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Review Article

Involvement of Inflammation in Venous Thromboembolic Disease

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Abstract

Recent evidence has been established that the inflammatory process is involved in the pathophysiology of Venous Thrombotic Events (VTE) and may have a significant role in prediction of the disease. It is likely that classical and non-classical risk factors modulate thrombosis through inflammatory mediators. Inflammation of the venous wall promotes the release of tissue factor inhibit the release of anticoagulant factors and hamper endogenous fibrinolysis. Recent studies also indicated that increased inflammatory response (interleukin storm) is related to prothrombotic state and thromboembolic events in patients with COVID-19. Inflammatory markers are also negatively related to thrombolysis and restoration of blood flow in the acute phase of Venous Thrombosis (VT). Despite the growing evidence of the involvement of inflammation in pathogenesis of VTE, the importance of anti-inflammatory treatment of this disease was overlooked. Aspirin was shown to be effective in the prevention of recurrent venous thrombosis after treatment with anticoagulant drugs. Some anti-inflammatory drugs like nonsteroidal anti-inflammatory agents may have prothrombotic effect and increase risk of VTE. Therefore, the recent research was dedicated to searching new specific anti-inflammatory drug inhibitors of inflammatory markers, which were shown to be involved in the pathogenesis of VTE. As thrombus formation is based on the activation of coagulation system, provoked by inflammation, prevention and treatment of VTE, should include both anticoagulant and anti-inflammatory agents. To reduce bleeding complications of combined treatment, sub-therapeutic doses of both drugs should be used to improve the efficacy of management of VTE without increasing risk of bleeding.

Keywords: Inflammation; Venous thromboembolic events; Risk factors for thrombosis; COVID-19; Anti-inflammatory treatment

Introduction

The role of inflammation in the etiopathogenesis of arterial thrombosis has been elucidated. However, less is known about the relationship between inflammation and venous thrombosis. Recently, inflammation has been shown to be pathogenetic mechanism also in VTE through which different risk factors trigger thrombus formation in veins [1,2]. Inflammation of the vessel wall, which is usually induced by vessel wall damage, stimulates the coagulation system. Not only mechanical factors (turbulent blood flow) but also biochemical factors, in combination with a pro-coagulant state, provoke thrombus formation. Disease processes with inflammatory components such as cancer, inflammatory bowel disease and some rheumatic diseases lead to increased release of inflammatory cytokines that stimulate coagulation cascade and platelet activation. Inflammation also damages endothelium, which consequently loses its anticoagulant properties and provokes blood coagulation [3]. Further increased thromboembolic risk of Coronavirus Disease 2019 (COVID-19) is associated with inflammatory response and elevated levels of pro-inflammatory cytokines which cause damage of endothelium and leads to pro-thrombotic endothelial dysfunction [4].

Interrelationship between Inflammation and Hemostasis

Thrombus formation is attributed to three main groups of factors including alteration in blood flow, endothelial injury and hypercoagulable state, known as Virchow's triade [5]. Recently, growing body of evidence suggests a role of inflammation as a major contributor to pathogenesis of VTE [6], by enhancing the hypercoagulable state and increasing endothelial damage. The key event in the initiation of VT is most probably vein wall inflammation. Thrombus formation most probably 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 induction of Tissue Factor (TF) release. Monocytic TF and activation of the intrinsic pathway with neutrophils promote thrombus formation [4]. The link between coagulation system and inflammation is also supported by polyphosphate, which is present in human platelet dense granules and is released upon platelet activation. It stimulates coagulation by increasing activation of factor V, decreasing Tissue Factor Pathway Inhibitor (TFPI) activity, and delaying load lyses by activation Thrombin Activatable Fibrinolysis Inhibitor (TAFI) [7]. Inflammatory markers increase the number of micro particles through leukocyte activation and concentration of tissue factor on the particle surface. Microparticles bearing tissue factor and P-Selectin Glycoprotein Ligand-1 (PSGL-1) [8]. Recently, it was demonstrated that there exists an association between VTE and several markers of inflammation such as C-Reactive Protein (CRP), IL-6, IL-8, and

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tumor necrosis factor α [2,9]. These pro-inflammatory cytokines play an important role in VTE by promoting a pro-coagulant state primarily by inducing the expression of tissue factor. Several immune system components (cytokines, chemokines and various leukocyte sub-types) are involved in the inflammatory process of VTE [10]. Additionally, inflammatory mediators such as polyphosphates, bradykinin, and others may directly activate the extrinsic coagulation pathway [11].

The involvement of inflammation in the pathogenesis of VT is supported by increased levels of markers of inflammation such as C-Reactive Protein (CRP), Interleukin-6 (IL-6) and Interleukin-8 (IL-8) and Tumor Necrosis Factor alpha (TNF-α) [12,13]. In one of our studies, it was shown that patients with idiopathic venous thrombosis in its stable phase (3-4 months after acute disease) have increased levels of circulating markers of inflammation (CRP, IL-6, IL-8). In this group of patients with idiopathic venous thrombosis also anti-inflammatory interleukin-10 was significantly decreased. It indicates that patients in the stable phase of the disease had an increased systemic inflammatory response, which was related to markers of endothelial dysfunction [14]. To elucidate the dilemma if increased levels of inflammatory markers in patients with VTE are consequence of the disease or the cause, this group of patients was followed up for 4 years and in patients with or without complete recanalization of previously occluded veins, inflammatory markers (CRP, IL-8) were increased and anti-inflammatory IL-10 was again decreased. It indicates that a systemic inflammatory response is most probably not the consequence of the disease but is involved in its pathogenesis [15]. The inflammatory markers, particularly pro-inflammatory cytokines, play an important role in pathogenesis of VTE by promoting a pro-coagulant state, primarily by inducing the expression of tissue factor [10].

Therefore, it is an extensive crosstalk between coagulation and inflammation. Whether by, activation of one system may amplify activation of the other [16]. Coagulation process also stimulates inflammatory response. Tissue factor triggers not only the generation of coagulation factors, but it induces Protease-Activated Receptor (PAR) - mediated signaling, with release of more inflammatory cytokines, abregulate leukocytes and vascular cell adhesion molecules and suppress vasculo-protective molecules, such as thrombomodulin [17]. Therefore, activated coagulation proteases may affects specific receptors on inflammatory cells and endothelial cells and thereby modulate the inflammatory response [18].

Inflammation and Fibrinolysis

Inflammation plays a central role in initiation and resolution of venous thrombi. Neutrophils infiltrate the venous thrombus early and play a critical role during the early phase of venous thrombus resolution and collagen lysis [19,20]. Neutrophils also facilitate the recruitment of monocytes into the thrombus, where they produce various chemokines and matrix-degrading proteases and stimulate thrombus resolution. However, inflammatory markers, particularly Interleukins (interleukin-6) inhibit fibrinolysis and have been linked to fibrotic reorganization of thrombus. The neutralization of IL-6 with antibodies was shown to accelerate thrombus resolution and decrease vein wall fibrosis [21]. In the study which included patient with superficial venous thrombosis where the recanalization rate and extent of thrombus was followed up to 1 year, it was shown that the recanalization rate was negatively correlated with levels of inflammatory markers. Patients with a lower recanalization rate had increased levels of CRP, IL-6 and TNF-α [22]. In contrast, TNF-α antibody or TNF-α inhibitor (ETANER-OEPT) inhibited venous thrombus resolution [21].

In tissue injury and disease, the proteases FXa, FVIIa, thrombin, plasmin and tissue Plasminogen Activator (tPA) not only participate in coagulation or fibrinolysis but also mediate inflammation and tissue remodeling [23]. TNFα and IL-1 decrease tPA levels in human umbilical vein endothelial cells [24]. Recent evidence also suggests that PAI-1 is tightly associated with inflammation and that PAI-1 levels are locally enhanced in inflammatory cites [25].

COVID-19, VTE, and Inflammation

Recent findings indicate that there is increased risk of VTE associated with corona virus disease (COVID-19). Covid related VTE is associated with higher risk of morbidity and mortality [26]. Meta-analysis showed that thromboembolism significantly increase the odds of mortality of covid patients by as high as 74%. There exist different mechanisms through which COVID-19 contribute to elevated thromboembolism risk. Most probably, systemic inflammatory process represents the basic mechanism of increased pro-thrombotic state. Abnormally elevated levels of pro-inflammatory cytokines (cytokines storm) have been found in patients infected with novel coronavirus [27]. Several studies suggested that cytokines levels, particularly IL-1, TNF-α and IL-6 correlated directly with lung injury and multi-organ failure [28]. The increased systemic inflammation complete with endothelial injury leads to pro-thrombotic endothelial dysfunction [29]. The recent autopsy study found that almost no organ in the body is spared to thrombosis [30]. Significant macrovascular and microvascular thrombosis was found in multiple organs. The rates of VTE in covid patients are higher than in other viral pandemics experienced in the past [31], and there is correlation between disease severity and the risk of thromboembolism among covid infected individuals. It could be the consequence of increased platelet adhesion and aggregation, and high release of inflammatory cytokines (cytokines storm) that activate the coagulation cascade [32]. The enhanced cytokine production during virus infections also stimulates pro-coagulant reactions, with increased tissue factor expression, a major initiator of the coagulation. Thrombin which leads to fibrin formation, enhanced platelet activation, alters fibrinolysis are the major mediators of inflammatory response. As inflammation results in further tissue factors expression, thrombin generation represents initiation of vicious circle, which promote pro-coagulant state [33]. Neutrophil extracellular drops and damage-associated molecular patterns may also be involved in the pro-coagulant profile in patients with COVID-19 [34].

Inflammation Therapeutic Target in Management of VTE

In the recent clinical setting, anticoagulation therapy represents a successful option in preventing the propagation of venous thromboembolic events. However, not only prevention of thrombus propagation but faster resolution of the thrombus is the key for the improvement of disease prognosis. Inflammation most probably represents 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 stimulate recanalization of thrombotic occlusions of veins [35]. In the past, for the prevention of VTE, aspirin, which also has anti-inflammatory properties, was used. When given for antithrombotic prophylaxis in higher-risk medical or surgical patients, aspirin was shown to reduce the incidence of venous thromboembolism in some clinical studies. However, the evidence of efficacy of aspirin in the primary prevention of venous thromboembolism was too weak for general recommendation to use aspirin in the primary prevention of VTE [36].

In contrast, recent studies and meta-analysis indicated 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 1/3, without significantly increasing the risk of bleeding [37]. In the study of Brighton, et al. aspirin, as compared to placebo, did not significantly reduce the rate of recurrence of venous thromboembolism, but resulted in a significant reduction in the rate of major vascular events. This indicates that aspirin, when it is given to patients after initial anticoagulant therapy of unprovoked venous thrombosis, is of therapeutic benefit [38]. Antithrombotic effect of aspirin based on its anti-inflammatory activity.

The results of these studies point out the importance of anti-inflammatory treatment for prevention and management of patients with VTE. However, the studies indicated that effects of anti-inflammatory drugs on coagulation and thrombus formation differ. It was shown that nonsteroidal anti-inflammatory drugs or Cyclooxygenase-2-selective inhibitors (COX-2) increase risk of VTE [39]. A recent systemic review and meta-analysis indicated that the risk ratio among Non-Steroid Anti-Inflammatory Drugs (NSAID) users is 1.8-times for VTE [40]. As a relationship between some inflammatory markers (interleukins, selectins) and VTE was shown, the interest for searching new anti-inflammatory drugs - inhibitors of inflammatory markers, are growing. The pivotal role of P-selectin in the pathophysiology of venous thrombosis has prompted researchers to evaluate different ways of inhibiting this pathway [41]. P-selectin inhibition promotes thrombus resolution and prevents vein wall fibrosis. In a model of murine thrombosis induction, a selectin inhibition with its inhibitor has been shown to decrease inflammation and venous thrombosis [7]. As the studies with interleukins and tumor necrosis factor-alpha inhibitors indicated to be effective in prevention of atherosclerotic cardiovascular events [42], recently are investigated as potential drugs for prevention and treatment of VTE.

In COVID-19 patients beside anticoagulant drugs also antiplatelet agents such as aspirin, ticagrelor and dipyridamole drugs for prevention of thrombosis are used and preliminary results showed that they could be effective [43].

Further, drugs with a pleiotropic anti-inflammatory effect like statins are reported to reduce the occurrence of VT [44]. 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 [45].

Heparins also have reported to have anti-inflammatory properties and act to reduce several components of inflammation [46]. Heparins also reduced inflammation through their ability to inhibit factor-Xa and thrombin [47].

New oral anticoagulants NOACs also showed direct anti-inflammatory potential [48] which may explain higher recanalization rate of VTE than warfarin [49].

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