

# Inflammation and venous thromboembolic disease

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## Abstract

Recent evidence has been established that the inflammatory process is involved in the pathophysiology of 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, whereas other coagulation factors inhibit the release of anticoagulant factors and hamper endogenous fibrinolysis. Inflammatory markers are also negatively related to thrombolysis and restoration of blood flow in the acute phase of the disease. 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 NSID may have negative 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.

## 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 accepted as possible mechanism 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, including inflammatory components such as cancer, inflammatory bowel disease and some rheumatic diseases lead to increased release of inflammatory cytokines that may stimulate platelet activation and damage of endothelium, which consequently loses its anticoagulant properties and provokes blood coagulation [3].

## Interrelationship between inflammation and haemostasis

The first event in thrombus formation is most probably activation of endothelial cells, platelets and leukocytes with formation of micro particles that trigger the coagulation system through the induction of tissue factor (TF). Monocytic TF and activation of the intrinsic pathway with neutrophils promote thrombus formation [4]. Therefore the key event in the initiation of VT is most probably vein wall inflammation. The involvement of inflammation in the pathogenesis of VT is also supported by markers of inflammation such as C-reactive protein (CRP), interleukin-6 (IL-6) and interleukin-8 (IL-8) and tumour necrosis factor alpha (TNF- $\alpha$ ) [5,6]. In one of our studies it was shown that patients with idiopathic venous thrombosis in its stable phase have increased levels of circulating markers of inflammation (CRP, IL-6, IL-8). 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 [7]. In this group of patients with idiopathic venous thrombosis also anti-inflammatory interleukin-10

was significantly decreased. 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 were significantly decreased. It indicates that a systemic inflammatory response is most probably not the consequence of the disease but is involved in its pathogenesis [8]. 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 [9].

## 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 collagenolysis [10,11]. 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), have been linked to fibrosis and inhibit fibrinolysis. The neutralisation of IL-6 with antibodies was shown to accelerate thrombus resolution and decrease vein wall fibrosis [12]. In the study which included patient with superficial venous thrombosis

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**Key words:** Pathogenesis of thrombosis, thrombolysis, inflammatory markers, anti-inflammatory drugs

**Received:** January 07, 2019; **Accepted:** January 14, 2020; **Published:** January 17, 2020

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-alpha [13].

### 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, 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. 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 [14]. 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 [15].

In contrast, recent studies and meta-analysis indicated that aspirin is effective in the prevention of 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 recurrence by more than 1/3, without significantly increasing the risk of bleeding [16]. 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 [17].

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 [18]. A recent systemic review and meta-analysis indicated that the risk ratio among NSAID users is 1.8-times for VTE [19]. 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 [20]. 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 [21]. As the studies with interleukins and tumour necrosis factor-alpha inhibitors indicated to be effective in prevention of atherosclerotic cardiovascular events [22], recently are investigated as potential drugs for prevention treatment of VTE.

Further, drugs with a pleiotropic anti-inflammatory effect like statins are reported to reduce the occurrence of VT [23]. 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 [24].

Heparins also have reported to have anti-inflammatory properties and act to reduce several components of inflammation [25]. Heparins also reduced inflammation through their ability to inhibit factor-Xa and thrombin [26].

### Authorship and contribution

This review was written by single author – Pavel poredoš, who collected the data from published papers and findings from his research group.

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