Hypercoagulability and Hypofibrinolysis and Risk of Deep Vein Thrombosis and Splanchnic Vein Thrombosis
Similarities and Differences


Abstract—In this review, we provide an overview of the risk factors for venous thromboembolism, focusing on hypercoagulability and hypofibrinolysis. In the first part of this review, we discuss the risk factors for commonly occurring venous thrombosis, in particular deep vein thrombosis and pulmonary embolism. In the second part, we provide an overview of the risk factors for the Budd-Chiari syndrome and portal vein thrombosis. These are rare, life-threatening forms of venous thromboembolism located in the splanchnic veins. There are many similarities in the risk profiles of patients with common venous thrombosis and splanchnic vein thrombosis. Inherited thrombophilia and hypofibrinolysis increase the risk of both common venous thrombosis and splanchnic vein thrombosis. However, there are also apparent differences. Myeloproliferative neoplasms and paroxysmal nocturnal hemoglobinuria have a remarkably high frequency in patients with thrombosis at these unusual sites but are rarely seen in patients with common venous thrombosis. There are also clear differences in the underlying risk factors for Budd-Chiari syndrome and for portal vein thrombosis, suggesting site specificity of thrombosis even within the splanchnic venous system. These clear differences in underlying risk factors provide leads for further research on the site specificity of venous thrombosis and the development of thrombosis at these distinct sites. (Arterioscler Thromb Vasc Biol. 2011;31:485-493.)

Key Words: coagulation ■ fibrinolysis ■ venous thrombosis ■ pulmonary embolism ■ portal vein thrombosis ■ Budd-Chiari syndrome ■ site specificity

V enous thromboembolism (VTE), with deep vein thrombosis (DVT) and pulmonary embolism (PE) as its 2 most common manifestations, is the third leading cause of cardiovascular morbidity and mortality in developed countries.1 VTE has an age-dependent incidence of 1 to 2 cases per 1000 person-years, ranging from 1 in 100 000 in children to 1 in 100 in advanced age.2-4 The main complications of VTE are the postthrombotic syndrome in DVT and acute death in case of PE.5

The term thrombophilia defines conditions that are associated with an increased risk of VTE and are characterized by a hypercoagulable state or alterations in the fibrinolytic system leading to hypofibrinolysis.5,6 Common clinical features of thrombophilia are thrombosis at a young age; recurrent venous thrombosis; a positive family history of VTE; obstetric complications; and thrombosis located at unusual venous sites, such as the veins of the upper extremities, cerebral sinus and veins, retinal, or splanchnic veins.7 The role of thrombophilia in the pathogenesis of common VTE has long been established. Traditionally, the role of thrombophilia in the development of thrombosis at these uncommon venous locations has received relatively little attention.

However, the understanding of the etiology of splanchnic vein thrombosis (SVT) has considerably increased during the past 10 years. SVT includes hepatic vein thrombosis (Budd-Chiari syndrome [BCS]) and portal vein thrombosis (PVT), which are 2 rare but life-threatening forms of venous thrombosis.8 In the first part of this review, we provide a concise overview of the risk factors that are associated with the development of DVT and PE, with an emphasis on the role of hypercoagulability and hypofibrinolysis. In the second part, we focus on the risk factors for BCS and PVT. Finally, we discuss similarities but also apparent differences in the risk profile between common VTE and BCS and PVT.

Risk Factors for Common VTE
Risk factors for common venous thrombosis can be divided into acquired or environmental factors and genetic risk factors. Acquired risk factors include immobilization, plaster casts, surgery, trauma, cancer, obesity, increasing age, my-
eloproliferative neoplasms (MPNs), antiphospholipid syndrome, hormone replacement therapy, use of oral contraceptives, pregnancy, and puerperium. Most of these acquired factors cause stasis or hypercoagulability of blood, both known to predispose to venous thrombosis. Known genetic risk factors for venous thrombosis are deficiencies of antithrombin, protein C, protein S, and the factor V Leiden (FVL) mutation and prothrombin 20210A gene variant (reviewed in\textsuperscript{7}).

High plasma levels of hemostasis factors, especially factors stimulating secondary hemostasis (hypercoagulability), such as factor VIII, and factors inhibiting fibrinolysis (hypofibrinolysis), such as plasminogen activator inhibitor type 1 (PAI-1), have been associated with increased risk of VTE. Both hypercoagulability and hypofibrinolysis factors are often the result of the above mentioned acquired and genetic factors and are considered to be direct intermediates in the pathophysiology of VTE (Figure).

Venous thrombosis is a multifactorial disease and is only rarely caused by a single risk factor. Thrombosis occurs most often when 2 or more risk factors are present at the same time.\textsuperscript{9} The addition of a temporary risk factor in a patient with genetic thrombophilia can trigger the development of venous thrombosis, as is observed, for instance, in FVL carriers who start to use oral contraceptives.\textsuperscript{10} A general population study showed that about half of all VTEs were secondary to the presence of 1 or more triggering risk factors. The most common triggering factors were hospitalization (52%), cancer (48%), and surgery (42%).\textsuperscript{11}

An overview of the main risk factors for VTE is provided in the Table and is discussed further in the following sections.

**Hypercoagulability in Common VTE**

Hypercoagulability can be the result of common variation or specific mutations in coagulation factor genes. Testing for genetic risk factors has been shown to be effective in identifying individuals at risk for venous thrombosis. However, not all these genetic variants are consistently associated with risk of VTE.

The strongest association with risk of a first venous thrombosis is seen for genetic variations that result in antithrombin, protein C, or protein S deficiencies, with approximately 5- to 10-fold, 4- to 6-fold, and 1- to 10-fold increases in risk, respectively.\textsuperscript{12,13} Because these deficiencies are rare, the estimates come from retrospective studies, although prospective studies in asymptomatic family members showed similar results.\textsuperscript{14} These deficiencies are also associated with an increased risk of VTE recurrence.

Consistent associations with venous thrombosis are observed with the prothrombin G20210A variant and FVL mutation, which are associated with 3- and 7-fold increased risks, respectively.\textsuperscript{15,16} However, the association with VTE recurrence is unclear. Some studies reported an increased risk of recurrence for heterozygous carriers,\textsuperscript{17,18} but other, more recent studies did not confirm these findings.\textsuperscript{19–22} Heterozygosity for these genetic variants therefore does not have any

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**Table.** Prothrombotic or Other Predisposing Factors in DVT/PE, BCS, and PVT

<table>
<thead>
<tr>
<th>Factor</th>
<th>DVT/PE</th>
<th>BCS</th>
<th>PVT</th>
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<tbody>
<tr>
<td><strong>Hypercoagulability factors</strong></td>
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<tr>
<td>Protein C deficiency</td>
<td>++</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Protein S deficiency</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>++</td>
<td>+</td>
<td>+</td>
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<tr>
<td>FVL mutation</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Prothrombin gene G20210A</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Fibrinogen levels</td>
<td>+</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Factor VIII levels</td>
<td>+</td>
<td>NS</td>
<td>+/−</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>++</td>
<td>+</td>
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<td><strong>Hypofibrinolysis</strong></td>
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<tr>
<td>Overall hypofibrinolysis</td>
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<td>+</td>
<td>NS</td>
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<tr>
<td>PAI-1</td>
<td>+</td>
<td>+</td>
<td>NS</td>
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<tr>
<td>TAFI</td>
<td>+</td>
<td>+/−</td>
<td>NS</td>
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<tr>
<td><strong>Other risk factors</strong></td>
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<tr>
<td>Immobilization</td>
<td>++</td>
<td>−</td>
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<tr>
<td>Malignancy*</td>
<td>++</td>
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<td>Surgery†</td>
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<td>Paroxysmal nocturnal hemoglobinuria</td>
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<tr>
<td>Other autoimmune diseases§</td>
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<td><strong>Local factors</strong></td>
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<tr>
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<tr>
<td>Liver cyst, parasitic mass</td>
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<td>+</td>
<td>−</td>
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<tr>
<td>Local inflammation¶</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Hepatobiliary malignancies*</td>
<td>−</td>
<td>+</td>
<td>+</td>
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†Indicates not considered a risk factor; +/−, contradictory results in the literature; +, weak risk factor; ++, strong risk factor; +++, very strong risk factor; NS, not studied.

*Hepatobiliary malignancies are associated with the development of PVT and, to a lesser extent, BCS.

†Abdominal surgery in which iatrogenous injury to the portal vein may occur (e.g., splenectomy) and general abdominal surgery are associated with development of PVT.

‡Includes oral contraceptive use, hormone replacement therapy, pregnancy, and puerperium.

§Including inflammatory bowel disease, sarcoidosis, vasculitis, and connective tissue disease.

¶Intraabdominal infection/inflammation, eg, pancreatitis, cholecystitis, diverticulitis, appendicitis, and omphalitis.
consequence for the duration or intensity of anticoagulant treatment, but homozygosity and combinations with other risk factors are associated with an increased recurrence risk and may need long-term treatment.23 However, a recent study found that homozygosity for the FVL mutation or the prothrombin variant or double heterozygosity for the FVL mutation and the prothrombin variant did not result in a high risk of recurrent venous thrombosis.24 Interestingly, the FVL mutation is a stronger risk factor for DVT than for isolated PE, which has been designated the FVL paradox.25 To date, no explanation for this remarkable difference has been found.26

Individuals with anti-phospholipid antibodies (APA) have also a rather pronounced (5-fold) increase in risk of a first venous thrombosis, and also the risk of recurrence is consistently increased.27 The combination of venous or arterial thrombosis and the presence of APA, or a combination of obstetric complications and the presence of APA, is defined as the antiphospholipid syndrome.

For prothrombotic conditions or changes in coagulation factors levels, such as acquired activated protein C resistance and increased levels of factor VIII, IX, XI, and fibrinogen, the effects are moderate and not consistent.7,28,29 Determining these conditions or factor levels may increase knowledge about the etiology but will not directly affect the treatment of patients.

Hypercoagulability can be assessed using overall tests of coagulation, such as the endogenous thrombin generation potential. Thrombin converts fibrinogen into fibrin and is essential for acceleration of the coagulation cascade by activating several other coagulation factors. An increased endogenous thrombin potential has been associated with an increased risk of first VTE.30,31 Measurement of thrombin generation has also been shown to be of use in identifying patients with a high risk of recurrence risk of VTE,32–34 although this was not observed in all studies.31

**Hypofibrinolysis in Common VTE**

Fibrinolysis is the process of degradation of a fibrin clot and limits thrombus extension beyond the site of endothelial damage. Plasmin, formed on activation of its inactive precursor plasminogen, is the key enzyme of fibrinolysis and cleaves fibrin into fibrin degradation products. Regulation of the fibrinolytic system is a complex interaction of several proteins. Eventually, plasminogen can be converted from plasminogen to the active plasmin by tissue-type plasminogen activator (t-PA) and urokinase plasminogen activator. Several proteins control the fibrinolytic system. PAI-1 is the primary inhibitor of t-PA and urokinase plasminogen activator, thereby reducing the conversion of plasminogen to plasmin. Thrombin-activatable fibrinolysis inhibitor (TAFI) potently attenuates fibrinolysis by removing carboxy-terminal lysine residues from partially degraded fibrin, thereby reducing the binding of plasminogen and t-PA to fibrin. Finally, α2-antiplasmin (plasmin inhibitor) is responsible for directly inhibiting plasmin (reviewed in35).

The overall fibrinolytic potential, which is the net effect of both activating and inhibitory factors on fibrinolysis, can be assessed using global tests of fibrinolysis. Until 2005, no clear indications for a role of a decreased overall fibrinolytic potential in the pathogenesis of venous thrombosis were observed. In these older studies, the fibrinolytic potential was studied using global tests, such as the euglobulin clot lysis time (CLT) and the dilute whole blood clot lysis assay. Both of these tests have a number of limitations.6 However, recent findings in 2 large case-control studies demonstrated an association between hypofibrinolysis and risk of VTE. In these studies, a plasma-based, tissue factor–initiated, and t-PA–induced clot lysis assay was used. The CLT denotes the time needed from half-maximal clot formation to half-maximal lysis of a plasma clot and represents a marker for the overall fibrinolytic capacity.36 In the Leiden Thrombophilia Study, a case-control study on 469 patients with a first DVT and 469 healthy controls, a 2-fold increase in risk of DVT in individuals with a CLT above the 90th percentile was observed.37 In the Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis study, involving >2000 patients with VTE and >2500 controls, these findings were confirmed, showing a similar relationship between risk of DVT or PE and hypofibrinolysis.38 The combination of hypofibrinolysis and risk factors associated with hypercoagulability was shown to result in a substantially greater risk than expected on the basis of the individual risks.38 In this study, oral contraceptive use in women with hypofibrinolysis was associated with a more than 20-fold increased risk of VTE. Hypofibrinolysis does not appear to be associated with risk of recurrence of VTE.39

When considering individual fibrinolytic factors, the literature on the role of PAI-1 and t-PA in venous thrombosis has been controversial. In the Longitudinal Investigation of Thromboembolism Etiology study, a large, population-based prospective study on venous thrombosis in middle-aged and elderly patients, no association was found between levels of PAI-1 or t-PA/PAI-1 complex and the risk of venous thrombosis.40 Several other studies also failed to show an association between t-PA and PAI-1 and the risk of venous thrombosis.41–43 However, more recently, the above-mentioned Leiden Thrombophilia Study demonstrated that elevated PAI-1 levels were associated with an elevated CLT, indicative of hypofibrinolysis, and with the risk of venous thrombosis.44 In this study, t-PA levels were associated with venous thrombosis but not with CLT, suggesting that t-PA levels are more likely to reflect other underlying risk factors.

High TAFI levels have also been shown to be associated with a mildly increased risk of VTE, although not in thrombophilic families.45 In the Leiden Thrombophilia Study, TAFI levels above the 90th percentile increased the risk for VTE 1.7-fold compared with TAFI levels below the 90th percentile,46 which was later confirmed in an independent cohort.47 In addition, high TAFI levels have been associated with an increased risk of recurrence of VTE.48 TAFI levels and activity are partly determined by several common genetic variations, which have also been associated with risk of VTE.49

Studies on levels of plasminogen or α2-antiplasmin and the risk of venous thrombosis are scarce and often in small patient groups only.50–52 At this point, there is no clear evidence for a role of plasminogen or α2-antiplasmin levels in the development of VTE.6
Other Acquired Risk Factors for Common VTE

Hospitalized patients have an increased risk for VTE because they are often exposed to 1 or more acquired risk factors for VTE, such as immobility, cancer, surgery, congestive heart failure, infections, or chronic kidney disease. Recent hospitalization for an acute medical disease is independently associated with a 8-fold increased risk of VTE and accounts for almost one fourth of all VTE events.

Cancer patients have an increased risk of venous thrombosis as a result of multiple factors, such as activation of coagulation by tumor cells, resulting in hypercoagulability: compression of veins by the tumor; hospitalization; surgery; and chemotherapy. VTE can be diagnosed in 4% to 20% of patients with cancer and is one of the leading causes of death in these patients. MPNs are also associated with an increased risk of thrombotic complications, including venous and arterial thrombosis and microcirculatory disorders, such as erythromelalgia. Risk of these complications is most pronounced in polycythemia vera and essential thrombocytosis.

The risk of venous thrombosis in surgery depends on the type of surgery and patient characteristics. Surgery induces an acute phase reaction, and plasma levels of many hemostasis factors increase in the days after surgery, which contributes to the prothrombotic condition in that period.

Another well-known triggering risk factor is immobility. Immobility, mostly defined as bed rest for at least 4 days, increases risk, probably by stasis of blood flow in the venous system. Clinical settings with immobility are bed rest and plaster casts or paresis of the legs. Shorter periods of bed rest and minor injuries have also been associated with an increased risk of venous thrombosis.

Obesity (body mass index above 30 kg/m²) leads to a 2- to 3-fold increase in the risk of VTE, and this increase in risk is even larger with severe obesity. Obesity is associated with hypercoagulability and hypofibrinolysis because of, among other factors, increased plasma levels of fibrinogen, factor VIII, and especially PAI-1.

Risk Factors for SVT

BCS is defined as an obstruction of the hepatic venous outflow tract from the level of the small hepatic veins to the entrance of the inferior vena cava into the right atrium. BCS is a rare disorder with an annual incidence of 0.2 to 0.8 per million inhabitants in the Western world, predominantly affecting young females. The classical triad of symptoms in BCS consists of abdominal pain, ascites, and hepatomegaly, frequently accompanied by a variable degree of alterations in liver biochemical tests. However, clinical presentation may range from the absence of symptoms, in the case of preservation of hepatic veins or formation of collaterals, to fulminant hepatic failure, with an acute or chronic development of symptoms ranging from weeks to months. With contemporary management, the survival rate is 87% at 1 year and 82% at 2 years.

In PVT, the obstruction is located in the extrahepatic portal vein, but involvement of the intrahepatic portal, superior mesenteric, and splenic vein may occur. Although PVT is considered a rare disorder, a recent autopsy study reported a prevalence of 1%. Clinically, PVT can be classified as acute or chronic, which represent successive stages of the same disease and share similar causes. Complications of portal hypertension, such as gastrointestinal bleeding from esophageal varices and splenomegaly, are the most important clinical manifestations of PVT. Furthermore, if thrombosis extends into the mesenteric vein, there is a substantial risk of bowel infarction, which is the most severe complication of acute PVT. The prognosis of patients with PVT is determined mainly by the underlying cause of thrombosis.

BCS is considered primary when obstruction of the venous tract is the result of thrombosis and secondary when obstruction results from invasion by a local malignant tumor or from extrinsic compression by a tumor, cyst, or abscess. The latter can also be accompanied by a hypercoagulable state. PVT is considered primary in the absence of liver cirrhosis and local malignant tumors, which are the leading risk factors. Other frequent local risk factors are inflammatory foci in the abdomen and surgical trauma to the portal vein, which are often accompanied by an additional prothrombotic condition. A local precipitating factor can be identified in approximately one third of PVT patients, whereas local factors related to the development of thrombosis are rarely identified in patients presenting with BCS.

In many patients with BCS and PVT, a genetic or acquired disorder in hemostasis is present. Several well-known risk factors that predispose to common forms of venous thrombosis also contribute to the pathogenesis of thrombosis at these unusual sites. However, some marked differences also exist.

The most prominent risk factors for SVT are displayed in the Table and are further explored below.

Hypercoagulability in SVT

The prevalence of inherited deficiencies of the natural anticoagulants antithrombin, protein C, and protein S is difficult to determine in BCS and PVT patients, because acquired deficiencies of these coagulation inhibitors can occur because of liver synthetic dysfunction, which is a frequent complication in these patients. In addition, most of these patients are treated with long-term anticoagulant treatment with vitamin K antagonists, which hampers the diagnosis of protein C and protein S deficiency. In these patients, an inherited deficiency may be diagnosed by evaluating a panel of coagulation tests (eg, factors II, V, and X). A clear isolated deficiency in comparison with other coagulation tests may be indicative of a genetic deficiency. Studies that have taken these factors explicitly into account have reported a prevalence of antithrombin deficiency of 0% to 5% in both BCS and PVT, a prevalence of protein C deficiency of 4% to 20% in BCS and 0% to 7% in PVT, and a prevalence of protein S deficiency of 0% to 7% in BCS and 0% to 30% in PVT. A case-control study by Janssen et al showed that, among the 3 factors, only protein C deficiency was significantly associated with both BCS and PVT, whereas Primignani et al did not find a significant association between these factors and PVT. Although the data are not entirely consistent, primary deficiencies of these coagulation inhibitors are likely to
contribute to the pathogenesis of BCS and PVT and should be included in a diagnostic workup.

In BCS patients, the prevalence of the FVL mutation ranges between 7% and 32%, which is in the same order of magnitude as in patients with DVT. The prevalence of the FVL mutation in patients with PVT is lower, ranging between 3% and 9%, whereas a recent metaanalysis reported a 2-fold risk of PVT in FVL carriers. As in patients with more common forms of venous thrombosis, the FVL mutation is often accompanied by other prothrombotic states or risk factors in these patients. On the contrary, the prothrombin G20210A gene variant is more common in PVT than in BCS, with a prevalence ranging from 3% to 8% in BCS, compared to 3% to 22% in PVT. A recent metaanalysis reported a 4- to 5-fold increase in risk of BCS, whereas a recent metaanalysis reported a 2-fold risk of PVT in FVL carriers. So far, the difference in prevalence of the FVL mutation and the prothrombin gene variant in BCS and PVT remains unknown.

Although considered a risk factor for BCS and PVT, APA have received relatively little attention in etiologic studies. The prevalence of APA in BCS and PVT has been estimated to be around 5% to 15%, but its importance as a risk factor is difficult to assess because anti-cardiolipin antibodies are also frequently found in patients with chronic liver disease without thrombosis. However, large studies confirming and quantifying the relationship between antiphospholipid syndrome and BCS and PVT are still lacking, in particular studies correctly using the recently updated Sapporo criteria for the antiphospholipid syndrome.

The contribution of increased levels of individual coagulation factors to the pathogenesis of thrombosis of the splanchnic veins has yet not been fully established. Few case reports and small series have suggested a potential role of increased factor VIII levels in the etiology of PVT. However, the interpretation of factor VIII levels in these disorders is complicated. Factor VIII is an acute phase protein and is also increased in patients with liver insufficiency, which is frequently seen in BCS and PVT patients. Recently, Martinelli et al described significantly elevated factor VIII levels in patients with primary PVT.

Few studies have focused on the recurrence risk of thrombosis in BCS patients. Condant et al assessed the outcome of PVT in relation to prothrombotic conditions in a cohort of 136 patients, of whom 84 received anticoagulant therapy. In this study, an incidence rate of 5.5 per 100 person-years for all types of thrombotic events was reported, and an underlying prothrombotic state was shown to be an independent predictor of recurrent thrombosis.

An elevated endogenous thrombin potential has been associated with an increased risk of VTE. It might be expected that an increased endogenous thrombin potential also contributes to the development of BCS or PVT, but this has not yet been investigated.

### Hypofibrinolysis in SVT

Few studies have assessed the role of the fibrinolytic system in the pathogenesis of BCS and PVT. De Bruin et al observed an association between SVT and genetic variation in the TAFI gene. A decreased risk of SVT in 147Thr/Thr homozygotes and a slightly, but not significantly, increased risk in carriers of the 325Ile variant was observed, suggesting a role for TAFI in the pathogenesis of SVT. Interestingly, the genotypes associated with an increased risk of SVT are associated with decreased TAFI levels, whereas an association between high TAFI levels and VTE risk has been consistently reported. There was a high degree of linkage disequilibrium between these 2 single-nucleotide polymorphisms, making it difficult to assess the contribution of the individual single-nucleotide polymorphisms. The increased risk of SVT in carriers of the 325Ile allele may be related to a TAFI variant with a greater antifibrinolytic potential but lowered antigen levels. The mechanism behind the contribution of the Ala147Thr single-nucleotide polymorphism to an increased risk of thrombosis is unknown.

Dayal et al measured t-PA and PAI-1 levels in a relatively small study of 27 BCS patients. In this study, only 3 patients showed mildly increased levels of t-PA and PAI-1 compared with healthy controls. More recently, Hoekstra et al extensively investigated components of the fibrinolytic system in 101 BCS patients. This study found significantly higher PAI-1 levels in BCS patients compared with controls, whereas TAFI and α2-antiplasmin levels were significantly lower. A subgroup of BCS patients showed clearly elevated CLTs, indicative of hypofibrinolysis. A CLT above the 90th or 95th percentile of controls was associated with a 2.4-fold or 3.4-fold increase in risk of BCS, respectively. Of note, analysis of single-nucleotide polymorphisms of fibrinolysis proteins revealed no significant differences between cases and controls, but the number of individuals studied was limited and probably too small for analysis of genetic factors. These findings suggest that an impaired fibrinolytic potential contributes to the development of BCS. Although additional studies are warranted, both these studies indicate that, as in other forms of venous thrombosis, impaired fibrinolysis may also play a role in the pathogenesis of thrombosis of the splanchnic veins.

### Other Risk Factors for SVT

MPNs are the most common underlying cause and can be identified in nearly half of BCS and about one third of PVT patients, which is strikingly higher than in other forms of VTE. The most common gain of function mutation leading to development of MPN is JAK2 Val617Phe, which is found in nearly all cases of polycythemia vera and about half the cases of essential thrombocytopenia and primary myelofibrosis. The JAK2 Val617Phe mutation has been described in 17% to 45% of unselected BCS and PVT patients. Screening for JAK2 Val617Phe is an important diagnostic tool to detect MPN in these patients and is now part of the standard diagnostic workup in BCS and PVT. Portal hypertension, resulting from pre- or posthepatic venous obstruction, can lead to hypersplenism and hemodilution. Both these conditions may...
mask the characteristic peripheral blood cell changes and make diagnosis of MPN notoriously difficult. Therefore, bone marrow histology should also be performed, allowing for MPN diagnosis in patients without the JAK2 Val617Phe mutation. About half of the BCS and PVT patients with the JAK2 Val617Phe mutation as the only indication of an underlying MPN develop an overt MPN during follow-up.99 A recent metaanalysis showed that JAK2 Val617Phe is rare in other forms of venous thrombosis, confirming the unique role of MPN in the pathogenesis of thrombosis at these distinct sites.99 The exact pathogenic mechanism of thrombotic complications in MPN remains elusive, but besides the characteristic erythrocytosis and thrombocytosis, platelet and leukocyte functional abnormalities seem critical.100

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired hematologic disorder of hematopoietic stem cells, which frequently has a devastating course and is specifically related to thrombosis at unusual sites. Remarkably, thrombosis of the splanchnic veins is a frequent complication, particularly of the hepatic veins and the inferior vena cava, in which more than 45% of the thrombotic episodes are located, accounting for the majority of deaths in this disorder.101 PNH has been reported in 9% to 19% of tested BCS patients,74,102 whereas a prevalence of 0% to 2% has been reported in PVT.72,73 Several mechanisms, including intravascular hemolysis, increased platelet activation and aggregation, procoagulant microparticles resulting from complement-mediated platelet damage, hypofibrinolysis, and increased tissue factor expression, may contribute to the pathogenesis of venous thrombosis in PNH.103,104 Patients with a PNH cell population above 60% of the granulocytes appear to be at greatest risk for thrombosis.103 Testing for PNH should be routinely performed in all BCS and PVT patients.

A number of systemic, autoimmune-mediated diseases have been implicated in the pathogenesis of both BCS and PVT. Of these, Behçet disease is particularly associated with BCS. It represents the leading cause of BCS in areas where Behçet disease is highly prevalent.105 Other systemic diseases include inflammatory bowel disease, vasculitis, sarcoidosis, and connective tissue disease. However, these accounts for only a minority of cases.66,70

Oral contraceptive use, pregnancy, and puerperium are known risk factors for venous thrombosis, and are also estimated MPN and PVT. Of these, Behçet disease is particularly associated with BCS. It represents the leading cause of BCS in areas where Behçet disease is highly prevalent.106 Other systemic diseases include inflammatory bowel disease, vasculitis, sarcoidosis, and connective tissue disease. However, these accounts for only a minority of cases.66,70

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Recently, a potentially new factor in the pathogenesis of BCS was identified. Talens et al initially showed, using a proteomic approach, that apolipoprotein A1 was decreased in 9 BCS patients compared with controls and subsequently validated these findings in a cohort of 101 BCS patients, in which apolipoprotein A1 levels were also significantly lower compared with controls.106 Apolipoprotein A1 is the principal component of high-density lipoprotein cholesterol, which has been shown to be inversely associated with other forms of venous thrombosis,107–109 although this association was not observed in all studies.110 Low apolipoprotein A1 levels have also been associated with an increased risk of recurrence of common VTE.111

Multifactorial Etiology in SVT

Even more notably than in patients with DVT or PE, the etiology of primary BCS and PVT must be considered multifactorial. The recent European Network for Vascular Disorders of the Liver (EN-Vie) studies reported a combination of 2 or more genetic or acquired prothrombotic factors in 46% of BCS and 48% of PVT patients.68,73 In this series of BCS patients, 18% of the patients even displayed 3 risk factors. Based on these findings, a complete hemato logic workup, including for inherited thrombophilia, APA, MPN, and PNH, should always be performed in BCS and PVT patients, irrespective of whether one prothrombotic factor has already been identified. This is particularly relevant for identifying MPNs, which are also often accompanied by other prothrombotic factors and require additional treatment, such as aspirin, or antiproliferative treatment.

Clues for Site Specificity of Thrombosis: DVT Versus SVT

It is still unresolved why some patients develop thrombosis of the splanchnic veins, whereas most others with similar prothrombotic factors develop DVT or PE. In contrast to the vasculature of the lower extremities, the splanchnic vasculature does not contain venous valves, which are well known to be involved in the pathogenesis of DVT.112 Further research is needed to identify local factors that are involved in the pathogenesis of thrombosis at these distinct sites. In this respect, it has been speculated that endothelial cells of the splanchnic veins may interact with activated platelets or leukocytes and increased microparticles, which are characteristic features of MPN and PNH, 2 hematologic disorders with a remarkable high frequency in SVT.113 Recently, the JAK2 Val617Phe mutation was demonstrated in the endothelial cells of 2 BCS patients, which indeed suggests a contribution of the endothelium to the development of thrombosis.114 An underlying mechanism, however, remains elusive. In addition, endothelial cells of the splanchnic veins are exposed to gut-derived oral antigens and bacterial components from the gastrointestinal tract. Hepatic sinusoidal endothelial cells display immune tolerance, which prevents a response to these factors.115 However, there is no evidence that the endothelial cells of the portal vein are similarly protected.113 It has therefore been hypothesized that these endothelial cells are chronically activated, making them particularly vulnerable to the disease-specific changes of PNH and MPN.113 These factors may be prothrombotic, resulting in an increased risk for SVT.

Interestingly, there are also apparent differences in the etiology of BCS and PVT (Table). Although MPNs are the most frequent prothrombotic factor in both BCS and PVT, MPNs are clearly more common in BCS than in PVT. In addition, it is clear that the FVL mutation is more strongly associated with BCS than with PVT, whereas the opposite is true for the prothrombin gene variant. In BCS patients, the FVL mutation has even been specifically associated with involvement of thrombosis of the inferior vena cava.27 Finally, it is evident that PNH is more strongly associated with the development of BCS than of PVT.
The understanding of the interaction of prothrombotic disorders and local factors in the etiology of BCS and PVT will play an essential role in the understanding of the pathogenesis of thrombosis at these unusual sites. Identification of distinct differences in the etiology with more common forms of venous thrombosis, and the remarkable differences in etiology even between BCS and PVT, needs further research.

Conclusion

The understanding of the etiology of VTE has improved over the years. VTE must be considered a multifactorial disease, in which the interplay of genetic or acquired factors is required for thrombosis formation. This prothrombotic tendency is caused by abnormalities in the coagulation of fibrinolysis pathways, leading to hypercoagulability or an impaired fibrinolysis. More general risk factors also contribute, partly through these pathways, to the development of thrombosis. An interesting aspect of VTE is its site specificity. In contrast to DVT or PE, the cause of venous thrombosis at unusual sites, such as the splanchnic veins, remains to be elucidated. Although the etiology shows a considerable overlap with common forms of VTE, there are several remarkable differences that may prove to be a means toward a better understanding of the site specificity of venous thrombosis.

Disclosures

None.

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