Hemostasis based on a novel 'two-path unifying theory' and classification of hemostatic disorders

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Hemostasis is the most important protective mechanism for human survival following harmful vascular damage caused by internal disease or external injury. Physiological mechanism of hemostasis is partially understood. Hemostasis can be initiated by either intravascular injury or external bodily injury involving two different levels of damage [i.e., limited to the endothelium or combined with extravascular tissue (EVT)]. In intravascular injury, traumatic damage limited to local endothelium typically is of no consequence, but disease-induced endothelial damage associated with systemic endothelial injury seen in sepsis and other critical illnesses could cause generalized 'endotheliopathy'. It triggers no bleeding but promotes serious endothelial molecular response. If intravascular local trauma extends beyond the endothelium and into EVT, it causes intravascular 'bleeding' and initiate 'clotting' via normal hemostasis. In external bodily injury, local traumatic damage always extends to the endothelium and EVT, and triggers 'bleeding' and 'clotting'. Systemic endotheliopathy activates only unusually large von Willebrand factor multimers (ULVWF) path and mediates 'microthrombogenesis', producing 'microthrombi' strings. This partial activation of hemostasis with ULVWF path leads to vascular microthrombotic disease. But localized traumatic injury extending to the endothelium and EVT activates both ULVWF and tissue factor paths. Combined activation of ULVWF and tissue factor paths provides normal hemostasis in external bodily injury, but causes 'macrothrombus' formation in intravascular injury. This 'two-path unifying theory' concept succinctly elucidates simplified nature of hemostasis in intravascular and external bodily injuries. It also clarifies different pathogenesis of every hemorrhagic disease and thrombotic disorder related to internal vascular disease and external vascular injury. *Blood Coagul Fibrinolysis* 29:573–584

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Introduction

Hemostasis is defined as natural process that causes bleeding to stop at injured blood vessel and keep blood within the vascular space. Clinical experience and laboratory studies in hemorrhagic diseases and thrombotic disorders have provided valuable insights on the nature of hemostasis. In hemostasis, essential participating components are [1–5]

(1) Endothelium
(2) Unusually large von Willebrand factor multimers (ULVWF) from the endothelium
(3) Platelets
(4) Tissue factor (TF) from the extravascular tissue (EVT)
(5) Coagulation factors

The physiological hemostatic mechanism is partially understood. Several theoretical concepts are proposed for the mechanisms in hemostasis and thrombosis. Among them are in-vivo cell-based TF–FVIIa-initiated coagulation [2], endothelial collagen binding and platelet aggregation to make hemostatic plug [3–5], balance shift between procoagulants and anticoagulants [1,4,6], and von Willebrand factor (VWF) and platelet interaction (primary hemostasis) and activated coagulation factors producing cross-linked fibrin meshes (secondary hemostasis) [1,7].

In this review article, the axiom of hemostasis will be formulated and a novel hemostatic theory will be proposed based on the knowledge and insights learned from physiopathological mechanism of microthrombogenesis.

Proposed principles and theory of hemostasis

Hemostatic principles

No matter what the true nature of hemostasis may be, the unwavering normal hemostasis in vascular injury must confirm the following five principles:

(1) Hemostasis can be activated only by vascular injury.
(2) Hemostasis must be activated through ULVWF path and/or TF path.
(3) Hemostasis is the same process in both hemorrhage and thrombosis.

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(4) Hemostasis is the same process in both arterial thrombosis and venous thrombosis.
(5) The levels of vascular damage (endothelium and/or EVT) determine the phenotypes of hemorrhagic syndrome and generate different phenotypes of the thrombotic disorder.

An exception is pathologic hemostasis in which thrombotic disorder occurs without vascular injury. This rare situation is known to occur only in two diseases: one is microthrombosis in thrombotic thrombocytopenic purpura (TTP) via activated 'aberrant' ULVWF path and the other is fibrin clots [i.e., disseminated intravascular coagulation (DIC)] in acute promyelocytic leukemia (APL) via activated 'aberrant' TF path, which will be discussed later.

To date, unresolved mystery of the mechanism of hemostasis associated with hemorrhage and thrombosis has been still hiding within the wall of the endothelium, behind the EVT and in circulation. The concept of microthrombosis and macrothrombosis, mucosal hemorrhagic syndrome in von Willebrand disease (VWD), pathogenesis of genetic thrombophilia [8], character of focal thrombotic syndrome, vascular microthrombosis in DIC [9,10], combined thrombohemorrhagic syndrome, and many others could not be accounted by contemporary theories of hemostasis.

Two-path unifying theory of hemostasis

In the advent of recognition of vascular microthrombotic disease (VMTD)/disseminated intravascular microthrombosis (DIT) as a distinct disease entity, its identification of molecular pathogenesis [11,12], which knowledge gained from the concept of microthrombogenesis [11,12], is shedding light upon the pathophysiological mechanism of hemostasis and its role in various hemorrhagic syndromes and thrombotic disorders. Perhaps paradigm shift in resolving hemostasis puzzles and rational therapeutic strategy in treating hemostatic diseases could be at hand.

To account for clinical phenotypes of the hemorrhagic diseases and thrombotic disorders, a novel 'two-path unifying theory of hemostasis' is proposed as illustrated in Fig. 1. In the settings of intravascular injury and extravascular bodily injury, all five hemostatic components must be properly functional for normal hemostasis to produce healthy hemostatic plug. Physiological hemostasis should be achieved through the activation of two independent but simultaneously cooperating hemostatic paths.

First, ULVWF-induced microthrombotic path (ULVWF path) must be activated in vascular endothelial injury. Endothelial injury causes platelet activation and endothelial exocytosis of ULVWF from Weibel–Palade bodies and promotes sufficient release of these prothrombotic multimers [5,13–15]. ULVWF become anchored to the edge of damaged endothelial cells with support of collagen as long elongated strings [5] and recruit platelets. Both components together form platelet-ULVWF complexes, which become 'microthrombi' strings that are tightly attached to endothelial membrane [5,11–15]. This process, forming microthrombi, is called microthrombogenesis [11,12].

Second, in normal hemostasis, TF-initiated fibrinogenic path (TF path) also must be activated in vascular injury. If the injury, in addition to the endothelium, extends into the TF-rich EVT, TF is released into the local vascular injury site and activates FVII in circulation to FVIIa. According to 'cell-based model of coagulation' [2,16], TF–FVIIa complexes activate FX to FXa. FXa with FVa that is activated from FV forms FXa–FVa complex (prothrombinase). Prothrombinase activates prothrombin to make small priming amounts of thrombin, which is called initiation phase. This priming amount of thrombin promotes FVIIIa–FIXa complex (tenase) feedback. This complex converts FX to FXa and markedly increases thrombin generation in amplification phase. In final stage, thrombin will convert sufficient amount of fibrinogen to fibrin to make enough 'fibrin meshes' [1,13,17]. This process, forming fibrin meshes, can be called fibrinogenesis.

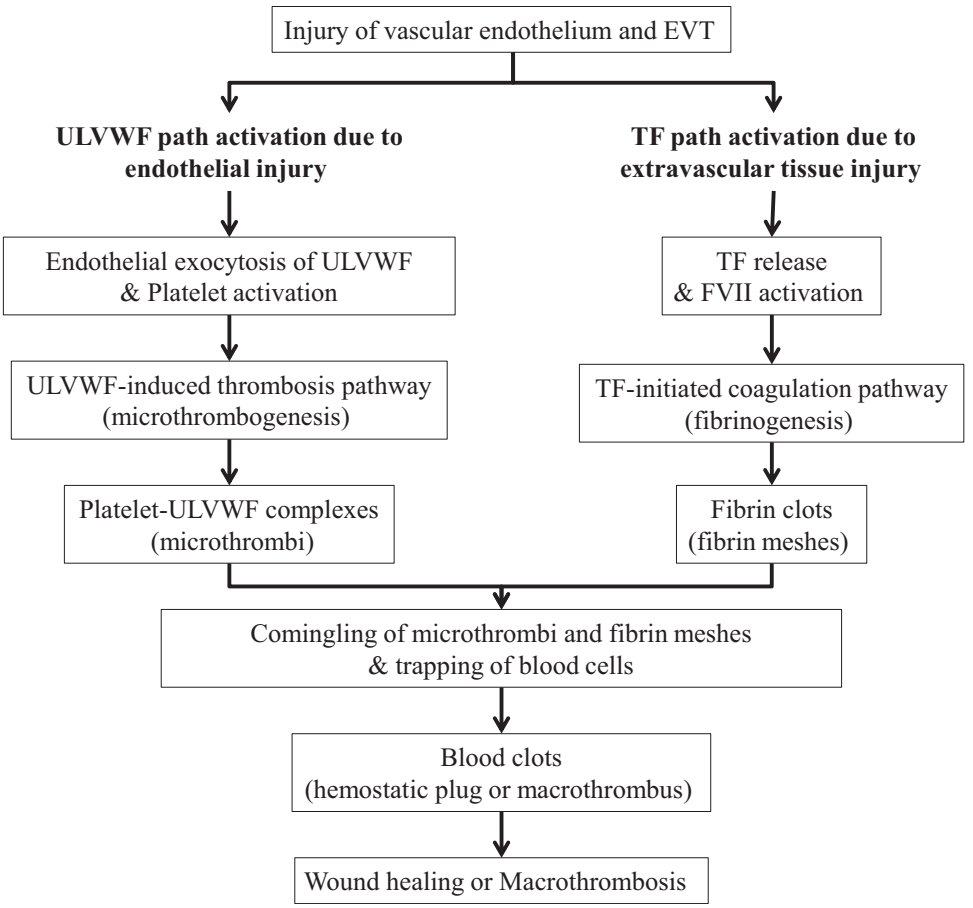
In ULVWF path, microthrombogenesis assembles 'microthrombi' strings. In TF path, through activated coagulation cascade, fibrinogenesis molds 'fibrin meshes'. Both microthrombi and fibrin meshes comingle at the site of endothelial injury and perhaps with help of adhesion molecules become unified together and trap blood cells to produce interconnected 'blood clots'. These blood clots become healthy 'hemostatic plug' preventing unnecessary hemorrhage at external vascular injury site, but also become pathologic 'macrothrombus' in intravascular injury site as illustrated in Fig. 1.

Newly released and anchored to the endothelial membrane but yet uncleaved ULVWF by ADAMTS13 initiate normal local hemostasis, as they possess a very high affinity to platelets [3–5,18]. This extremely efficient character of ULVWF is the essential ingredient limiting hemorrhage from the onset at vascular injury site. However, later we will discover that, in many critical illnesses such as sepsis and severe trauma, the same character of ULVWF also ignites a deadly pathologic microthrombotic disorder (i.e., VMTD) via disseminated microthrombogenesis. ULVWF is the strange protagonist symbol of Dr Jekyll and Mr Hyde.

Hemorrhagic syndromes

Hemorrhagic syndrome develops following vascular injury as a consequence of impaired hemostasis associated with underlying hemorrhagic disease. Even with hemorrhagic diseases (e.g., thrombocytopenia, VWD,

Fig. 1



Normal hemostasis based on the 'two-path unifying theory'. The concept of this theory is derived from the physiopathological logic of hemostasis (five principles described in the text). The nature has endowed human with only 'one' normal blood clotting system. Hemostasis protects human from unnecessary bleeding in external bodily injury and aids in self-wound healing, but also guards from unnecessary self-inflicted injury and hostile environmental insult, which cause intravascular vascular injury, leading to deadly thrombotic disorders. This is the true irony of the nature that the exact same normal hemostasis not only provides wound healing but also can lead to life-threatening thrombosis, which, I believe, is a nature's warning to human for a good reason. In normal hemostasis, there must be two paths, which have to be unified to make normal hemostasis or macrothrombus. In a certain disease (endotheliopathy-associated vascular microthrombotic disease), typically only unusually large von Willebrand factor multimers path is activated, and in another disease (acute promyelocytic leukemia), only tissue factor path is activated. The former produces microthrombi, and the latter produces fibrin clots. If both paths were activated normally and simultaneously, macrothrombus would occur. These are explained in the text and their genesis noted in Table 3. APL, acute promyelocytic leukemia; EA-VMTD, endotheliopathy-associated vascular microthrombotic disease; EVT, extravascular tissue; TF, tissue factor; ULVWF, unusually large von Willebrand factor multimers.

hemophilia), bleeding and hemostasis do not occur unless vascular injury compromises the integrity of the endothelial barrier (*hemostasis principle* 1). Following vascular injury in a patient with hemorrhagic disease, the character of the disease and extent of the injury determine the expression of bleeding. Thus, minimal vascular injury could lead to severe hemorrhagic syndrome in a hemorrhagic disease.

The levels of vascular damage (endothelium and/or EVT) determine the phenotype of hemorrhagic syndrome (*hemostasis principle* 5). In intravascular trauma, if the damage were limited to local endothelium (e.g., detachment of small atheromatous cholesterol plaque, or mild trauma following coronary artery intervention procedure), typically intravascular bleeding would be minimal and transient. But, if the damage extended beyond the endothelium and into EVT (e.g., large atheromatous rupture in coronary artery or severe injury due to intravascular catheter procedure), endothelial damage would activate ULVWF path leading to 'bleeding' and 'microthrombi', and subsequently, EVT damage activates TF path promoting 'fibrin clots', resulting in 'macrothrombus' as well as 'bleeding'.

Bleeding due to external bodily injury is always associated with damage to the endothelium and EVT by its nature. Depending upon the hemorrhagic disease and extent of the vascular injury, different hemorrhagic phenotypes could develop; some are due to defective

Table 1 Classification of the causes of the hemorrhagic syndrome associated with vascular injury

Associated with defective ULVWF path			
Platelet diseases (e.g., petechiae)		ULVWF diseases (e.g., mucosal bleeding)	
Hereditary	Acquired	Hereditary	Acquired
Thrombocytopenia (e.g., TAR syndrome)	Thrombocytopenia (e.g., ITP, leukemia)	VWD with quantitative defect (e.g., types 1 and 3)	Autoimmune VWD Heyde's syndrome Henoch–Schonlein purpura
Thrombocytopathia (e.g., Bernard–Soulier syndrome)	Thrombocytopathia (e.g., aspirin)	VWD with qualitative defect (e.g., types 2A, 2B, 2N)	
Associated with defective TF Path			
Coagulation diseases (e.g., musculoskeletal bleeding)			
Hereditary		Acquired	
Hemophilia A		Hepatic coagulopathy	
Hemophilia B		Type 1: chronic liver disease (e.g., liver cirrhosis)	
Prothrombin deficiency		Type 2: acute fulminant hepatic failure (e.g., VMTD, acute hepatitis)	
FVII deficiency		Vitamin K deficiency	
FV deficiency		DIC (e.g., APL[a])	
Hypofibrinogenemia		Drug-induced coagulopathy (e.g., heparin, Coumadin)	
VWD types 1 and 3		Acquired hemophilia	
VWD type 2N			

APL, acute promyelocytic leukemia; DIC, disseminated intravascular coagulation; DIT, disseminated intravascular microthrombosis; ITP, immune thrombocytopenic purpura; TAR, thrombocytopenia with absent radius; TF, tissue factor; ULVWF, unusually large von Willebrand factor multimers; VMTD, vascular microthrombotic disease; VWD, von Willebrand disease; VWF, von Willebrand factor multimers. [a] APL is not due to vascular injury, but is due to increased TF expression, leading to 'aberrant' activation of TF path, which is pathologic hemostasis. Please see the text and Table 3 for detail.

ULVWF path disease, which causes bleeding as a result of endothelial damage (e.g., petechiae, mucosal bleeding); the others are defective TF path disease, which causes tissue bleeding and hematoma associated with EVT damage (e.g., hemarthrosis, tissue hematoma, cavitary bleeding).

Defective ULVWF path-associated hemorrhagic syndromes occur due to either quantitative or qualitative defect of platelets or ULVWF diseases (Table 1). But defective TF path-associated hemorrhagic syndromes occur due to deficiency of coagulation factor(s) (Table 1).

Hemorrhagic syndrome due to unusually large von Willebrand factor multimers path diseases

In ULVWF path, hemorrhagic syndrome occurs due to endothelial injury in the patient with the platelet disease or ULVWF disease. The ULVWF disease is currently called 'VWD'. Endothelial damage results in inadequate microthrombogenesis due to thrombocytopenia/thrombocytopathia or quantitative/qualitative defect of ULVWF. The outcome would be insufficient production of endothelial cell-anchored 'microthrombi' strings, which limit their ability of unifying with fibrin meshes.

The examples of the platelet disease are hereditary thrombocytopenia (e.g., thrombocytopenia with absent radius syndrome) and thrombocytopathia (e.g., Bernard Soulier syndrome, Glanzmann's thrombasthenia), and acquired thrombocytopenia (e.g., immune thrombocytopenic purpura, hypersplenism) and thrombocytopathia (e.g., aspirin, clopidogrel) as shown in Table 1. The examples of the ULVWF disease are hereditary VWD and acquired VWD, including Heyde's syndrome and Henoch–Schonlein purpura as shown in Table 1.

Without major vascular injury, the common hemorrhagic phenotype of the platelet disease is 'petechiae', but common phenotype of ULVWF path associated with 'VWD' is 'mucosal hemorrhagic syndrome'. The bleeding time, which tests the integrity of the endothelium and function of ULVWF path, is prolonged in the ULVWF path disease.

Hemorrhagic syndrome due to tissue factor path diseases

In the TF path disease, hemorrhagic syndrome occurs due to vascular injury that penetrates into the EVT in the patient with one or more of coagulation factor deficiency as shown in Table 1. EVT damage causes inadequate fibrinogenesis due to deficient activation of TF–FVIIa complex-initiated cascade. Insufficient production of fibrins causes less fibrin meshes, which limit their ability of unifying with microthrombi strings for hemostasis.

The examples of the coagulation disease are hereditary coagulation factor deficiency and acquired coagulopathy as illustrated in Table 1. Hereditary coagulation disease includes factor deficiency (e.g., hemophilia A, hemophilia B, FVIII deficiency associated with VWD types 1, 2N, and 3). Acquired coagulopathy includes hepatic coagulopathy, vitamin K deficiency, drug-induced coagulopathy (e.g., warfarin, heparin), and acquired autoimmune hemophilia.

Typical hemorrhagic phenotype of defective TF path diseases is internal hemorrhage, leading to hemarthrosis,

tissue and organ hematoma as well as external hemorrhage following external bodily injury. The bleeding time is sometimes prolonged in hemophilia A. It was not correlated to severity of the disease or preceding transfusion [19,20]. Although its mechanism could not be explained [19,20], this author suspects it might be related to the technical issue. When the test needle penetrates into the EVT in a person with more EVT mass or due to testing technique (vertical vs. horizontal), TF path could be activated locally for hemostasis. But insufficient fibrinogenesis in FVIII deficiency would artificially prolong the bleeding time *in vivo*.

Pathogenesis of the phenotypes of hemorrhagic syndrome

Petechial syndrome

Common manifestation of the platelet disease, which causes defective ULVWF path, is petechiae, but sometimes mucosal bleeding could occur. In small dermal bleeding under the skin, red cells could escape into the interstitial spaces from anatomically intact capillaries [21]. Even though ULVWF is sufficient, if thrombocytopenia is severe, locally insufficient platelet-sufficient ULVWF complexes may not be able to prevent red cell passage through the cytoplasmic break of the endothelium. This dislocation of the red cells probably causes petechiae [21].

Platelets are abundant in circulation. In a local vascular injury, they are readily available from blood for hemostasis even in the patient with significant thrombocytopenia. Of course, adequate number of the platelet must be available for hemostasis when major injury or polytrauma occurs. Typically, thrombocytopenia-related hemorrhagic tendency is uncommon in the absence of associated coagulopathy or severe trauma.

In clinical practice, platelet transfusion is not routinely recommended in acute transient thrombocytopenia without bleeding unless the count is less than 12 000/μl. Chronic immune thrombocytopenia should not be treated just to raise the platelet number artificially above 25 000/μl, as hemostasis is adequate even with moderate thrombocytopenia and the drug treatment is expensive and inconvenient with significant undesirable side effects. Furthermore, platelet transfusion is often not beneficial and may be dangerous for conditions such as VMTD as it accelerates microthrombogenesis.

Mucosal hemorrhagic syndrome

This syndrome occurring in the ULVWF path disease is a very unique hemorrhagic syndrome. ULVWF are packaged and stored within Weibel–Palade bodies of endothelial cells to be available immediately for hemostasis in vascular injury. Decreased quantity or quality of endothelial ULVWF in VWD causes insufficient release of ULVWF, resulting in insufficient platelet-ULVWF strings anchored to endothelial cells.

The mucus membrane that covers the surface of internal organs is a delicate structure that rubricates and protects the tissue, and is well supplied with blood through capillaries. But it is only covered by epithelial membrane without the skin protection. Thus, in vascular injury, the mucous membrane, protecting the capillary endothelium with insufficient ULVWF in 'VWD', would be more vulnerable to minimal injury causing membrane disruption. In the absence of the protective skin, sufficient platelet-insufficient ULVWF microthrombi could lead to 'mucosal hemorrhagic syndrome'. This syndrome can be manifested as epistaxis, oral mucosal bleeding, intestinal bleeding, hematuria, and heavy menstrual flow.

EVT hemorrhagic syndrome

Without a detectable external bodily injury in coagulation factor deficiency, an internal EVT injury associated with external blunt trauma or internal injury could cause a serious hemorrhagic syndrome within the tissue, cavity, and organ. For example, in hemophilia A, if the release of TF following EVT injury activates TF path, but with deficient FVIII, it would cause local tissue bleeding and continue to increase internal tissue hemorrhage due to insufficient fibrin meshes that mold hemostatic fibrin clots. The result is musculoskeletal hemorrhage such as hemarthrosis, cavitary hemorrhage, and tissue/organ hematomas [22].

Combined mucosal and EVT hemorrhagic syndrome

This syndrome is another interesting syndrome supporting 'two-path unifying theory' of hemostasis. It occurs in VWD types 1, 2N, and 3 as these hereditary diseases cause both defective ULVWF and TF paths due to deficient ULVWF and FVIII deficiency [23].

FVIII deficiency occurs due to the decrease of cleaved smaller size VWF in these types of VWD. VWF is an indirect participant in fibrinogenesis as VWF acts as a carrier/protector for FVIII in circulation, which is an essential component in activating TF path. VWF maintains normal level of FVIII by decreasing its clearance approximately by five-fold. If smaller VWF are decreased, it cannot protect FVIII from degradation. Therefore, hemorrhagic phenotype of VWD types 1, 2N, and 3 is combined mucosal and EVT hemorrhagic syndrome [23,24].

Thrombotic disorders

Thrombotic disorders occur as a result of 'normal' hemostasis following intravascular injury. Sometimes, thrombogenesis can be accentuated with 'enhanced' hemostasis in certain situations such as thrombophilia, endotheliopathy, hereditary, or acquired vasculitis. In addition, to make the thrombogenesis more complex, atypical thrombotic disorders, which are not caused by normal hemostasis, occur without intravascular injury.

Table 2 Classification of hemostatic thrombotic disorders

Due to local intravascular injury	Due to focal endotheliopathy	Due to systemic endotheliopathy
Local: TF and ULVWF path activation Due to intravascular injury (e.g., postsurgery, trauma, vascular access)	Focal: ULVWF path activation Due to hereditary focal endotheliopathy (e.g., hereditary focal VMTD) Due to acquired focal microvascular injury (e.g., atheromatous erosion of coronary artery)	Disseminated: ULVWF path activation Due to acquired endotheliopathy [e.g., EA-VMTD (TTP-like syndrome)] Due to ADAMTS13 deficiency[a] [e.g., hereditary TTP, autoimmune TTP (TTP)]
Character of thromboses and vascular sites		
Macrothrombosis In both venous or arterial system	Microthrombosis In arterioles, capillaries, and venules	Microthrombosis In capillary and smaller arterial system
Examples of disorders		
DVT Hereditary thrombophilia-associated (e.g., FV Leiden, protein C deficiency) Acquired DVT (e.g., postsurgery, trauma; vascular access) IVC-filter induced thrombosis syndrome Thromboembolism Pulmonary thromboembolism Arterial thrombosis Aortic aneurysm-associated thrombosis Vascular access steal syndrome	Hereditary focal VMTD HERNS syndrome Fabry's disease (?) Acquired focal VMTD Susac's syndrome Degos endotheliopathy (?) Coronary vascular microthrombosis (e.g., unstable angina) Cerebral vascular microthrombosis (e.g., TIA)	Hereditary VMTD Hereditary TTP (GA-VMTD)[a] Acquired VMTD Autoimmune TTP (AA-VMTD)[a] TTP-like syndrome (EA-VMTD) (e.g., HUS, ARDS, FHF, DIT, AI)

AA-VMTD, antibody-associated VMTD; FHF, fulminant hepatic failure; AI, adrenal insufficiency; ARDS, acute respiratory distress syndrome; DIT, disseminated intravascular microthrombosis; DVT, deep vein thrombosis; EA-VMTD, endotheliopathy-associated VMTD; GA-VMTD, gene mutation-associated VMTD; HERNS, hereditary endotheliopathy with retinopathy, nephropathy, and stroke; HUS, hemolytic uremic syndrome; IVC, inferior venal cava; TF, tissue factor; TIA, transient ischemic attack; TTP, thrombotic thrombocytopenic purpura; ULVWF, unusually large von Willebrand factor multimers; VMTD, vascular microthrombotic disease. [a]TTP is not due to vascular injury, but is due to increased ULVWF expression associated with ADAMTS13 deficiency, leading to 'aberrant' activation of ULVWF path, which is pathologic hemostasis. Please see the text and Table 3 for detail.

Atypical thrombotic disorders

As mentioned earlier, among thrombotic disorders few exceptions caused by nonvascular injury are TTP, APL, and also heparin-induced thrombocytopenia with thrombosis syndrome (HIT-TS). Out of these three nonvascular injury-associated thrombotic disorders, TTP and APL still can be best classified as thrombotic disorders, but occurring as a result of 'abnormal' hemostasis for a logical reason [*hemostasis principle 2*]. These two disorders develop thrombosis through 'aberrant' hemostatic path without intravascular injury. TTP utilizes aberrant ULVWF path to produce 'microthrombi' and causes VMTD, and APL utilizes aberrant TF path to produce 'fibrin clots' and causes true DIC (consumptive coagulopathy) (*hemostatic principle 2*) as succinctly illustrated in Table 3. This proposition adding TTP and true DIC [25] to the hemostatic disorder associated with 'aberrant' hemostatic paths is a very clear and important concept in the understanding of 'normal' hemostasis and 'abnormal' hemostasis, especially in clinical medicine. This concept is also utilized in the classification and genesis of the hemostatic thrombotic disorders in Tables 2 and 3, which is self-explanatory.

HIT-TS is not caused by hemostasis as there is no evidence it utilizes either ULVWF path and/or TF path. Following heparin administration, heparin-platelet factor 4 antibodies can be formed. The complex of heparin-platelet factor 4 antibodies activates platelets, leading to intravascular aggregation of platelets, and produces the multiple large platelet thrombi. This syndrome is truly platelet thrombosis occurring both venous and arterial systems, especially in lower extremities, which has been called 'white clots'.

As 'normal' hemostatic thrombosis develops only in the situation of intravascular injury, the presence of thrombosis without underlying diseases such as TTP, APL, and HIT-TS should assert that the intravascular endothelial damage has occurred with or without the EVT damage. Therefore, in the absence of intravascular injury, 'thrombophilia' by itself could not cause thrombosis yet; it is because hemostasis cannot be initiated without activated ULVWF and/or TF paths. This important fact would critically influence the clinician's decision for the timing of prophylactic anticoagulation therapy in the thrombophilic patient.

Genesis of microthrombi, macrothrombus, and fibrin clots

Focusing on the nature of thrombus itself rather than on the process of thrombogenesis would make it easier for the clinician to understand the pathophysiological mechanism of different phenotypic thrombotic disorders.

The longstanding enigmatic puzzle on how blood coagulation causes thrombosis in intravascular space has created so many debates in coagulation community [26–33].

Table 3 Genesis of microthrombi, fibrin clots, and macrothrombus via normal and pathologic hemostasis

	Normal hemostasis		Pathologic hemostasis	
Hemostatic path	Normal path		'Aberrant' path	
Injury/pathology	Intravascular injury		TTP	APL
Activated path Injury level/pathology	ULVWF path Endothelium	ULVWF path + TF path Endothelium and EVT	ULVWF path ADAMTS13 deficiency	TF path ↑ TF expression
Participant	ULVWF Platelet	ULVWF Platelet TF Coagulation factors (FVIIa, FXa, FVa, FIXa, FVIIIa, FII, fibrinogen)	ULVWF Platelet	TF Platelet (?) Coagulation factors (FVIIa, FXa, FVa, FIXa, FVIIIa, fibrinogen)
Genesis	Microthrombogenesis	Microthrombogenesis and fibrinogenesis	Microthrombogenesis	Fibrinogenesis
Nature of clots	Platelet-ULVWF complex	Platelet-ULVWF complex and fibrin mesh	Platelet-ULVWF complex	Fibrin mesh
Thrombosis form	Microthrombi Focal VMTD (e.g., HERNS syndrome)	Macrothrombus	Microthrombi	Fibrin clots
Examples of clinical disorders	TTP-like syndrome (e.g., EA-VMTD)	DVT Thromboembolism (e.g., PE) Arterial thrombosis STEMI	TTP (e.g., GA-VMTD; AA-VMTD)	True DIC of APL

AA-VMTD, antibody-associated VMTD; APL, acute promyelocytic leukemia; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; EA-VMTD, endotheliopathy-associated VMTD; EVT, extravascular tissue; GA-VMTD, gene mutation-associated VMTD; HERNS, hereditary endotheliopathy, retinopathy, nephropathy, and stroke; PE, pulmonary embolism; STEMI, ST-elevation myocardial infarction; TF, tissue factor; TTP, thrombotic thrombocytopenic purpura; ULVWF, unusually large von Willebrand factor multimers; VMTD, vascular microthrombotic disease.

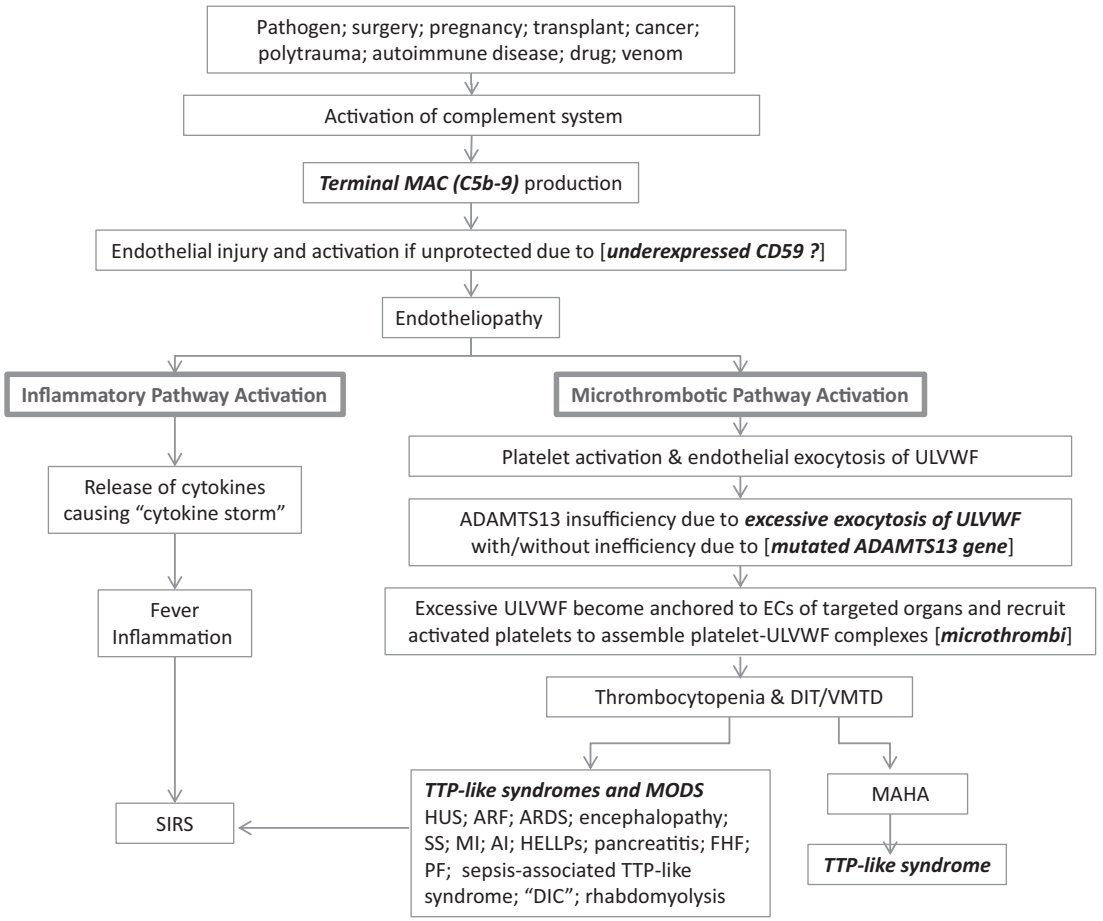
The major controversy has been centered on how TF becomes available within the endothelium and in circulation, and how it interacts with coagulation factors [1,2,29–33]. After several decades of clinical, laboratory, biological, and molecular research, the understanding of thrombogenesis is still far from completion.

The author's opinion is the conceptual groundwork on thrombosis and thrombogenesis should be reassessed and revised as it is a fact that in-vivo TF is not endowed in the endothelium and circulation [27] for a good reason. To identify the mechanism of complicated thrombogeneses, we are focusing mainly on the role of TF, cross-talk between inflammation and coagulation, balance shift between anticoagulant and procoagulant. Instead, we have to go back to the basic logics of 'vascular injury' and nature of 'microthrombi/thrombus/blood clots'. We know very well that microthrombi occur without TF-initiated coagulation as illustrated in Figs. 1 and 2 [11,12]. It is also true that TF has no role in the activation of ULVWF path. Furthermore, not all thrombi are generated in the same manner as clearly observed in deep vein thrombosis (DVT) and 'DIC' (i.e., DIT). These puzzles can be solved through the analysis of the logics of vascular injury and characters of microthrombi, fibrin clots, and macrothrombus with application of the concept of 'two-path unifying theory of hemostasis'.

The different levels of vascular damage (endothelium and/or EVT) produce dissimilar thrombotic disorders (*hemostasis principle* 5). According to novel 'two-path unifying theory of hemostasis', thrombosis model is governed by the same rule of hemostatic principle as in the hemorrhagic syndrome and follows exactly the same path of normal hemostasis (Fig. 1 and Table 2). If an intravascular injury is limited only to the endothelium, which occurs in many critical illnesses such as endotheliopathy-associated VMTD (EA-VMTD) and TTP-like syndrome, solely ULVWF path becomes activated as a result of endothelial damage, and disseminated 'microthrombi' are formed via microthrombogenesis [11,12]. Thus, microthrombosis, which clinical phenotype is VMTD, is the characteristic lesion of DIT [11,12]. On the other hand, if an intravascular injury extends to the EVT by local trauma, which results in DVT in the venous system and arterial thrombosis in the arterial system, both ULVWF and TF paths become activated simultaneously due to combined endothelial and EVT damage (*hemostasis principle* 4). In this case, 'macrothrombus' (Fig. 1) [34] is formed via activation of local microthrombogenesis and fibrinogenesis. The outline of the genesis of microthrombi and macrothrombus is shown in Fig. 1 and Table 3.

For example, following coronary intervention procedure, it is not uncommon to encounter transient and localized coronary thrombotic episode of 'microthrombi', which develop due to traumatic endothelial injury that activates ULVWF path [35,36]. At other times, intracoronary 'macrothrombus' can occur during/after percutaneous coronary intervention [34], which is a very serious condition caused by coronary intravascular catheter injury not only damaging the endothelium but also penetrating

Fig. 2



Molecular pathogenesis of unusually large von Willebrand factor multimers path in endotheliopathy-associated vascular microthrombotic disease. The 'two-activation theory of the endothelium' has been proposed to explain the pathogenesis of 'endotheliopathy' in endotheliopathy-associated vascular microthrombotic disease. There are two sequential paths. First is complement activation and second is activation of inflammatory pathway and microthrombotic pathway, which lead to inflammation and microthrombosis. In second path, inflammatory pathway and microthrombotic pathway are completely independent. However, clinical scientists have interpreted these two clinical phenotypes must cross-talk to link inflammation and coagulation, which is a vague concept that cannot explain all the phenotypic clinical features in endotheliopathy-associated vascular microthrombotic disease such as disseminated intravascular microthrombosis, microangiopathic hemolytic anemia, consumptive thrombocytopenia, thrombotic thrombocytopenic purpura-like syndrome, systemic inflammatory response syndrome, and multiorgan dysfunction syndrome. AI, adrenal insufficiency; ARDS, acute respiratory distress syndrome; ARF, acute renal failure; DIT, disseminated intravascular microthrombosis; EA-VMTD, endotheliopathy-associated vascular microthrombotic disease; EC, endothelial cell; FHF, fulminant hepatic failure; HELLPs, hemolysis, elevated liver enzymes, low platelet syndrome; HUS, hemolytic uremic syndrome; MAC, membrane attack complex; MAHA, microangiopathic hemolytic anemia; MI, myocardial infarction; MODS, multiorgan dysfunction syndrome; PF, purpura fulminans; SIRS, systemic inflammatory response syndrome; SS, stroke syndrome; TTP, thrombotic thrombocytopenic purpura; ULVWF, unusually large von Willebrand factor multimers.

beyond the endothelium and into the EVT (i.e., myocardium) of the heart. The result could lead to ST-elevation myocardial infarction (MI).

Yet, there is another clotting situation that is caused by activation of TF path alone without intravascular injury and without activation of ULVWF path. This unique coagulation disorder is seen in true DIC, example of which is APL. The expressed TF from leukemic cells activates FVII–FVIIa, which leads to activation of cell-based model coagulation cascade [2] and depletes FVIII and FV with consumption of fibrinogen. The end result is the formation of fibrin meshes, which become 'fibrin clots', as illustrated in Fig. 1. This is abnormal hemostasis that is led by 'aberrant' activation of TF pathway. No doubt is that this is still hemostatic disease.

Indeed, now we can reconcile the long-standing mystery of the difference between in-vitro extrinsic coagulation pathway and in-vivo cell-based fibrinogenic pathway that is incorporated in the 'two-path unifying theory'. In retrospect, the 'fibrin clots' that we have observed in-vitro clotting test tubes must be the same 'fibrin clots' occurring in in-vivo fibrinogenesis of activated TF path occurring in APL. Therefore, in-vitro TF coagulation cascade alone just constitutes incomplete hemostatic

function. In another word, in-vitro laboratory tests for fibrinogenesis pathway [i.e., prothrombin time (PT), activated partial thromboplastin time, thrombin time (TT), and fibrinogen assay] only represent partial tests evaluating of normal hemostasis, in which ULVWF path participation is completely unaccounted.

Localized thrombotic disorder

Localized arterial or venous thrombosis develops in intravascular endothelial injury, which occurs in extensive surgery, trauma, vascular access steal syndrome, and many others, always extending to the EVT because of the extent and nature of the injury. The damage induces the activation of ULVWF and TF paths (Tables 2 and 3) (*hemostasis principle* 2 and 4). This combined damage leads to local endothelial exocytosis of ULVWF and platelet activation as well as TF release and activation of coagulation cascade. These activated ULVWF and TF paths produce 'macrothrombus'. It is made of comingled unified complexes of microthrombi strings, fibrin-meshes, and blood cells with help of adhesion molecules. Thus, the result of this localized hemostasis is ' true blood clots' as blood cells trapped within the thrombus.

Venous thrombus (i.e., DVT) is a typical example that could occur at venous wound due to external trauma or internal injury sufficient enough to make a localized damage. Thrombus parts may get detached from mother thrombus and travel to the lungs (i.e., pulmonary emboli) and other organs. Perhaps because of slow venous circulation [1], venous thrombus is heavily trapped with blood cells (red/dark clots) and loosely attached to the vessel wall. Localized arterial thrombosis, which incidence is less common compared with DVT, also can develop following internal trauma (e.g., aortic aneurysm-associated thrombus, vascular access steal syndrome, and surgical injury) at arterial vasculature. Arterial thrombus is lightly loaded with blood cells (pale/white clots) and firmly adherent to the vessel wall. Detached emboli may travel to the lower extremity, brain, kidney, and other organs.

Hereditary thrombophilia

Based on 'two-path unifying theory', thrombophilia can be defined as 'passively enhanced thrombogenic state'. Even in hereditary thrombophilia, thrombosis cannot occur without intravascular injury (*hemostasis principle* 1). Intravenous injury involving the endothelium and EVT initiates thrombogenesis and forms 'blood clot' (macrothrombus). Most of the time, in nonthrombophilic person, localized DVT would be spontaneously resolved due to physiological fibrinolytic process. However, hereditary thrombophilia such as FV Leiden, protein C (PC) deficiency, protein S deficiency, and antithrombin (AT) III deficiency would passively enhance the genesis of DVT once vascular injury has occurred in the venous system. This 'enhanced thrombogenic state' is caused by the following mechanisms; activated FV Leiden becomes resistant to activated PC-induced inactivation of FVa Leiden [37]; PC deficiency and protein S deficiency cannot inactivate VIIIa and/or FVa [38]; and AT III deficiency cannot neutralize FIIa, FXa, and FIXa [39]. These mechanisms would create persistent action of FVa Leiden, FVIIIa, FVa, FIIa, FXa, or FIXa, which can be called 'passively enhanced thrombogenic state in TF path', and potentiate the progression of DVT despite of physiologic fibrinolysis.

Focal thrombotic disorder

Focal thrombotic disorder occurs due to focal intravascular endothelial damage (e.g., hereditary endotheliopathy, cholesterol plaque) without damage extending into the EVT. Although the mechanism of hereditary and acquired focal thrombotic disorder is not clearly established at this time, ULVWF path may play a critical role as hereditary endotheliopathies are characterized by vascular occlusive disease and hypoxic organ dysfunction. It is speculated that the release of small amounts of ULVWF could focally activate ULVWF path. At injured focal endothelial sites, 'microthrombi' strings could be formed and result in focal thrombotic syndrome such as retinopathy, nephropathy, myocardiopathy, and stroke (HERNS).

Acquired focal thrombotic syndromes are not uncommon, which includes arterial ischemic stroke syndrome associated with decreased ADAMTS13 level in children, myocardial ischemic syndrome, and perhaps sudden death syndrome in athletes due to sharp multiple cardiac traumas during the sports game, activating hemostatic path. It is likely that focally activated ULVWF path in the brain and heart could cause focal microthrombosis. It also can be multifocal, which can become more serious microthrombosis.

The syndrome can be termed 'focal endotheliopathy' or 'focal VMTD' (Table 2). Hereditary focal VMTD occurs in HERNS syndrome [40]. In addition to the brain and heart, hereditary and acquired focal VMTD can develop in other organs as seen in Susac's syndrome [41] and Degos endotheliopathy [42].

Disseminated vascular microthrombotic disease

There are three different kinds of the disseminated VMTD as follows [43]:

(1) EA-VMTD: TTP-like syndrome
(2) Gene mutation-associated VMTD (GA-VMTD): hereditary TTP
(3) Antibody-associated VMTD (AA-VMTD): autoimmune TTP

VMTD, which hematologic phenotype is consumptive thrombocytopenia, microangiopathic hemolytic anemia (MAHA) and organ dysfunction syndromes, is hemostatic

disorder caused by activated ULVWF path without TF path activation [43]. To make the situation more complicated, EA-VMTD occurs in normal hemostasis due to activated ULVWF path, but GA-VMTD and AA-VMTD occurs in pathologic hemostasis due to activated 'aberrant' ULVWF path. Refer to Table 3 for genesis of TTP.

EA-VMTD (i.e., TTP-like syndrome) is seen in patients with critical illnesses such as sepsis, trauma, complications of pregnancy, surgery and transplant, and drug/toxins, in which complement activation occurs [43–45]. The terminal complex C5b-9 damages the endothelium leading to endotheliopathy, which activates microthrombotic pathways via activated ULVWF path of normal hemostasis. The result is microthrombogenesis at endothelial cells as illustrated in Fig. 2 and it orchestrates multiple clinical phenotypes of DIT.

On the other hand, GA-VMTD and AA-VMTD (i.e., TTP) are seen in patients with ADAMTS13 deficiency due to either hereditary TTP or autoimmune TTP. ADAMTS13 deficiency, which occurs due to decreased production in hereditary TTP and occurs due to autoantibody production in autoimmune TTP, leads to excess of ULVWF in circulation, which triggers pathologic hemostasis through activation of 'aberrant' ULVWF path causing microthrombi formation in microcirculation [46].

Both TTP-like syndrome and TTP produce similar pathological conditions of vascular microthrombosis/microvascular thrombosis; however, the former is through normal hemostasis in endothelial injury and the latter is through pathologic hemostasis without endothelial injury. TTP-like syndrome (i.e., EA-VMTD) is much more common thrombotic disorder than TTP in clinical medicine [11,12,43–45]. 'DIC' that is characterized by vascular microthrombosis that has been erroneously attributed to TF path-activated coagulopathy [47] is found to be the same disorder to TTP-like syndrome [44,45].

For example, for EA-VMTD, pathogen in sepsis provokes the activation of complement as a part of innate immune response, which generates terminal complement complex (C5b-9) to kill the pathogen. If endothelial protectin CD59 of the host were downregulated [48,49], C5b-9 would induce endotheliopathy to the innocent bystander endothelial cells as illustrated in Fig. 2. Endotheliopathy activates the platelet and promotes endothelial exocytosis of ULVWF and triggers activation of ULVWF path of hemostasis, but TF path is not activated as typically EVT damage does not occur in sepsis and critical illnesses [50]. EA-VMTD results in dissemination of large amount of 'microthrombi'. EA-VMTD is also characterized by inflammation, systemic inflammatory response syndrome, multiorgan dysfunction syndrome (MODS), and hematologic phenotype of TTP-like syndrome as shown in Fig. 2. The organ phenotype syndromes of MODS include hemolytic uremic syndrome, acute respiratory distress syndrome, central nervous system dysfunction, fulminant hepatic failure (FHF), MI, pancreatitis, adrenal insufficiency and shock, rhabdomyolysis, many combined syndromes, and others.

Is 'disseminated intravascular coagulation' hemorrhagic syndrome or thrombotic disorder?

The simple answer is 'DIC' is a thrombotic disorder, developing as a result of activated ULVWF path due to endotheliopathy [44], which is consistent with EA-VMTD/DIT. Although this issue has been discussed in recent publications in great detail [11,12,43,44], I will repeat it only briefly for the clinical scientist of hemostasis.

Since coined by McKay [51] in 1950, the contemporary ironclad concept of 'DIC' has been based on activated TF path disorder [52–54]. However, disseminated 'micro blood clots' has been poorly defined and presumed to be composed of platelets and fibrins with participation of coagulation factors. Now, this notion can be easily dispelled by 'two-path unifying theory' of hemostasis as presented in Fig. 1. The medical conditions (i.e., critical illnesses) associated with 'DIC', pathologic findings of DIT, hematologic phenotypes of thrombocytopenia and MAHA, and clinical phenotypes of MODS are the same as TTP-like syndrome. It is no wonder why generalized endotheliopathy does not cause macrothrombosis. This theory firmly supports the contention that 'DIC' is misnomer and it should be renamed as DIT. 'DIC' has been misinterpreted and misrepresented.

The next very important question is how does acute (decompensated, overt) 'DIC' occurs in sepsis and other critical illnesses, as it presents with prolonged prothrombin time (PT) and activated partial thromboplastin time (PTT), hypofibrinogenemia, and elevated fibrin degradation products as well as thrombocytopenia? These features certainly are consistent with activation of both ULVWF path and TF path. Coagulation scientists have tried to decipher 'DIC' mystery using TF encryption/decryption theory [55], thiol path TF regulation theory [56], TF transfer theory [57], and inflammation and coagulation interaction theory [9,52,58–60]. All of them are still controversial.

The explanation for abnormal coagulation profile is EA-VMTD/DIT in sepsis and other critical illnesses leads to microvascular thrombosis in the liver and causes acute hepatic necrosis. Its clinical phenotype includes liver failure [61], hepatorenal syndrome [62,63], and hepatic encephalopathy [63,64], resulting in type 2 acute hepatic coagulopathy (Table 1) [11,12,43,44]. Indeed, the association of hepatic disease in 'DIC' has been well documented by McKay himself [51,65] and many authors in the medical literature [66–68]. It is clear that 'acute DIC' is a combined hemostatic disorder of activated ULVWF

path due to endotheliopathy and activated TF path due to secondary hepatic coagulopathy. That means 'acute DIC' is the misinterpretation for combined thrombohemorrhagic syndrome of EA-VMTD/DIT.

In conclusion, our current understanding of hemostasis is incomplete. However, newly proposed 'two-path unifying theory of hemostasis' offers a clear and logical interpretation of normal hemostasis *in vascular injury*, and clarifies the pathogenesis of every hemorrhagic syndrome and thrombotic disorder through the understanding of the *simple concept of external bodily injury and intravascular injury*. In addition, we also can understand the pathophysiological mechanisms of mucosal hemorrhagic syndrome of VWD, thrombophilia in DVT, genesis of microthrombosis, macrothrombosis and fibrin clots, focal endotheliopathy-associated thrombotic disorder, EA-VMTD, difference between TTP and TTP-like syndrome, and activated 'aberrant' path of hemostasis in atypical thrombotic disorders as well as the mystery of 'DIC'. Finally, through the novel concept of hemostasis based on 'two-path unifying theory', the pathophysiological mechanism of hemorrhagic disease/syndrome and thrombotic disorder can be merged together. Our next task is how we can utilize this conceptual framework in designing the prevention and therapeutic intervention of hemostatic disorders.

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Conflicts of interest

J.C.C., MD has neither actual nor potential personal or financial conflicts of interest in regard to this article.

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