Involvement of Inflammation in Venous Thromboembolic Disease: An Update in the Age of COVID-19

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Abstract

The inflammatory process is strongly involved in the pathophysiology of venous thromboembolism (VTE) and has a significant role in disease prediction. Inflammation most probably represents a common denominator through which classical and nonclassical risk factors stimulate thrombotic process. Inflammation of the venous wall promotes the release of tissue factor, inhibits the release of anticoagulant factors, and hampers endogenous fibrinolysis. Systemic inflammatory response also inhibits restoration of blood flow in the occluded vessel. Recent studies indicate that increased inflammatory response ("cytokine storm") is related to prothrombotic state and thromboembolic events in patients with coronavirus disease 2019 (COVID-19). The growing evidence of involvement of inflammation in the pathogenesis of VTE indicates the importance of anti-inflammatory treatment and prevention of VTE. While aspirin was shown to be effective in prevention of recurrent venous thrombosis after treatment with anticoagulant drugs, some other anti-inflammatory drugs like nonsteroidal anti-inflammatory agents may have prothrombotic effect, thus potentially increasing the risk of VTE. Recently, new specific anti-inflammatory drug inhibitors of inflammatory markers that have been shown to be involved in the pathogenesis of VTE are being searched. As thrombogenesis is based on activation of coagulation provoked by inflammation, then prevention and treatment of VTE should include both anticoagulant and anti-inflammatory agents. Combined treatment is related to increased risk of bleeding complications, therefore subtherapeutic doses of both drugs should be used to improve the efficacy of management of VTE without increasing the risk of bleeding.

Keywords
- inflammation
- venous thromboembolism
- risk factors
- COVID-19
- anti-inflammatory treatment

Systemic inflammation represents a potent prothrombotic stimulus. It is well known that inflammation is involved in the pathogenesis of atherothrombosis and recently it has been shown that inflammation also represents one of the basic pathogenetic mechanisms of venous thromboembolism (VTE). Inflammation most probably represents a common denominator through which different risk factors damage vessel wall, evoke inflammation, and trigger thrombus formation.[1,2]

Not only mechanical factors (turbulent blood flow) but also biochemical factors, in combination with a procoagulant state, stimulate thrombus formation. Inflammation of the vessel wall, which is usually induced by vessel wall injury, activates the coagulation system through an increase of tissue

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Table 1 Procoagulant effects of inflammation

Mechanisms	Procoagulant effects
Activation of inflammatory cells	
Platelets	Release of polyphosphate from dense granules: • Activation of FV, FXII. • Inhibition of TFPI activity. • Activation of TAFI.
Neutrophils	NETS formation: • Activation of FXI, FXII. • Impairment of thrombomodulin-dependent protein C activation. • Inhibition of TFPI.
Activation of procoagulant factors	Direct activation of TF driven coagulation pathways
Microparticles formation	Release of PSGL-1: • Activation of TF.
Endothelial damage	Endothelial dysfunction and loss of antithrombotic properties

Abbreviations: NET, neutrophil extracellular trap; PSGL-1, P-selectin glycoprotein ligand-1; TAFI, thrombin activatable fibrinolysis inhibitor; TF, tissue factor; TFPI, tissue factor pathway inhibitor.

factor expression. Inflammatory diseases, such as inflammatory bowel disease, some rheumatic diseases, and cancer lead to increased release of inflammatory cytokines that stimulate coagulation and platelet activation. Inflammation also damages the endothelium, which consequently loses its anticoagulant properties and triggers blood coagulation.[3] Further, increased thromboembolic risk of coronavirus disease 2019 (COVID-19) is associated with inflammatory response when elevated levels of pro-inflammatory cytokines cause damage to endothelium and lead to prothrombotic endothelial dysfunction.[4]

Therefore, systemic inflammation is a potent prothrombotic stimulus which upregulates procoagulant factors, downregulates natural anticoagulants, and inhibits fibrinolytic activity.

In patients with COVID-19, especially in the critical form of disease, an exaggerated inflammatory response defined as a "cytokine storm" has been reported.[5] This resembles other hyperinflammation syndromes, falling into the broader definition of cytokine release syndrome.

Interrelationship between Inflammation and Coagulation

Thrombus formation is attributed to three main groups of factors, including alteration in blood flow, endothelial injury, and hypercoagulable state, which contribute to the well-known Virchow's triade.[6] Recently, a growing body of evidence suggests a role of inflammation as a major contributor to pathogenesis of VTE,[7] by enhancing the hypercoagulable state and causing endothelial damage. The key event in the initiation of VTE is most probably venous wall inflammation. Thrombus formation starts with activation and damage of endothelial cells, platelets, and leukocytes which subsequently initiate inflammation and microparticle formation that trigger the coagulation system through the stimulation of tissue factor (TF) release. Monocytic TF and activation of the intrinsic pathway with neutrophils promote thrombus formation.[4]

Neutrophils represent important but under-recognized players, not only in the immune system as launching the first line of defense against invading microorganisms, but also promoting coagulation. Activated neutrophils release their decondensed chromatin as a network of extracellular fibers—neutrophil extracellular traps (NETs).[8] NETs are composed of DNA and histones that exert antimicrobial properties.[9] Further, NETs also stimulate the activation of coagulation (both extrinsic and intrinsic pathways) and platelet adhesion. Chromatin network activates coagulation also through binding of factor XII and XI, impairs thrombomodulin-dependent protein C activation, and inhibits TF pathway inhibitor.[10]

The link between coagulation and inflammation is also supported by polyphosphate, which is present in human platelet dense granules and released upon platelet activation. Polyphosphate stimulates coagulation by increasing activation of factor V, decreasing TF pathway inhibitor (TFPI) activity, and delaying clot lysis by activation of thrombin activatable fibrinolysis inhibitor (TAFI).[11] Inflammatory markers increase the number of microparticles through leukocyte activation and concentration of TF at particle surfaces. Microparticles bearing TF and P-selectin glycoprotein ligand-1 (PSGL-1) allow TF to express coagulant activity[12] (►**Table 1**, ►**Fig. 1**). Recently, an association between VTE and several markers of inflammation such as C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor α (TNFα) has been demonstrated.[2,13] These pro-inflammatory cytokines play an important role in pathogenesis of VTE by promoting a procoagulant state primarily by inducing TF expression. Several immune system components (cytokines, chemokines, and various leukocyte subtypes) are involved in the inflammatory process of VTE.[14] Additionally, other inflammatory mediators such as polyphosphates and bradykinin may directly activate TF driven coagulation pathways.[15]

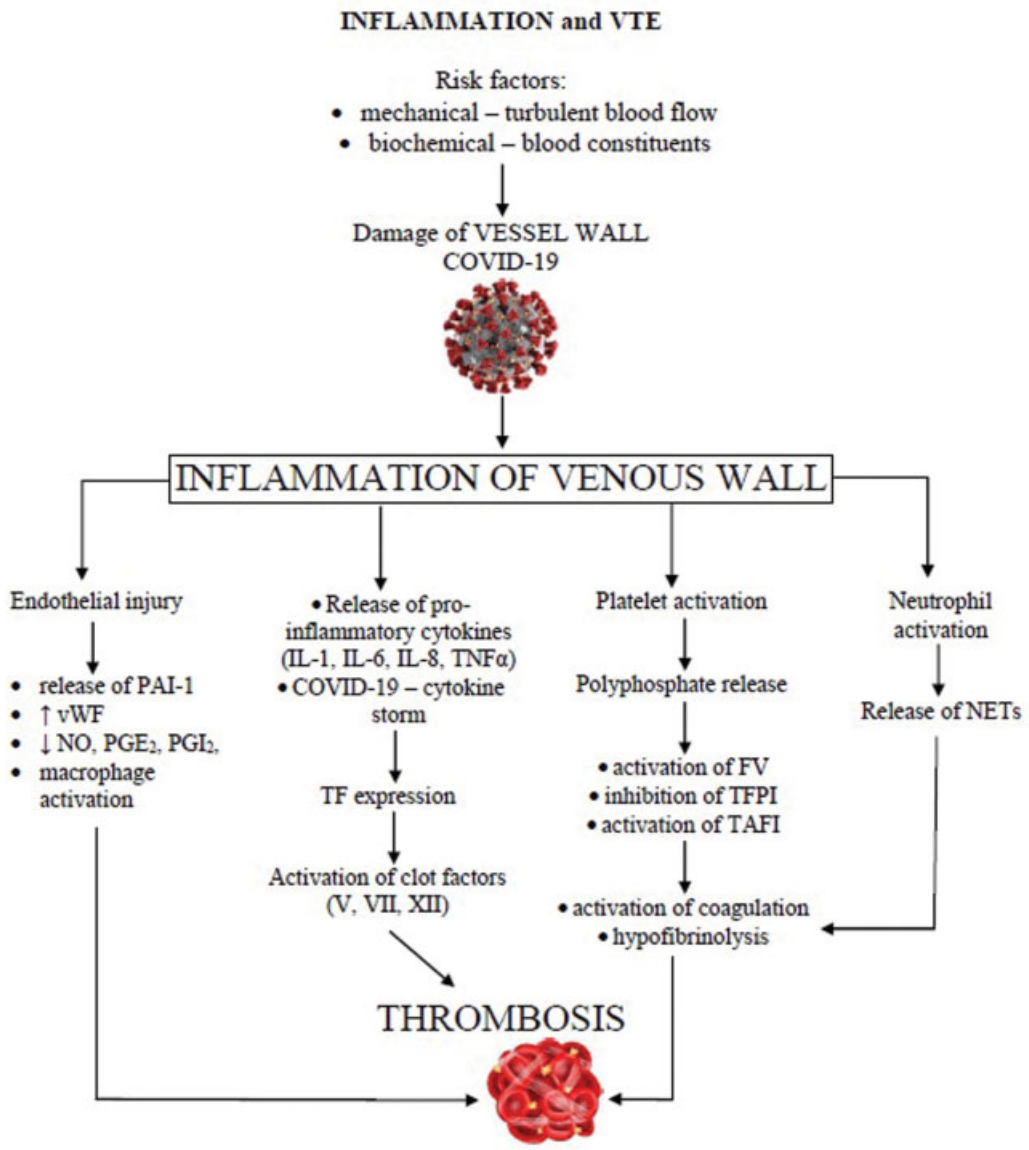

Fig. 1 Involvement of inflammation in venous thrombosis. IL-1, IL-6, IL-8, interleukins; TAFI, thrombin activatable fibrinolysis inhibitor; TFPI, tissue factor pathway inhibitor; TNFα, tumor necrosis factor α; VWF, von Willebrand factor; VTE, venous thromboembolic disease.

The relationship between inflammation and VTE is supported by increased levels of markers of inflammation such as CRP, IL-6, IL-8, and TNF-α.[16,17] One study showed that patients with idiopathic venous thrombosis in stable phase (3–4 months after acute disease) have increased levels of circulating markers of inflammation (CRP, IL-6, IL-8); also, anti-inflammatory interleukin-10 (IL-10) was significantly decreased. This would indicate that patients still had increased systemic inflammatory responses after the acute phase of disease. Increased inflammatory markers were related to markers of endothelial dysfunction.[18] To elucidate the dilemma if increased levels of inflammatory markers in patients with VTE are active players or simple bystanders, this group of patients was followed up for 4 years. In patients without a complete recanalization of previously occluded veins, inflammatory markers (CRP, IL-8) were increased, and anti-inflammatory IL-10 was again decreased. This indicates that a systemic inflammatory response is most probably not the consequence of the disease but is actively involved in its pathogenesis.[19] These results confirmed that the inflammatory markers, particularly pro-inflammatory cytokines, are involved in the pathogenesis of VTE by promoting a procoagulant state.[14]

Therefore, there is an extensive crosstalk between coagulation and inflammation, whereby activation of one system may amplify activation of the other.[20] Vice-versa coagulation processes stimulate inflammatory responses. TF triggers not only the generation of active coagulation factors, but also induces protease-activated receptor-mediated signaling, which stimulates the release of more inflammatory cytokines, activates leukocytes and vascular cell adhesion molecules and suppresses vasoprotective molecules, such as thrombomodulin.[21] Therefore, activated coagulation proteases stimulate specific

receptors on inflammatory cells and endothelial cells and thereby modulate the inflammatory response.[22]

The Relationship between Inflammation, Coagulation Factor XII and Thrombosis

The crosstalk between coagulation and inflammation is further indicated by the activity of factor XII driven contact pathway, which is involved in coagulation and inflammation via the intrinsic pathway of coagulation and the bradykinin-producing kallikrein–kinin system.[23] Coagulation factor XII is plasma protein, and the zymogen form of factor XIIa, an enzyme of the serin protease class. In vitro, FXII is activated to FXIIa after binding to negatively charged surfaces, such as glass. In vivo, FXII is activated by contact with polyanions. Contact to polyphosphates released by activated platelets activates FXII and this then promotes fibrin formation via the intrinsic pathway of coagulation.[24] FIIa cleaves plasma kallikrein and generates active kallikrein which in turn reciprocally activates additional FXII. Besides activation of the intrinsic pathway of coagulation, this process also liberates the inflammatory mediator bradykinin by kallikrein-mediated cleavage of high molecular weight kininogen.[24] Therefore, excessive FXII activity is associated with a life-threatening inflammatory disorder called hereditary angioedema. The contact system and its activator polyphosphate have been recognized as important contributors to thromboembolic and inflammatory disorders. On the other hand, balanced and targeting FIIa and polyphosphate interferes with the polyphosphate/FXII axis, providing safe thromboprotection and anti-inflammatory activity. Therefore, polyphosphatase may serve as a potent anti-inflammatory agent in reducing FIIa-driven complement and bradykinin effects.[25]

Inflammation and Fibrinolysis

Inflammation is involved in initiation and resolution of venous thrombi. Neutrophils in venous thrombus play a critical role during the early phase of venous thrombus resolution and collagen lysis.[26,27] In addition, neutrophils facilitate the recruitment of monocytes into the thrombus, where they produce various chemokines and matrix-degrading proteases and stimulate thrombus resolution. In contrast, some inflammatory markers, particularly interleukins (e.g., IL-6) inhibit fibrinolysis and can be involved in fibrotic reorganization of thrombus. In the study of Nosaka and coworkers, it was shown that neutralization of IL-6 with specific antibodies accelerated thrombus resolution and decreased vein wall fibrosis.[28] One of our studies, which included patients with superficial venous thrombosis where the recanalization rate and extent of thrombus was followed up to 1 year, showed that the recanalization rate is negatively associated with level of inflammatory biomarkers. Patients with a lower recanalization rate had increased levels of CRP, IL-6, and TNF-α.[29] In contrast, administration of exogenous TNF-α accelerated thrombus resolution in mice and TNF-α antibody (TNF-α inhibitor) retarded venous thrombus resolution.[28]

In tissue injury and disease, the proteases that activate factor X and VII (to FXa, FVIIa), thrombin, plasmin and tissue plasminogen activator (t-PA) not only participate in coagulation or fibrinolysis but also mediate inflammation and tissue remodeling.[30] TNFα and IL-1 decrease t-PA levels in human umbilical vein endothelial cells.[31] Recent evidence also suggests that plasminogen-activator inhibitor-1 (PAI-1) is tightly associated with inflammation and that PAI-1 levels are locally enhanced in inflammatory sites of vessel wall.[32]

COVID-19, VTE, and Inflammation

Recent findings indicate that there is increased risk of VTE associated with COVID-19. COVID-19-related VTE is associated with higher risk of morbidity and mortality.[33] Meta-analysis has shown that thromboembolism significantly increases the odds of mortality of COVID-19, which can be as high as 74%.[33] Risk factors of thromboembolic complications in patients with the COVID-19 have not been completely elucidated. A meta-analysis of studies that reported thromboembolisms in patients with COVID-19 showed that increasing age was associated with a higher prevalence of VTE and pulmonary embolism, while increased body-mass index was associated only with increased prevalence of pulmonary embolism.[34] The mortality of patients with COVID-19 is related to the seriousness of the disease. Data from the RIETE registry (Registro Informatizado della Enfermedad ThromboEmbolica) showed that 10-day mortality among patients at a hospital ward was 9.1% whereas it was 19.0% among those treated in intensive care units.[35] To reduce thromboembolism occurrence, thromboprophylaxis in patients hospitalized because of COVID-19 is now well established. The studies also showed that post-discharge thromboprophylaxis is beneficial, particularly in higher risk patients, and revealed lower incidence of VTE.[36]

There exist different mechanisms through which COVID-19 contributes to elevated thromboembolism risk. Most probably, systemic inflammatory processes represent the basic mechanism of increased prothrombotic state. Abnormally elevated levels of pro-inflammatory cytokines (cytokine storm) have been found in COVID-19 patients.[37] Several studies suggested that cytokines levels, particularly IL-1, TNF-α and IL-6 correlated directly with lung injury and multiple organ failure.[38] The increased systemic inflammation causes endothelial injury and leads to pro-thrombotic endothelial dysfunction.[39] One recent autopsy study found that almost no organ in the body is saved from thrombosis.[40] Significant macrovascular and microvascular thrombosis was found in multiple organs. As the disease progresses, widespread thrombosis and multiorgan dysfunction syndrome appear.[41]

The rates of VTE in COVID-19 patients are higher than in other viral pandemics experienced in the past,[42] and there is a correlation between disease severity and the risk of thromboembolism among SARS-CoV-2 infected individuals. Higher infectious dose is followed by active and prolonged viral replication in pneumocytes, macrophages and other immune cells.[43]

Activation of coagulation during virus infections could be the consequence of increased platelet adhesion and aggregation, and high release of inflammatory cytokines

("cytokine storm").[44] The enhanced cytokine production also stimulates procoagulant reactions, with increased TF expression, a major initiator of the coagulation. Thrombin, which leads to fibrin formation, enhances platelet activation and alters fibrinolysis, both of which are also major mediators of inflammatory response. As inflammation results in further TF expression, thrombin generation represents initiation of a vicious cycle, which promotes the procoagulant state.[23,45] Neutrophil extracellular traps and damage-associated molecular patterns may also be involved in the procoagulant profile in patients with COVID-19.[46]

Inflammation Therapeutic Target in the Management of VTE

Anticoagulation therapy represents an effective option in preventing VTE and the propagation of VTE events. However, not only prevention of thrombus propagation but faster resolution of the thrombus is the key for improvement of disease prognosis. As inflammation represents one of the basic pathogenetic mechanism of VTE and is involved in thrombolysis and elimination of thrombus, it is expected that inhibition of inflammation, together with anticoagulation, may improve the efficacy of prevention of thromboembolic events and induce recanalization of thrombotic occlusions of veins.[47] One of the first drugs which was used for the prevention of VTE was aspirin, which also has anti-inflammatory properties.[48] It was shown that in higher-risk medical or surgical patients, aspirin reduces the incidence of VTE. However, the evidence of efficacy of aspirin in the primary prevention of VTE was too weak for general recommendation to use aspirin in the primary prevention of VTE.[49]

However, recent studies and meta-analysis have shown that aspirin is effective in the prevention of recurrent VTE as extended treatment of patients who completed initial anticoagulant treatment. The INSPIRE collaboration study showed that aspirin, after anticoagulant treatment of patients with the first unprovoked VTE, reduces the overall risk of VTE reoccurrence by more than one-third, without significantly increasing the risk of bleeding.[50] In another study where aspirin was compared to placebo, aspirin did not significantly reduce the rate of recurrent VTE, but it significantly reduced the rate of major vascular events. This result shows that in patients, aspirin may have some antithrombotic therapeutic benefits[51] after initial anticoagulant therapy with unprovoked venous thrombosis, which is presumably based on its anti-inflammatory activity.

Although the studies highlight the importance of inflammation in pathogenesis of VTE and anti-inflammatory treatment for prevention and management of patients with thrombotic diseases, the studies indicated that the effects of anti-inflammatory drugs on coagulation and thrombus formation differ. It was shown that nonsteroidal anti-inflammatory drugs (NSAID) or cyclooxygenase-2-selective (COX-2) inhibitors increase the risk of VTE.[52] A recent meta-analysis indicated that NSAID users have 1.8-times higher risk for VTE.[53] As a relationship between some inflammatory markers (interleukins, selectins) and VTE was shown, the interest for the search of new anti-inflammatory drugs (which are also inhibitors of inflammatory markers) is growing. P-selectin, which is involved in the pathophysiology of VTE, has stimulated researchers to evaluate the ways of its inhibition.[54] It was shown that P-selectin inhibition promotes thrombus resolution and prevents vein wall fibrosis. In a model of murine thrombosis induction, P-selectin inhibition with its inhibitor has been shown to decrease inflammation and reduce the risk for VTE.[11] Interleukin and TNF-α inhibitors have shown effectiveness in prevention of atherosclerotic cardiovascular events.[55] Therefore, they are being investigated as potential drugs also for the prevention and treatment of VTE.

In COVID-19 patients beside anticoagulant drugs also antiplatelet agents such as aspirin, ticagrelor, and dipyridamole drugs for the prevention of thrombosis are used and preliminary results showed that they could be effective.[56]

Further, drugs with a pleiotropic anti-inflammatory effect like statins are reported to reduce the occurrence of VTE.[57] Therefore, current evidence would support a favorable effect of statins as adjuvant therapy in patients with COVID-19.[58] Statins have shown anti-inflammatory effects in rodent models of thrombosis with the reduction of inflammatory biomarkers, including cytokines and P-selectins, neutrophil, and macrophage infiltrations within the thrombi and vessel wall.[59]

Heparins also have reported to have anti-inflammatory properties and reduce different mediators of inflammation.[60] Heparins reduced inflammation in relation to their ability to inhibit factor Xa and thrombin.[61] Newer direct oral anticoagulants (DOACs) have also shown direct anti-inflammatory potential.[62] It may explain their profibrinolytic potential and higher recanalization rates of VTE in DOAC anticoagulated patients compared to warfarin.[63]

Conclusion

There is an extensive crosstalk between coagulation and inflammation. Inflammation promotes prothrombotic state through TF expression, thrombin generation, inhibition of release of anticoagulant factors, and activation of inflammatory cells. Further, inflammation inhibits endogenic fibrinolysis and causes prothrombotic endothelial dysfunction. Vice-versa, activation of the coagulation system may importantly affect inflammatory response by different mechanisms. In patients with COVID-19, an intensive inflammatory response known as "cytokine storm" is most probably responsible for the hypercoagulable state leading to widespread thrombosis.

As inflammation represent one the basic pathogenetic mechanisms of VTE, it is expected that inhibition of inflammation together with anticoagulation may improve efficacy of prevention and treatment of thromboembolic events. Therefore, recent interest for searching new anti-inflammatory drugs, particularly inhibitors of inflammatory markers, is growing.

Conflict of Interest
None declared.

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