Challenging dogmas in pancreatic surgery: biliary drainage, outcome and beyond

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Effect of Preoperative Biliary Drainage on Coagulation and Fibrinolysis in Severe Obstructive Cholestasis

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ABSTRACT

Goals
To evaluate the function of coagulation and fibrinolysis in cholestatic patients before and after preoperative biliary drainage (PBD).

Background
Cholestasis owing to an obstructive biliary malignancy is associated with postoperative complications related to a proinflammatory state, an impaired hepatic synthesis function, and a potential derangement of hemostasis. Hence, PBD is advocated for cholestatic patients undergoing major surgery.

Study
Plasma coagulation and fibrinolytic parameters were assessed in 24 cholestatic patients and 10 controls. In 9 cholestatic patients, the parameters were reassessed at least 4 weeks after PBD.

Results
Compared to controls, cholestatic patients showed lower concentrations ($P<0.001$) of plasma vitamin K-dependent factors II and VII, whereas prothrombin time, activated partial thromboplastin time, and factor V were unaltered. Thrombin generation was increased in cholestatic patients, as reflected by higher plasma concentrations of thrombin-antithrombin complexes and D-dimers. Fibrinolysis was significantly impaired as evidenced by low plasminogen activator activity (PAA) owing to an increase in plasminogen activator inhibitor-1. Elevated markers for thrombin generation (thrombin-antithrombin) decreased after PBD from $10.7 \pm 1.2$ to $5.7 \pm 0.7$ng/mL ($P<0.05$). Additionally, impairment of fibrinolysis in cholestatic patients resolved after PBD (plasminogen activator inhibitor-1 levels decreased from $19 \pm 1$ to $10 \pm 1$IU/mL and plasminogen activator activity increased from $82 \pm 3\%$ to $110 \pm 4\%$, respectively). D-dimers remained unaltered after PBD, likely because of normalization of coagulation and fibrinolytic activity.

Conclusions
Obstructive cholestasis is associated with a procoagulant state, despite an impaired vitamin K-dependent coagulation factor synthesis. Virtually all alterations in coagulation and fibrinolysis were reversed by biliary drainage.
INTRODUCTION

Patients with severe cholestasis in consequence to biliary tract obstruction are at risk for postoperative complications when undergoing procedures, such as pancreatoduodenectomy and extended liver resection\textsuperscript{1-4}. These complications have been associated with impaired hepatic protein synthesis and a pro-inflammatory state\textsuperscript{1}. A derangement of hemostasis could also play a role. Analysis of global routine coagulation parameters, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) at the time of surgery are typically near or within the normal range in cholestatic patients. Whether a more detailed analysis of coagulation and fibrinolysis results in out-of-range values, as was shown in a rabbit model of cholestasis\textsuperscript{6}, is unknown.

The liver plays a central role in the regulation of coagulation and fibrinolysis. Hepatocytes synthesize the vast majority of coagulation factors, their inhibitors, and compounds of the fibrinolytic system. The hepatic clearance of activated clotting proteases and protease inhibitor complexes further modulates coagulation activation. Obstructive cholestasis may impair the synthesis of coagulation factors as a result of bile acid-induced hepatocyte damage\textsuperscript{7} and a diminished absorption of fat-soluble vitamin K from the gut\textsuperscript{8,9}, which is required for the synthesis of vitamin K-dependent coagulation factors [e.g., factors (f)II, VII, IX, and X and proteins C and S]. An imbalance in secondary hemostasis may lead to increased blood loss during major surgery, although compromised hepatic synthesis of fibrinolytic components may alleviate the hemostatic disorder.

This disequilibrium may be even more pronounced, as cholestasis and bile acid deficiency in the intestinal lumen are associated with an impaired intestinal immune defense, enhanced intestinal permeability, and, consequently an increased exposure of Kupffer cells and sinusendothelial cells in the portal circulation to bacterial wall constituents, such as lipopolysaccharide, leading to a diminished clearance function of Kupffer cells and cytokine-mediated aggravation of hepatocyte secretion failure.\textsuperscript{10,11} The interaction of lipopolysaccharide with Hageman factor (intrinsic pathway) and the effect on thrombin formation does not seem to play a major role in the relation between inflammation and coagulation.\textsuperscript{12} Nevertheless, the inflammatory response as a consequence of obstructive cholestasis could result in a procoagulant state initiated through tissue factor and amplified by the downregulation of physiological anticoagulant pathways and endogenous fibrinolysis.\textsuperscript{6,13} This may ultimately lead to microvascular or clinically evident thrombotic events and/or disseminated intravascular coagulation.\textsuperscript{14}

Preoperative biliary drainage (PBD) is generally advocated to improve the surgical outcome in patients with cholestasis undergoing major surgery. Although beneficial results of PBD have been demonstrated in experimental studies,\textsuperscript{15} the exact role of PBD in patients with obstructive cholestasis remains unclear.\textsuperscript{16} Moreover, endoscopic stent placement harbors specific complications that negatively affect the overall treatment outcome.\textsuperscript{17,18} To date, studies on the effect of severe cholestasis on the systemic
inflammatory state are limited in scope and did not include an incisive analysis of 
coagulation and fibrinolysis. Therefore, this study was conducted to assess the 
activation state of coagulation and fibrinolysis in cholestatic patients before and after 
PBD.

MATERIALS AND METHODS

Study Population
Patients with obstructive cholestasis owing to a suspected pancreatic or periamp-
illary malignancy were recruited at the Academic Medical Center in Amsterdam 
between March 2007 and June 2008 and were scheduled to undergo resection (pan-
creatoduodenectomy) with curative intent. For this study all patients or their legal 
representatives provided written informed consent before inclusion. The study was 
approved by the institute’s medical ethics committee as part of an ongoing clin-
ical trial on the effect of PBD (trial number: ISRCTN31939699). Eligible patients 
had obstructive cholestasis with total bilirubin plasma levels of ≥50µmol/L and were 
scheduled for operation. Exclusion criteria were prior biliary drainage attempts, 
going cholangitis, defined as elevation in temperature to ≥38.5°C with a suspected 
biliary cause, and the need for an intervention. Other exclusion criteria included the 
use of anticoagulants, antibiotic therapy, and/or vitamin K substitution. Twenty-four 
patients were included of whom 12 were randomized to an early-surgery strategy 
without PBD, and 12 patients were randomized to a biliary drainage strategy with 
PBD for a median duration of 6 (range 4 – 8) weeks by endoscopic biliary stent place-
ment followed by surgery.

The control group consisted of patients with newly diagnosed colon carcinoma, 
pre-operatively sampled, who had not received (neoadjuvant) chemotherapy or other 
form of treatment.

Sampling
Blood was obtained before endoscopic stent placement (t=0) and after a minimum 
of 4 weeks internal biliary drainage (t=1). Nine of the twelve drained patients were 
sampled after PBD. The other 3 patients were not followed up because of sampling 
failure (n=1), hospital transfer (n=1), and the occurrence of multiple episodes of chol-
angitis with stent exchanges (n=1). Patients who underwent early surgery without 
PBD within 1 week after diagnosis were sampled at one time point only (t=0).

Blood was collected into Vacutainer tubes containing EDTA for the determination 
of blood counts, heparin for the determination of bilirubin, alkaline phosphatase 
(AP), and other routine chemical measurements, and citrate for the determination of 
coagulation and fibrinolysis parameters. Blood was centrifuged at 5,000×g for 15min 
at 4°C and plasma was separated and processed immediately or stored at -80°C until 
 further use.
Assays

Cholestasis, hepatic damage, and other routine parameters
Total bilirubin and AP were measured by routine laboratory assays to confirm obstructive cholestasis. Similarly, aspartate aminotransferase, alanine aminotransferase, and C-reactive protein (CRP) were assayed in heparinized plasma as markers for hepatocellular damage and inflammation. Blood counts (leukocytes and platelets) and hemoglobin were measured by conventional clinical chemistry from whole blood samples.

Coagulation and fibrinolysis parameters
Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were measured directly after sampling on a STA-R analyzer. PT was expressed as international normalized ratio. Citrate-anticoagulated plasma samples that had been stored at -80°C were used for the determination of factors II, V, and VII by a 1-stage clotting assay on the STA-R analyzer with STA reagents (Diagnostica Stago, Asnières, France). Antithrombin III was also determined on the STA-R using a chromogenic substrate assay. Thrombin-antithrombin (TAT) complexes (Enzygnost, Behring, Marburg, Germany) and D-dimers (D-dimer Vidas DD, bioMérieux, Paris, France) were measured by ELISA. Plasma levels of fibrinogen were assayed using STA fibrinogen reagent (Diagnostica Stago) according to the method of Clauss.22

Citrate-anticoagulated plasma samples were used for the determination of plasminogen activator activity (PAA) and plasminogen activator inhibitor-1 (PAI-1). PAA was measured by an automated amidolytic assay.23 Briefly, 25µL of plasma was mixed with 0.1mol/L Tris-HCl, pH=7.5, 0.1% (v/v) Tween-80, 0.3mmol/L S-2251 (Chromogenix, Mölndal, Sweden), 0.15µmol/L plasminogen (Chromogenix) and 0.12mg/mL cyanogen bromide-digested fibrinogen fragments (Chromogenix) in a final volume of 250µL. The amount of plasmin formed under these conditions is proportional to the PAA concentration and can be detected spectrophotometrically after the conversion of the chromogenic substrate. PAI-1 activity was measured by an amidolytic method as described earlier.24 Plasma was incubated with a fixed excess of tissue-type plasminogen activator (tPA) (40IU/mL) (Chromogenix) for 10 minutes at room temperature. The residual tPA activity was assayed by incubation with 0.13µmol/L plasminogen, 0.12mg/mL cyanogen bromide-digested fibrinogen fragments, and 0.11mmol/L S-2251 (Chromogenix). Under these conditions, the plasmin generated is inversely proportional to the amount of PAI-1 present. Both PAA and PAI-1 activity were measured using normal human plasma as reference.

Statistics
Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, Chicago, IL). Results are presented as mean ± SEM. Differences were tested using the Mann-Whitney U test and the Wilcoxon signed-rank test for two related samples. A P-value of <0.05 was considered statistically significant.
RESULTS

Patients
Ten control patients and 24 cholestatic patients were included in the study. In 9 of the cholestatic patients, blood was sampled before PBD (t=0) and at least 4 weeks after PBD (t=1). The mean age was 66 (range 43–77), the number of male and female patients was 16 (67%) and 8 (33%), respectively. The mean age of patients with colon carcinoma (control group) was 65 years (range 54–80), consisting of 7 males and 3 females. The histopathologically confirmed diagnoses in the cholestatic group were pancreatic ductal carcinoma, n=11; cholangiocarcinoma, n=2; adenocarcinoma of the ampulla of Vater, n=2; and adenocarcinoma not otherwise specified, n=9.

Biochemical Markers of Cholestasis, Hepatic Damage, and Inflammation
The results for total plasma bilirubin, AP, hepatic damage parameters, and other routine measurements are presented in Table 1. The mean values calculated in the group of 9 PBD patients were compared statistically with the mean values of the total cholestatic group (n=24). The data indicate that this relatively small subgroup of patients was representative for a broader group of cholestatic patients.

PBD resulted in adequate biliary decompression as documented by significant reduction in serum bilirubin levels and AP activity. PBD was also associated with substantially lowered hepatocellular damage as evidenced by marked decreases in serum aspartate aminotransferase and alanine aminotransferase activity. Hemoglobin concentration and platelet and leukocyte counts were not affected by PBD. Finally, CRP concentrations were slightly increased in the presence of cholestasis, indicating a low grade inflammatory state. PBD had no effect on CRP concentrations.

Table 1 Routine laboratory findings of cholestatic patients included in the study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>24 cholestatic patients (t=0)</th>
<th>9 cholestatic patients before PBD (t=0)</th>
<th>9 cholestatic patients after PBD (t=1)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (µmol/L)</td>
<td>201 (±15)</td>
<td>214 (±35)</td>
<td>15 (±3)</td>
<td>0.01</td>
</tr>
<tr>
<td>AP (U/L)</td>
<td>669 (±118)</td>
<td>989 (±297)</td>
<td>181 (±21)</td>
<td>0.01</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>271 (±83)</td>
<td>464 (±218)</td>
<td>36 (±4)</td>
<td>0.01</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>401 (±80)</td>
<td>547 (±192)</td>
<td>48 (±5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hemoglobin (mmol/L)</td>
<td>8.0 (±0.2)</td>
<td>8.1 (±0.3)</td>
<td>8.4 (±0.3)</td>
<td>0.34</td>
</tr>
<tr>
<td>Platelets (10^9/L)</td>
<td>298 (±16)</td>
<td>325 (±34)</td>
<td>283 (±28)</td>
<td>0.59</td>
</tr>
<tr>
<td>Leucocytes (10^9/L)</td>
<td>8.0 (±0.6)</td>
<td>8.8 (±0.8)</td>
<td>8.1 (±0.5)</td>
<td>0.46</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>11 (±1)</td>
<td>11 (±2)</td>
<td>9 (±4)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Results are given as mean ± SEM. *Wilcoxon signed-rank test for t=0 vs. t=1. PBD, preoperative biliary drainage; AP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein.
Coagulation Activation

The coagulation and fibrinolysis parameters are summarized in Figure 1 and Table 2. The mean values calculated in the group of 9 PBD patients were representative for a broader group of cholestatic patients with the exception of factor II that was 6% lower in the total cholestatic group ($n=24$, $P<0.05$). Cholestatic patients had normal aPTT, PT, and factor V values, which did not change after PBD (Fig. 2A, B). However, vitamin K-dependent factor II and factor VII were both slightly decreased in the presence of cholestasis and increased by 15% and 30%, respectively, after PBD (Figs. 2C, D). Activation of coagulation and consequent thrombin generation were reflected by plasma levels of TAT complexes. The plasma concentration of TAT complexes was increased in the presence of cholestasis and reduced by 90% after PBD (Fig. 2E). Levels of ATIII and fibrinogen were increased before biliary drainage (possibly reflecting the acute phase behavior of these proteins) and were almost normalized (reduced by 30% and 20%, respectively) after the procedure. These data indicate that vitamin K-dependent coagulation factors were reduced and markers of coagulation activation were enhanced in the presence of cholestasis, all tending to normalize after PBD.

Figure 1  Secondary hemostasis in the presence of cholestasis and the effect of preoperative biliary drainage: the tissue factor (TF) and common pathways of coagulation activation and fibrinolysis pathway. The TF pathway is initiated at the site of injury in response to the release of TF. Roman numerals represent the respective coagulation factor.
whereby "a" indicates an activated state. The thrombus, that forms as a result of platelet aggregation (primary hemostasis) and the formation of fibrin, is enzymatically cleaved into fibrin degradation products as a consequence of fibrinolysis. Fibrinolysis is initiated by the conversion of plasminogen to plasmin by tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA), a process that is inhibited by plasminogen activator inhibitors (PAI-1). Physiological anticoagulants are delineated in the upper left corner and comprise antithrombin III (ATIII), which binds to thrombin resulting in TAT complexes, protein C (PC) complexed with protein S (PS) as cofactor, and tissue factor pathway inhibitor (TFPI). Black arrows represent disturbances in the presence of cholestasis in comparison with control and transparent arrows represent the effect of biliary drainage (delineated in the upper right corner).

### Table 2: Coagulation and fibrinolytic factors in patients included in the study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>10 control patients</th>
<th>24 cholestatic pts before PBD</th>
<th>9 cholestatic pts after PBD</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT [sec.]</td>
<td>34 (±1)</td>
<td>33 (±1)</td>
<td>35 (±1)</td>
<td>34 (±2)</td>
</tr>
<tr>
<td>INR</td>
<td>1.0 (±0.04)</td>
<td>1.0 (±0.03)</td>
<td>0.9 (±0.05)</td>
<td>1.0 (±0.05)</td>
</tr>
<tr>
<td>fII (%)</td>
<td>102 (±2)</td>
<td>87** (±2)</td>
<td>92** (±2)</td>
<td>107 ± (±3)</td>
</tr>
<tr>
<td>fV (%)</td>
<td>101 (±2)</td>
<td>101 (±2)</td>
<td>100 (±3)</td>
<td>99 (±4)</td>
</tr>
<tr>
<td>fVII (%)</td>
<td>101 (±2)</td>
<td>85** (±2)</td>
<td>86 (±3)</td>
<td>114 ± (±3)</td>
</tr>
<tr>
<td>ATIII (%)</td>
<td>103 (±2)</td>
<td>137** (±6)</td>
<td>138 (±7)</td>
<td>105 (±2)</td>
</tr>
<tr>
<td>TAT [ng/mL]</td>
<td>5.0 (±0.5)</td>
<td>11.5** (±0.5)</td>
<td>10.7 (±1.2)</td>
<td>5.7 (±0.7)</td>
</tr>
<tr>
<td>Fibrinogen [g/L]</td>
<td>3.8 (±0.4)</td>
<td>6.0** (±0.2)</td>
<td>6.2 (±0.3)</td>
<td>5.1 (±0.4)</td>
</tr>
<tr>
<td>D-dimer [mg/L]</td>
<td>0.5 (±0.1)</td>
<td>0.9* (±0.3)</td>
<td>0.7 (±0.2)</td>
<td>0.8 (±0.3)</td>
</tr>
<tr>
<td>PAA (%)</td>
<td>104 (±3)</td>
<td>85** (±2)</td>
<td>82 (±3)</td>
<td>110 (±4)</td>
</tr>
<tr>
<td>PAI-1 [IU/mL]</td>
<td>8.3 (±0.5)</td>
<td>16.9** (±0.8)</td>
<td>19.2 (±0.8)</td>
<td>9.5 (±0.7)</td>
</tr>
</tbody>
</table>

Results are given as mean ± SEM. *=p<0.05 and **=p<0.001 vs. control (Mann-Whitney U test). †Significantly different in comparison to 24 cholestatic patients (Mann-Whitney U test). #Wilcoxon signed-rank test for t=0 vs. t=1.
PBD, preoperative biliary drainage; aPTT, activated partial thromboplastin time; INR, international normalized ratio; f, factor; AT, Antithrombin; TAT, thrombin-antithrombin; PAA, plasminogen activator activity; PAI, plasminogen activator inhibitor.

### Fibrin Formation and Fibrinolysis

The fibrinolytic response to fibrin formation includes the endothelial release of tPA and urokinase-type plasminogen activator (uPA), which convert plasminogen to its active form, plasmin, that is responsible for the degradation of fibrin. Plasmin activation is coupled to increases in PAI-1 activity for properly balancing hemostasis. Figure 3A shows that PAA (reflecting tPA and uPA activity) is inhibited in the presence of cholestasis, probably owing to increased PAI-1 levels (Fig. 3B). PAI-1 levels returned to baseline after biliary drainage resulting in the restoration of endogenous fibrinolysis (15% increase in PAA, Fig. 3A). These data indicate that impairment of fibrinolysis in obstructive cholestasis is, in part, restored after PBD. The net effect on the reduction of coagulation activation and normalization of fibrinolysis after PBD is reflected by the stable concentrations of D-dimer levels that were increased in cholestatic patients and remained unaltered after PBD (0.7±0.2 to 0.8±0.3mg/L, P=0.53, Table 2).
As postoperative complications occurred in only 4 patients, an analysis of the correlation between these complications and coagulation and fibrinolysis parameters was meaningless.

**DISCUSSION**

The present study shows that severe obstructive cholestasis is associated with decreased vitamin K-dependent coagulation factor synthesis, an overall procoagulant state, and a generally impaired fibrinolytic state. The majority of coagulation and fibrinolysis parameters were normalized to baseline values 4 weeks after endoscopic PBD.

The beneficial action of PBD is considered to be twofold. First, inflammation is reduced as a result of restored bile levels in the gut lumen enabling the binding of endotoxin by bile salts, improvement of gut integrity, and restitution of the gut flora composition. Second, the accumulation of hydrophobic bile acids in the liver ceases leading to a marked decrease in hepatocyte injury and improvement of hepatocellular function. In addition, cholestasis leads to vitamin K deficiency. Although standard coagulation tests such as the PT and aPTT typically remained unimpaired, our study directly confirmed a cholestasis-induced reduction of vitamin K-dependent fII and fVII plasma levels. PBD resulted in a systemic increase in these vitamin K-dependent coagulation factors, probably due to restoration of gut flora and improvement of intestinal absorption.

Despite the decreased vitamin K-dependent coagulation factor synthesis in cholestatic patients, thrombin generation was increased as evidenced by the increased TAT complex levels. It is likely that the increased thrombin generation was because of systemic inflammatory response in patients with obstructive cholestasis. As the reduced plasma levels of factors II and VII are likely to the result of a compromised vitamin K-dependent hepatic synthesis, it is plausible that levels of protein C and protein S, both also vitamin K-dependent proteins, were decreased in the presence of cholestasis, which may have further exacerbated the procoagulant conditions.

Also, TAT levels might be increased because of a decreased clearance of the complexes by the liver. Although somewhat counterbalanced by the low levels of vitamin K-dependent factors II, VII, and possibly IX and X, physicians should note that patients with obstructive cholestasis seem to be in a procoagulant rather than an anticoagulant state.

There is substantial evidence demonstrating an impairment of fibrinolysis in the presence of cholestasis. These findings are supported by the low PAA values and increased PAI-1 levels found in this study.
Figure 2  Cholestatic patients (t=0, ●) undergoing adequate endoscopic biliary drainage (t=1, ●) show a decreased vitamin K-dependent coagulation factor synthesis and a procoagulant state. Plasma levels of (A) prothrombin time, given as international normalized ratio (INR) values, (B) factor V, (C) prothrombin (factor II), (D) factor VII, and (E) thrombin-antithrombin (TAT)-complexes are depicted. P-values pertain to the Wilcoxon signed-rank test for two related samples. The boxplots (●) depicted on the left hand site are values obtained in the 10 controls.
The mechanistic implications of PAI-1 production by endothelial cells and hepatocytes in the context of cholestasis is currently elusive, although believed to be driven by a tumor necrosis factor-α-mediated stimulus.27,28 Experiments in mice with targeted disruption of genes encoding components of the plasminogen–plasmin system showed that fibrinolysis plays a major role in cholestasis-induced fibrosis,29-31 whereby the enhanced suppression of fibrinolysis by PAI-1 and a consequentially accelerated degradation of fibrin led to a reduction in liver injury.29,30 Conversely, blocking of tPA exacerbated liver injury after bile duct ligation (i.e., cholestasis induction).31 Moreover, a pathophysiologic role of PAI-1 in thromboembolic disease is putatively inferred by the association between elevated PAI-1 levels and thrombotic tendency.32 Thus, the procoagulant state in the presence of cholestasis is amplified as a result of an impaired fibrinolytic system but significantly reduced by PBD owing to the normalization of the fibrinolytic system.

Malignant disease is associated with increased PAI-1 activity33 and certain cancers, especially pancreatic carcinoma, are associated with thrombosis. In patients diagnosed with pancreatic carcinoma, the plasma concentration of several coagulation factors is increased, namely TF, thrombin, and fibrinogen.34 Furthermore, venous thromboembolism and pancreatic carcinoma are typically associated with advanced disease or a diagnosis of metastatic cancer within 4 months.35 Our results in patients with mainly pancreatic carcinoma showed that the anomalies of the coagulation system were almost completely reversed after PBD. This indicates that cholestasis itself and not the underlying malignancy is the cause of the coagulopathy. It should be noted that the positive effects of PBD were in part attributable to the selection of patients without advanced disease who were in relatively good general condition to undergo major surgery.

Whereas PBD yielded beneficial effects in experimental models, conflicting results have been reported in human studies.16,18 For distal obstructions PBD should not be carried out routinely, as the improvements of biliary drainage do not outweigh the complications affiliated with endoprosthesis, for example, cholangitis, hemorrhagic complications, and even gut or bile duct perforations.36 However, in selected patients with distal obstructions and high bilirubin levels and cholestatic patients requiring extensive liver resection, such as in the case of hilar cholangiocarcinoma, PBD may be advantageous in reducing overall complications.26,37 The results of this study show the beneficial effects of PBD on hemostasis.

In conclusion, severe obstructive cholestasis, although accompanied by mild impairment of vitamin K-dependent coagulation factor synthesis, is associated with procoagulant activity most likely owing to a mild proinflammatory state with coagulation activation and inhibition of fibrinolysis. Hemostatic alterations because of cholestasis are almost completely reversed after PBD, indicating that cholestasis itself and not the underlying malignancy is the cause of coagulopathy. Improvement of hemostatic changes after PBD could contribute to a better outcome after major surgery in selected cholestatic patients.
Figure 3  Fibrinolysis was significantly impaired in the presence of cholestasis (t=0, ●) and normalized after biliary drainage (t=1, ●). Plasma levels of (A) plasminogen activator activity (PAA) and (B) plasminogen activator inhibitor (PAI)-1 are depicted. P-values pertain to the Wilcoxon signed-rank test for two related samples. The boxplots (□) depicted on the left hand site are values obtained in the 10 controls.
Chapter 4 Effect of Preoperative Biliary Drainage on Coagulation

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