Thromboelastometry Shows Early Hypercoagulation in Patients with Spontaneous Subarachnoid Hemorrhage

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■ BACKGROUND: **The ability to achieve hemostasis after spontaneous subarachnoid hemorrhage (SAH) plays a pivotal role in outcome. Changes in coagulation in the early hours after SAH have been only sparsely investigated.**

■ OBJECTIVE: **To investigate changes in coagulation after SAH and illuminate underlying mechanisms.**

■ METHODS: **We enrolled 46 patients with spontaneous aneurysmal SAH. Blood samples were collected at admission and 24 hours after symptom onset. Thromboelastometry (ROTEM) was performed using the standard assays EXTEM, INTEM, and FIBTEM. Platelet maximum clot elasticity was calculated based on ROTEM results. Thrombin generation, levels of thrombin-antithrombin complex, fibrinogen, and coagulation factor XIII were measured. All data were compared with a gender-matched healthy control group.**

■ RESULTS: **At admission (median, 3 hours 39 minutes from symptom onset), maximum clot firmness (EXTEM, $P < 0.0001$; INTEM, $P = 0.08$; FIBTEM, $P < 0.0001$) and platelet maximum clot elasticity ($P < 0.0001$) were higher in patients with SAH than in healthy controls. Thrombin generation showed higher, although nonsignificant, endogenous thrombin potential in patients with SAH than in healthy controls ($P = 0.06$), and thrombin-antithrombin complex levels were above the reference interval. Median fibrinogen and coagulation factor XIII levels were both within the reference parameters and remained increased 24 hours after symptom onset, whereas endogenous thrombin potential ($P = 0.01$) and thrombin-antithrombin complex levels decreased ($P < 0.0001$).**

■ CONCLUSIONS: **Patients with SAH were in a hypercoagulable state at admission and remained so 24 hours after SAH. Increased clot firmness could be caused by increased platelet function, because platelet maximum clot elasticity was increased despite normal fibrinogen and coagulation factor XIII levels.**

INTRODUCTION

Spontaneous subarachnoid hemorrhage (SAH) is most often caused by a ruptured aneurysm and occurs primarily in healthy individuals.[1,2] The mortality ranges from 30% to 50% within the first 6 months,[3,4] and surviving patients continue to have cognitive and neurologic disabilities several months after SAH.[1,2]

Treatment guidelines are controversial regarding antifibrinolytic drugs,[5,6] yet, treatment with tranexamic acid (TXA) has proved to be effective in reducing the risk of rebleeding.[7] Rebleeding often occurs within the first 2–3 hours after ictus,[8] and

Key words
- Blood coagulation tests
- Factor XIII
- Platelets
- Subarachnoid hemorrhage
- Thromboelastography

Abbreviations and Acronyms
aPTT: Activated partial thromboplastin time
CT: Computed tomography
DCI: Delayed cerebral ischemia
FXIII: Coagulation factor XIII
IQR: Interquartile range
LI30: Lysis index after 30 minutes
MCE: Maximum clot elasticity
MCF: Maximum clot firmness
MRI: Magnetic resonance imaging
ROTEM: Thromboelastometry
SAH: Subarachnoid hemorrhage
S100B: Serum s100 calcium binding protein B
TAT: Thrombin-antithrombin
TXA: Tranexamic acid
UFH: Unfractionated heparin

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antifibrinolytic treatment does not seem to reduce mortality.[7] SAH complications such as rebleeding, hydrocephalus, vasospasms, and delayed cerebral ischemia (DCI) significantly affect mortality and functional outcome.[9] Previous studies have investigated coagulation within 24 hours after SAH (**Figure 1**).[10-18] Studies indicate activated coagulation, after SAH, mainly reflected by increased thrombin-antithrombin (TAT) complex levels[10,13-15] and increased fibrin D-dimer compared with healthy individuals.[11,14-18]

Some studies link the pathogenesis behind DCI to the development of microthrombi, possibly caused by increased platelet activation.[19-21]

Thromboelastometry/thromboelastography (ROTEM/TEG [Tem International GmbH, Munich, Germany]) evaluates coagulation from clot initiation to termination, including clot strength.[22] ROTEM/TEG has also been applied in patients with SAH from 12 hours to days after symptom onset.[12,23-26] Thrombin generation is a dynamic assay used to measure the amount of thrombin generated.[27] Analysis of thrombin generation detects both hypocoagulable and hypercoagulable conditions; however, thrombin generation determined by this dynamic assay has not been previously reported in patients with SAH.

Evaluation of coagulation in the very early hours after symptom onset with global and dynamic coagulation assays may increase our insight into changes in coagulation in the acute phase of SAH and could improve our knowledge of post-SAH pathology.

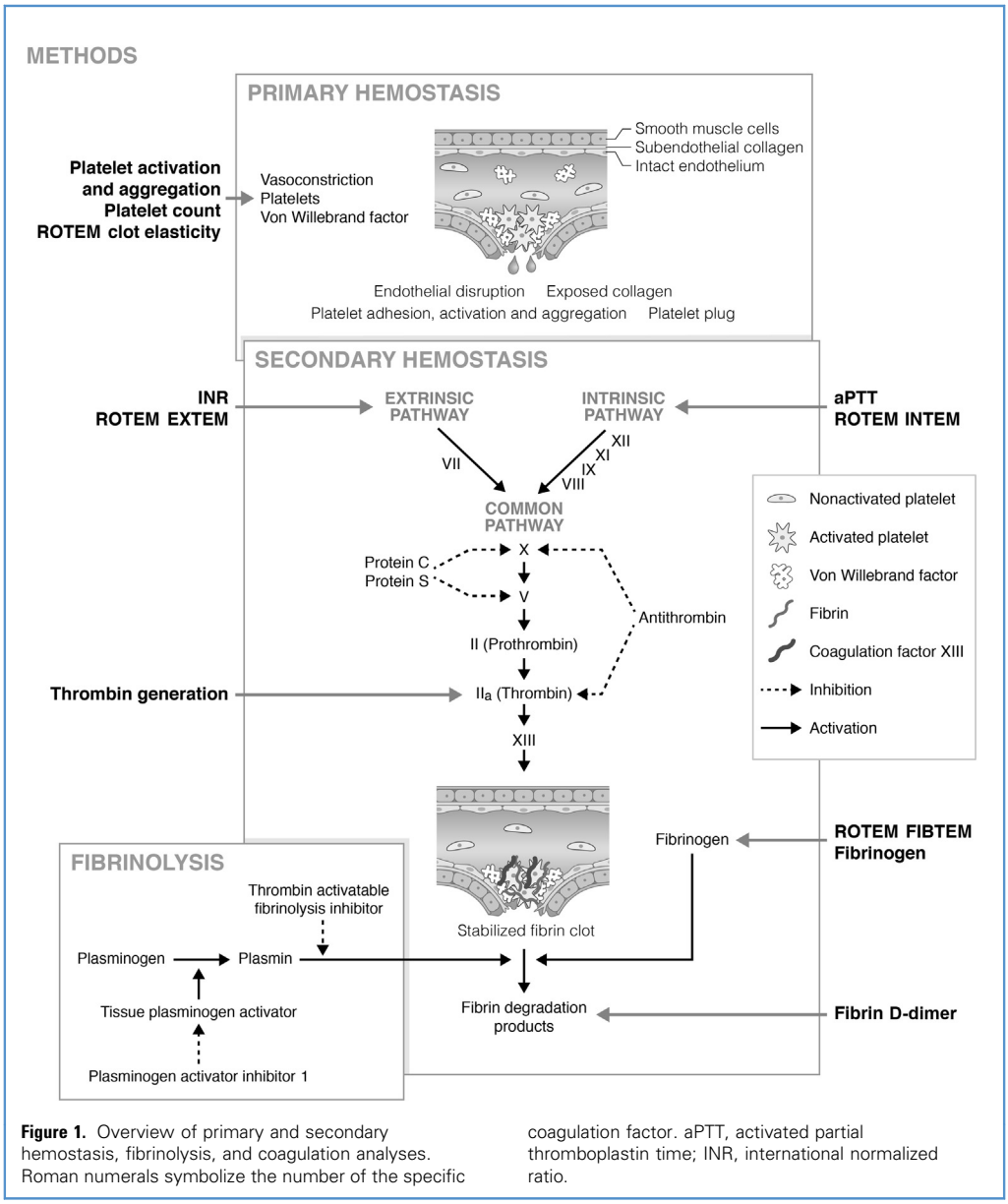

Figure 1. Overview of primary and secondary hemostasis, fibrinolysis, and coagulation analyses. Roman numerals symbolize the number of the specific coagulation factor. aPTT, activated partial thromboplastin time; INR, international normalized ratio.

By using dynamic coagulation analyses, we aimed to investigate coagulation after aneurysmal SAH and to illuminate underlying mechanisms behind possible changes. We hypothesized that patients with SAH show activated coagulation in the acute phase compared with healthy individuals.

METHODS

Study Population

This prospective cohort study enrolled 46 patients with aneurysmal SAH admitted to the Department of Neurosurgery, Aarhus University Hospital, Denmark from June 18, 2014 to August 31, 2016. Blood samples were collected at admission and again 24 hours after symptom onset. Part of this study population has been published previously.[28] Inclusion criteria were spontaneous SAH diagnosed by cerebral computed tomography (CT) or magnetic resonance imaging (MRI). The location of the aneurysm was diagnosed by CT angiography or digital subtraction angiography. Exclusion criteria were younger than 18 years, perimesencephalic subarachnoid bleeding (defined as hemorrhage restricted to the cisterns surrounding the brainstem with a negative cerebral angiography result), pregnancy, known bleeding disorder, active cancer or chemotherapy within the previous 3 months, liver cirrhosis, current infection, treatment with antithrombotic or antiplatelet drugs, and hemorrhage triggered by arteriovenous malformation, brain tumor or trauma, and hence, traumatic SAH was also excluded.

Information about the time of SAH onset was based on information provided by patients or their relatives. Clinical data were obtained from medical records. We documented the Glasgow Coma Scale score and applied the World Federation of Neurological Surgeons grading system for subarachnoid hemorrhage and the Hunt and Hess classification at admission. The APACHE II (Acute Physiology and Chronic Health Evaluation) score was calculated during the first 24 hours of hospitalization. The modified Fisher grading scale was obtained from CT scans performed at admission. The attending physician decided when rescans were required for each patient with SAH. All scans were retrospectively evaluated, and the presence of DCI was recorded. DCI was defined as a new focal neurologic deficit or decrease in the level of consciousness, with identified cerebral infarction on CT or MRI after exclusion of procedure-related infarctions.

ROTEM data were compared with a gender-matched healthy control group (14 men, 32 women), with a mean age of 44 years (range, 21–60 years), extracted from a previously reported population of healthy individuals.[29] Thrombin generation data were compared with gender-matched healthy controls (14 men, 32 women), with a mean age of 52 years (range, 33–65 years), also extracted from a previously reported healthy population.[30]

Clinical outcome was evaluated after 30 days using the Modified Rankin Scale. The Modified Rankin Scale score and information on 30-day mortality were obtained from medical records. The attending neuroradiologist and neurosurgeon decided if coil treatment was possible or surgical clipping should be performed. According to local clinical practice and the decision of the attending neurosurgeon/neuroradiologist, treatment with 1 g of TXA commenced immediately when SAH was diagnosed (if within 48 hours from symptom onset) and coil procedure was not possible within the next 6 hours. Further treatment consisted of 1 g of TXA 2 hours after the initial dose and 1 g every 6 hours thereafter.

According to local clinical practice, patients with SAH were treated with 1–3 L of isotonic fluid therapy during the first 24 hours. The standard procedure after endovascular coiling was treatment with 5000 international units of unfractionated heparin (UFH) (administered once) immediately when coils were in position. The day after the procedure, 75 mg of aspirin was initiated and administrated twice daily for 1 month. Thus, antiplatelet therapy was intitiated after the final blood sample, which was obtained 24 hours after symptom onset.

The Central Denmark Region Committees in Biomedical Research Ethics and Data Protection Agency approved the study (incompetent patients case number 1–10–72–95–14, version 3, 05052014 and competent patients case number 1–10–72–94–14, version 4, 27042014). Patients or their legal proxies gave written informed consent before enrollment (incompetent patients case number 1–16–02–225–14 and competent patients case number 1–16–02–224–14). The Helsinki Declaration was followed in all aspects.

Laboratory Analyses

ROTEM analyses were sampled in tubes containing 3.2% sodium citrate (Vacuette [Greiner bio-one GmbH, Kremsmuenster, Austria]) and performed within 2 hours using the standard assays EXTEM, INTEM, and FIBTEM. Clot initiation was evaluated by clotting time. Clot propagation was evaluated using the maximum velocity of clot formation and time to maximum velocity. Clot strength was evaluated by maximum clot firmness (MCF). Fibrinolysis was evaluated by the lysis index after 30 minutes (LI30) in EXTEM. LI30 describes the degree of fibrinolysis relative to MCF after a 30-minute runtime of the ROTEM analyzer (% clot firmness lost). Calculation of the platelet component, maximum clot elasticity (platelet MCE), was derived from ROTEM tests performed with and without platelet inhibition as described by Solomon et al.[31] First, MCE was calculated for both EXTEM MCF and FIBTEM MCF using the following formula: MCE = (100 × MCF)/(100 − MCF) for each parameter. Second, clot elasticity attributable to platelets was calculated as: platelet MCE = MCE EXTEM−MCE FIBTEM.[31]

Thrombin generation was sampled in tubes containing 3.2% sodium citrate (Vacuette) and quantified in platelet-poor plasma with the addition of tissue factor (5 pM) and phospholipids (4 μM) using a calibrated automated thrombogram (Thrombinoscope BV, Maastricht, the Netherlands). We obtained the following thrombin generation parameters: lag time, time to peak, peak, and endogenous thrombin potential.

Blood samples for the measurement of TAT complex levels were sampled in tubes containing 3.2% sodium citrate (Vacuette), and the TAT levels were determined using an enzyme-linked immunoassay (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany). The reference interval was provided by the manufacturer.

Blood for the analysis of activated partial thromboplastin time (aPTT), fibrinogen (functional, Clauss method), fibrin D-dimer, international normalized ratio, and thrombin time was sampled in tubes containing 3.2% sodium citrate (Vacuette) and analyzed

using CS2100i (Sysmex, Kobe, Japan). aPTT results are presented with 2 reference intervals because the Department of Clinical Biochemistry, Aarhus University Hospital changed the aPTT assay on April 5, 2016, which altered the reference interval. The coagulation factor XIII (FXIII) was analyzed using ACL TOP 500 (Instrumentation Laboratory, Munich, Germany), and analysis of serum samples of S100 calcium binding protein B (S100B) and lithium heparin samples of C-reactive protein were performed using the COBAS 6000 C and E (Roche, Basel, Switzerland).

Ethylene diamine tetra acetic acid samples for hemoglobin, platelet count, and erythrocyte volume fraction were analyzed with Sysmex XE-5000 (Sysmex, Kobe, Japan).

Statistical Analysis

The sample size calculation was based on FIBTEM MCF levels in a population of healthy controls obtained at the Department of Clinical Biochemistry, Aarhus University Hospital, Denmark.[29] The mean FIBTEM MCF level was 14 mm (standard deviation, ± 3 mm) in healthy individuals. The standard deviation for patients with SAH was estimated to be ±4.5 mm, because we assumed that the standard deviation was higher in patients with SAH than in healthy individuals. We chose the minimum relevant difference between patients and healthy individuals to be 3 mm. With a significance level at 5% (2α) and a test power at 90% (1-β), a minimum of 41 patients needed to be included.

The data were checked for normal distribution using histograms and QQ-plots. Data are presented as median with interquartile range (IQR). Differences in laboratory results between patients with SAH at admission and healthy controls, and differences in coagulation test results between the patients, divided according to clinical outcome, were tested using the unpaired t test, unless assumptions were not fulfilled and the Wilcoxon Mann-Whitney test was applied. Differences in laboratory test results between admission and 24 hours after symptom onset were tested using the paired t test, and assumptions were checked using Bland-Altman and QQ-plots. The Wilcoxon signed-rank test was used if assumptions were not fulfilled. Statistical analysis was performed using STATA 13 (StataCorp LLC, College Station, Texas, USA). Graphs were designed with Prism 6.0 (GraphPad, La Jolla, California, USA) and presented with the boxplots Tukey method for plotting the whiskers and outliers.

The article was prepared in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[32]

RESULTS

Patient Demographics and Clinical Characteristics

Table 1 shows the main characteristics of the 46 enrolled patients. The median age was 58 years (range, 37–87 years) and 32 patients (70%) were women. Patients enrolled in the study had low comorbidity, with hypertension being the most frequent medical condition. Thirteen patients (28%) had a history of smoking, 16 patients (35%) had never smoked, and the smoking history for 17 patients (37%) was missing. Fourteen patients (30%) died within 30 days.

At admission, 45 of the included patients with SAH underwent a CT scan. One patient was diagnosed with SAH on admission with MRI, but had a CT scan performed immediately after the MRI. The median Fisher grade was 4, (IQR, 3–4). Of the included 46 patients, 23 (50%) received the coil procedure and 12 (26%) had a surgical procedure with clips performed. Sixteen patients (70%) had their aneurysm coiled within 24 hours from symptom onset. One patient received both the coil and clips procedure. Nine patients (20%) did not receive the coil procedure or an operation

Table 1. Demographic and Clinical Characteristics of 46 Patients With Spontaneous Subarachnoid Hemorrhage

Variables	Value
Age (years), mean (range)	59 (37–87)
Females, n (%)	32 (70)
Clinical status at admission, n (%)	
Intubated	20 (43)
Comorbidity, n (%)	
Hypertension (N = 42)	11 (24)
Diabetes (N = 45)	1 (2)
Medication before admission, n (%)	
Statins (N = 46)	8 (17)
Antihypertensive medication (N = 45)	11 (24)
Selective serotonin reuptake inhibitors (N = 45)	2 (4)
Scores at admission and 24 hours	
Glasgow Coma Scale, median (IQR)	13 (4–15)
Hunt and Hess, median (IQR)	3 (2–4)
World Federation of Neurological Surgeons score, median (IQR)	3 (1–5)
Acute Physiology and Chronic Health Evaluation II score (0–71), median (IQR)	17 (12–23)
Radiologic findings at admission	
Modified Fisher grading scale (0–4), median (IQR)	4 (3–4)
Intraventricular bleeding, n (%)	29 (63)
Parenchymal hemorrhage, n (%)	18 (39)
Aneurism treatment, n (%)	
Surgical, clips	13 (28)
Endovascular, coil	23 (50)
Both coil and clips (>1 aneurysm)	1 (2)
External liquid drainage, n (%)	19 (41)
No surgical treatment, n (%)	9 (20)
Scores, day 30	
Modified Rankin Score day 30, median (IQR)	4 (1–6)
Mortality day 30, n (%)*	14 (30)

Data are presented as the median (interquartile range) except for age, which is presented as the mean (range).
IQR, interquartile range.
*Missing follow-up data in 1 patient.

because they died shortly after admission (8 patients) or because the aneurysm could not be located (1 patient). Admission samples were obtained within a median of 3 hours and 39 minutes (IQR, 2 hours 46 minutes–6 hours 36 minutes) from symptom onset. The sample time at 24 hours after symptom onset was 23 hours and 40 minutes (IQR, 22 hours 31 minutes–24 hours 26 minutes).

Among the 46 included patients, 4 received TXA before arrival at the hospital, and the information concerning TXA administration was missing for 1 patient. Therefore, 41 patients (89%) had an admission sample obtained before administration of TXA. One gram of TXA was administered 1–6 times during the first 24 hours. Seven patients (15%) never received TXA treatment.

Patients with SAH at Admission versus Healthy Controls

We found no difference in ROTEM results at admission when comparing patients with SAH who did not receive TXA with patients who received TXA (EXTEM MCF, $P = 0.56$; INTEM MCF, $P = 0.38$; FIBTEM MCF, $P = 0.71$). Results reported are therefore based on all patients enrolled in the study.

At admission, patients with SAH had a higher clot strength than healthy controls as indicated by a higher MCF in EXTEM ($P < 0.0001$), INTEM ($P = 0.08$), and FIBTEM ($P < 0.0001$), as presented in Figure 2. In addition, Figure 2 shows that the platelet MCE was higher in patients with SAH than in healthy controls ($P < 0.0001$).

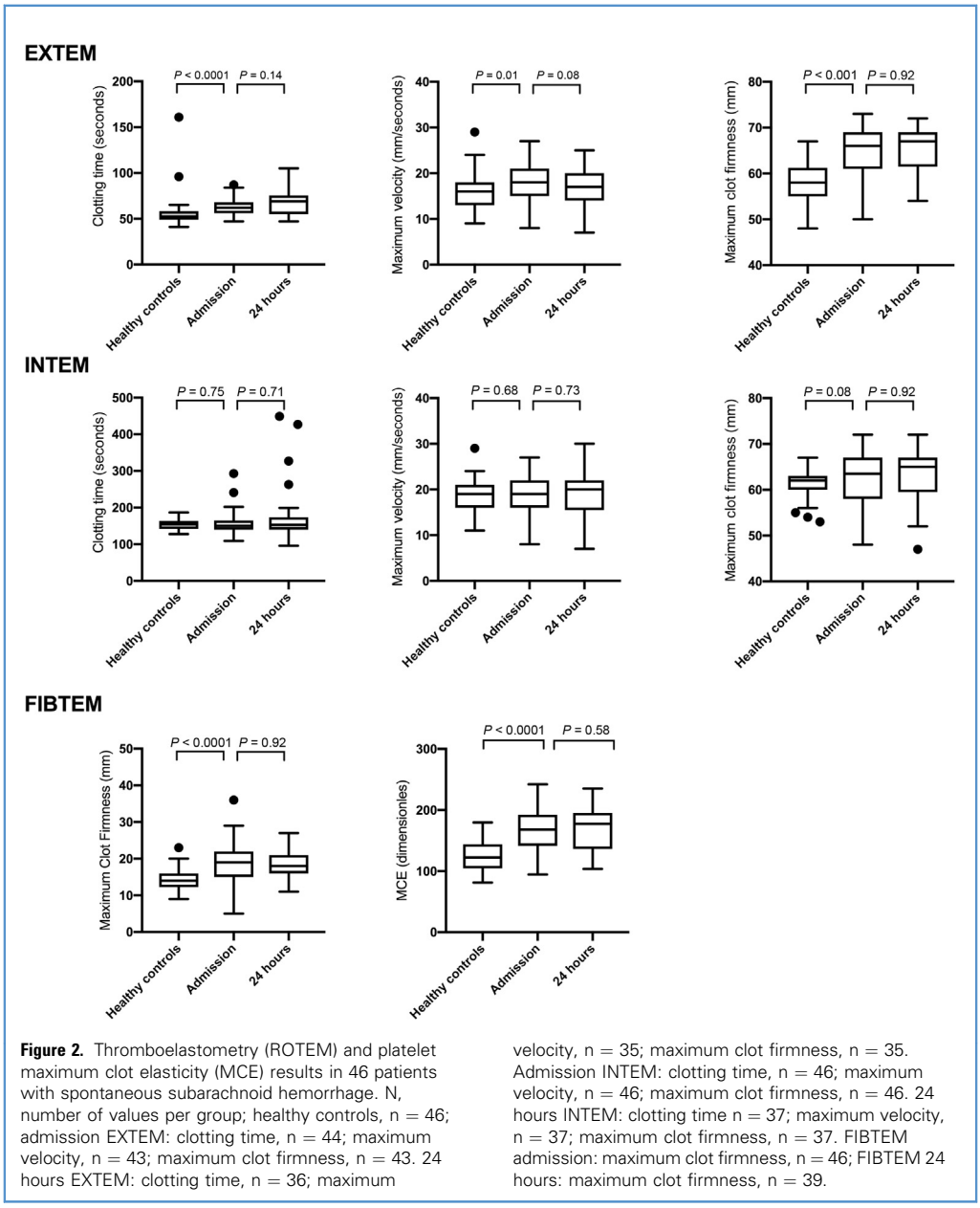

Figure 2. Thromboelastometry (ROTEM) and platelet maximum clot elasticity (MCE) results in 46 patients with spontaneous subarachnoid hemorrhage. N, number of values per group; healthy controls, n = 46; admission EXTEM: clotting time, n = 44; maximum velocity, n = 43; maximum clot firmness, n = 43. 24 hours EXTEM: clotting time, n = 36; maximum velocity, n = 35; maximum clot firmness, n = 35. Admission INTEM: clotting time, n = 46; maximum velocity, n = 46; maximum clot firmness, n = 46. 24 hours INTEM: clotting time n = 37; maximum velocity, n = 37; maximum clot firmness, n = 37. FIBTEM admission: maximum clot firmness, n = 46; FIBTEM 24 hours: maximum clot firmness, n = 39.

Figure 3 shows that thrombin generation in patients with SAH was characterized by shorter lag time ($P < 0.0001$), shorter time to peak ($P < 0.0001$), and a higher thrombin peak ($P < 0.0001$) compared with healthy controls. Endogenous thrombin potential was higher in patients with SAH than in healthy controls, although not statistically significant ($P = 0.06$). Median TAT complex levels were above the upper limit of the reference interval (Table 2). Conventional coagulation tests were within the reference interval except for fibrin D-dimer, which was slightly increased (Table 2). In 20 patients (43%), S100B concentrations were higher than the reference interval.

Patients with SAH after 24 Hours

No ROTEM parameters changed significantly from admission to 24 hours after symptom onset (Figure 2), and the platelet MCE remained increased ($P = 0.42$) (Figure 2). LI30 results were within the reference interval at admission and showed no change within 24 hours (Table 2). Thrombin generation showed an increase in lag time ($P < 0.0002$) and time to peak ($P = 0.03$), as well as a decrease in peak ($P = 0.01$) and endogenous thrombin potential ($P = 0.01$) (Figure 3). TAT complex levels decreased ($P < 0.0001$), and whereas international normalized ratio and aPTT showed only subtle changes, fibrinogen increased ($P = 0.01$) and FXIII decreased significantly ($P < 0.0001$) (Table 2). Fibrin D-dimer did not change from admission to 24 hours after symptom onset ($P = 0.30$) and neither did the S100B levels ($P = 0.05$).

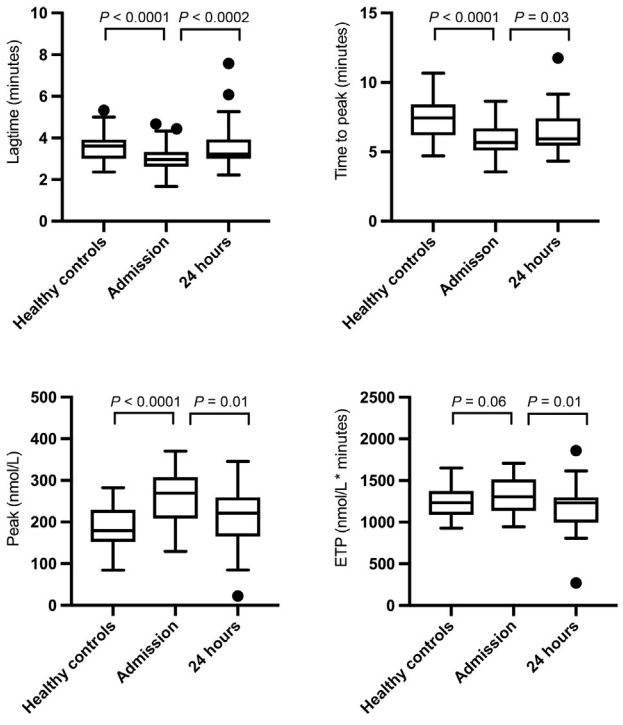

Figure 3. Thrombin generation results in 46 patients with spontaneous subarachnoid hemorrhage. ETP, endogenous thrombin potential; N, number of values per group; healthy controls, n = 46; admission, n = 44, 24 hours, n = 30.

Patients with SAH 24 Hours after Symptom Onset with Omission of Results Influenced by UFH. Results from 8 patients were influenced by UFH as judged by prolonged thrombin time and/or prolonged aPTT and no thrombin generation. After omission of results from these 8 patients, analyses were performed for parameters that could be affected by UFH. No significant changes were found from admission to 24 hours after symptom onset in thrombin time ($P = 0.26$), INTEM CT ($P = 0.26$), INTEM MCF ($P = 0.89$), EXTEM MCF ($P > 0.99$), or FIBTEM MCF ($P = 0.92$). The median of aPTT at admission was 27 seconds (range, 20–39 seconds), whereas it was 30 seconds (range, 22–39 seconds) at 24 hours ($P < 0.0001$).

Clinical Outcomes

Rescans were performed in 29 patients between day 4 and day 14 at the attending physician's discretion, and DCI was diagnosed in 9 of these patients (31%). Table 3 presents laboratory test results with patients divided into groups according to clinical outcome with or without DCI and in survivors versus nonsurvivors. The median admission FIBTEM MCF was higher in patients with DCI than in patients without DCI ($P = 0.02$). Nonsurviving patients had higher TAT ($P = 0.002$) and fibrin D-dimer levels ($P = 0.001$) than did surviving patients. The level of S100B was higher in nonsurviving than in surviving patients ($P < 0.0001$).

DISCUSSION

Patients with SAH showed an increase in clot strength already at admission. Clot strength remained increased during the first 24 hours after symptom onset, although fibrinogen remained well within the reference interval and FXIII decreased significantly. These findings indicate that increased clot strength is potentially driven by platelet-related factors. Increased platelet MCE, both at admission and 24 hours after symptom onset, further supports this hypothesis.

The most recent studies investigating coagulation in patients with SAH using viscoelastic assays also reported increased clot strength, but not until 24–72 hours after symptom onset, and patients receiving antiplatelet drugs were not excluded.[12,23,26] Ramchand et al.[23] suggest that the increase in clot strength could be caused by increased platelet activation; however, these investigators did not present platelet activation marker, FXIII or, fibrinogen levels.

Studies concerning primary hemostasis after SAH report increased platelet aggregation within days to weeks after symptom onset,[33,34] increased platelet activation in patients with SAH developing DCI,[19-21,26,35] and higher levels of coated platelets in patients with SAH compared with healthy individuals.[36,37] Overall, these studies indicate increased platelet function after SAH. However, to clarify the potential role of platelets in the very acute phase of SAH, platelet function has to be analyzed in continuation of the indirect determination of MCE.

In our study, platelet MCE did not differ between patients with or without development of DCI, which is in accordance with the findings of Vahtera et al.[12] However, we evaluated coagulation within 24 hours after symptom onset, and DCI was investigated between day 4 and day 14. Further studies are needed to

Table 2. Laboratory Test Results in 46 Patients With Spontaneous Subarachnoid Hemorrhage

	Reference Intervals	Admission	24 Hours	*P* Value
Thrombin-antithrombin complex (μg/L)	2.0–4.2	23.0 (11.8–71.3)*	8.8 (5.0–13.7)†	<0.0001
Activated partial thromboplastin time (seconds)				
Before April 5, 2016 (n = 42)	25–38	27 (26–30)‡	30 (28–39)§	<0.0001
After April 5, 2016 (n = 4)	20–29	26 (21–27)	27 (22–36)	0.36
Thrombin time (seconds)	<21	16 (16–17)	16 (15–21)	0.02
Fibrinogen (μmol/L)	5.5–12.0	8.6 (7.5–10.0)‖	9.2 (8.1–10.1)§	0.01
Lysis index after 30 minutes, EXTEM (%)	>94	100 (100–100)	100 (100–100)	0.89
Fibrin D-dimer (mg/L fibrinogen equivalent units)	<0.50	1.4 (0.65–6.60)‖	1.2 (0.70–3.50)§	0.05
International normalized ratio	<1.2	1.1 (1.0–1.1)‖	1.1(1.1–1.2)§	<0.0001
Platelet count ($\times 10^9$/L)	145–400¶	217 (184–262)‖	203 (171–245)§	0.01
Coagulation factor XIII ($\times 10^3$ arbitrary units/L)	0.61–1.77	1.10 (0.93–1.33)‡	0.88 (0.68–1.1)†	<0.0001
Hemoglobin (mmol/L)				
Females (n = 32)	7.3–9.5	8.0 (7.5–8.5)	6.9 (6.5–7.3)#	<0.0001
Males (n = 14)	8.3–10.5	8.5 (7.8–9.1)	7.3 (7.0–7.7)‖	<0.0001
C-reactive protein (mg/L)	<8.0	2.0 (0.8–3.4)‖	16.5 (7.5–41.7)#	0.0001
Serum s100 calcium binding protein B (μg/L)	0.02–0.13	0.12 (0.05–0.33)‖	0.12 (0.05–0.21)**	0.30

Data are presented as median (interquartile range).
*2 missing values.
†8 missing values.
‡3 missing values.
§6 missing values.
‖1 missing value.
¶Reference interval for women and men together.
#5 missing values.
**7 Missing values.

investigate whether increased platelet function in patients with SAH influences pathogenesis such as DCI. The admission endogenous thrombin potential was not significantly different from that of healthy controls, whereas the TAT complex levels were increased at admission compared with the reference interval. Measurements of thrombin generation illustrate ex vivo thrombin generation in platelet-poor plasma, whereas the TAT complex levels reflect in vivo generated thrombin. Hence, the discrepancy between thrombin generation results and TAT complex levels supports that platelets might be the main drivers of the hypercoagulation found in the present study. Twenty-four hours after symptom onset, thrombin generation and TAT complex levels showed less activated coagulation, which might be because of a decrease in substrate.

We found higher TAT complex levels and fibrin D-dimer at admission in nonsurviving patients than in surviving patients. This finding is in accordance with previous studies[13,15,38-41] and indicates that increased thrombin generation is related to mortality and poor functional outcome. We did not find that platelet MCE was related to increased mortality in this study, possibly because of lack of power.

S100B, a marker of neurologic injury, showed higher levels at admission in nonsurviving patients than in surviving patients. Previous studies also report higher S100B levels in patients with poor functional outcome.[42-45] Of the present patients with SAH, 56% had S100B levels within the reference interval at admission.

The major strength of the present study is its multimodal dynamic coagulation analyses performed in the early phase after SAH. It is a single-center study, but the study population represents the general population of patients with SAH.[1] We carefully included patients who did not receive any antithrombotic treatment, and therefore, the results reflect the effect of SAH on systemic coagulation without the influence of antithrombotic treatment. Some limitations should be considered. Our sample size is relatively small and not adequate for prognostic interpretations. Healthy controls and patients are matched on gender but differ in age, because the group of patients with SAH included more elderly people. However, a previous study showed that the association between age and ROTEM and thrombin generation parameters is nonlinear.[46] Patients treated with endovascular coiling received UFH, and in 8 patients, this treatment was administrated so close to the 24-hour sample that these results were influenced by UFH. However, after omission of results from these 8 patients, the conclusions still remained. Rescans were not systematically performed, which limits

Table 3. Laboratory Test Results at Admission in 46 Patients With Spontaneous Subarachnoid Hemorrhage, With and Without Delayed Cerebral Ischemia at Rescans Within 14 Days From Admission and in Survivors Compared With Nonsurvivors

	Delayed versus No Delayed Cerebral Ischemia			Survivors versus Nonsurvivors		
Variables (Reference Intervals)	Delayed Cerebral Ischemia (n = 9)	No Delayed Cerebral Ischemia (n = 20)	*P* Value	Survivors (n = 32)	Nonsurvivors (n = 14)	*P* Value
FIBTEM, maximum clot firmness (8–20 mm)	22 (19–24)	17 (15–21)	0.02	19 (15–22)	18 (14–21)	0.17
Platelet maximum clot elasticity (74–165)	189 (155–210)	168 (142–192)*	0.21	174 (144–198)‡	157 (140–189)	0.56
Lysis index after 30 minutes %, EXTEM (>94%)	100 (100–100)*	100 (100–100)*	0.53	100 (100–100)†	100 (100–100)	0.72
Endogenous thrombin potential (1011–1551 nmol/L × minutes)	1303 (1208–1584)	1309 (1089–1508)*	0.42	1326 (1128–1514)*	1303 (1140–1541)*	1.00
Thrombin-antithrombin complex (2.0–4.2 µg/L)	23.0 (14.5–46.8)	21.0 (12.0–109.0)	0.59	16.7 (11.2–27.6)	53.4 (28.4–129.6)*	0.002
Fibrinogen (5.5–12.0 µmol/L)	8.6 (8.4–9.9)	8.4 (6.9–9.8)	0.31	9.2 (7.6–10.4)*	7.9 (6.8–8.6)	0.06
Fibrin D-dimer (<0.5 mg/L fibrinogen equivalent units)	1.3 (0.7–2.0)	2.3 (0.8–9.9)	0.18	0.92 (0.51–1.8)*	6.5 (2.0–10.9)	0.001
Serum s100 calcium binding protein B (0.02–0.13 µg/L)	0.10 (0.06–0.14)*	0.20 (0.07–0.71)*	0.23	0.07 (0.05–0.16)*	0.49 (0.13–1.94)*	<0.0001

Data are presented as median with interquartile range (IQR).
*1 missing value.
†2 missing values.
‡3 missing values.

documentation of rebleeding or DCI development. We do not have information on how many patients with SAH were admitted dead or died within a few minutes after admission before enrollment. Therefore, our data did not allow us to estimate the total eligible SAH population.

CONCLUSIONS

Patients with SAH were in a hypercoagulable state at admission and remained so despite a subtle decrease in thrombin generation 24 hours after symptom onset. The mechanisms behind the increased coagulation may be mediated by platelets. Further studies are needed to confirm whether platelets play a key role in coagulation and outcome after SAH.

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