated receptors.

increased procoagulants, or with decreased protective anticoagulants. It can also occur when abnormal proteins[20] initiate a process of microvascular occlusion and thrombosis.

A variety of factors contribute to the further development of the pathology. Their actions are often interdependent and, once activated, lead to further amplification of one another. Perhaps the most significant role is that of systemic inflammatory response.[21-23] There is an increased expression of proinflammatory cytokines, including tissue necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and IL-8. These cytokines induce the expression of prothrombotic factors with activation of the coagulation pathway.[24] Thrombin generation leads to activation of the PARs present in endothelial cells, platelets, and leukocytes, resulting in the activation of these cells.[25] The adhesive molecules P- and E-selectins are activated, leading to leukocyte migration and adhesion to the endothelium.[26] Neutrophil proteases cause further injury to the endothelium. A combination of these effects results in blockage of the circulation as well as in microthrombi formation. With microcirculatory occlusion, hypoxia and generation of reactive oxygen species (ROS) further lead to vasculopathy. A vicious circle is thereby established, resulting in an unfavorable outcome. In the case of localized occlu-

sion, there will be infarction of the affected organ. When the occlusion is generalized, multiorgan dysfunction syndrome will ensue.[27,28] The major organs involved are kidneys,[29] lungs,[30] liver,[31] and brain.[32] The mortality rate varies with different clinical settings, but typically exceeds 50%.[33]

The commonly encountered disorders with microvascular thrombosis, listed in Table 1, are reviewed in this article to illustrate different versions of the same pathogenic mechanisms.

Disorders with Microthrombosis due to Endothelial Injury

SEPSIS/SEVERE TRAUMA

In the critically ill patient with severe sepsis or trauma, a series of events often lead to multiorgan dysfunction syndrome.[28] A high mortality is associated with this complication. Studies exploring its pathogenesis have revealed a picture of endothelial injury with active systemic inflammatory response. Increased expression of cytokines and procoagulants are the major contributory factors in the development of severe disseminated intravascular coagulation (DIC)[13,34-36] with a thrombotic phenotype.[34] Widespread microthrombi have been

Table 1 Diseases with Microvascular Thrombosis

Disorders with Endothelial Injury

   Sepsis/severe trauma

   Tumor microvasculature

   Radiation injury

Disorders with Abnormal Blood Flow

   Aggregated platelets: TMA; heparin-induced thrombocytopenia

   Aggregated erythrocytes: Malaria; sickle cell disease;
     cold agglutinin disease

   Aggregated leukocytes: Leukostasis

   Reperfusion after interruption of blood flow: Postacute
     myocardial infarction; postsurgical reconstruction

Disorders with Abnormal Blood Components:
   Hypercoagulable States

   APS

   TBI

   SAH

   Warfarin necrosis

   Postvaricella purpura fulminans

TMA, thrombotic microangiopathy; APS, antiphospholipid syndrome; TBI, traumatic brain injury; SAH, subarachnoid hemorrhage.

observed in autopsied specimens[37,38] (Fig. 2). In severe sepsis, bacterial endotoxins such as lipopolysaccharides bind to endothelial receptors, triggering an inflammatory response. This amplifies the generation of cytokines, chemokines, adhesive molecules, and complement activation. As a result, the endothelial function is perturbed in several ways (Fig. 3). Multiple interactions between the activated inflammatory factors and the thrombotic factors occur, escalating the process until the vicious circle is broken.[39] The inflammatory response results in an increased expression of the inflammatory cytokines TNF-α, IL-1β, and IL-6.[22,23] Tissue factor, normally not expressed at the surface of the endothelium, is induced by these cytokines.[24] Upregulation of tissue factor is also found in monocytes and macrophages.[40] Recent observations show that tissue factor is present in
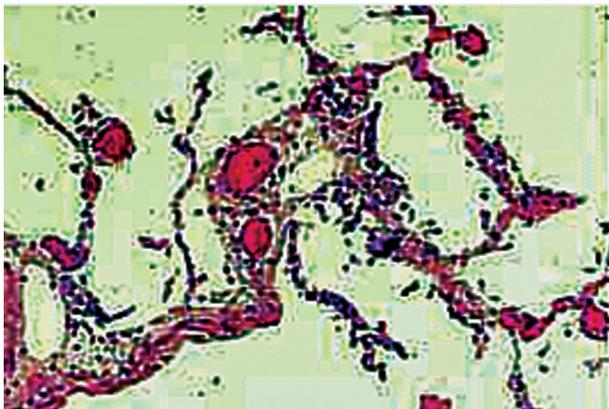

Figure 2 Microthrombi in the pulmonary alveolar capillaries in a patient who died of severe sepsis. Hematoxylin and eosin stain.

microparticles in the circulating blood with levels accentuated during sepsis.[41,42] The inflammatory cytokines also induce increased expression of E- and P-selectins, resulting in adherence of neutrophils to the endothelial surface.[26,43,44] The ensuing neutrophil-endothelial interaction results in release of proteases and ROS from the neutrophils, thus enhancing the endothelial injury. Complement activation leads to production of C3a and C5a and upregulation of C5a receptors in neutrophils, endothelial cells, lungs, cardiomyocytes, and neurons.[45] The prothrombotic role of C5a has been verified in experimental sepsis, with anti-C5a antibodies shown to attenuate the coagulopathy.[45,46]

Following endothelial injury, a coagulation response takes place, with increased expression of tissue factor in the endothelial cells, monocytes, and macrophages.[40] In the normal endothelium, a receptor for the anticoagulant protein C is present. This is, however, poorly expressed in capillaries, thus rendering the capillaries more susceptible to thrombosis. The function of protein C is also impaired in sepsis,[21,22,47] thus favoring the development of microthrombosis. Clinical trials of recombinant form of human activated protein C (rhAPC), drotrecogin alfa, in patients with sepsis showed mixed results.[48] In the phase 3 PROWESS trial, a significantly reduced mortality was found in the rhAPC treated group.[49] The patients who benefited most were those with severe sepsis[50] and overt DIC.[51] However, in a subsequent trial (ADDRESS),[52] designed to test efficacy of rhAPC in patients with low APACHE score (<25), no difference in the 28-day mortality rate was found. The addition of heparin to rhAPC adds minimally to the survival benefit but significantly reduced stroke complications.[53] Due to the high cost of rhAPC, justification for its use in low grade sepsis is questionable,[54] while more clinical trials are evaluating its benefit in those with severe sepsis.[48,55–57]

The functions of two other naturally occurring anticoagulants, antithrombin and TFPI, are also adversely affected in sepsis.[39] Antithrombin levels are low, due to consumption by the increased thrombin generation in sepsis, decreased synthesis, and degradation by elastase released by activated neutrophils. The administration of recombinant antithrombin has been shown to reduce thrombin generation[58] but did not lower the mortality in sepsis.[59] TFPI is normally anchored to the endothelium by glycosyl phosphatidyl-inositol.[60] In sepsis, TFPI is detached and thus has reduced function.[61] A clinical trial of recombinant TFPI in severe sepsis showed reduction of the coagulopathy but did not lower mortality.[62]

The fibrinolytic system is also perturbed in sepsis. Under various forms of stress, including the development of DIC, tPA is released from the endothelium. The resulting increased fibrinolytic activity is counterbalanced by an increase in circulating PAI-1, in part due
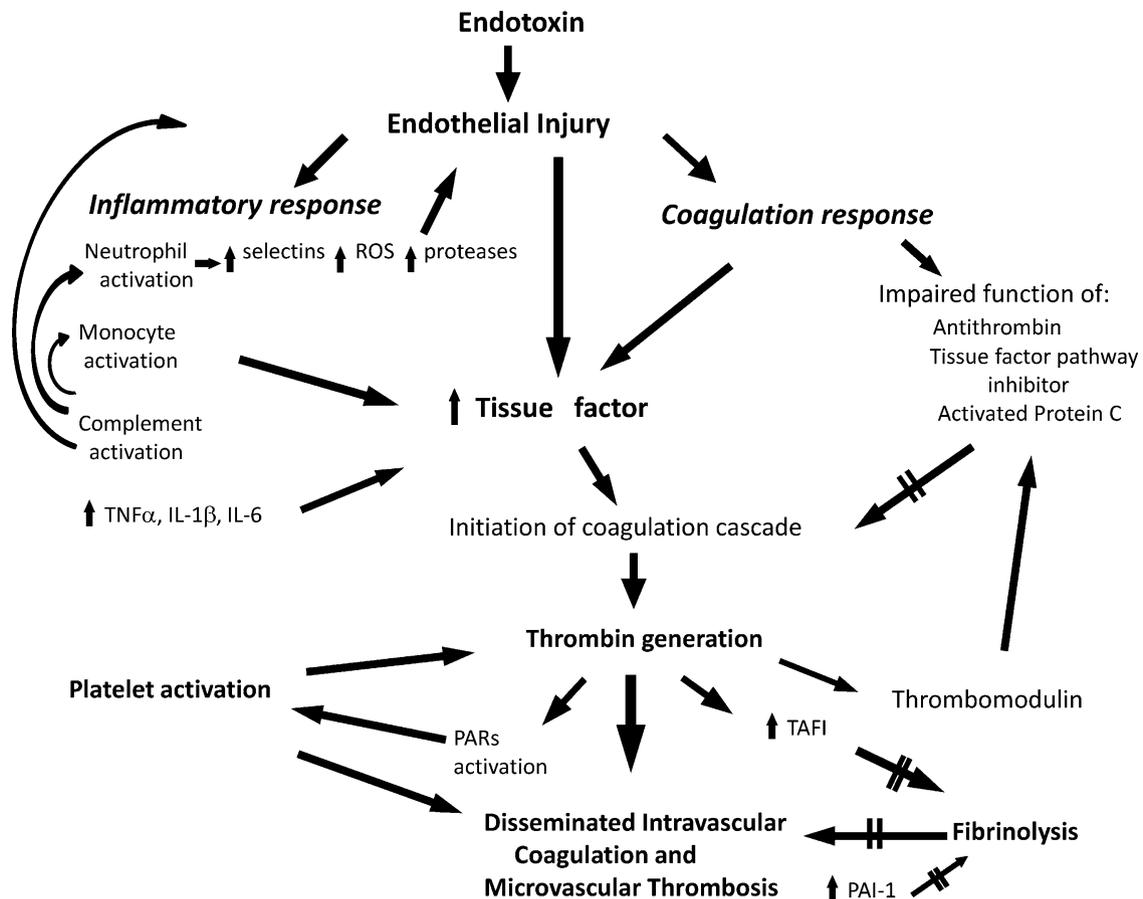
Figure 3 Multiple pathways showing interactions among contributory factors in acute sepsis. IL-1β, interleukin 1β; IL-6, interleukin 6; PAI-1, plasminogen activator inhibitor type 1; PARs, protease activated receptors; ROS, radical oxygen species; TAFI, thrombin activable fibrinolytic inhibitor; TNFα, tumor necrosis factor α.

to the action of inflammatory cytokines, such as TNF-α.[63] In experimental sepsis, the increased PAI-1 was found to be the dominant effect.[64] Fibrinolysis is also impaired by the activation of the thrombin activatable fibrinolytic inhibitor (TAFI).[65] In addition, the activated TAFI displays carboxypeptidase activity, and, through this pathway, can modulate inflammation.[66]

Thrombin and several coagulation proteases activate the PARs.[25] Members of the PAR family, PAR-1 to PAR-4, are present in the endothelial cells, platelets, monocytes, and neutrophils. Activated PARs in turn activate these cells in a concerted effort to enhance the prothrombotic process.

Additional factors are frequently present in critical care unit patients, such as hypoxia, hypotension, and fever. These can magnify the progression of DIC and microthrombosis leading to multiorgan failure. Thus, in any given patient, the appropriate management should take into consideration the multiple and complex nature of the pathogenesis.

TUMOR MICROVASCULATURE

Microthrombi are frequently present in many types of tumors and are considered part of the pathology. A generalized microthrombi formation is, however, mostly seen in metastatic cancer, with findings similar to those seen in thrombotic microangiopathy (TMA), also known as microangiopathic hemolytic anemia.[67–70] The features of cancer-associated TMA are distinct from those of acute idiopathic thrombotic thrombocytopenic purpura (TTP) and of hemolytic-uremic syndrome (HUS), in that there is no preferential localization of the microthrombotic lesions in the brain and kidneys.[70–72] In contrast to TTP, there is systemic coagulopathy and the microthrombi are rich in fibrin. The pathogenesis in cancer-associated thrombosis is also different. In the tumor microenvironment, in addition to invasion of tumor cells into the microvasculature, tumor angiogenesis results in malformed vessels with aberrant blood flow.[15] These vessels are irregular in size, with increased permeability. There is hypoxia with increased vascular endothelial growth factor (VEGF) activity.[73,74] Tumor cells themselves also produce proinflammatory cytokines such as TNF-α and IL-6, inducing increased tissue factor expression by the endothelial cells. In addition, tissue factor is also produced by many types of tumor cells. As tumor cells undergo apoptosis, exteriorization of phospholipids to the surface of cell

membrane leads to activation of tissue factor. Thus, apoptotic cells are more thrombogenic.[75] Tissue factor bearing microparticles are also found in the blood of patients with cancer[76] and acute leukemia.[77] These are submicron cellular fragments that may contribute to the prothrombotic state.[78] Yet, it is unclear why microthrombi are not seen as fragments as expected.

Microthrombi are more frequently seen in two organs, the renal glomeruli being involved in 26% of autopsied specimens of cancer patients,[79] while the lung is also a common site for microthrombi.[80,81] These microthrombi do not contain tumor cells. Whether they form the basis for metastasis is not still unknown. On the other hand, microthrombi in low grade brain tumors (astrocytoma) may signal progression toward glioblastoma.[82]

RADIATION INJURY

Vascular injury due to ionizing radiation is well recognized, with the capillaries being most sensitive. The effects of ionizing radiation on the endothelial cells include apoptosis, increased endothelial permeability, expression of chemokines, and adhesion molecules.[16,83] The natural antithrombotic state of the endothelium is impaired with increased VWF,[84] tissue factor,[85] impaired protein C function,[86] and reduced fibrinolytic activity.[87] Thrombotic occlusion of small vessels is a common feature of focal radiation necrosis following radiation to the brain.[88] As local radiation is the major therapeutic modality for head and neck cancer, a common complication is osteoradionecrosis of bone.[89,90] Endothelial cell damage with necrosis of microvasculature along with an inflammatory response is believed to be leading pathogenic factors.

Disorders with Microthrombosis due to Abnormal Blood Flow

The microvasculature can be blocked by circulating cellular elements, including erythrocytes, leukocytes, and platelets (Table 2). The consequences are dependent on the nature of the occluding elements.

AGGREGATED PLATELETS: THROMBOTIC MICROANGIOPATHY (TMA)

The characteristic microvascular lesion in TMA, consists of a microthrombus rich in platelets with variable amounts of fibrin and erythrocytes. The clinical manifestation is one of microangiopathic hemolytic anemia and thrombocytopenia. TMA is present in a wide spectrum of diseases. The classical TMA is acute idiopathic TTP,[71] while the other forms of TMA are HUS, and TM secondary to cancer, pregnancy, connective tissue disorders, tissue transplantation, infection, and drug toxicity.[91] Acute idiopathic TTP is an autoimmune disorder with an immunoglobulin G (IgG) autoantibody directed against ADAMTS13, an enzyme that cleaves VWF.[71,92] The lack of ADAMTS13 results in the accumulation of ultralarge multimers of VWF at locations with high shear stress, causing extensive platelet aggregation with platelet thrombi formation in arterioles, capillaries, and rarely in venules. The characteristic lesion is a platelet-rich thrombus partially occluding a small blood vessel (Fig. 4). Impaired endothelial function such as decreased prostacyclin synthesis and impaired fibrinolytic activity also contributes to the pathology. Microvascular endothelial cells derived from the brain, kidneys, and heart have been found in vitro to be most susceptible to this form of injury, while those from lungs and liver are not.[93,94] This observation is supported by the clinical picture in which neurological abnormalities and renal failure are the most common presenting features. The mortality rate is over 95% when left untreated. In contrast, survival with more than 90% remission can be achieved with early diagnosis and appropriate management with therapeutic plasma exchange and immunosuppression. The acute idiopathic TTP should be distinguished from HUS, where microthrombi are localized to the renal glomeruli. Two forms of HUS are present.[95] The diarrhea associated form

Table 2 Microthrombosis as Result of Blockage of Microvasculature

Disorder	Occluding Elements	Mechanism	Local/General
TTP/HUS	Platelets	Severe deficiency of ADAMTS13	Brain, heart, kidney
HIT	Platelets	Antibody against PF4/heparin	Skin, adipose tissue
Malaria	Erythrocytes	Changes in infected red cells	Brain
Sickle cell	Erythrocytes	Sickling	Brain, lungs/generalized
Cold agglutinin disease	Erythrocytes	Agglutination from antibodies	Generalized
Leukostasis	Leukemic cells	Increased adhesive molecules	Brain, heart, lungs
DIC	Fibrin	Endothelial damage	Kidney/generalized
Warfarin necrosis	Fibrin	Low protein C	Skin, adipose tissue
Miscellaneous	Cryoglobulin	Erythrocyte aggregation	Generalized
Miscellaneous	Paraproteins	Erythrocyte aggregation	Generalized

TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type1 motif, member 13; HIT, heparin-induced thrombocytopenia; DIC, disseminated intravascular coagulation.
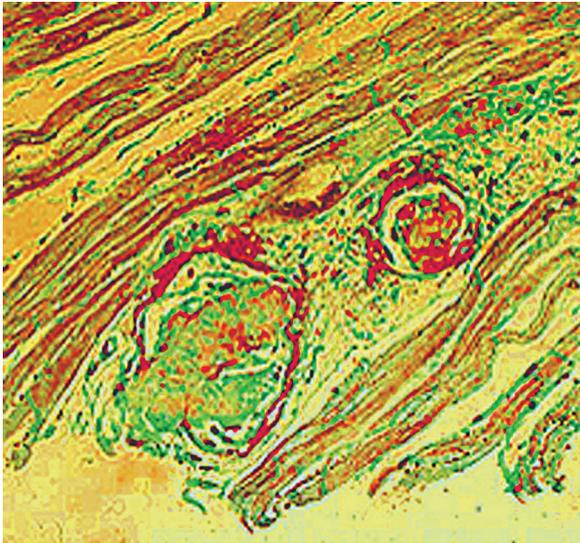
Figure 4 The characteristic microthrombotic lesion in the myocardium in thrombotic thrombocytopenic purpura, showing a capillary partially occluded by a platelet-rich thrombus. Lendrum stain with platelets shown as green and fibrin shown as red.

(D[+]HUS) is seen in hemorrhagic enterocolitis caused by Shiga toxin from *Escherichia coli* infection.[72,96] The renal glomerular microvascular endothelium is most sensitive to the toxin, resulting in renal failure.[97] The illness is usually self-limited after clearing the Shiga toxin. On the other hand, in the atypical form (D[−]HUS or aHUS) severe renal disease is the rule.[98] It is associated with genetic defects of the complement system including factor H, factor I, membrane cofactor protein (MCP/CD46), and defect of the *CFHR1* gene that regulates C5 convertase.[99] Autoantibodies against factor H are also found in aHUS.[100]

In the other forms of TMAs, the formation of microthrombi is secondary to an underlying disease.[101]

Some of them are associated with endothelial damage, such as in connective tissue disorders, infection, and drug toxicity. The concomitant presence of hypercoagulability, such as in cancer, further increases the thrombotic risk.

AGGREGATED PLATELETS: HEPARIN-INDUCED THROMBOCYTOPENIA

Platelet-rich microthrombi are commonplace in heparin-induced thrombocytopenia.[102] IgG immune complexes of antiplatelet factor 4/heparin activate platelets, causing thrombocytopenia and hypercoagulability. The immune complexes also interact with endothelial cells, amplifying the endothelial injury.[103] The platelet thrombi initially start in the microvasculature of skin and adipose tissues (Fig. 5A, B), but often extend to larger vessels causing serious arterial and venous thrombotic complications.

AGGREGATED ERYTHROCYTES

Under physiological conditions, a smooth passage of erythrocytes through the microcirculation requires specific rheological characteristics.[104] Erythrocytes are highly deformable and orient their shape with the stream of blood flow. They also aggregate to form linear arrays like a stack of coins known as rouleaux. Aggregate formation is dependent on the deformability of erythrocytes, adhesiveness of the erythrocyte membrane as well as plasma proteins, especially fibrinogen, and flow characteristics. Erythrocyte aggregation is encountered in several disorders with microthrombosis as a common complication.[105] Some examples are reviewed here.

Malaria In *Plasmodium falciparum* infection, impaired microcirculation has been observed in brain,[106] retina,[107] and spleen.[108] The brain abnormalities account for much of the neurological symptoms. Because of the clinical
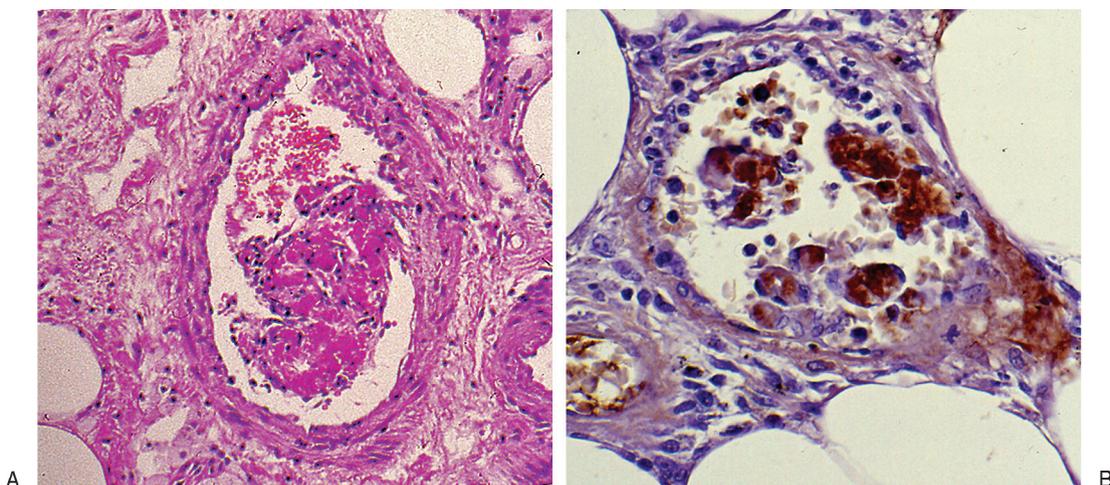

Figure 5 A small artery in the subcutaneous tissue occluded by a microthrombus in a patient with heparin-induced thrombocytopenia. (A) Hematoxylin and eosin stain. (B) Immunostaining with anti-Gp1b (CD42) identified the nature of the components of the microthrombus as platelets.
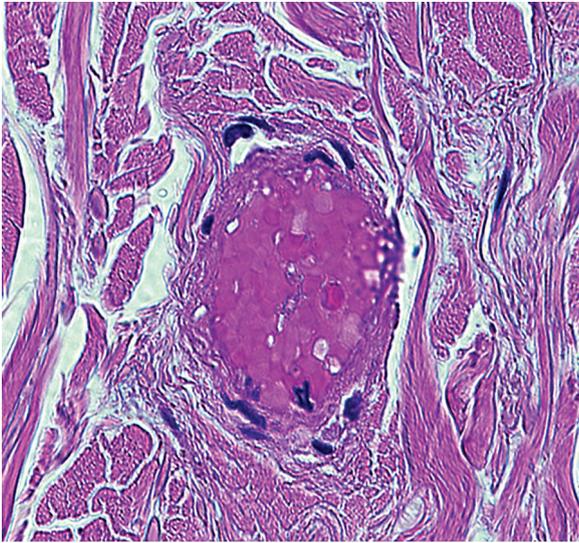
Figure 6 A small arteriole in the subcutaneous tissue occluded by aggregated erythrocytes in a severe case of *Plasmodium falciparum* infection. Hematoxylin and eosin stain.

severity of cerebral malaria, most investigations are centered on *P. falciparum*. In severe cases, microthrombi are also found in sites other than the brain (Fig. 6). The older concept that altered properties of the infected erythrocyte such as decreased plasticity and increased adhesiveness cause the vascular obstruction, has now given way to viewing the microvascular lesion as the combined result of multiple events. In addition to changes in the erythrocytes, platelet activation occurs.[109,110] A membrane protein, *P. falciparum* erythrocyte membrane protein, present on *P. falciparum* infected erythrocytes,[111] is believed to mediate a series of interactions including adhesion between the parasite and endothelium, binding of platelets and erythrocytes via CD36 (an adhesive molecule on microvascular endothelial cells). Other adhesive molecules, including ICAM-1, VCAM-1, P-selectin, E-selectin, are also involved.[112] Evidence of endothelium activation has also been observed.[113] In addition, the *P. falciparum*-infected erythrocytes induce tissue factor expression in the endothelium and lead to activation of the coagulation pathway.[114] Thrombin generation results in PAR activation and release of inflammatory cytokines, amplifying many of the above interactions.[115]

Microparticles derived from endothelial cells have also been detected in patients with severe malaria and their number correlate with plasma TNF levels.[116] As malaria is still an important worldwide disease, and cerebral malaria carries a high mortality, it is hoped that some of these findings may be translated to a better therapeutic approach.[117]

Sickle Cell Disease Although erythrocyte sickling can offer a rheological blockade to the microcirculation,

events that lead to the vasculopathy are much more complex.[118,119] Hemolysis releases hemoglobin and impairs the arginine-nitric oxide (NO) pathway by scavenging NO. Arginase is also released from hemolyzed erythrocytes, reduces the NO synthetase activity, and further decreases the availability of NO. It also shifts the metabolism of L-arginine to L-ornithine, producing polyamines and L-proline, substances that promote smooth muscle cell growth and fibrosis.[120] There are also changes in the coagulation profile, toward a prothrombotic state[121] with enhanced thrombin generation,[122] tissue factor activity,[123] decreased anticoagulants,[124] abnormal fibrinolysis,[125] and platelet activation.[126] However, it is unclear to what extent these factors contribute directly to the microvascular occlusion.[127] The roles played by factors such as endothelial activation and inflammatory cytokines are considered more important. Many of these changes correlate with the hemoglobin levels, reflecting the degree of hemolysis. These findings led to the concept that vascular complications are dependent on the level of hemolysis and the resulting NO scavenging.[118,119,128,129] Those patients with a high degree of hemolysis would be expected to have pulmonary hypertension, leg ulceration, priapism, and stroke, while others with less hemolysis would be expected to have vaso-occlusion (presumably from rheological obstruction of the sickled erythrocytes) with pain crisis, acute chest syndrome, and osteonecrosis. However, this concept of NO scavenging, while attractive, has recently been questioned[130] as the vasculopathy is not seen in other severe hemolytic disorders with higher levels of free plasma hemoglobin, such as paroxysmal nocturnal hemoglobinuria. Furthermore, clinical trials designed to abrogate the deleterious effects of NO did not show benefits. An example is seen in the clinical trial of hydroxyurea. Although the degree of hemolysis was reduced in patients treated with this compound, the pulmonary hypertension was not affected.[131] Another example was the clinical trial of the phosphodiesterase (PDE) inhibitor, sidenafil. Inhibition of PDE was expected to enhance the effect of NO on guanylate cyclase. However, the trial was terminated due to excessive rate of pain crises.[132] It is clear that the underlying mechanism for microvascular occlusion in sickle cell disease is complex and that the temporal (massive hemolysis, crisis) and spatial (difference with different vessels, e.g., pulmonary vs. bone) changes have to be taken into consideration.

Cold Agglutinin Disease In contrast to malaria, microcirculatory blockade by agglutinated erythrocytes is less common in autoimmune hemolytic anemia. However, widespread vascular occlusion can occur and the profound effects of agglutinated erythrocytes are frequently not recognized. This is mostly seen in cold agglutinin disease. As erythrocytes aggregate at low temperature, the skin microvasculature is more prone

Figure 7 Extensive livedo reticularis developed in a patient with cold autoimmune hemolytic anemia right after administration of intravenous immunoglobulin.

to occlusion, with livedo reticularis as the leading clinical manifestation.[133] The severity can be intensified by additional risk factors. This was illustrated in a patient with cold autoimmune hemolytic anemia refractory to immunosuppressive therapy. Following the intravenous administration of immunoglobulin, which increased the blood viscosity and the erythrocyte aggregation, severe generalized microvascular occlusion abruptly took place with profound livedo reticularis, the patient succumbed to coma (Fig. 7). Another example is seen when autoimmune hemolytic anemia developed in a patient with cryoglobulinemia, resulting in catastrophic mesenteric thrombosis and cerebral infarction. At postmortem extensive mesenteric thrombi were found in the small arterioles, capillaries, and venules, and consisted mostly of agglutinated erythrocytes (Fig. 8).[134]

AGGREGATED LEUKOCYTES: LEUKOSTASIS

The microcirculatory obstruction can be severe and life-threatening. It may impair blood flow to the brain, eyes, myocardium, lungs, and kidneys, and progress to multi-organ failure (Fig. 9A, B). Initially, the microvasculature is obstructed by the leukocytes without significant activation of hemostasis, but as the obstruction progresses,
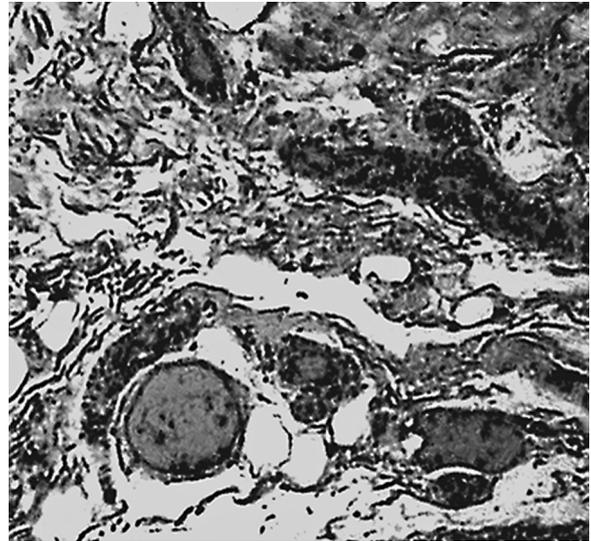

Figure 8 Microthrombi in the submucosa of small intestines in a patient with catastrophic mesenteric thrombosis from combined cryoglobulinemia and cold autoimmune hemolytic anemia.

thrombosis will develop and can lead to extensive arterial and venous thromboembolism. Involvement of both the brain and lungs is associated with a high mortality rate.[135,136] In acute leukemia, the risk of leukostasis is increased when the peripheral blast count exceeds $100,000/\mu L$. The frequency of hyperleukocytosis ranges from 5 to 13% in adult acute myelogenous leukemia (AML) and from 12 to 25% in pediatric AML.[136–138] Acute leukemia with monocytic differentiation (FAB classification: myelomonoblastic [M4], monoblastic [M5]) often presents with hyperleukocytosis as a common complication.[139] Nearly 40% of patients presenting with poorly differentiated monoblastic leukemia have white blood cell counts greater than $100,000/\mu L$ at diagnosis.[140] Myelo-monoblasts, especially in the M4, M5 subtypes, are larger and less deformable, and thus
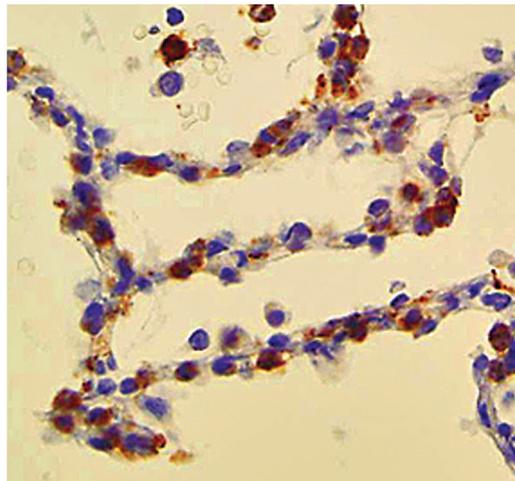
Figure 9 Pulmonary alveolar capillaries blocked by myelomonoblasts in a patient with acute monoblastic leukemia. (A) Wright stain; (B) Positive CD 33 immunostain.

more frequently cause leukostasis. This picture is often seen in AML in infants as the leukemia is often M4 or M5 and shows high blast counts.[141]

The cause of leukostasis was previously thought to be due to hyperleukocytosis. However, this concept was recently challenged. It is now generally believed that adhesive molecules in both endothelium and leukemic blasts play an essential role. In vitro studies showed an increased expression of adhesive molecules by endothelial cells and corresponding receptors in the myeloblasts.[142] Myeloblasts, through their production of cytokines including TNFα and IL-1β, were found to upregulate the expression of ICAM-1, VCAM-1, P-, and E-selectins by endothelial cells. At the same time, their corresponding receptors (e.g., CD11b) are present in the myeloblasts. In such a microenvironment, the endothelial cells are able to recruit additional myeloblasts, forming a vicious cycle where more leukemic cells are trapped leading to more leukostasis. In the M4 and M5 subtypes of AML, CD11b, a receptor of ICAM-1, ICAM-2, is highly expressed in the myeloblasts, whereas in M0, M1, M2, and M3 subtypes there is less expression of this receptor, thus providing another reason for the higher frequency of leukostasis in the M4 and M5 subtypes. This new concept has implications on the management of the leukostasis. Cytoreduction by leukapheresis, though popular, may not be sufficient to change the outcome.[90]

REPERFUSION AFTER INTERRUPTION OF BLOOD FLOW

Interruption of Blood Flow as Seen in Acute Myocardial Infarction The degree of restoration of myocardial function following acute myocardial infarction is dependent on early reperfusion.[143] Microvascular occlusion, also known as the "no-reflow" phenomenon, follows the reperfusion of the ischemic area. The microvascular endothelial cells show explosive swelling while neutrophils, erythrocytes, and platelets filled the vascular lumen.[17] There is loss of vasomotor tone. Hemorrhage and edema in the surrounding tissues are also present.[144] Metabolic injury to the surrounding myocytes results in loss of myocardial function and fibrosis. Increased understanding of the pathogenesis and the consequences of the microvascular occlusion has led to clinical approaches that require better assessment of the abnormal blood flow and to use of therapeutic agents to prevent the ischemic injury and salvage myocardial function.[145] This subject has been extensively studied both clinically and in experimental myocardial infarction models and reviewed elsewhere.[144,146–148]

Reperfusion after Surgical Reconstruction The current technique employing microvascular free-tissue transfer (free-flap reconstruction) has a remarkably suc-

cessful rate, up to 90 to 99%.[149] However, thrombosis still occurs in 8 to 14% cases.[18] The risk factors for thrombosis have been shown to be preexisting focal arterial thickening, prior radiation, hypercoagulable state such as that seen in cancer, smoking, diabetes, hypertension, and hypercholesterolemia.[150] Antiplatelet agents (aspirin, dextran) and anticoagulants are standard prophylactic measures in this procedure. The role of NO has also been investigated. It activates guanylate cyclase thus inhibiting platelet aggregation.[151] The NO inhibitor L-NAME has been found in experimental animal models to promote microvascular thrombosis in the setting of microvascular anastomosis.[152]

Disorders with Microthrombosis due to Abnormal Blood Components: Hypercoagulable States

ANTIPHOSPHOLIPID SYNDROME (APS)
Among the hypercoagulable states, thrombosis in APS[153–156] is a good example of how microthrombi can form in multiple organs, including the liver, intestines, brain, heart adrenals, and kidneys as well as in skin, retina, and nail fold. The hypercoagulable state in APS is associated with the presence of autoantibodies against phospholipid-binding plasma proteins (antiphospholipid antibodies; aPL) and β2-glycoprotein I. These autoantibodies, in particular the anti-ß2-glycoprotein I, bind to endothelial cells. They induce endothelial and platelet activation as well as expression of tissue factor, and adhesion molecules. The C3 and C5 components of the complement system are also activated. Although most individuals harboring aPL show little clinical manifestations, severe thrombotic complications can occur, with a major risk for morbidity and mortality. In less than 1% of patients, massive generalized thrombosis can develop over a short period of time, leading to the term "catastrophic APS."[157–159] In a review of 97 patients with intestinal involvement in the Catastrophic Antiphospholipid Syndrome Registry, microthrombosis had been observed in 4% of the classic APS in contrast with 75% in the catastrophic APS. A correspondingly higher mortality of 55% was seen in the catastrophic APS. In another prospective 5-year study of 1000 patients with APS,[160] the mortality was 5.3% with main cause of death being cerebral involvement in 27.2%, cardiac involvement in 19.8%, and infection in 19.8% cases. In catastrophic APS, rigorous antithrombotic measures along with intravenous immunoglobulin (IVIG), corticosteroids, and therapeutic plasma exchange have been shown to reduce the overall mortality.[161] For the noncatastrophic APS, the long-term use of anticoagulants is recommended for those with thrombotic complications while recognition of the autoimmune nature of aPL leads to new approach with immune suppression.

TRAUMATIC BRAIN INJURY (TBI)

Thrombotic complications may occur in the microvasculature as a result of the hypercoagulability observed in patients with TBI.[162] Abnormalities of coagulation parameters are present in the vast majority of patients following TBI. The severity of these changes also predicts the clinical outcome. Brain is rich in procoagulants, especially tissue factor,[163,164] while devoid of thrombomodulin, the cofactor of the anticoagulant protein C.[8] Thrombogenesis in TBI involves the release of tissue factor and the activation of the extrinsic coagulation pathway. Platelet activation takes place, the severity of which is also correlated with the outcome.[165] Following brain trauma, increase in inflammatory cytokines such as TNF-α and IL-6 further upregulates tissue factor expression in the endothelium and increase the procoagulant effect.[166] Locally, this can lead to formation of microthrombi[167–170] and systemically to the development of DIC.[171] Postmortem studies demonstrated microthrombi affecting arterioles, capillaries, and venules with diameter of 6 to 100 μm.[12] The extent of the microthrombosis has been shown to correlate with the degree of cerebral ischemia and selective neuronal necrosis. The fibrinolytic pathway is also activated, secondary to the local microthrombosis and to the systemic DIC. Evidence of increased fibrinolysis, such as increased fibrinogenolysis and decrease in α2-plasmin inhibitor had been shown to correlate with the incidence of intracranial bleeding and with poor outcome in TBI.[172] The above findings have been applied to the current therapeutic approach for TBI. Antithrombin had been tried, but this approach did not substantially influence the clinical outcome.[173] Low molecular weight heparin had been found to be of some benefit in rats,[174] but there are no conclusive data in humans. When used for thromboprophylaxis, low molecular weight heparin was shown to have low bleeding risk. In a recent clinical trial, only 1 in 287 patients had expansion of the intracranial hemorrhage.[175] Guidelines for reducing the morbidity of brain injury must await results of other clinical trials on a range of anticoagulant, antiplatelet, and anti-inflammatory approaches.

SUBARACHNOID HEMORRHAGE (SAH)

A similar pattern of coagulopathy is also present following SAH. For up to 10 days after SAH, there is an increased risk of delayed cerebral ischemia, which can progress to infarction.[176] This has generally been attributed to cerebral vasospasm. However, recent observations showing the lack of benefit from therapeutic use of endothelin antagonists, suggest that vasospasm alone may not account for all of the ischemia. The additional pathogenic factor is believed to be microthrombosis.[177] Transcranial Doppler studies have demonstrated microembolic signals in as many as 70% of patients with SAH.[178,179] Markers of platelet activation, elevated procoagulant activity in blood,

and increased tissue factor level in cerebrospinal fluid have been observed in the acute phase, before vasospasm and delayed cerebral ischemia set in. Increased markers of procoagulant activity are an early predictor of infarction. Postmortem studies also support the concept that cerebral vasospasm cannot account for most of the infarction and that microthrombosis plays a significant role. In an angiographic study, vasospasm was identified in only 37% of patients with infarction.[180] A recent observation confirmed the correlation between the microthrombi burden and evidence of ischemia based on clinical, radiological, and histological criteria.[181] As our concept shifts from vasospasm to microthrombosis, the current approach to management of SAH needs to be reexamined. Measures that can reduce thrombosis have been advocated. In a recent clinical trial of enoxaparin given for 3 weeks following SAH, there was a reduction of the incidence of delayed ischemic deficit and cerebral infarction 1 year later, without an increased risk of recurrent SAH or secondary bleeding.[182] On the other hand, the use of a prothrombotic approach, such as inhibitors of fibrinolysis or recombinant factor VII, has been found to reduce recurrent SAH, although long-term use may increase risk of cerebral ischemia.[183–185] Hopefully, clinical trials with larger number of patients will clarify the roles of these therapeutic agents.

WARFARIN NECROSIS

This occurs at the start of warfarin therapy in patients with heterozygous deficiency of protein C.[186,187] Warfarin produces a more rapid inhibition in the synthesis of protein C than that of factors VII, IX, X, and prothrombin. A hiatus of relative deficiency of protein C occurs in the first 24 to 72 hours following the initiation of warfarin. Patients with low baseline levels of protein C are at risk of developing local ischemic changes with microthrombosis and resulting in tissue necrosis. This is usually found in skin and adipose tissues (Fig. 10). In a study measuring protein C in patients who had recovered from warfarin necrosis, 11 of the 13 patients had abnormally low levels ranging from 23 to 69%.[188] This
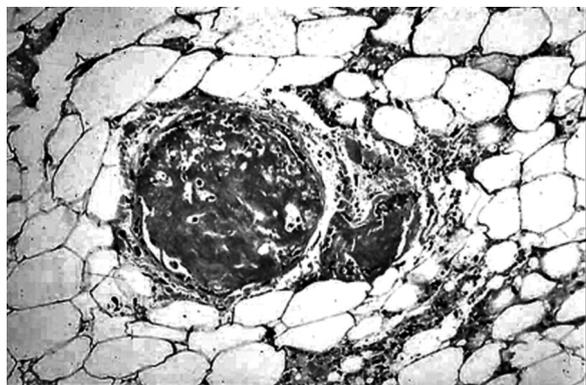

Figure 10 Fibrin thrombus in a small vessel in the breast in warfarin necrosis. Hematoxylin and eosin stain.

finding supports the role of protein C deficiency in the pathogenesis of warfarin necrosis. A similar association has also been reported in patients with deficiency of protein S,[189] factor V Leiden,[190] or antithrombin.[191]

POST-VARICELLA PURPURA FULMINANS

Although chicken pox is almost always a benign childhood illness, rare occurrences of purpura fulminans with microvascular thrombosis have been observed.[192,193] This complication has also been seen after streptococcal infections.[194] In the case of varicella, an autoimmune response may occur, with formation of antibodies against protein C and protein S leading to severe acquired protein C and protein S deficiency.[194,195] aPL have also been found.[196] The recognition of the autoimmune nature of this complication has led to successful use of immunosuppressive modalities such as corticosteroids, IVIG, or therapeutic plasma exchange.[197]

CONCLUSION

Microvascular thrombosis is the outcome of a series of events, triggered by many underlying disorders. Several factors, especially inflammatory response and coagulation activation, contribute to further progression, often with a poor outcome. Both the initiating disorder and the contributory factors play equally important roles. Without vigorous efforts to treat all of these factors concurrently, attempts to deal only with the primary triggering disorder have all too often been unsuccessful. With a new understanding of the mechanisms of action of many of the contributory factors, it is now possible to address them simultaneously. The appropriate management should be analogous to that of cancer, in which multiple modalities of combination chemotherapy, radiation, hormonal, immunologic, and targeted receptors inhibition are concurrently applied. This new paradigm is increasingly being addressed in ongoing clinical trials.

REFERENCES

1. Aird WC. Spatial and temporal dynamics of the endothelium. J Thromb Haemost 2005;3(7):1392–1406
2. Lipowsky HH. Microvascular rheology and hemodynamics. Microcirculation 2005;12(1):5–15
3. Baskurt OK, Meiselman HJ. Blood rheology and hemodynamics. Semin Thromb Hemost 2003;29(5):435–450
4. Aird WC. Phenotypic heterogeneity of the endothelium: I. Structure, function, and mechanisms. Circ Res 2007;100(2): 158–173
5. Aird WC. Phenotypic heterogeneity of the endothelium: II. Representative vascular beds. Circ Res 2007;100(2):174–190
6. Pries AR, Kuebler WM. Normal endothelium. Handb Exp Pharmacol 2006;176(176 Pt 1):1–40
7. Kwaan HC, Samama MM. The significance of endothelial heterogeneity in thrombosis and hemostasis. Semin Thromb Hemost 2010;36(3):286–300
8. Ishii H, Salem HH, Bell CE, Laposata EA, Majerus PW. Thrombomodulin, an endothelial anticoagulant protein, is absent from the human brain. Blood 1986;67(2):362–365
9. Esmon CT, Gu JM, Xu J, Qu D, Stearns-Kurosawa DJ, Kurosawa S. Regulation and functions of the protein C anticoagulant pathway. Haematologica 1999;84(4):363–368
10. Lippi G, Franchini M. Pathogenesis of venous thromboembolism: when the cup runneth over. Semin Thromb Hemost 2008;34(8):747–761
11. Lippi G, Franchini M, Favaloro EJ. Unsuspected triggers of venous thromboembolism—trivial or not so trivial? Semin Thromb Hemost 2009;35(7):597–604
12. Virchow R. Phlogose und Thrombose in Gefabsystem. In: Gesammelte Abhandlungen zur Wissenschaftlichen Medizin. Frankfurt, Germany: Von Meidinger Sohn; 1856: 458
13. Levi M, Schultz M, van der Poll T. Disseminated intravascular coagulation in infectious disease. Semin Thromb Hemost 2010;36(4):367–377
14. Galindo M, Gonzalo E, Martinez-Vidal MP, et al. Immunohistochemical detection of intravascular platelet microthrombi in patients with lupus nephritis and antiphospholipid antibodies. Rheumatology (Oxford) 2009;48(8): 1003–1007
15. Nagy JA, Chang SH, Shih SC, Dvorak AM, Dvorak HF. Heterogeneity of the tumor vasculature. Semin Thromb Hemost 2010;36(3):321–331
16. Rubin DB, Drab EA, Ward WF. Physiological and biochemical markers of the endothelial cell response to irradiation. Int J Radiat Biol 1991;60(1-2):29–32
17. Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. J Clin Invest 1974;54(6):1496–1508
18. Brands MT, van den Bosch SC, Dieleman FJ, Bergé SJ, Merkx MA. Prevention of thrombosis after microvascular tissue transfer in the head and neck. A review of the literature and the state of affairs in Dutch Head and Neck Cancer Centers. Int J Oral Maxillofac Surg 2010;39(2):101–106
19. Lecoq JP, Senard M, Hartstein GM, Lamy M, Heymans O. Thromboprophylaxis in microsurgery. Acta Chir Belg 2006; 106(2):158–164
20. Kwaan HC, Bongu A. The hyperviscosity syndromes. Semin Thromb Hemost 1999;25(2):199–208
21. Esmon CT. The impact of the inflammatory response on coagulation. Thromb Res 2004;114(5-6):321–327
22. Esmon CT. The interactions between inflammation and coagulation. Br J Haematol 2005;131(4):417–430
23. Levi M. The coagulant response in sepsis and inflammation. Hamostaseologie 2010;30(1):10–12, 14–16
24. Bevilacqua MP, Pober JS, Majeau GR, Fiers W, Cotran RS, Gimbrone MA Jr. Recombinant tumor necrosis factor induces procoagulant activity in cultured human vascular endothelium: characterization and comparison with the actions of interleukin 1. Proc Natl Acad Sci U S A 1986; 83(12):4533–4537
25. Coughlin SR. Thrombin signalling and protease-activated receptors. Nature 2000;407(6801):258–264
26. Bevilacqua MP, Nelson RM. Endothelial-leukocyte adhesion molecules in inflammation and metastasis. Thromb Haemost 1993;70(1):152–154
27. Gando S. Microvascular thrombosis and multiple organ dysfunction syndrome. Crit Care Med 2010;38(2, Suppl): S35–S42

28. Lee CC, Marill KA, Carter WA, Crupi RS. A current concept of trauma-induced multiorgan failure. Ann Emerg Med 2001;38(2):170–176

29. Hertig A, Rondeau E. Role of the coagulation/fibrinolysis system in fibrin-associated glomerular injury. J Am Soc Nephrol 2004;15(4):844–853

30. Welty-Wolf KE, Carraway MS, Ortel TL, Piantadosi CA. Coagulation and inflammation in acute lung injury. Thromb Haemost 2002;88(1):17–25

31. Dhainaut JF, Marin N, Mignon A, Vinsonneau C. Hepatic response to sepsis: interaction between coagulation and inflammatory processes. Crit Care Med 2001;29(7, Suppl): S42–S47

32. Papadopoulos MC, Davies DC, Moss RF, Tighe D, Bennett ED. Pathophysiology of septic encephalopathy: a review. Crit Care Med 2000;28(8):3019–3024

33. Stegmayr BG. Apheresis as therapy for patients with severe sepsis and multiorgan dysfunction syndrome. Ther Apher 2001;5(2):123–127

34. Levi M, Ten Cate H. Disseminated intravascular coagulation. N Engl J Med 1999;341(8):586–592

35. ten Cate H, Timmerman JJ, Levi M. The pathophysiology of disseminated intravascular coagulation. Thromb Haemost 1999;82(2):713–717

36. Lippi G, Cervellin G. Disseminated intravascular coagulation in trauma injuries. Semin Thromb Hemost 2010; 36(4):378–387

37. Kojima M, Shimamura K, Mori N, Oka K, Nakazawa M. A histological study on microthrombi in autopsy cases of DIC. Bibl Haematol 1983;(49):95–106

38. Shimamura K, Oka K, Nakazawa M, Kojima M. Distribution patterns of microthrombi in disseminated intravascular coagulation. Arch Pathol Lab Med 1983;107(10): 543–547

39. Schouten M, Wiersinga WJ, Levi M, van der Poll T. Inflammation, endothelium, and coagulation in sepsis. J Leukoc Biol 2008;83(3):536–545

40. Osterud B. Tissue factor expression by monocytes: regulation and pathophysiological roles. Blood Coagul Fibrinolysis 1998;9(Suppl 1):S9–S14

41. Meziani F, Delabranche X, Asfar P, Toti F. Bench-to-bedside review: circulating microparticles—a new player in sepsis?. Crit Care 2010;14(5):236

42. Soriano AO, Jy W, Chirinos JA, et al. Levels of endothelial and platelet microparticles and their interactions with leukocytes negatively correlate with organ dysfunction and predict mortality in severe sepsis. Crit Care Med 2005; 33(11):2540–2546

43. McEver RP. GMP-140: a receptor for neutrophils and monocytes on activated platelets and endothelium. J Cell Biochem 1991;45(2):156–161

44. Klintman D, Li X, Thorlacius H. Important role of P-selectin for leukocyte recruitment, hepatocellular injury, and apoptosis in endotoxemic mice. Clin Diagn Lab Immunol 2004;11(1):56–62

45. Ward PA. Role of the complement in experimental sepsis. J Leukoc Biol 2008;83(3):467–470

46. Laudes IJ, Chu JC, Huber-Lang M, et al. Expression and function of C5a receptor in mouse microvascular endothelial cells. J Immunol 2002;169(10):5962–5970

47. Esmon CT, Fukudome K, Mather T, et al. Inflammation, sepsis, and coagulation. Haematologica 1999;84(3): 254–259

48. Levi M, Lowenberg E, Meijers JC. Recombinant anti-coagulant factors for adjunctive treatment of sepsis. Semin Thromb Hemost 2010;36(5):550–557

49. Bernard GR, Vincent JL, Laterre PF, et al; Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344(10):699–709

50. Ely EW, Laterre PF, Angus DC, et al; PROWESS Investigators. Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis. Crit Care Med 2003;31(1):12–19

51. Dhainaut JF, Yan SB, Joyce DE, et al. Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation. J Thromb Haemost 2004;2(11):1924–1933

52. Abraham E, Laterre PF, Garg R, et al; Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) Study Group. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. N Engl J Med 2005;353(13):1332–1341

53. Levi M, Levy M, Williams MD, et al; Xigris and Prophylactic HepaRin Evaluation in Severe Sepsis (XPRESS) Study Group. Prophylactic heparin in patients with severe sepsis treated with drotrecogin alfa (activated). Am J Respir Crit Care Med 2007;176(5):483–490

54. Costa V, Brophy JM. Drotrecogin alfa (activated) in severe sepsis: a systematic review and new cost-effectiveness analysis. BMC Anesthesiol 2007;7:5

55. Barie PS. "All in" for a huge pot: the PROWESS-SHOCK trial for refractory septic shock. Surg Infect (Larchmt) 2007; 8(5):491–494

56. Barie PS. Current role of activated protein C therapy for severe sepsis and septic shock. Curr Infect Dis Rep 2008;10(5):368–376

57. Bernard GR, Margolis BD, Shanies HM, et al; Extended Evaluation of Recombinant Human Activated Protein C United States Investigators. Extended evaluation of recombinant human activated protein C United States Trial (ENHANCE US): a single-arm, phase 3B, multicenter study of drotrecogin alfa (activated) in severe sepsis. Chest 2004; 125(6):2206–2216

58. Leitner JM, Firbas C, Mayr FB, Reiter RA, Steinlechner B, Jilma B. Recombinant human antithrombin inhibits thrombin formation and interleukin 6 release in human endotoxemia. Clin Pharmacol Ther 2006;79(1):23–34

59. Warren BL, Eid A, Singer P, et al; KyberSept Trial Study Group. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. JAMA 2001;286(15):1869–1878

60. Ott I, Miyagi Y, Miyazaki K, et al. Reversible regulation of tissue factor-induced coagulation by glycosyl phosphatidylinositol-anchored tissue factor pathway inhibitor. Arterioscler Thromb Vasc Biol 2000;20(3):874–882

61. Brandtzaeg P, Sandset PM, Joø GB, Ovstebø R, Abildgaard U, Kierulf P. The quantitative association of plasma endotoxin, antithrombin, protein C, extrinsic pathway inhibitor and fibrinopeptide A in systemic meningococcal disease. Thromb Res 1989;55(4):459–470

62. Abraham E, Reinhart K, Opal S, et al; OPTIMIST Trial Study Group. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. JAMA 2003;290(2):238–247

63. van der Poll T, Levi M, Büller HR, et al. Fibrinolytic response to tumor necrosis factor in healthy subjects. J Exp Med 1991;174(3):729–732

64. Carmeliet P, Schoonjans L, Kieckens L, et al. Physiological consequences of loss of plasminogen activator gene function in mice. Nature 1994;368(6470):419–424

65. Bajzar L, Jain N, Wang P, Walker JB. Thrombin activatable fibrinolysis inhibitor: not just an inhibitor of fibrinolysis. Crit Care Med 2004;32(5, Suppl):S320–S324

66. Leung LL, Nishimura T, Myles T. Regulation of tissue inflammation by thrombin-activatable carboxypeptidase B (or TAFI). Adv Exp Med Biol 2008;632:61–69

67. Kwaan HC, Gordon LI. Thrombotic microangiopathy in the cancer patient. Acta Haematol 2001;106(1-2):52–56

68. Elliott MA, Letendre L, Gastineau DA, Winters JL, Pruthi RK, Heit JA. Cancer-associated microangiopathic hemolytic anemia with thrombocytopenia: an important diagnostic consideration. Eur J Haematol 2010;85(1):43–50

69. Zakarija A. Thrombotic microangiopathy syndromes. Cancer Treat Res 2009;148:115–136

70. Gordon LI, Kwaan HC. Cancer- and drug-associated thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Semin Hematol 1997;34(2):140–147

71. Kwaan HC, Boggio LN. The clinical spectrum of thrombotic thrombocytopenic purpura. Semin Thromb Hemost 2005; 31(6):673–680

72. Karpman D, Sartz L, Johnson S. Pathophysiology of typical hemolytic uremic syndrome. Semin Thromb Hemost 2010; 36(6):575–585

73. Baronzio G, Freitas I, Kwaan HC. Tumor microenvironment and hemorheological abnormalities. Semin Thromb Hemost 2003;29(5):489–497

74. Brat DJ, Van Meir EG. Vaso-occlusive and prothrombotic mechanisms associated with tumor hypoxia, necrosis, and accelerated growth in glioblastoma. Lab Invest 2004;84(4): 397–405

75. Wang J, Weiss I, Svoboda K, Kwaan HC. Thrombogenic role of cells undergoing apoptosis. Br J Haematol 2001;115(2): 382–391

76. Rak J. Microparticles in cancer. Semin Thromb Hemost 2010;36(8):888–906

77. Kwaan HC, Rego EM. Role of microparticles in the hemostatic dysfunction in acute promyelocytic leukemia. Semin Thromb Hemost 2010;36(8):917–924

78. Key NS, Kwaan HC. Microparticles in thrombosis and hemostasis. Semin Thromb Hemost 2010;36(8):805–806

79. Myhre-Jensen O, Hansen ES, Butrago B. Renal microthrombosis. Incidence in 500 consecutive autopsies. Clinicopathological relations. Acta Pathol Microbiol Scand [A] 1972;80(3):403–411

80. Shih HM, Lin CC, Shiao YW. Pulmonary tumor thrombotic microangiopathy. Am J Emerg Med 2011; 29(2):241, e3–e4

81. Chinen K, Tokuda Y, Fujiwara M, Fujioka Y. Pulmonary tumor thrombotic microangiopathy in patients with gastric carcinoma: an analysis of 6 autopsy cases and review of the literature. Pathol Res Pract 2010;206(10):682–689

82. Tehrani M, Friedman TM, Olson JJ, Brat DJ. Intravascular thrombosis in central nervous system malignancies: a potential role in astrocytoma progression to glioblastoma. Brain Pathol 2008;18(2):164–171

83. Hallahan D, Clark ET, Kuchibhotla J, Gewertz BL, Collins T. E-selectin gene induction by ionizing radiation is independent of cytokine induction. Biochem Biophys Res Commun 1995;217(3):784–795

84. Jahroudi N, Ardekani AM, Greenberger JS. Ionizing irradiation increases transcription of the von Willebrand factor gene in endothelial cells. Blood 1996;88(10):3801–3814

85. Verheij M, Dewit LG, van Mourik JA. The effect of ionizing radiation on endothelial tissue factor activity and its cellular localization. Thromb Haemost 1995;73(5):894–895

86. Hauer-Jensen M, Fink LM, Wang J. Radiation injury and the protein C pathway. Crit Care Med 2004;32(5, Suppl): S325–S330

87. Astedt B, Bergentz SE, Svanberg L. Effect of irradiation on the plasminogen activator content in rat vessels. Experientia 1974;30(12):1466–1467

88. Dropcho EJ. Neurotoxicity of radiation therapy. Neurol Clin 2010;28(1):217–234

89. Lyons A, Ghazali N. Osteoradionecrosis of the jaws: current understanding of its pathophysiology and treatment. Br J Oral Maxillofac Surg 2008;46(8):653–660

90. Madrid C, Abarca M, Bouferrache K. Osteoradionecrosis: an update. Oral Oncol 2010;46(6):471–474

91. Kwaan HC. Miscellaneous secondary thrombotic microangiopathy. Semin Hematol 1987;24(3):141–147

92. Kwaan HC. Thrombotic thrombocytopenic purpura: a diagnostic and therapeutic challenge. Semin Thromb Hemost 2005;31(6):615–624

93. Mitra D, Jaffe EA, Weksler B, Hajjar KA, Soderland C, Laurence J. Thrombotic thrombocytopenic purpura and sporadic hemolytic-uremic syndrome plasmas induce apoptosis in restricted lineages of human microvascular endothelial cells. Blood 1997;89(4):1224–1234

94. Laurence J, Mitra D. Apoptosis of microvascular endothelial cells in the pathophysiology of thrombotic thrombocytopenic purpura/sporadic hemolytic uremic syndrome. Semin Hematol 1997;34(2):98–105

95. Zipfel PF, Heinen S, Skerka C. Thrombotic microangiopathies: new insights and new challenges. Curr Opin Nephrol Hypertens 2010;19(4):372–378

96. Louise CB, Obrig TG. Shiga toxin-associated hemolytic-uremic syndrome: combined cytotoxic effects of Shiga toxin, interleukin-1 beta, and tumor necrosis factor alpha on human vascular endothelial cells in vitro. Infect Immun 1991;59(11):4173–4179

97. Louise CB, Obrig TG. Human renal microvascular endothelial cells as a potential target in the development of the hemolytic uremic syndrome as related to fibrinolysis factor expression, in vitro. Microvasc Res 1994;47(3):377–387

98. Dragon-Durey MA, Sethi SK, Bagga A, et al. Clinical features of anti-factor H autoantibody-associated hemolytic uremic syndrome. J Am Soc Nephrol 2010;21(12):2180–2187

99. Le Quintrec M, Roumenina L, Noris M, Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome associated with mutations in complement regulator genes. Semin Thromb Hemost 2010;36(6):641–652

100. Heinen S, Hartmann A, Lauer N, et al. Factor H-related protein 1 (CFHR-1) inhibits complement C5 convertase activity and terminal complex formation. Blood 2009; 114(12):2439–2447

101. Kwaan HC. Miscellaneous secondary thrombotic microangiopathy. Semin Hematol 1987;24(3):141–147

102. Kelton JG, Warkentin TE. Heparin-induced thrombocytopenia: a historical perspective. Blood 2008;112(7):2607–2616

103. Kwaan HC, Sakurai S. Endothelial cell hyperplasia contributes to thrombosis in heparin-induced thrombocytopenia. Semin Thromb Hemost 1999;25(Suppl 1):23–27

104. Baskurt OK, Meiselman HJ. Blood rheology and hemodynamics. Semin Thromb Hemost 2003;29(5):435–450

105. Kwaan HC, Wang J. Hyperviscosity in polycythemia vera and other red cell abnormalities. Semin Thromb Hemost 2003;29(5):451–458

106. Newton CR, Marsh K, Peshu N, Kirkham FJ. Perturbations of cerebral hemodynamics in Kenyans with cerebral malaria. Pediatr Neurol 1996;15(1):41–49

107. Beare NA, Harding SP, Taylor TE, Lewallen S, Molyneux ME. Perfusion abnormalities in children with cerebral malaria and malarial retinopathy. J Infect Dis 2009;199(2):263–271

108. Buffet PA, Safeukui I, Deplaine G, et al. The pathogenesis of Plasmodium falciparum malaria in humans: insights from splenic physiology. Blood 2011;117(2):381–392

109. Grau GE, Mackenzie CD, Carr RA, et al. Platelet accumulation in brain microvessels in fatal pediatric cerebral malaria. J Infect Dis 2003;187(3):461–466

110. Cox D, McConkey S. The role of platelets in the pathogenesis of cerebral malaria. Cell Mol Life Sci 2010;67(4):557–568

111. Baruch DI, Gormely JA, Ma C, Howard RJ, Pasloske BL. Plasmodium falciparum erythrocyte membrane protein 1 is a parasitized erythrocyte receptor for adherence to CD36, thrombospondin, and intercellular adhesion molecule 1. Proc Natl Acad Sci U S A 1996;93(8):3497–3502

112. Chakravorty SJ, Hughes KR, Craig AG. Host response to cytoadherence in Plasmodium falciparum. Biochem Soc Trans 2008;36(Pt 2):221–228

113. García F, Cebrián M, Dgedge M, et al. Endothelial cell activation in muscle biopsy samples is related to clinical severity in human cerebral malaria. J Infect Dis 1999; 179(2):475–483

114. Francischetti IM, Seydel KB, Monteiro RQ, et al. Plasmodium falciparum-infected erythrocytes induce tissue factor expression in endothelial cells and support the assembly of multimolecular coagulation complexes. J Thromb Haemost 2007;5(1):155–165

115. Francischetti IM, Seydel KB, Monteiro RQ. Blood coagulation, inflammation, and malaria. Microcirculation 2008;15(2):81–107

116. Combes V, Taylor TE, Juhan-Vague I, et al. Circulating endothelial microparticles in malawian children with severe falciparum malaria complicated with coma. JAMA 2004; 291(21):2542–2544

117. Milner DA Jr. Rethinking cerebral malaria pathology. Curr Opin Infect Dis 2010;23(5):456–463

118. Kato GJ, Hebbel RP, Steinberg MH, Gladwin MT. Vasculopathy in sickle cell disease: biology, pathophysiology, genetics, translational medicine, and new research directions. Am J Hematol 2009;84(9):618–625

119. Morris CR. Mechanisms of vasculopathy in sickle cell disease and thalassemia. Hematology (Am Soc Hematol Educ Program) 2008:177–185

120. Morris CR, Kato GJ, Poljakovic M, et al. Dysregulated arginine metabolism, hemolysis-associated pulmonary hypertension, and mortality in sickle cell disease. JAMA 2005;294(1):81–90

121. Francis RB Jr. Platelets, coagulation, and fibrinolysis in sickle cell disease: their possible role in vascular occlusion. Blood Coagul Fibrinolysis 1991;2(2):341–353

122. Peters M, Plaat BE, ten Cate H, Wolters HJ, Weening RS, Brandjes DP. Enhanced thrombin generation in children with sickle cell disease. Thromb Haemost 1994;71(2):169–172

123. Key NS, Slungaard A, Dandelet L, et al. Whole blood tissue factor procoagulant activity is elevated in patients with sickle cell disease. Blood 1998;91(11):4216–4223

124. Kurantsin-Mills J, Ofosu FA, Safa TK, Siegel RS, Lessin LS. Plasma factor VII and thrombin-antithrombin III levels indicate increased tissue factor activity in sickle cell patients. Br J Haematol 1992;81(4):539–544

125. Nsiri B, Gritli N, Bayoudh F, Messaoud T, Fattoum S, Machghoul S. Abnormalities of coagulation and fibrinolysis in homozygous sickle cell disease. Hematol Cell Ther 1996;38(3):279–284

126. Kurantsin-Mills J, Ibe BO, Natta CL, Raj JU, Siegel RS, Lessin LS. Elevated urinary levels of thromboxane and prostacyclin metabolites in sickle cell disease reflects activated platelets in the circulation. Br J Haematol 1994;87(3):580–585

127. Ataga KI, Orringer EP. Hypercoagulability in sickle cell disease: a curious paradox. Am J Med 2003;115(9):721–728

128. Gladwin MT, Kato GJ. Hemolysis-associated hypercoagulability in sickle cell disease: the plot (and blood) thickens! Haematologica 2008;93(1):1–3

129. Gladwin MT, Vichinsky E. Pulmonary complications of sickle cell disease. N Engl J Med 2008;359(21):2254–2265

130. Bunn HF, Nathan DG, Dover GJ, et al. Pulmonary hypertension and nitric oxide depletion in sickle cell disease. Blood 2010;116(5):687–692

131. Gordeuk VR, Campbell A, Rana S, et al. Relationship of erythropoietin, fetal hemoglobin, and hydroxyurea treatment to tricuspid regurgitation velocity in children with sickle cell disease. Blood 2009;114(21):4639–4644

132. Machado RF, Martyr S, Kato GJ, et al. Sildenafil therapy in patients with sickle cell disease and pulmonary hypertension. Br J Haematol 2005;130(3):445–453

133. Rose VL, Kwaan HC. Anti-Pr cold hemagglutination associated with livedo reticularis. Am J Hematol 1985;19(4):419–421

134. Ruch J, McMahon B, Ramsey G, Kwaan HC. Catastrophic multiple organ ischemia due to an anti-Pr cold agglutinin developing in a patient with mixed cryoglobulinemia after treatment with rituximab. Am J Hematol 2009;84(2):120–122

135. Blum W, Porcu P. Therapeutic apheresis in hyperleukocytosis and hyperviscosity syndrome. Semin Thromb Hemost 2007;33(4):350–354

136. Porcu P, Danielson CF, Orazi A, Heerema NA, Gabig TG, McCarthy LJ. Therapeutic leukapheresis in hyperleucocytic leukaemias: lack of correlation between degree of cytoreduction and early mortality rate. Br J Haematol 1997; 98(2):433–436

137. Vaughan WP, Kimball AW, Karp JE, Dragon LH, Burke PJ. Factors affecting survival of patients with acute myelocytic leukemia presenting with high wbc counts. Cancer Treat Rep 1981;65(11-12):1007–1013

138. Creutzig U, Ritter J, Budde M, Sutor A, Schellong G. Early deaths due to hemorrhage and leukostasis in childhood acute myelogenous leukemia. Associations with hyperleukocytosis

and acute monocytic leukemia. Cancer 1987; 60(12):3071–3079

139. Cuttner J, Conjalka MS, Reilly M, et al. Association of monocytic leukemia in patients with extreme leukocytosis. Am J Med 1980;69(4):555–558

140. Scott CS, Stark AN, Limbert HJ, Master PS, Head C, Roberts BE. Diagnostic and prognostic factors in acute monocytic leukaemia: an analysis of 51 cases. Br J Haematol 1988;69(2):247–252

141. Biondi A, Cimino G, Pieters R, Pui CH. Biological and therapeutic aspects of infant leukemia. Blood 2000;96(1):24–33

142. Stucki A, Rivier AS, Gikic M, Monai N, Schapira M, Spertini O. Endothelial cell activation by myeloblasts: molecular mechanisms of leukostasis and leukemic cell dissemination. Blood 2001;97(7):2121–2129

143. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. N Engl J Med 1993;329(10):673–682

144. Beek AM, Nijveldt R, van Rossum AC. Intramyocardial hemorrhage and microvascular obstruction after primary percutaneous coronary intervention. Int J Cardiovasc Imaging 2010;26(1):49–55

145. Patel B, Fisher M. Therapeutic advances in myocardial microvascular resistance: unravelling the enigma. Pharmacol Ther 2010;127(2):131–147

146. Bhavsar J, Rosenson RS. Adenosine transport, erythrocyte deformability and microvascular dysfunction: an unrecognized potential role for dipyridamole therapy. Clin Hemorheol Microcirc 2010;44(3):193–205

147. Bekkers SC, Yazdani SK, Virmani R, Waltenberger J. Microvascular obstruction: underlying pathophysiology and clinical diagnosis. J Am Coll Cardiol 2010;55(16):1649–1660

148. Buja LM. Myocardial ischemia and reperfusion injury. Cardiovasc Pathol 2005;14(4):170–175

149. Khouri RK. Free flap surgery. The second decade. Clin Plast Surg 1992;19(4):757–761

150. Ashjian P, Chen CM, Pusic A, Disa JJ, Cordeiro PG, Mehrara BJ. The effect of postoperative anticoagulation on microvascular thrombosis. Ann Plast Surg 2007;59(1):36–39, discussion 39–40

151. Radomski MW, Palmer RM, Moncada S. Endogenous nitric oxide inhibits human platelet adhesion to vascular endothelium. Lancet 1987;2(8567):1057–1058

152. Azizzadeh B, Buga GM, Berke GS, Larian B, Ignarro LJ, Blackwell KE. Inhibitors of nitric oxide promote microvascular thrombosis. Arch Facial Plast Surg 2003;5(1):31–35

153. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4(2):295–306

154. Cervera R, Piette JC, Font J, et al; Euro-Phospholipid Project Group. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002;46(4):1019–1027

155. Espinosa G, Cervera R. Antiphospholipid syndrome: frequency, main causes and risk factors of mortality. Nat Rev Rheumatol 2010;6(5):296–300

156. Mehdi AA, Salti I, Uthman I. Antiphospholipid syndrome: endocrinologic manifestations and organ involvement. Semin Thromb Hemost 2011;37(1):49–57

157. Cervera R, Asherton RA. Catastrophic antiphospholipid syndrome. Pathophysiol Haemost Thromb 2006;35(1-2):181–186

158. Asherson RA, Cervera R, Piette JC, et al. Catastrophic antiphospholipid syndrome. Clinical and laboratory features of 50 patients. Medicine (Baltimore) 1998;77(3):195–207

159. Asherson RA, Cervera R, Piette JC, et al. Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. Medicine (Baltimore) 2001;80(6):355–377

160. Cervera R, Khamashta MA, Shoenfeld Y, et al; Euro-Phospholipid Project Group (European Forum on Antiphospholipid Antibodies). Morbidity and mortality in the antiphospholipid syndrome during a 5-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis 2009;68(9):1428–1432

161. Bucciarelli S, Erkan D, Espinosa G, Cervera R. Catastrophic antiphospholipid syndrome: treatment, prognosis, and the risk of relapse. Clin Rev Allergy Immunol 2009;36(2-3):80–84

162. Stein SC, Smith DH. Coagulopathy in traumatic brain injury. Neurocrit Care 2004;1(4):479–488

163. Astrup T. Assay and content of tissue thromboplastin in different organs. Thromb Diath Haemorrh 1965;14(3-4):401–416

164. Goodnight SH, Kenoyer G, Rapaport SI, Patch MJ, Lee JA, Kurze T. Defibrination after brain-tissue destruction: A serious complication of head injury. N Engl J Med 1974;290(19):1043–1047

165. Jacoby RC, Owings JT, Holmes J, Battistella FD, Gosselin RC, Paglieroni TG. Platelet activation and function after trauma. J Trauma 2001;51(4):639–647

166. Nekludov M, Antovic J, Bredbacka S, Blombäck M. Coagulation abnormalities associated with severe isolated traumatic brain injury: cerebral arterio-venous differences in coagulation and inflammatory markers. J Neurotrauma 2007;24(1):174–180

167. Dietrich WD. Morphological manifestations of reperfusion injury in brain. Ann N Y Acad Sci 1994;723:15–24

168. Dietrich WD, Alonso O, Halley M. Early microvascular and neuronal consequences of traumatic brain injury: a light and electron microscopic study in rats. J Neurotrauma 1994;11(3):289–301

169. Maeda T, Katayama Y, Kawamata T, Aoyama N, Mori T. Hemodynamic depression and microthrombosis in the peripheral areas of cortical contusion in the rat: role of platelet activating factor. Acta Neurochir Suppl (Wien) 1997;70:102–105

170. Stein SC, Graham DI, Chen XH, Smith DH. Association between intravascular microthrombosis and cerebral ischemia in traumatic brain injury. Neurosurgery 2004;54(3):687–691, discussion 691

171. Kaufman HH, Hui KS, Mattson JC, et al. Clinicopathological correlations of disseminated intravascular coagulation in patients with head injury. Neurosurgery 1984;15(1):34–42

172. Kushimoto S, Yamamoto Y, Shibata Y, Sato H, Koido Y. Implications of excessive fibrinolysis and alpha(2)-plasmin inhibitor deficiency in patients with severe head injury. Neurosurgery 2001;49(5):1084–1089, discussion 1089–1090

173. Grenander A, Bredbacka S, Rydvall A, et al. Antithrombin treatment in patients with traumatic brain injury: a pilot study. J Neurosurg Anesthesiol 2001;13(1):49–56

174. Wahl F, Grosjean-Piot O, Bareyre F, Uzan A, Stutzmann JM. Enoxaparin reduces brain edema, cerebral lesions, and improves motor and cognitive impairments induced by a traumatic brain injury in rats. J Neurotrauma 2000;17(11): 1055–1065

175. Dudley RR, Aziz I, Bonnici A, et al. Early venous thromboembolic event prophylaxis in traumatic brain injury with low-molecular-weight heparin: risks and benefits. J Neurotrauma 2010;27(12):2165–2172

176. Roos YB, de Haan RJ, Beenen LF, Groen RJ, Albrecht KW, Vermeulen M. Complications and outcome in patients with aneurysmal subarachnoid haemorrhage: a prospective hospital based cohort study in the Netherlands. J Neurol Neurosurg Psychiatry 2000;68(3):337–341

177. Vergouwen MD, Vermeulen M, Coert BA, Stroes ES, Roos YB. Microthrombosis after aneurysmal subarachnoid hemorrhage: an additional explanation for delayed cerebral ischemia. J Cereb Blood Flow Metab 2008;28(11):1761–1770

178. Romano JG, Forteza AM, Concha M, et al. Detection of microemboli by transcranial Doppler ultrasonography in aneurysmal subarachnoid hemorrhage. Neurosurgery 2002; 50(5):1026–1030, discussion 1030–1031

179. Giller CA, Giller AM, Landreneau F. Detection of emboli after surgery for intracerebral aneurysms. Neurosurgery 1998;42(3):490–493, discussion 493–494

180. Crompton MR. The pathogenesis of cerebral infarction following the rupture of cerebral berry aneurysms. Brain 1964;87:491–510

181. Stein SC, Browne KD, Chen XH, Smith DH, Graham DI. Thromboembolism and delayed cerebral ischemia after subarachnoid hemorrhage: an autopsy study. Neurosurgery 2006;59(4):781–787, discussion 787–788

182. Wurm G, Tomancok B, Nussbaumer K, Adelwöhrer C, Holl K. Reduction of ischemic sequelae following spontaneous subarachnoid hemorrhage: a double-blind, randomized comparison of enoxaparin versus placebo. Clin Neurol Neurosurg 2004;106(2):97–103

183. Roos Y; STAR Study Group. Antifibrinolytic treatment in subarachnoid hemorrhage: a randomized placebo-controlled trial. Neurology 2000;54(1):77–82

184. Chwajol M, Starke RM, Kim GH, Mayer SA, Connolly ES. Antifibrinolytic therapy to prevent early rebleeding after subarachnoid hemorrhage. Neurocrit Care 2008;8(3):418–426

185. Starke RM, Kim GH, Fernandez A, et al. Impact of a protocol for acute antifibrinolytic therapy on aneurysm rebleeding after subarachnoid hemorrhage. Stroke 2008; 39(9):2617–2621

186. Pabinger I, Karnik R, Lechner K, Slany J, Niessner H. Coumarin induced acral skin necrosis associated with hereditary protein C deficiency. Blut 1986;52(6):365–370

187. McGehee WG, Klotz TA, Epstein DJ, Rapaport SI. Coumarin necrosis associated with hereditary protein C deficiency. Ann Intern Med 1984;101(1):59–60

188. Rose VL, Kwaan HC, Williamson K, Hoppensteadt D, Walenga J, Fareed J. Protein C antigen deficiency and warfarin necrosis. Am J Clin Pathol 1986;86(5):653–655

189. Sallah S, Abdallah JM, Gagnon GA. Recurrent warfarin-induced skin necrosis in kindreds with protein S deficiency. Haemostasis 1998;28(1):25–30

190. Dahlbäck B. New molecular insights into the genetics of thrombophilia. Resistance to activated protein C caused by Arg506 to Gln mutation in factor V as a pathogenic risk factor for venous thrombosis. Thromb Haemost 1995;74(1): 139–148

191. Kiehl R, Hellstern P, Wenzel E. Hereditary antithrombin III (AT III) deficiency and atypical localization of a coumarin necrosis. Thromb Res 1987;45(2):191–193

192. Fluri S, Kaczala GW, Leibundgut K, Alberio L. Chickenpox is not always benign: postvaricella purpura fulminans requires prompt and aggressive treatment. Pediatr Emerg Care 2010;26(12):932–934

193. Sharma VK, Dubey TN, Dave L, Agarwal A. Postvaricella purpura fulminans with no evidence of disseminated intravascular coagulation (DIC) or protein S deficiency. J Indian Med Assoc 2010;108(8):529–530

194. Francis RB Jr. Acquired purpura fulminans. Semin Thromb Hemost 1990;16(4):310–325

195. Josephson C, Nuss R, Jacobson L, et al. The varicella-autoantibody syndrome. Pediatr Res 2001;50(3):345–352

196. Manco-Johnson MJ, Nuss R, Key N, et al. Lupus anticoagulant and protein S deficiency in children with postvaricella purpura fulminans or thrombosis. J Pediatr 1996;128(3):319–323

197. Busuttil DP, Hay CR, Lewis MA, Wynn RF. Aggressive multiple modality therapy for varicella-associated purpura fulminans. Br J Haematol 2000;110(4):1012–1013