Decreased TFPI-dependent anticoagulant capacity in patients with cirrhosis who have decreased protein S but normal TFPI plasma levels

Wilma Potze¹, Freeha Arshad¹, Jelle Adelmeijer¹, Hans Blokzijl², Arie P. van den Berg², Joost C.M. Meijers³, Robert J. Porte⁴, Ton Lisman¹⁴

British Journal of Haematology 2013; 162(6):819-26

¹Surgical Research Laboratory, Department of Surgery, University of Groningen, University Medical Centre Groningen, The Netherlands.
²Department of Gastroenterology, University of Groningen, University Medical Centre Groningen, Groningen.
³Department of Experimental Vascular Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands.
⁴Section of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.
Abstract

Protein S acts as a cofactor for tissue factor pathway inhibitor (TFPI) in down regulation of thrombin generation, and acquired and congenital protein S deficiencies are associated with a concomitant TFPI deficiency. In contrast, in patients with liver diseases, decreased protein S, but normal or increased levels of TFPI have been reported. We compared TFPI and protein S plasma levels between 26 patients with cirrhosis and 20 healthy controls and found that TFPI levels were comparable between patients (111 ± 38%) and controls (108 ± 27%), despite reduced protein S levels (74 ± 23% in patients vs. 98 ± 10% in controls). Subsequently, we quantified the activity of the TFPI-protein S system by measuring thrombin generation in the absence and presence of neutralizing antibodies to protein S or TFPI. Ratios of peak thrombin generation in the absence and presence of these antibodies were calculated. Both the protein S and the TFPI ratios were increased in patients with cirrhosis compared to controls. Protein S ratios were 0.62 [0.08-0.93] in patients vs. 0.32 [0.20-0.54] in controls; TFPI ratios were 0.50 [0.05-0.90] in patients vs. 0.18 [0.11-0.49] in controls. Thus, although the acquired protein S deficiency in patients with cirrhosis is not associated with decreased TFPI levels, the TFPI/protein S anticoagulant system is functionally impaired.
Introduction

Protein S is a vitamin K-dependent plasma protein that is synthesized in the liver and by endothelial cells. It is well known that protein S acts as a cofactor for activated protein C (APC) in the proteolytic inactivation of coagulation factors Va and VIIIa [1]. It has been shown that protein S also effectively inhibits thrombin generation in plasma in the absence of APC [2,3]. This APC-independent anticoagulant property of protein S was especially observed at low TF concentrations. These observations led to the identification of a new role of protein S as a cofactor for tissue factor pathway inhibitor (TFPI) in the inhibition of factor Xa (FXa) [4]. Based on these findings, it has been proposed that protein S deficiency not only increases the risk of thrombosis by impairing the protein C system, but also by reducing the ability of TFPI to down-regulate the coagulation pathway. In fact, it has been shown that TFPI plasma levels are reduced in both congenital and acquired protein S deficiency [5], which is most probably due to the existence of a complex between protein S and TFPI in plasma. Deficiency of either protein is associated with an increased risk of venous thrombosis [6,7].

Castoldi et al. [5] assessed the functional consequences of combined (partial) protein S and TFPI deficiency by comparing thrombin generation in plasma from heterozygous type I protein S-deficient individuals with age- and sex-matched controls. At a low TF concentration, thrombin generation in plasma from patients with a protein S deficiency was 3-fold higher than in plasma from healthy individuals. Furthermore, simultaneous normalization of both protein S and TFPI levels completely corrected the elevated thrombin generation, while normalization of the protein S level alone hardly affected thrombin generation and normalization of the TFPI level alone reduced the peak height of thrombin generation by half.

In addition, Maurissen et al. [8] quantified the activity of the TFPI-protein S system in plasma by measuring thrombin generation in the absence and presence of neutralizing antibodies to protein S or TFPI. These studies showed that protein S and TFPI ratios, determined as the ratio of thrombin peaks in the absence and presence of neutralizing antibodies, were elevated in protein S-deficient individuals, indicating an impairment of the TFPI-protein S system. Furthermore, both ratios correlated well with full-length TFPI levels, which were significantly lower in protein S-deficient patients compared to family members with normal levels of protein S. This decrease in TFPI levels in conjunction with protein S deficiency was proposed to exacerbate the hypercoagulable phenotype of protein S deficiency [5].

We recently reported that plasma levels of protein S are markedly reduced, with median levels of only 16% of normal, in patients with acute liver failure [9]. Also, protein S levels were reported to be decreased in plasma from patients with cirrhosis [10,11]. Whether this decrease can be fully attributed to decreased synthesis, or whether protein S consumption also contributes is at present unclear. TFPI is not produced by the liver, but the microvascular endothelium is thought to be the principal source of TFPI [12]. Therefore, it has previously been proposed that patients with liver disease have normal plasma levels of TFPI. However, the literature is scarce and also conflicting. Increased TFPI levels have been described in patients with hepatic inflammatory diseases [13,14]. Also in those patients with acute liver failure, in whom we reported substantially decreased protein S levels, plasma levels of TFPI were substantially increased, by more than 2-fold, as compared to healthy controls [15]. In contrast, another study reported normal levels of the inhibitor in patients with advanced chronic hepatocellular disease [16]. In yet another study, patients with chronic hepatocellular disease appeared to have normal or elevated levels of TFPI, but patients with fatal hepatic
dysfunction had either low, normal, or high levels of TFPI [17]. Finally, one study has shown that the TFPI concentration decreases in advanced liver disease [18].

Although the literature is not consistent, several studies have shown normal or even increased levels of TFPI in patients with liver disease, despite a reduced plasma level of protein S. Thus, liver disease may be an exception to the rule that protein S deficiency is accompanied by TFPI deficiency. Here we studied protein S and TFPI levels in a well characterized cohort of patients with cirrhosis. In addition, we studied the functionality of the TFPI/protein S system in these patients by comparing thrombin generation profiles generated in plasma of cirrhotic patients to profiles generated in plasma from healthy individuals in the presence and absence of inhibitory antibodies to protein S or TFPI.

Patients and methods

Patients
Twenty-six adult patients with a previous clinical diagnosis of liver cirrhosis, who were under routine control for their disease by the Department of Hepatology of the University Medical Center Groningen (UMCG) or who were admitted to the Hepatology ward of the UMCG, were included in the study. The patients were classified according to the Child-Pugh classification [19]. Ten patients with Child’s A cirrhosis, ten patients with Child’s B cirrhosis, and six patients with Child’s C cirrhosis were studied. Exclusion criteria were documented history of congenital coagulation disorders, presence of active infection (<2 weeks), presence of acute liver failure, use of anticoagulant drugs in the past 10 days, pregnancy, human immunodeficiency virus (HIV) positivity, and recent (<7 days) transfusion with blood products.

The control group consisted of twenty adult healthy volunteers working at our institution. Exclusion criteria for the control group were documented history of congenital coagulation disorders, document history of hepatic disease, recent viral infection (<2 weeks), use of anticoagulant drugs in the past 10 days, pregnancy, use of oral contraceptives, and HIV positivity.

This study was approved by the local medical ethical committee and informed consent was obtained from each subject before inclusion in the study.

Plasma samples
Blood samples from each patient and control were drawn by clean venepuncture and collected into vacuum tubes containing 0.129 mol/l trisodium citrate as an anticoagulant, at a blood to anticoagulant ratio of 9:1, and was stored at room temperature for a maximum of 1 hour. Platelet-poor plasma (PPP) was prepared by double centrifugation at 2000 and 10,000 g, respectively for 10 min at 18°C. Plasma was aliquoted, snap-frozen and stored at -80°C until use.

Thrombin generation-based assays for measurement of the activity of the TFPI-protein S system
Thrombin generation was determined using calibrated automated thrombography. Methods were based on the thrombin generation-based assays to measure the activity of the TFPI-protein S system described by Maurissen et al. [8]. Plasma (68 µl) was incubated for 15 min at 37°C with 4 µl of corn trypsin inhibitor (CTI, 33 µg/ml final concentration; Hematologic Technologies, Essex Junction, VT, USA) and 8 µl of either HEPES-NaCl buffer (25 mmol/l
HEPES, pH 7.4, 175 mmol/l NaCl), polyclonal antibodies to protein S (to a final concentration of 2.80 µmol/l; DakoCytomation, Glostrup, Denmark), or monoclonal antibodies to TFPI (to a final concentration of 0.66 µmol/l; Sanquin, Amsterdam, The Netherlands). Coagulation was initiated with 20 µl PPP 5 pmol/l reagent (Thrombinscope B.V., Maastricht, The Netherlands) diluted with 0.9% NaCl, to obtain a final concentration of 2.0 pmol/l TF and 1.6 µmol/l phospholipids in the reaction mixture. After addition of 20 µl of CaCl₂ and fluorogenic substrate (Thrombinscope B.V.), substrate conversion by thrombin was followed in a Fluoroskan Ascent reader (Thermo Labsystems, Helsinki, Finland) with 390 nm excitation and 460 nm emission filter sets. Peak heights of thrombin generation were calculated using software obtained from Thrombinscope B.V. [20]. The TFPI cofactor activity of protein S was expressed as the ratio of thrombin peaks determined in the absence and presence of anti-protein S antibodies (protein S ratio). Furthermore, the activity of the TFPI-protein S system was expressed as the ratio of thrombin peaks determined in the absence and presence of anti-TFPI antibodies (TFPI ratio).

**Determination of factor levels in plasma**

Total protein S antigen was assayed by enzyme-linked immunosorbent assay (ELISA) using antibodies from DAKO (Glostrup, Denmark). Free protein S was measured by precipitating the C4b-binding protein-bound fraction with polyethylene glycol 8000 and measuring the concentration of free protein S in the supernatant. Plasma TFPI levels were measured by ELISA as previously described [8]. Levels of protein S and TFPI were expressed as percentages of pooled normal plasma, which was obtained by combining plasma samples from >200 healthy volunteers.

**Statistical analysis**

Data are expressed as means (with standard deviations [SDs]), medians (with ranges), or numbers (with percentages) as appropriate. Means of two groups were compared by Student’s t-test or Mann–Whitney U-test as appropriate. Multiple groups were compared using one-way analysis of variance (ANOVA; with the Bonferroni post-test) or Kruskal–Wallis H-test (with Dunn’s post-test) as appropriate. Spearman’s correlation coefficient was used to assess correlation between continuous variables and Pearson chi-square or Fisher’s exact test with Pearson Correlation Coefficient for dichotomous variables. P-values of 0.05 or less were considered statistically significant. GRAPHPAD PRISM (San Diego, CA, USA) and IBM SPSS STATISTICS 20 (New York, NY, USA) were used for analyses.

**Results**

**Patient characteristics**

The main characteristics of the study population are reported in Table 1. Twenty-six patients with cirrhosis (14 males and 12 females; mean age 55 ± 11 years) were included and categorized according to the severity of liver disease as expressed by the Child Pugh score [19]. The most common aetiologies of cirrhosis were alcoholic disease and non-alcoholic steatohepatitis (NASH). Twenty healthy subjects (10 males and 10 females; mean age 35 ± 11 years) were included as controls. None of the patients or controls used oral contraceptives or hormone replacement therapy.
**Plasma protein S and TFPI levels**

Plasma TFPI levels were comparable between patients and controls (108 ± 27% in patients vs. 111 ± 38% in controls, P = 0.815; Table 2). In contrast, protein S levels were substantially decreased in patients (total Protein S: 74 ± 23% in patients vs. 98 ± 10% in controls, P < 0.001; free protein S: 83 ± 23% in patients vs. 103 ± 12% in controls, P = 0.0006), and the decrease in protein S levels was proportional to the severity of the disease (Table 2).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Child A</th>
<th>Child B</th>
<th>Child C</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>55 [20-72]</td>
<td>54 [41-61]</td>
<td>58 [53-68]</td>
<td>.497</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>5 (50)</td>
<td>5 (50)</td>
<td>4 (67)</td>
<td>.781</td>
</tr>
<tr>
<td>BMI</td>
<td>26.0 [5.3]</td>
<td>28.9 [6.0]</td>
<td>30.5 [6.9]</td>
<td>.320</td>
</tr>
<tr>
<td>Smoking</td>
<td>4 (40)</td>
<td>2 (20)</td>
<td>2 (33.3)</td>
<td>.668</td>
</tr>
<tr>
<td>Alcohol (U per week)</td>
<td>0 [0-10]</td>
<td>0 [0-7]</td>
<td>0 [0-130]</td>
<td>.408</td>
</tr>
<tr>
<td><strong>Aetiology of liver disease:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic</td>
<td>3 (30)</td>
<td>2 (20)</td>
<td>6 (100)</td>
<td>.005</td>
</tr>
<tr>
<td>HCV</td>
<td>0 (0)</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>NASH</td>
<td>2 (20)</td>
<td>2 (20)</td>
<td>0 (0)</td>
<td>.639</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>0 (0)</td>
<td>2 (20)</td>
<td>0 (0)</td>
<td>.323</td>
</tr>
<tr>
<td>PBC</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>PSC</td>
<td>0 (0)</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Auto-immune</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Alcoholic + NASH</td>
<td>0 (0)</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Alcoholic + HCV</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hemochromatosis + NASH</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Co-morbidity:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>4 (40)</td>
<td>2 (20)</td>
<td>0 (0)</td>
<td>.258</td>
</tr>
<tr>
<td>DM</td>
<td>4 (40)</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>.227</td>
</tr>
<tr>
<td><strong>Plasma levels:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum bilirubin (µmol/L)</td>
<td>10 [4-26]</td>
<td>40 [18-121]</td>
<td>93 [63-255]</td>
<td>.0001</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>42.7 [3.9]</td>
<td>33.1 [4.8]</td>
<td>27.2 [2.6]</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Serum creatinin (µmol/L)</td>
<td>62.4 [19.2]</td>
<td>72.8 [32.3]</td>
<td>86.7 [18.5]</td>
<td>.193</td>
</tr>
<tr>
<td>Haemoglobin (mmol/L)</td>
<td>8.7 [0.6]</td>
<td>7.2 [0.9]</td>
<td>6.3 [0.8]</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Leukocytes (10^9/L)</td>
<td>6.9 [2.7]</td>
<td>4.9 [2.1]</td>
<td>6.5 [3.7]</td>
<td>.238</td>
</tr>
<tr>
<td>INR</td>
<td>1.1 [0.1]</td>
<td>1.3 [0.2]</td>
<td>1.6 [0.2]</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Table 1. Demographic and clinical characteristics of the study population
Data are expressed as number (%), mean [SD], or median [range].

**Thrombin generation**

Plasma from cirrhotic patients and controls were incubated with CTI in the absence or presence of neutralizing antibodies to protein S or TFPI for 15 min at 37°C. Thrombin generation was then initiated with a low TF concentration (2.0 pmol/l). The median peak heights in the absence of antibodies were 25.7 [9.6-66.5] nmol/l (median [range]) in plasma from controls and 61.4 [3.2-132.7] nmol/l in plasma from patients (P = 0.01). Peak heights of thrombin generation without antibodies were significantly higher in Child class B (81.1 [3.2-132.7] nmol/l) and Child class C (81.0 [48.8-116.5] nmol/l) cirrhotic patients compared...
to healthy controls ($P = 0.04$ and $P = 0.007$ respectively). Addition of antibodies to protein S increased the thrombin peaks to 78.1 [41.2–147.4] nmol/l in controls and to 97.7 [34.8–188.6] nmol/l in patients ($P = 0.203$; Table 2; Fig 1). Furthermore, in the presence of protein S antibodies, average peak heights were no longer significantly higher in the Child class B and C cirrhotic patients compared to controls (Table 2), suggesting that decreased protein S levels in cirrhotic patients explain the difference in thrombin generation between cirrhotic Child class B and C patients and healthy controls. Complete inhibition of the TFPI-protein S system was achieved through addition of inhibitory antibodies against TFPI, resulting in further increases of peak heights to 128.2 [90.4–202.2] nmol/l in controls and 116.2 [59.4–197.7] nmol/l in patients (Table 2; Fig 1).

The anticoagulant activities of protein S and TFPI were expressed as the ratio of peak heights obtained in the absence and presence of the respective inhibitory antibodies. The median protein S ratios were 0.32 and 0.62 in controls and patients respectively. In other words, protein S, via its TFPI cofactor activity, reduced thrombin generation by approximately 68% in controls and by 38% in patients. The median TFPI ratios were 0.18 and 0.55, respectively, indicating that the TFPI-protein S system as a whole reduced thrombin generation by approximately 82% in controls and by 45% in patients. Both protein S and TFPI ratios were significantly increased in patients compared to controls, $P = 0.03$ and $P = 0.009$, respectively (Fig 2). In particular in Child class B and C patients, both ratios were markedly increased compared to controls (Table 2).

**Figure 1.** Effects of anti-protein S and anti-tissue factor pathway inhibitor (TFPI) antibodies on thrombin generation at a low tissue factor concentration (2.0 pmol/l). Average of (A) 20 separate thrombin generation curves in plasma of healthy controls and (B) 26 separate thrombin generation curves in plasma of patients with cirrhosis, without addition of antibodies (dotted line), with anti-protein S antibodies (dashed line) or with anti-TFPI antibodies (solid line).

**Figure 2.** Functional tissue factor pathway inhibitor (TFPI)–protein S assays in controls and in patients with Child A, B, or C cirrhosis. (A) Protein S ratio in plasma from controls and patients. (B) TFPI ratio in plasma from controls and patients.
Interestingly, peak thrombin generation in the absence of inhibitory antibodies (basal peak thrombin generation) was strongly correlated to protein S ratios, both in patients and controls (r = 0.88; P < 0.0001 and r = 0.82, P < 0.0001 respectively). This positive correlation was also observed between basal peak thrombin generation in plasma and TFPI ratios (r = 0.92; P < 0.0001 and r = 0.87, P < 0.0001, respectively; Fig 3).

Figure 3. Correlation between basal peak thrombin generation (nmol/l) and (A) protein S ratio and (B) TFPI ratio, in plasma from 20 healthy individuals (●) and 26 patients with cirrhosis (●).

Furthermore, plasma protein S levels strongly correlated with the protein S ratio in patients (r = -0.66, P = 0.0002; Fig 4). Plasma protein S levels were also correlated with the TFPI ratio in both patients (r = -0.76, P < 0.0001) and controls (r = -0.51, P = 0.02; Fig 4). Free plasma protein S levels also correlated with both the protein S ratio (r = -0.41, P = 0.04) and the TFPI ratio (r = -0.48, P = 0.01) in patients. In addition, plasma TFPI levels strongly correlated with the TFPI ratios in both patients (r = -0.67, P < 0.0001) and controls (r = -0.75, P = 0.0001; Fig 5). No correlation between plasma TFPI levels and protein S ratios was observed in both patients and controls.

Figure 4. Correlations between total protein S levels and (A) protein S ratio and (B) TFPI ratio, in plasma from 20 healthy individuals (●) and 26 patients with cirrhosis (●).
Figure 5. Correlations between tissue factor pathway inhibitor (TFPI) levels and TFPI ratio in plasma from 20 healthy individuals (●) and 26 patients with cirrhosis (●).

Table 2. Tissue factor pathway inhibitor (TFPI)–protein S parameters in cirrhotic patients and controls. Data are expressed as mean [SD] or median [range]. *P < 0.05; **P < 0.01.
Discussion

Protein S and TFPI act together in down-regulating thrombin formation [4] and it has been shown that both hereditary and acquired protein S deficiency states are accompanied by a partial deficiency of full-length TFPI [5]. However, we show that in patients with cirrhosis the acquired protein S deficiency is not accompanied by a decrease in TFPI plasma levels. Furthermore, patients with cirrhosis showed a reduced activity of the TFPI-protein S system when compared to healthy controls.

Despite the substantial decrease in protein S plasma levels in cirrhotic patients, TFPI levels are comparable between patients and controls. In addition, we have previously shown increased TFPI levels despite substantially decreased protein S levels in patients with acute liver failure [15]. This indicates that the decrease in TFPI levels in conjunction with acquired protein S deficiency as described previously [5] does not occur in patients with liver diseases.

A possible explanation for normal TFPI levels in patients with liver diseases despite decreased plasma levels of protein S may be that TFPI release in these patients is substantially increased compared to that in healthy individuals, but that this increased TFPI release is masked, in part, by the protein S deficiency. In both chronic and acute liver diseases, continuous activation of the endothelium is common, resulting in increased plasma levels of endothelial-derived proteins, such as von Willebrand factor [21,22]. The combination of continuous endothelial cell activation and protein S deficiency may thus result in normal to slightly elevated TFPI levels. Endothelial activation was probably absent in the acquired protein S deficiencies studied by Castoldi et al (use of oral contraceptives or vitamin K antagonists) [5], explaining the divergent results between our study and the published data.

Protein S and TFPI levels are significantly lower in females than in males [8,23]. In this study there were slightly more males in the patient group (14 males and 12 females) than in the control group (10 males and 10 females). However, this could not explain the differences in protein S levels between patients (with lower protein S levels) and controls observed here. Furthermore, the mean age in the patient group was substantially higher than in the control group. However, levels of TFPI are hardly influenced by age [7] and only in females does total protein S levels increase with increasing age [23] which is unlikely to explain the decreased protein S levels in the (older) patients compared to the (younger) controls observed here.

The decreased TFPI-dependent anticoagulant capacity in patients with cirrhosis resulted in an increased thrombin generation as compared to controls. The difference in peak thrombin generation between patients and controls largely disappeared upon addition of anti-protein S antibodies, indicating that the low protein S levels were responsible for the impairment of the TFPI-protein S system in the patients with cirrhosis.

We have previously proposed that the haemostatic system in patients with liver disease is in a ‘rebalanced’ status due to a concomitant decrease in pro- and anticoagulants [24]. Furthermore, we proposed the rebalanced haemostatic status of patients with liver disease to be unstable, resulting in a propensity to switch to both a hypo- and hypercoagulable status. The experiments performed in this study suggest that the haemostatic status of a patient with liver disease also depends on the strength of the initiating trigger. At the suboptimal concentrations of TF and lipids used in this study, thrombin generation profiles in healthy individuals are clearly marginal (Fig 1A), and plasma from patients with cirrhosis clearly
generate more thrombin compared to that in healthy volunteers (Fig 1B). This hypercoagulable phenotype was much less pronounced when thrombin generation in the same patients was tested using a high TF trigger (data not shown).

The observed increased peak thrombin generation in this study is in line with the clinical observation of thrombotic complications in patients with cirrhosis. Several studies have shown an increased risk of venous thromboembolism (VTE) in patients with cirrhosis [25-27]. Portal vein thrombosis forms another frequently occurring venous thrombosis in patients with cirrhosis [28]. These thrombotic complications cause increasing morbidity and mortality. The increase in factor VIII in combination with decreased protein C is proposed to be responsible for the hypercoagulable status in patients with chronic liver disease [29]. However, in the current study we have shown that the impaired activity of the TFPI-protein S system in patients with cirrhosis may also contribute to this hypercoagulable state, especially at a low TF concentration. Thus, the increased risk of thrombotic complications, such as venous thrombosis and portal vein thrombosis, which are probably not associated with massive exposure of TF, may be explained by the decreased TFPI-dependent anticoagulant capacity in patients with cirrhosis.

In conclusion, the acquired protein S deficiency in patients with cirrhosis is not associated with a decrease in TFPI plasma levels. Despite normal TFPI plasma levels, the TFPI/protein S anticoagulant system is functionally impaired in patients with cirrhosis, which may contribute to thrombotic complications.
References


