Thrombelastographic changes and early rebleeding in cirrhotic patients with variceal bleeding

T N Chau, Y W Chan, D Patch, S Tokunaga, L Greenslade, A K Burroughs

Abstract

***Background*—Routine coagulation tests do not necessarily reflect haemostasis in vivo in cirrhotic patients, particularly those who have bleeding varices. Thrombelastography (TEG) can provide a global assessment of haemostatic function from initial clot formation to clot dissolution.**

***Aim*—To evaluate TEG changes in cirrhotic patients with variceal bleeding and their association with early rebleeding.**

***Patients/Methods*—Twenty cirrhotic patients with active variceal bleeding had serial TEG and routine coagulation tests daily for seven days. The TEG variables before the day of rebleeding (n = 6) were compared with those of patients without rebleeding (n = 14).**

***Results*—Baseline characteristics of the rebleeding and non-rebleeding groups were comparable apart from a higher incidence of uncontrolled infection on the day of rebleeding in the rebleeding group (p = 0.007). The patients in the rebleeding group were more hypocoagulable before the day of rebleeding as shown by longer *r* (42 *v* 24 mm, p<0.001) and *k* (48 *v* 13 mm, p<0.001) and smaller *a* (12 *v* 38°, p<0.001) compared with the mean of daily results of the non-rebleeding group. Routine coagulation tests, however, showed no significant differences between the two groups.**

***Conclusion*—The results of serial TEG measurements suggest that hypocoagulability may be associated with early rebleeding in cirrhotic patients.**

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Keywords: thrombelastography; variceal bleeding; early rebleeding; cirrhosis

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Variceal haemorrhage in cirrhotic patients carries a high early death rate ranging from 30 to 60%,[1 2] even when balloon tamponade, drugs, or emergency sclerotherapy are used as first line treatments. Rebleeding usually occurs within the first week after admission.[3] After the first week, early rebleeding within six weeks occurs in 19–31%.[3 4] Up to 60% of deaths within six months of variceal bleeding are related to rebleeding.[3] However, the risk factors associated with early rebleeding remain unclear.[5 6] In some studies, it was found to be related to the degree of liver failure[5] and bacterial infection,[5 7] while another study showed that age, endoscopic stigmata of recent bleeding, and the severity of the index bleed were the predictors.[6] Feu *et al* found that the risk of rebleeding is related to portal pressure.[8]

The liver plays a central role in the production of clotting and fibrinolytic factors, and coagulation abnormalities are one of the cardinal features of liver disease.[9 10] However, attempts to correlate the incidence of bleeding with coagulation status have had limited success. This may be related to the fact that coagulation abnormalities are both complex and multifactorial and depend on the balance between hepatic synthesis and clearance of activated coagulation proteins and their inhibitors, the presence or absence of dysfibrinogenaemia, thrombocytopenia, abnormal platelet function, and disseminated intravascular coagulation. Hence routine coagulation tests do not necessarily reflect coagulation in vivo in cirrhotic patients.[10]

The thrombelastograph (TEG) (Haemoscope Corp and Launch Diagnostics, Skokie, Illinois, USA) is a mechanically operated system that allows global assessment of haemostatic function from a single blood sample, documenting the interaction of platelets with the protein coagulation cascade from the time of the initial platelet-fibrin interaction, through platelet aggregation, clot strengthening, and fibrin cross linkage to eventual clot lysis.[11] A comparison of TEG with routine coagulation tests has shown a clear relation. TEG variables also contain additional information on the haemostatic process, which makes TEG more sensitive to changes in the haemostatic balance of coagulation and related systems.[12] Clinically, TEG has been used mainly in directing coagulation factor transfusion during and after liver transplantation.[13 14] It is also useful in assessing the risk for haemorrhage in patients after cardiopulmonary bypass[15] or after transplant renal biopsy.[16] Despite this evidence, TEG has not entered routine clinical practice and has never been evaluated for monitoring patients with gastrointestinal bleeding. Bleeding gastro-oesophageal varices is an ideal situation where TEG may be useful. Cirrhotic patients are frequently hypocoagulable on laboratory testing. In addition, clotting factors are routinely given, although the evidence that this affects the outcome is negligible, and nor is it known whether changes in coagulation reflect early rebleeding.

The aims of our study were (*a*) to examine TEG abnormalities in patients with variceal bleeding, (*b*) to compare the TEG variables of patients with variceal rebleeding and those who did not rebleed, and (*c*) to examine the clinical utility of TEG.

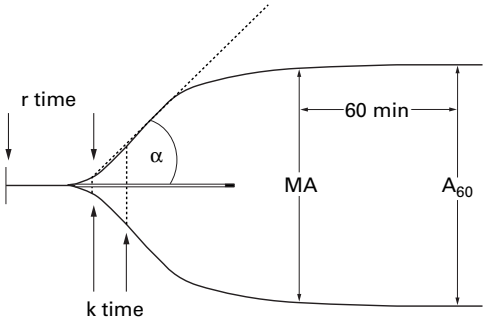

Figure 1 Thrombelastographic (TEG) variables: reaction time (r; normal range 19–28 mm) is related to the rate of initial fibrin formation. k (range 8–13 mm) is clot formation time. Maximum amplitude (MA; range 48–60 mm) represents the strength of the clot. Alpha angle (α; range 29–43°) represents the rate of clot formation. A_{60} is a measure of clot retraction or lysis.

Patients and methods

Twenty three cirrhotic patients presenting consecutively as an emergency with upper gastrointestinal tract haemorrhage, as shown by either haematemesis or melaena, or both, were admitted to the Royal Free Hospital. Two were excluded because oeosphagitis in one and a gastric ulcer in the other were the source of bleeding. Another patient, who developed uncontrolled variceal bleeding and died within 24 hours despite all medical treatment, was also excluded.

A diagnosis of cirrhosis was confirmed by relevant clinical, biochemical, radiological, or histological data. All the patients were confirmed by endoscopy to have varices. Physical examination and laboratory analysis were performed on admission. All patients were initially managed by active resuscitation including blood transfusion. Emergency upper endoscopy was performed in all cases within 12 hours of the index bleed. Endoscopic sclerotherapy and banding were carried out in eight and 12 patients respectively. In all patients, intravenous terlipressin 2 mg was administered four hourly for two days. Balloon tamponade was used for haemorrhage that persisted despite endoscopic banding and vasoactive drugs (six cases). A sepsis work up, including blood, sputum, urine, and ascitic fluid (if any) culture, and chest *x* ray were performed on admission, and intravenous cefotaxime was given prophylactically in all patients for seven days. Sepsis work up was repeated if previous positive cultures were found or whenever patients showed signs of infection.

Whole blood coagulation was assessed using a computerised TEG (Haemoscope Corp and Launch Diagnostic, UK) as recommended by the manufacturer. The TEG consists of two mechanical parts: a heated (37°C) oscillated cup and a pin which is suspended freely from a torsion wire.[11] A 0.25 ml volume of whole blood is pipetted into a plastic cup, and mineral oil is placed on the surface of the sample to eliminate the blood-air interface and prevent drying during analysis. While the freshly drawn blood in the cup remains liquid, the motion of the cup does not affect the pin. When a clot starts to form, the fibrin strands couple the motion of the cup to the pin, and the shear modulus and elasticity of the clot is then transmitted through the pin and amplified to give the TEG trace on heat sensitive paper as well as a computer record. The native TEG was measured with no anticoagulant or celite added. The TEG was allowed to run for about two hours or 60 minutes after the maximum amplitude on the TEG trace was achieved. The TEG variables reaction time (*r*), clot formation time (*k*), angle (α), maximum amplitude (MA), and amplitude 60 minutes after the MA (A_{60}) were measured and documented (fig 1).

r is the time from sample placement in the TEG cup until the TEG trace amplitude reaches 2 mm (normal range 19–28 mm). This represents the rate of initial fibrin formation and is related functionally to plasma clotting factors and circulating inhibitor activity. Prolongation of the *r* time may be a result of coagulation factor deficiencies, or severe hypofibrinogenaemia. *k* is measured from *r* to the point where the amplitude of the tracing reaches 20 mm (normal range 8–13 mm). It is the time taken to reach a standard clot firmness and is affected by the activity of the intrinsic clotting factors, fibrinogen and platelet. MA is the maximum amplitude on the TEG trace (normal range 48–60 mm). It reflects the strength of the clot and is a direct result of the function of platelets and plasma factors and their interaction. *α* is the angle formed by the slope of the TEG tracing from the *r* to the *k* value (normal range 29–43°). It represents the rate of clot growth and describes the polymerisation of the structural elements involved in clotting.[17] Clot growth is a function of platelets and plasma components residing on the platelet surfaces. Hypocoagulability may be reflected by the prolongation of *r* or *k*, or the increase in α, or the decrease in MA depending on the haemostatic problem of the patients. A_{60} is a measure of clot retraction or lysis. The whole blood clot lysis index (WBCLI) can be calculated by dividing A_{60} by MA and multiplying by 100 to express the index as a percentage. A WBCLI of less than 80% indicates fibrinolysis.

The first TEG was performed within 24 hours of admission, and then 24 hourly till one week after admission or patients developed rebleeding. TEG variables on the day of rebleeding were defined as the last TEG performed before the rebleeding episode—that is, the TEG variables evaluated were always before clinical rebleeding was diagnosed. Coagulation tests including prothrombin time (PT) and activated partial thromboplastin time (APTT) as well as a full blood count were also carried out daily. Rebleeding was defined as the recurrence of haemorrhage (new haematemesis, melaena, or gastric aspirate containing blood), associated with a transfusion requirement of two units of blood or more and occurring more than 24 hours after the index bleeding. Rebleeding episodes were treated in the same way as index bleeds. Emergency TIPSS (transjugular intrahepatic portosystemic stent shunt) was performed whenever medical and endoscopic treatment failed to control bleeding.

Table 1 Baseline characteristics of patients in the rebleeding and non-rebleeding groups

	Rebleeding group (n=6)	*Non-rebleeding group (n=14)*	*p Value*
Age (y)	57 (40–61)	52 (37–73)	0.48
Sex (M/F)	5/1	5/9	0.63
Underlying diagnosis of cirrhosis			
Primary biliary cirrhosis	1 (17)	5 (36)	
Post-hepatitic	2 (33)	4 (29)	
Alcoholic	1 (17)	4 (29)	
Cryptogenic	2 (33)	1 (7)	0.37
Presence of hepatocellular carcinoma	0 (0)	1 (7)	0.86
History of variceal bleeding	4 (67)	4 (29)	0.64
Ascites	4 (67)	12 (85)	0.55
Encephalopathy	5 (83)	6 (43)	0.16
Child's classification			
A or B	4 (67)	7 (50)	
C	2 (33)	7 (50)	0.82
Units of blood transfused within 24 hours after admission	5 (0–10)	7 (0–12)	0.64
Sepsis			
On admission	3 (50)	6 (43)	0.61
On day of rebleeding/end of the study	5 (83)	2 (14)	**0.007**
Laboratory results on admission			
Haemoglobin (g/dl)	9.8 (6.6–11.6)	10.8 (5.9–12.6)	0.93
White cell count ($\times 10^9$ /l)	9.2 (7.2–13.2)	9.0 (3.4–31)	0.59
Platelet count ($\times 10^9$/l)	117 (44–144)	80 (30–152)	0.34
Prothrombin time (seconds)	19 (15–31)	24 (15–39)	0.93
Activated partial thromboplastin time (seconds)	35 (32–85)	45 (26–75)	0.84
Serum albumin (g/l)	37 (21–48)	30 (21–39)	0.39
Bilirubin (μmol/l)	71 (5–527)	70 (10–355)	0.90
Alkaline phosphatase (U/l)	65 (49–174)	110 (39–271)	0.25
Alanine aminotransferase (U/l)	23 (6–365)	29 (12–390)	0.87
Urea (mmol/l)	11 (5–15)	10 (2–25)	0.10
Creatinine (μmol/l)	73 (50–208)	85 (51–251)	0.68

Where applicable, results are expressed as median (range). Other values in parentheses are percentages.

STATISTICAL METHODS

Descriptive statistics of the baseline characteristics of patients with or without rebleeding were expressed as median and range when appropriate. For binary or categorical data, Fisher's test of exact probability was used, and Wilcoxon rank sum test was used for continuous data. Student's *t* test was applied for the comparison of TEG variables and other coagulation tests (*a*) on the day of rebleeding and the mean of daily results in patients without rebleeding and (*b*) on the first day of testing in both groups. Measurements with positively skewed distribution, *r*, *k*, PT, APTT, and platelet count were log transformed. Analysis of covariance was also used to compare the two groups, adjusting for baseline characteristics. The appropriate model was selected using backward elimination. Child's classification, number of units of blood transfused within the first 24 hours, age, and sex were selected as the covariates in the analysis of covariance model. Univariate logistic regression was used to determine the odds ratio for the TEG and other coagulation tests in relation to the risk of early rebleeding. All analyses were carried out using Stata (Stata Corp, Texas, USA).

Table 2 Comparison of thromboelastographic variables and routine coagulation tests on the day of rebleeding and the mean of daily results in the non-rebleeding group

	Rebleeding group (n=6)	*Non-rebleeding group (n=14)*	*p Value**
r (mm)	42 (34–56)	24 (2–120)	**<0.001†**
k (mm)	48 (23–85)	13 (2–79)	**<0.001†**
MA (mm)	45 (33–81)	58 (13–96)	0.28
a (degree)	12 (5–20)	38 (11–69)	**<0.001**
Platelet count ($\times 10^9$/l)	42 (26–131)	71 (26–518)	0.60†
Prothrombin time (seconds)	27 (17–34)	20 (15–43)	0.19†
Activated partial thromboplastin time (seconds)	46 (33–81)	39 (26–94)	0.44†
WBCLI (%)	84 (66–95)	88 (82–98)	0.72

Results are expressed as median (range).
*Student's *t* test.
†Comparison after log transformation of data.
WBCLI, whole blood clot lysis index.

Table 3 Difference in thromboelastographic variables and routine coagulation tests on the day of rebleeding in those who rebled and the mean of daily results in the non-rebleeding group assessed by analysis of covariance

	Difference between rebleeding and non-rebleeding group	*p Value*	*Variables used for adjustment**
log [*r*]	0.65 (0.37 to 0.94)	**0.001**	Age
log [*k*]	1.11 (0.66 to 1.56)	**0.001**	Sex, Child's class, number of units of blood transfused
MA	5.53 (5.85 to 16.9)	0.32	
a	−17.9 (−27.3 to −8.4)	**0.001**	Child's class
log [platelet]	−0.18 (−0.71 to 0.34)	0.47	
log [PT]	−0.16 (−0.01 to 0.33)	0.07	
log [APTT]	0.004 (−0.14 to 0.14)	0.45	
WBCLI	2.5 (−1.1 to 3.4)	0.88	

Results are given with 95% confidence intervals in parentheses.
*Variables were selected by the model using backward elimination of baseline characteristics.
PT, prothrombin time; APTT, activated partial thromboplastin time; WBCLI, whole blood clot lysis index.

Results

During the study period, 20 patients were enrolled. Six developed recurrent upper gastrointestinal bleeding between 24 hours and seven days after admission. One of the non-rebleeding group, who developed uncontrolled pneumonia despite multiple antibiotics, died on day 5 after admission. There were no statistically significant differences in the baseline clinical and laboratory characteristics of patients with and without rebleeding (table 1). Five patients who developed early rebleeding had evidence of sepsis (three with chest infection, one with staphylococcal septicaemia secondary to leg ulcer, one with central line related septicaemia) on the day of rebleeding while only two without recurrent bleeding had uncontrolled infection (one with chest infection and one with spontaneous bacterial peritonitis) at the end of the study period. This difference was statistically significant (p = 0.007).

Table 4 Univariate logistic regression between the occurrence of rebleeding and daily measurement of thromboelastographic variables and routine coagulation tests

	Odds ratio	*Standardised odds ratio*	*p Value*
log [*r*]	11.1 (1.4 to 89.8)	4.6 (1.2 to 17.1)	**0.02**
log [*k*]	6.7 (1.7 to 27.5)	5.6 (1.6 to 19.7)	**0.01**
MA	0.98 (0.93 to 1.03)	0.69 (0.3 to 1.62)	0.40
α	0.78 (0.65 to 0.95)	0.015 (0.0005 to 0.40)	**0.01**
log [platelet]	0.61 (0.15 to 2.52)	0.73 (0.30 to 1.78)	0.49
log [PT]	6.3 (0.4 to 99.1)	1.71 (0.76 to 3.85)	0.19
log [APTT]	2.2 (0.1 to 38.7)	1.24 (0.57 to 2.71)	0.58
WBCLI	0.99 (0.97 to 1.01)	0.72 (0.41 to 1.71)	0.91

Results are given with 95% confidence intervals in parentheses.
PT, prothrombin time; APTT, activated partial thromboplastin time; WBCLI, whole blood clot lysis index.

Table 2 gives a summary of the TEG variables and coagulation tests on the day of rebleeding in those patients who rebled and the mean of all daily results of patients without rebleeding. *r*, *k*, and α on the day of rebleeding showed significant differences when compared with the mean of the daily results in patients without rebleeding ($p<0.001$). Analysis of covariance showed that the difference between *r*, *k*, and α on the day of rebleeding and the mean of daily results in the non-rebleeding group remained statistically significant after being adjusted with the baseline variables selected by backward elimination (table 3). Conversely, MA, WBCLI, and other coagulation results showed no significant difference between the rebleeding and non-rebleeding groups by *t* test or analysis of covariance. There were no statistically significant differences in any TEG variables and coagulation tests within 24 hours of admission between patients with and without rebleeding. Only one patient with rebleeding, who had a chest infection, had a WBCLI of less than 80% within 24 hours of admission as well as on the day of rebleeding.

Univariate logistic regression showed that the odds ratio of log *r*, log *k*, and α were 11.1, 6.7, and 0.78 respectively (table 4). In order to compare the effect of the different parameters, the standardised odds ratio (the odds ratio for the increase of one SD) was also computed. α was shown to have the greatest statistical significance (table 4).

Discussion

In this study, patients in the early rebleeding and non-rebleeding groups did not show any significant difference in any TEG variable within 24 hours of admission. This may have been because the initial blood products transfused can correct the coagulation defects.[18–20] However, the progressive increase in *r* and *k*, and decrease in α in the patients who eventually rebled suggest a hypocoagulable state related to hypofibrinogenaemia or coagulation factor deficiencies. The reason for the hypocoagulability in these particular patients (compared with those who did not rebleed) is uncertain. Only one patient who rebled had TEG evidence of fibrinolysis, which may suggest that disseminated intravascular coagulation is not the major contributing factor for early rebleeding. Although there is a correlation between the TEG results and the severity of liver cirrhosis, our analysis of covariance suggests that it cannot be fully explained by it. Another possible cause of the hypocoagulability identified in our study is the presence of uncontrolled infection. Bacterial infection associated with rebleeding in patients after admission for variceal bleeding has been reported,[5 7] but a causal relation between variceal bleeding and bacterial infection remains controversial.[7 21–24] In our study, uncontrolled infection despite the use of prophylactic antibiotics preceded recurrent bleeding in five of six patients with rebleeding. The numerous circulatory and blood coagulation derangements induced by infection[23 24] in cirrhotic patients may theoretically trigger variceal bleeding.

Patients with cirrhosis suffer from complex haemostatic disturbance, which may be due to impaired synthesis of clotting factors, a hyperfibrinolytic syndrome, and/or altered platelet function.[9 10] Thus it is not surprising that routine coagulation tests may not reflect the risk of bleeding, and indeed previous studies on patients having laparoscopic liver biopsies also showed no correlation between standard tests such as PT and platelet count and the "liver bleeding time".[25] To date, studies on rebleeding in patients with cirrhosis have not reported standard coagulation profiles as being useful predictors.[3 26–28] This implies that standard blood coagulation values do not reflect in vivo haemostasis or that coagulopathy is not associated with early rebleeding. However, in the present study, the TEG variables *r*, *k*, and α were predictively associated with early variceal rebleeding in cirrhotic patients, whereas the routine coagulation tests did not appear to show any significant difference between the rebleeding and non-rebleeding group.

TEG has become an accepted tool in the monitoring of coagulation during liver transplantation. We speculate that it could be used with clinical benefit for cirrhotic patients with variceal bleeding. Specific blood product replacement could be administered as in liver transplantation. It remains to be seen whether targeted correction of TEG abnormalities prevents early rebleeding. In addition, the role of sepsis in altering TEG variables and its association with early rebleeding needs to be explored. Further studies of the use of TEG for cirrhotic patients should answer these questions.

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