Basic Mechanisms and Pathogenesis of Venous Thrombosis

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Abstract

In 1856 Virchow proposed a triad of causes for venous thrombosis, postulating that stasis, changes in the vessel wall or changes in the blood could lead to thrombosis. We now know that abnormally high levels of some coagulation factors and defects in the natural anticoagulants contribute to thrombotic risk. Among these, factor V Leiden, which renders factor Va resistant to activated protein C, is the most prevalent with approximately 5% of the Caucasian population having this genetic alteration. These genetically controlled variants in coagulation factors work in concert with other risk factors, such as oral contraceptive use, to dramatically increase thrombotic risk. While these abnormalities in the blood coagulation proteins are associated with thrombotic disease propensity, they are less frequent contributors to thrombosis than age or cancer. Cancer increases thrombotic risk by producing tissue factor to initiate coagulation, by shedding procoagulant lipid microparticles or by impairing blood flow. Age is the strongest risk factor for thrombosis. Among possible reasons are fragility of the vessels potentially contributing to stasis, increased coagulation factor levels, impaired function of the venous valves, decreases in the efficacy of natural anticoagulants associated with the vessel wall, increased risk of immobilization and increased risk of severe infection.

Keywords

Venous thrombosis; venous valves; P-selectin; tissue factor; ischemia; obesity; sex hormones; stasis; microparticles

A. Introduction

Virchow's triad predicts that the causes of thrombosis are changes in blood coagulability, changes in the vessel wall or stasis (Figure 1). More recent studies have provided a mechanistic understanding for some of the processes that cause each of these alterations to contribute to thrombosis. A combination of genetically manipulated mouse models and human epidemiology have revealed that a variety of genetic risk factors can contribute to venous thrombosis, but the site of the thrombotic risk varies depending on the defect^{1,2}.

One of the major concepts involved in either hemostasis or thrombosis is that the processes are localized. Simply increasing coagulation enzyme concentrations with or without added negatively charged phospholipid vesicles leads to thrombin generation, but this thrombin

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generation is widespread, usually leading to disseminated intravascular coagulation rather than either hemostasis or thrombosis^{3,4}.

A. Where does venous thrombosis begin and why?

Except in thrombosis associated with surgery, examination of the thrombus in the human veins seldom indicates evidence of injury⁵, raising the question of how venous thrombosis is initiated. Venous thrombosis is believed to begin at the venous valves^{1,6}. These valves play a major role in helping with blood circulation in the legs. They are also areas where stasis and hypoxia may occur. Direct evidence from autopsy studies and phlebography have established the venous valvular sinus as a frequent location of thrombosis initiation^{5,7-9}. This phenomenon has been attributed to stasis, one of the components of Virchow's triad. Contrast media lingers in valve sinuses taking an average of 27 min to clear post-venography¹⁰. Valvular sinus stasis has also been associated with hypoxia and increased hematocrit¹¹, constituting a potentially hypercoagulable micro-environment. Furthermore, in animal models, oxygen tension drops very rapidly once blood flow is halted¹¹. Abnormalities in these valves as a contributor to thrombotic risk have not been studied extensively at the molecular level. In a recent preliminary study, several of the important vessel based antithrombotic proteins, including thrombomodulin and endothelial protein C receptor (EPCR), were shown to be regionally expressed on the valves¹². Furthermore, the expression of these proteins showed considerable inter-individual variation. Since expression of these anticoagulant proteins is sensitive to the environment, either hypoxia or inflammation could lead to down regulation, possibly contributing to the initiation of thrombosis¹³⁻¹⁵. In addition, hypoxia can lead to up-regulation of procoagulant activity including tissue factor on endothelium¹⁵⁻¹⁷. Further studies are needed to explore the possibility that changes in the ratio of procoagulant to anticoagulant properties of the valves make a contribution to venous thrombotic risk.

A. The role of blood cells versus vascular contribution to venous thrombosis

In addition to modulating the pro and anticoagulant properties of the endothelium, hypoxia also up regulates the expression of P-selectin on endothelium leading to the recruitment of leukocytes or leukocyte microparticles containing tissue factor which can serve as the nidus for initiation of the thrombotic response^{18,19} (Figure 2). Microparticles bearing tissue factor appear to play a role in thrombus formation^{20,21}. This contrasts to the conventional notion that initiation of coagulation involves exposure of tissue factor on cells surrounding the vessel other than endothelium. This conventional model is attractive because as soon as the vessel is compromised blood comes in contact with extravascular tissue factor sealing the lesion²².

There is general agreement that venous thrombosis involves tissue factor as the initiator of the coagulation response. The source of the tissue factor remains somewhat controversial in part because of the model systems used to induce the thrombus in animal models. Most of these involve some type of overt vessel damage. There are clear examples of model systems in which blood borne tissue factor, probably associated with blood cells or microparticles derived from the blood cells, probably leukocytes, is involved in the genesis of the thrombus. One of the first examples where this was shown involved passing human native blood over glass plates covered in collagen. Fibrin clots developed over the slides and this thrombus formation was blocked by antibodies to tissue factor²¹.

Under arterial and venous flow conditions, thrombus also appears to involve P-selectin, an adhesion molecule that can contribute to cell-cell interactions with cells expressing PSGL-1, a major ligand for P-selectin. Under arterial flow conditions, thrombus formation was blocked by inhibitors of P-selectin²³. Tissue factor and P-selectin appear to both be necessary for thrombus formation and they appear to both be resident on microparticles derived from monocytes, as indicated by the presence of monocyte proteins on the microparticles^{19,20}. In a

baboon venous stasis model of thrombosis, P-selectin inhibition was found to prevent thrombus development and facilitate clot resolution^{24,25}. In most of these models, it is difficult to determine whether the tissue factor-P-selectin involvement in thrombus formation is due to cellular interactions or microparticles²⁶.

It is possible that the interference with thrombosis caused by selectin inhibition is due to inhibiting platelet function or the interaction of platelets with leukocytes and/or leukocyte derived particles in the thrombus. A venous clot is composed of two regions. The red cell rich fibrin clot that appears to lie adjacent to the apparently intact endothelium and lines of platelet rich white thrombus, sometimes called the lines of Zahn, further inside the clot that separate regions of red thrombus^{5,27}. It would seem possible that disrupting the white thrombus areas might render the clot more fragile and/or more susceptible to clot lysis.

A different view of tissue factor involvement in venous thrombosis comes from studies of mice where tissue factor is selectively dramatically reduced in blood cells²⁸. In these mice, the blood borne tissue factor contributed little to stasis induced venous thrombosis, indicating that the tissue factor is derived from the vessel wall.

Obviously, these two models seem to be at odds with each other raising questions about why this may be the case. Perhaps the major problem is that each of the models involves vessel injury but the nature and extent of the injury varies. As mentioned previously, except in thrombosis associated with surgery, examination of the human thrombus in the vein seldom indicates evidence of vein injury in the region⁵ and thus most human deep vein thrombosis differs from animal models where injury of the vein, even if only by ligation, is usually an initiating event. By injuring the vein, procoagulant membrane surfaces are exposed and adhesive molecules are made available so that leukocytes and platelets will be recruited to the injury site.

A. Additional potential mechanisms for stasis induced venous thrombosis

Many of the anticoagulant pathways are triggered by endothelial cell surface components including thrombomodulin, EPCR, tissue factor pathway inhibitor and heparin like proteoglycans. EPCR and thrombin bound to thrombomodulin initiate the protein C pathway responsible for the inactivation of critical cofactors Va and VIIIa, tissue factor pathway inhibitor blocks tissue factor initiated coagulation and heparin like proteoglycans stimulate antithrombin's inhibitor activity toward coagulation enzymes like thrombin, reviewed in²⁹. Although the concentration of these proteins does vary somewhat among vascular beds, a major difference is determined by the ratio of endothelial cell surface to blood volume³⁰. Therefore, as the blood moves from the larger vessels into the microcirculation, the efficacy of the natural anticoagulants increases dramatically^{31,32}, in large part because of the vastly greater endothelial cell area exposed to blood in the capillaries compared to the major arteries or veins. Presumably, by stasis increasing the residence time in the large vessels, the natural mechanisms for controlling coagulation through interaction with the anticoagulants in the microcirculation are impaired and the propensity to develop thrombi increases with residence time of the blood in the large vessels. This model would be consistent with the known importance of these vascular anticoagulants in preventing thrombosis and the observation that stasis is a major contributor to thrombotic risk^{33,34}.

A. Changes in blood coaguability

Increased levels of coagulation factors, particularly factor VIII, von Willebrand factor, factor VII and prothrombin are associated with an increased risk of thrombosis, reviewed in^{2,35}. The increased risk of thrombosis with the elevation in factor VIII may be due to its inherent instability following activation and hence the need for replenishment to obtain a stable

thrombus. In the case of prothrombin, in addition to the potential increase in thrombin generation, prothrombin is also an effective inhibitor of activated protein C anticoagulant activity³⁶ and hence elevation in prothrombin may function as a double edged sword by directly enhancing thrombin production and by decreasing inhibition of the prothrombin activation.

In thrombophilic families, deficiencies of the main coagulation inhibitors occur in 15%, prothrombin 20210 A occurs in 20% and factor V Leiden occurs in 40-60%³⁷. Among the most common changes in blood that increase blood coagulability are defects in natural anticoagulants pathways. There are three major natural anticoagulant pathways; the heparin-antithrombin pathway, the protein C anticoagulant pathway and the tissue factor inhibitor pathway. Of these, defects in antithrombin, and each of the components of the protein C anticoagulant pathway, protein C^{37,38}, protein S³⁹, thrombomodulin⁴⁰ and possibly EPCR⁴¹, are associated with increased risks of thrombotic disease in humans. Tissue factor pathway inhibitor defects in human disease remain uncertain, in large part because the majority of the protein is associated with the endothelium and as a result, measuring circulating TFPI levels may not be informative. For all three systems, one or more components of the pathway function at the vessel wall and hence may be sensitive to vascular diseases including inflammation and hypoxia.⁴²⁻⁴⁴

A. The influence of aging on thrombosis risk

The risk of thrombosis increases dramatically with aging (Figure 3). The basis for this increase in thrombotic risk with aging remains uncertain. From a population perspective, all of the following increase with age: there are increases in procoagulant levels with age without concomitant increases in natural anticoagulants like protein C⁴⁵, there is an increase in body mass with age⁴⁶, activity decreases often with extended periods of immobilization due to illness, the frequency of acute serious infections rises, frailty increases and the number of co-morbidities tends to mount with age⁴⁷. Surprisingly, although exercise decreases the risk of venous thrombosis slightly in younger individuals, exercise increases this thrombotic risk in the elderly⁴⁸. In addition to the dramatically increased risk of venous thrombosis associated with age, there are also increases in markers of intravascular coagulation such as D-dimer and prothrombin fragment 1-2⁴⁵ indicating that there is a persistent hypercoagulable state. At present, we do not know if this is due primarily to changes in the vessel wall, perhaps the valves, or the blood. The extent of changes in the circulating blood cells as opposed to the plasma components that might contribute to the increased coagulation is also not known. A better understanding of the basis for the age dependent hypercoagulability might aid in more effective therapies. This is especially important since the bleeding risk on oral anticoagulants rises sharply in the elderly⁴⁹, making patient management more complex.

Arterial thrombotic risk rises with age in part, presumably, because of increased systemic inflammation such as an increase in IL-6 or C reactive protein⁵⁰ but these modest constitutive changes in inflammation appear to have little influence on venous thrombotic risk⁵¹. However, acute infections do increase risk markedly of both venous thrombosis and pulmonary embolism⁵². Whether the increases in risk are attributable to the acute inflammatory response, increased immobilization or both remains to be determined.

A. Venous thrombosis

A single factor abnormality is seldom enough to cause venous thrombosis leading to “the multiple hit hypothesis.” Although based on human population studies, it is clear that coagulation factor or natural anticoagulant factor levels influence the risk of venous thrombosis, it is equally clear that other factors contribute to thrombotic risk. For example, in some families with protein C deficiency, the incidence of thrombosis is low whereas in other families it is high. In one extended family, the high and low frequencies of thrombosis segregates in certain branches of the family with the protein C deficiency⁵³ suggesting that

there is a strong synergy between multiple factors. Other examples are that while obesity and oral contraceptives independently increase the risk of venous thrombosis, the two together increase the risk synergistically⁵⁴. After correcting for age and sex, obesity >30 Kg/m² increased the risk of thrombosis two-fold⁵⁴. Obese individuals have increased levels of coagulation factor VIII and IX possibly contributing to the increased risk of thrombosis, but the risk associated with obesity remains even after adjustment for clotting factor levels. Oral contraceptives increase the risk of thrombosis approximately fourfold, and this risk increases to approximately seven-fold for patients with factor V Leiden and 35-fold for patients with factor V Leiden who use oral contraceptives³⁷. Likewise, Factor V Leiden and heterozygous protein C deficiency have similar cooperative influences on the risk of thrombosis and this risk remains elevated in the elderly³⁷. All of this suggests that there is a thrombosis threshold where the propensity to generate thrombin is not adequately regulated by antithrombotic mechanisms.

A. Pregnancy

Like oral contraceptives⁵⁵, pregnancy carries an increased risk of developing venous thrombosis⁵⁶ that is increased still further in patients with thrombophilia. This increased risk is present in all trimesters of pregnancy and in the post partum period. Potential contributing factors might be disturbed blood flow and hormonal changes⁵⁶.

A. Cancer

Cancer is a major risk factor for venous thrombosis, increasing the risk about 6-10 fold⁵⁷⁻⁶⁰. Patients with cancer contribute approximately 20% of the new cases of venous thrombosis occurring in the community⁶¹. Tumors shed membrane particles that contain procoagulant activity⁶² including tissue factor⁶³ and membrane lipids that propagate the coagulation response. Adhesion molecules on the shed particles can help to concentrate the particles at sites where the appropriate ligands for the receptors are present, for instance P-selectin in ischemic areas. By concentrating the procoagulant and procoagulant lipid particles, it is possible to develop a localized thrombus rather than DIC, although DIC is found in some cancer patients. In addition, some tumors may compress one or more veins contributing to stasis.

A. Lupus Anticoagulants

Paradoxically the presence of lupus anticoagulants in patients is associated with an increased risk of thrombosis despite the fact that these lupus anticoagulant antibodies increase coagulation times *in vitro*. There are two major mechanisms that might contribute to the thrombotic risk. The antibodies bind to the platelets and endothelium possibly eliciting an inflammatory response^{64,65}. These antibodies also lead to complement activation which appears to contribute to fetal loss⁶⁶. These inflammatory contributions may help to explain why some patients with lupus anticoagulants have increased risks of arterial and/or venous thrombosis. On the venous side, one frequently observed candidate is inhibition of the protein C anticoagulant pathway⁶⁷⁻⁷⁰. In addition, antibodies against thrombomodulin are often found in this patient group and in patients with idiopathic thrombosis,⁷¹ potentially leading to impairment of the protein C anticoagulant pathway.

A. Post operative thrombosis

Post operative thrombosis is a complication of surgery especially knee, hip and cancer surgery^{61,72}. In the case of knee and hip surgery, damage to the veins in combination with stasis are thought to be major contributing factors⁷². In addition, materials released into the blood stream from the surgical sites can augment coagulation. In the case of cancer surgeries, candidates for contributing to thrombosis include the release of tumor procoagulants, host inflammatory responses and responses to chemotherapeutics.⁶¹

A. Conclusion

While epidemiology has identified factors which predispose to venous thrombotic risk, we still lack fundamental knowledge of the basis for the initiation of thrombosis, how exactly the valves are involved in the process and what specific factors are altered with advancing age that contribute so markedly to thrombotic risk. Given the increased risk of major bleeding in the elderly on oral anticoagulants, a better understanding of the basis for the increased risk of thrombosis in the elderly could provide information essential to the design of safer antithrombotics.

A. Research Agenda

- Prediction of thrombotic risk in the elderly
- Underlying mechanisms of increasing thrombotic risk with age
- Basis for increased bleeding risk on oral anticoagulants with age
- The role of the venous valves in thrombus initiation
- Establishing better animal models of venous thrombosis

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Virchow's Triad

Potential Causes of Thrombosis

Figure 1.

A modified version of Virchow's triad focusing on the findings that chronic low level inflammation has little impact on venous thrombosis (unlike arterial thrombosis), but that acute inflammation does increase venous thrombosis.

Figure 2. A model venous valve involvement in the initiation of thrombosis

The region just downstream of the valve is prone to hypoxia leading to endothelial cell activation. This upregulates adhesion molecules like P-selectin, which in turn can bind to leukocytes or leukocyte microparticles. Since the microparticles contain tissue factor, the interaction with the activated endothelium results in concentrating tissue factor to trigger coagulation that is rapid enough to result in thrombus formation.

Figure 3. The relationship between age and venous thrombotic risk

Figure 3a: The risk of deep vein thrombosis (DVT) rises markedly with increasing age in both men and women. *Figure 3b:* The risk of pulmonary embolism (PE) also rises with increasing age. (Reproduced by kind permission of American Medical Association from Silverstein et al: Trends in the incidence of deep vein thrombosis and pulmonary embolism. A 25-year population-based study. Arch Intern Med, Mar 23, 158:585-593, copyright © (1998) American Medical Association. All rights reserved.)