

## Mechanistic View of Risk Factors for Venous Thromboembolism

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**Abstract**—Venous thromboembolism is an episodic disease with an annual incidence of 2 to 3/1000 per year that is associated with a high morbidity and mortality. Risk factors for venous thromboembolism come in many guises. They fit into an extended version of Virchow's triad and they tilt the hemostatic balance toward clot formation. This can be achieved by decreasing blood flow and lowering oxygen tension, by activating the endothelium, by activating innate or acquired immune responses, by activating blood platelets, or by increasing the number of platelets and red blood cells or modifying the concentrations of pro- and anticoagulant proteins in the blood. In this narrative review we will discuss the known common risk factors within this pathophysiological framework. (*Arterioscler Thromb Vasc Biol.* 2012;32:563-568.)

**Key Words:** endothelium ■ platelets ■ pulmonary embolism ■ risk factors ■ Venous thrombosis

Venous thromboembolism (VTE) is the third most common vascular disease after myocardial infarction and ischemic stroke. The annual incidence of symptomatic and objectively confirmed VTE, the collective term generally used for deep venous thrombosis, pulmonary embolism or both, is 2 to 3 per thousand inhabitants.<sup>1</sup> The incidence varies strongly with age from 0.1 in adolescence to 8 per 1000 in those above the age of 80 years.<sup>1</sup>

The mechanistic framework that helps to understand and group the causes of VTE is an extension of the triad of Virchow, which postulates that thrombosis is caused by changes in (1) blood flow, (2) the state of the vessel wall, and/or (3) the composition of blood.<sup>2</sup> In a more current reductionist's view, stasis and low oxygen tension, activation of the endothelium, activation of innate (involving monocytes and granulocytes) and acquired immunity, activation of blood platelets, the concentration and nature of microparticles (MPs), and the individual concentrations of pro- and anticoagulant proteins all claim a role (see the Figure). In addition, red blood cells are present in venous clots. We will use this reductionist's framework to group and discuss the known common risk factors for VTE that are summarized in Table.

### Blood Flow, Oxygen Tension, and Endothelial Activation

Prolonged stasis in a vein, in particular in deepest parts of the pocket of a venous valve, causes lowered oxygen tension.<sup>3</sup> This oxidative stress will lead to the upregulation of multiple stress-response genes including hypoxia inducible factor 1- $\alpha$ , P-selectin (CD62), and other adhesion receptors.<sup>4,5</sup>

The resulting proinflammatory state of the endothelium supports the local recruitment of monocytes, granulocytes, platelets, and MPs. The recruitment of these actors and their activation may lead to the local exposure of tissue factor (TF),<sup>6</sup> thus initiating the extrinsic pathway of coagulation. When damaged granulocytes start releasing neutrophil extracellular traps, DNA, and RNA, factor XII may become activated thus triggering the intrinsic pathway of coagulation and further facilitating the formation of a thrombus.<sup>7,8</sup> The intrinsic pathway can also be triggered when activated platelets release inorganic polyphosphates.<sup>9</sup>

Low blood flow in veins occurs in conjunction with several classical risk factors for VTE, including bed rest and plaster cast, and in some forms of orthopedic surgery in which the blood flow is temporarily interrupted in order to facilitate the procedure.<sup>10,11,12</sup>

Travel-related VTE is to some extent due to impaired blood flow in the limbs,<sup>13</sup> and the thrombotic risk that is associated with obesity may in part be due to the fact that individuals with a high body mass index have a chronically raised intra-abdominal pressure and decreased blood velocity in the femoral vein, and are more likely to have a sedentary lifestyle than nonobese individuals.<sup>14</sup>

In pregnant women, venous stasis already begins in the first trimester and is assumed to be caused by progesterone-induced venodilation, whereas compression of the pelvic veins by the gravid uterus becomes more important in the second and third trimester of pregnancy.<sup>15</sup>

Smoking is a risk factor for VTE, although the effect is much less than for arterial thrombosis and the evidence less

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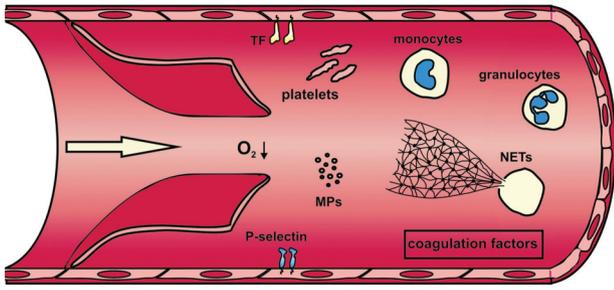
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**Figure.** The figure depicts a venous segment near a valve. Oxygen tension may become particularly low in the pocket of the valve when blood flow is impaired. This will result in procoagulant and proinflammatory conditions involving tissue factor (TF), P-selectin, platelets, microparticles (MPs) monocytes, and granulocytes. Damaged granulocytes may release neutrophil extracellular traps (NETs). The strength of the procoagulant response is strongly dependent on the concentration of coagulation factors in the blood.

consistent.<sup>16</sup> There are no mechanistic studies on the relationship between VTE and smoking, but it may be safe to postulate an inflammatory state of the endothelium, also involving components of innate immunity (see below).

Blood coagulation reactions and platelet activation are in part dependent on blood flow. How and to what extent this dependence influences thrombotic risk when flow is impaired is unknown.

**Innate and Acquired Immunity**

As a consequence of the processes described above, systemic activation of innate immunity will activate monocytes and

**Table. Common and Well-Established Risk Factors And Their Presumed Point(s) of Action**

Risk Factors	Presumed Points of Action
Surgery	Stasis, microparticles, innate immunity
Trauma	Stasis, vascular damage, microparticles, innate immunity
Venous catheters	Vascular damage
Prolonged bed rest	Stasis
Plaster cast	Stasis, microparticles
Long haul travel	Stasis
Malignancies	Microparticles, innate immunity, platelet numbers
Chemotherapy	Microparticles, innate immunity
Pregnancy	Stasis, coagulation factor concentrations
Puerperium	Vascular damage, coagulation factor concentrations
Oral contraceptives	Coagulation factor concentrations
Hormone replacement therapy	Coagulation factor concentrations
Obesity	Stasis, coagulation factor concentrations, platelets
Infection	Innate immunity
Inflammatory disease	Innate and acquired immunity
Smoking	Innate immunity, platelets, coagulation factor concentrations
Lupus anticoagulant	Innate and acquired immunity, platelets
Genetic factors	Coagulation factor concentrations

granulocytes and the endothelial lining of the blood vessels, and thus may facilitate the formation of a blood clot in susceptible areas of the vasculature. Such a systemic activation may be acute, for example in the case of infection. Indeed there is ample evidence that acute infection leads to an increased risk for VTE.<sup>17</sup>

Chronic inflammatory diseases like rheumatoid arthritis, inflammatory bowel disease, and psoriasis, but also smoking, increase the risk of VTE, and again the involvement of activated leukocytes, although not proven, is a likely mechanism.<sup>18</sup>

A well-established cause of VTE involving acquired immunity is the antiphospholipid syndrome.<sup>18</sup> This syndrome is caused by autoantibodies against phospholipid-binding plasma proteins, most commonly against beta2-glycoprotein I and prothrombin. These antibodies, in cooperation with the complement system, promote the activation of monocytes, granulocytes, and platelets, thus leading to an inflammatory state that predisposes to venous (and in this case also arterial) thrombosis.<sup>19</sup>

Obesity is also associated with a chronic inflammatory state, probably involving the production of adipokines, and it is conceivable that this will increase thrombotic risk.<sup>20</sup>

There is also genetic evidence for the involvement of inflammation in VTE. A candidate gene study of the interleukin 1 locus on chromosome 2 suggested that a certain haplotype of the gene encoding the interleukin 1 receptor antagonist increased thrombotic risk.<sup>21</sup> A more recent whole genome association study found evidence that genetic variation in the *HIVEP1* gene predisposes to VTE.<sup>22</sup> *HIVEP1* encodes a protein that participates in the transcriptional regulation of inflammatory target genes.

Despite these studies in favor of a role for (chronic) inflammation, a large population-based prospective study failed to find evidence for preexisting increased levels of inflammatory markers in individuals who later developed VTE.<sup>23</sup> Therefore, it cannot be excluded that the reported relationships between inflammation and VTE are in part the result of VTE rather than the cause.

**Platelets**

Venous blood clots are structures consisting of successive layers of fibrin, platelets, red blood cells, and leukocytes.<sup>3</sup> Compared to arterial clots, the number of platelets is relatively low. Older work also suggests that primary venous thrombi are platelet free, confirming the notion that platelets are not involved in the formation of the original nidus.<sup>24</sup> Based on these structural characteristics, platelets have historically been ignored in studies of VTE. Several lines of research indicate though that platelets play a determining role. First, the older work shows that as the formation of the thrombus propagates, the successive layers do contain platelets.<sup>24</sup> Second, (activated) platelets are important catalysts of both intrinsic and extrinsic thrombin generation and thus fibrin production.<sup>25</sup> Third, the platelet collagen receptor glycoprotein 6 was recently identified in a genome-wide association study that searched for novel risk factors for VTE.<sup>26</sup> Fourth, the use of aspirin may decrease the risk of first and recurrent VTE.<sup>27</sup>

Platelets thus may play a mechanistic role in supporting the formation of a venous clot, and some of the common risk factors for VTE can be ascribed to alterations in platelet number or function. The predisposition of obese individuals to VTE is in part determined by increased ADP-induced platelet aggregation, which in turn may be determined by the increased leptin levels that are often found in obese individuals.<sup>28</sup> As mentioned above, platelet activation may also play a role in antiphospholipid syndrome.

Myeloproliferative diseases such as polycythemia vera and essential thrombocytosis lead to increases in platelet number and function and VTE occurs in a large proportion of patients.<sup>29</sup> It is likely that this risk increase is a direct consequence of the change in platelet number rather than the presence of the JAK2V617F mutation that is present in virtually all patients with polycythemia and in about half of those with essential thrombocytosis.<sup>30</sup>

### Red Blood Cells

Primary erythrocytosis is related to venous thrombosis, but the mechanisms are complex and debated.<sup>31</sup> With respect to the association of hematocrit with venous thrombosis, the data are scarce and conflicting.<sup>32,33</sup> The most recent study, a large prospective study in the general population, shows a hazard ratio of 1.25 per % rise in hematocrit.<sup>34</sup> Whether the relation is causal or not remains unanswered.<sup>35</sup>

### Microparticles

Over the past 10 years, MPs have emerged as a potential key player in thromboembolic events.<sup>36</sup> MPs are submicron vesicles (sizes ranging from 50–1000 nmol/L) that are shed from the surface of intravascular cells, among which platelets, endothelial cells, and leukocytes. The repertoire of MP-exposed membrane proteins reflects that of the cell of which they were shed and one of these proteins is TF. TF is the primary initiator of the coagulation cascade, especially the association between TF-positive MPs (TF-MPs), and VTE has been studied. Although TF is normally not expressed by intravascular cells, certain pathological states such as sepsis upregulate TF expression on these cells and consequently on MPs.<sup>37</sup>

MPs generated from platelets form the majority (approximately 80%) of all MPs found in plasma,<sup>38</sup> but procoagulant activity of these MPs is limited. Both platelets and platelet MPs were recently suggested to express TF,<sup>39–41</sup> but this remains controversial. More likely, platelet MPs acquire TF through fusion with TF-positive MPs from other cellular sources, such as monocytes. Indeed, monocyte- and endothelium-derived MPs expose TF *in vitro* and show significant clotting activity.<sup>42,43</sup>

Several, but not all studies, found that either plasma TF-MP concentration or TF-MP procoagulant activity positively correlates with the risk of VTE.<sup>41,43–46</sup> An explanation for these inconsistent findings may be that detection of MPs is often inaccurate because of their small size. With regard to the recurrence of VTE, a clearer picture emerges. TF-MP activity and concentrations in plasma unambiguously correlate with the risk of recurrent VTE.<sup>41,47</sup>

Patients suffering from malignancy have a clearly elevated risk of VTE. Several studies indicate that cancer patients with VTE have significantly higher TF-MP activity and levels than cancer patients without VTE,<sup>48–51</sup> and such an association between TF-MP and VTE is confirmed by mechanistic studies.<sup>52</sup> Chemotherapy further increases the risk of VTE in cancer patients and a correlation with TF-MP activity has been suspected. Nevertheless, TF-MP activity in these patients does not appear to correlate with VTE.<sup>49,53</sup>

Surgery, trauma and delivery are risk factors for VTE, but any link between TF-MPs and surgery/trauma/delivery remains largely unexplored. However, blood from patients undergoing cardiopulmonary bypass surgery contains substantial amounts of MP-TF activity.<sup>54</sup> As detection methods for MPs in plasma continue to improve, it may be expected that the near future will see an accumulation of literature on TF-MPs in VTE.

### Coagulation Factor Concentrations

The best-studied determinants of venous thrombotic risk are concentrations of individual coagulation factors. These concentrations are in part, up to 50%, determined by genetic factors, but also lifestyle and other environmental factors play an important role.

#### Genetic Factors

We know 6 (moderately) strong genetic risk factors for VTE. The first 3 are heterozygous deficiencies of the natural anticoagulants antithrombin, protein C, and protein S. The prevalence of these deficiency states is low in the general population (in all races), and their genetic architecture is complex with several hundred documented mutations in the human gene mutation database (<http://www.hgmd.org/>).<sup>55</sup> In some populations particular mutations occur often because of founder effects.<sup>56</sup> Venous thrombotic risk may be increased up to 10-fold in these deficiency states.<sup>55</sup> There is no consistent evidence that deficiencies of other natural anticoagulants—such as TF pathway inhibitor, thrombomodulin, endothelial protein C receptor, and heparin cofactor II—are also strong risk factors for VTE. Partial deficiency of these natural anticoagulants are associated with other episodic or chronic diseases, like atypical hemolytic uremic syndrome in the case of thrombomodulin.<sup>57</sup>

The other 3 moderately strong genetic factors are associated with an increase, directly or indirectly, of the procoagulant potential of the blood: factor V Leiden, prothrombin G2021A, and blood group non-O.<sup>55</sup> The genetic architecture of these risk factors is simple. The prevalence in Caucasians varies from 3% to 15% for factor V Leiden and prothrombin G2021A, depending on the geographical location; in other races these 2 risk factors are extremely rare.<sup>58</sup> The increase in thrombotic risk is about 2- to 3-fold for prothrombin G2021A and 3- to 5-fold for factor V Leiden. Blood group non-O is the most common prothrombotic genetic risk factor and approximately doubles the risk of VTE and does so in all races.<sup>59</sup>

In addition to these 6 “classical” risk factors, a growing list of weak genetic risk factors has been discovered. These weak risk factors are generally common single nucleotide polymorphisms in coagulation factor genes—eg, those encoding

for fibrinogen, factor V, factor XI, et cetera—that have a small effect on gene function, and consequently a small effect on thrombotic risk.<sup>55</sup> One exception may be a single nucleotide polymorphisms in the fibrinogen gamma gene that increases thrombotic risk about 2-fold.<sup>60</sup> This single nucleotide polymorphisms influences the level of the fibrinogen  $\gamma$ -prime isoform, which is inversely related to thrombotic risk.<sup>60</sup>

The list of weak but common risk factors is expected to grow considerably in the near future as the large-scale genome wide association studies that are currently underway deliver their results.<sup>26</sup> Moreover, deep resequencing studies are expected to start soon, whether based on a candidate gene approach or genome-wide, which will yield unprecedented insight in the extent to which rare genetic variation determines individual thrombotic risk.

#### **Oral Contraceptives and Hormone Replacement Therapy**

Combined oral contraceptives contain both an estrogen and a progestagen. Hormonal contraceptive use is associated with changes in the coagulation system at different levels. Cross-over studies have demonstrated an increase in coagulation factors II, VII, VIII, and X in women using oral contraceptives,<sup>61</sup> a decrease of the levels of the natural anticoagulant protein S,<sup>62</sup> and a decrease of fibrinolytic activity, mainly through an increase of thrombin-activatable fibrinolysis inhibitor.<sup>63</sup> The use of oral contraceptive leads to increased resistance to the natural anticoagulant activity of activated protein C, which is partly explained by decreases of free protein S and free TF pathway inhibitor.<sup>64,65</sup> The prothrombotic state as measured by coagulation and fibrinolysis assays directly translates into observed epidemiological risks associated with different components of oral contraceptives. For example, combined oral contraceptives that contain desogestrel, gestodene, drospiridone, or cyproterone as a progestagen induce a more pronounced activated protein C resistance than those containing levonorgestrel,<sup>66,67</sup> and there is convincing evidence that users of such oral contraceptives have an increased risk of VTE as compared to users of contraceptives with levonorgestrel.<sup>68</sup>

Oral hormonal replacement therapy has very similar effects on coagulation and fibrinolysis variables as use of oral contraceptives, all pointing toward a prothrombotic effect. In particular oral estrogen-containing hormone replacement therapy decreases the levels of the natural coagulation inhibitors antithrombin, protein C, and protein S and increases activated protein C resistance.<sup>69–71</sup> However, a systematic review of trials comparing the effects of transdermal hormone replacement therapy with oral hormone replacement therapy on markers concluded that these effects are absent or at least lower with transdermal hormone replacement therapy use.<sup>72</sup> The effects of tibolone on markers of VTE risk are also less than in oral hormone replacement therapy or absent.<sup>69–71</sup> These findings are in line with the observed VTE risk.<sup>73</sup>

#### **Pregnancy/Puerperium**

The hormonal changes in pregnancy lead to a hypercoagulable state caused by decreased anticoagulant activity, increased procoagulant activity, and decreased fibrinolysis. The decrease in anticoagulant activity is mainly due to a decrease

in protein S concentration and an increase in activated protein C resistance. The increase in procoagulant activity is a result of an increase in plasma levels of factors V, VII, VIII, IX, and X and fibrinogen.<sup>74</sup> Finally, increases in levels of plasminogen activator inhibitor-1 and -2 activity and a decrease in tissue plasminogen activator lead to a hypofibrinolytic state.

#### **Obesity**

The relationship between obesity and VTE has been established in several epidemiological studies.<sup>14</sup> Obese subjects have increased plasma levels of procoagulant factors VII, VIII, and XII and fibrinogen, whereas fibrinolysis is decreased as reflected by increased levels of plasminogen activator inhibitor-1.<sup>75–77</sup> On the other hand, levels of the anticoagulant factors protein C and protein S are higher, and tissue plasminogen activator levels are lower under obese conditions, which might be considered to be a compensatory response to the hypercoagulable state.<sup>78,79</sup>

It is noteworthy that studies evaluating the effect of weight loss on hemostatic parameters showed that levels of TF, factor VII, plasminogen activator inhibitor-1, and tissue plasminogen activator decreased on weight loss, resulting in a decrease in thrombin generation.<sup>80,81</sup>

### **Conclusion**

Our current understanding of the etiology of VTE remains faithful to the 19<sup>th</sup> century concept of Virchow's triad, but more details are now known. Nevertheless, there remain gaps in the evidence that links epidemiological data with fundamental mechanistic insights. Filling these gaps in the understanding of the mechanism of action of classical risk factors for VTE will ultimately lead to benefits of patients in prevention and treatment of VTE. This is already true for risk factors that are well understood and are modifiable, such as obesity and prudent prescription of oral contraceptives and hormone replacement therapy. Identification of pregnant women or patients with malignancy who are at a particularly high risk to develop VTE is likely to be possible in the coming years. Finally, gaining more mechanistic insights in the etiology of recurrent venous thrombosis should lead toward fine-tuning/tailoring anticoagulant therapy in patients with a first thrombotic event.

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### **Disclosures**

None.

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