Changes in the Coagulation and Fibrinolytic System of Patients with Subarachnoid Hemorrhage

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Abstract

The aim of this study was to investigate the dynamic changes in the coagulation and fibrinolytic system with subarachnoid hemorrhage. The blood coagulation enzyme-AT complex (TAT), anticoagulant enzyme (AT), tissue plasminogen activator (tPA), plasminogen activin inhibitor (PAI-1), and mean blood flow velocity were measured. The TAT level was significantly higher 6 h after subarachnoid hemorrhage (SAH), whereas AT was significantly lower. These changes were maintained at 12 h to 1 d after SAH, returned to normal at 3 d, significantly changed again at 7 d to 14 d. The tPA level gradually increased after SAH and peaked at 14 d, and then returned to normal at 21 d. The PAI-1 levels were significantly lower than those in the control group 1 d after SAH gradually increased, and returned to normal at 21 d. In the cerebral vasospasm (CVS) groups, the levels of TAT, and AT significantly changed compared to the non-CVS groups after SAH. The PAI-1 levels were higher at 7 d and 14 d, but the changes were not significant. In groups Fisher III and IV as well as Hunt III to V, the TAT, AT, tPA, and PAI-1 levels were significantly higher than those in both Fisher and Hunt I and II 6 h, 12 h, 1 d, 7 d, and 14 d after SAH. The changes in the coagulation and fibrinolytic system of patients with SAH are correlated with the progress and symptoms of SAH as well as the blood content and CVS.

Key words: coagulation, fibrinolysis, subarachnoid hemorrhage, cerebral vasospasm

Introduction

Spontaneous subarachnoid hemorrhage (SAH) is mainly caused due to the rupture of intracranial aneurysms.[1] Most patients can receive satisfactory treatment via surgical clipping or interventional therapy.[2] However, some patients do not choose surgery or intervention and opt to receive conservative treatment. Thus, changes in the blood coagulation and fibrinolytic system need to be understood.[3] Research shows that blood is at a high coagulation state during the acute phase of bleeding, and then the fibrinolytic system changes.[4,5] Understanding these phenomena could aid the selection and use of effective anticoagulation and hemostatic drugs. The life-threatening complication for patients after SAH is cerebral vasospasm (CVS).[6] CVS causes cerebral blood flow changes that can lead to ischemia, oxygen deficiency, and encephalopathy.[7,8] CVS can be effectively prevented and controlled by maintaining the blood pressure at moderate levels, increasing the blood volume, and keeping the blood diluted

via the triple-H (hemodilution, hypervolemia, and hypertension) treatment.[9] Therefore, the relationship of blood coagulation and fibrinolytic system changes with CVS need to be determined to select the best conservative treatment for a patient. Research has shown that blood coagulation and fibrinolytic system changes are related to CVS.[10]

Some studies have reported on the occurrences of blood coagulation and fibrinolytic changes at a certain time after SAH.[5] However, dynamic observations for a large number of conservative treatment patients are difficult to carry out.

Materials and Methods

I. Subjects

A total of 30 patients with intracranial aneurysm (SAH) in the Second Hospital of Shandong University from October 2009 to November 2011 were enrolled in the current study. All participants were SAH patients who had quitted surgical clipping or coil embolization and asked for conservative treatment. The patients included 15 males and 15 females aged 43 to 72 years (average = 65.2 ± 7.3 years). All patients were confirmed by head computed tomography (CT) and

digital subtraction angiography (DSA) examination. They were hospitalized in neurosurgical intensive care units and received symptomatic treatment including strict immobilization, oxygen uptake, purgation, sedation, blood pressure control, and so on. The amount of bleeding was classified according to the Fisher CT classification: level I, 5 patients; level II, 10 patients; level III, 10 patients; and level IV, 5 patients. The severity of the illness was classified according to the Hunt classification: level I, 6 cases; level II, 12 cases; level III, 7 cases; and level IV to V, 5 patients. All patients did not take anticoagulants and drugs influencing fibrinolytic activity in the last 1 month. A total of 20 healthy individuals served as the control group, with 8 males and 12 females aged 42 to 66 years (average 61.3 ± 8.2). Both patient and control groups had no liver and blood disease history. This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the Second Hospital of Shandong University. Written informed consent was obtained from all participants.

II. Indicators

The blood coagulation enzyme-AT complex (TAT) was detected by the enzyme linked immunosorbent assay (ELISA) method. Measured samples were placed on trifluralin-coated plates containing rabbit anti-human blood coagulation enzyme polyclonal antibody. Mouse anti-human monoclonal antibody was then added, and the TAT content was determined by the color change in o-phenylendiamine.

The anticoagulant enzyme (AT) was measured by diffusing test samples in a coagulation enzyme gel board containing heparin for 18 h to 24 h covered by a fibrinogen solution. The bottom of the coagulation enzyme gel board was pale ivory due to the existence of fibrin. The covered part presented an empty circular spot due to thrombin deactivation. The empty spot diameter size was positively correlated with AT III activity.

The tissue plasminogen activator (tPA) was detected by the chromogenic substance method. Plasminogen is converted into plasmin under the action of tPA and its covalent complex. This complex induces the release of chromogenic substance into chromophore groups, and the color depth was positively correlated with tPA.

The plasminogen activin inhibitor (PAI-1) was measured indirectly using the chromogenic substance method.

About 4 mL of empty stomach peripheral venous blood from all patients were stored 6 h, 12 h, 1 d, 3 d, 7 d, 14 d, and 21 d after SAH. The blood samples were for TAT, AT, tPA, and PAI-1 according

to the above procedures. Patients in the same time period were examined by transcranial Doppler ultrasonography, respectively. A mean blood flow velocity in the middle cerebral artery (VMCA) > 120 cm/S was considered as CVS.[1–5,7–11] VMCA severity was classified as follows (cm/S): mild, 120 to 139; moderate, 140 to 200; and severe, > 200. Blood from the control group was drawn after relaxation for 30 min, and tested similarly as that of the patients.

III. Statistical analyses

Data were analyzed using the Studen-Newman-Keuls test, and groups of small samples were treated with the *t* test.

Results

I. Blood coagulation and anticoagulation index changes

Compared to the control group, 6 h after SAH, TAT sharply increased and At significantly decreased ($P < 0.01$). TAT maintained the high level at 12 h to 1 d ($P < 0.05$) and gradually recovered at 3 d ($P > 0.05$). However, at 7 d to 14 d, TAT increased and AT significantly decreased ($P < 0.05$). TAT gradually returned to normal at 21 d (Table 1).

II. Fibrinolytic activity index

After SAH, tPA gradually increased and its activity significantly increased at 7 d compared to the control group ($P < 0.05$). The tPA level reached a peak until 14 d ($P < 0.01$), and then returned to normal. On the other hand, plasma PAI-1 activity was significantly lower than that in the control group 1 d after SAH ($P < 0.05$). The activity gradually increased as time progressed (Table 1, Fig. 1).

III. Relationship among TAT, AT, tPA, PAI-1, and CVS

Comparing the SAH concurrent with CVS group and the SAH without CVS group, TAT and AT showed significant differences at 6 h, 12 h, 1 d, 7 d, and 14 d ($P < 0.05$). The former plasma PAI-1 activity was significantly higher than the latter at 7 d and 14 d ($P < 0.05$). The plasma tPA activity at different time points between two groups showed no significant differences (Table 2, Fig. 2).

IV. Relationship among TAT, AT, tPA, PAI1, SAH amount of bleeding, and the severity of illness

In the SAH group, Fisher CT levels III and IV were higher than levels I and II ($P < 0.05$), except at 3 d and 21 d (Table 3, Fig. 3). Hunt levels III and IV were also higher than levels I and II, except at 3 d and 21 d ($P < 0.05$) (Table 4, Fig. 4).

Table 1 Dynamic change of blood coagulation, fibrinolysis index (x ± s)

Group	Cases	TAT (μg/L)	AT (mg/L)	tPA (μg/L)	PAI (μg/L)	T/P
Control	20	1.5 ± 0.4	275 ± 36	5.3 ± 2.3	16.0 ± 5.3	0.33
SAH 6 h	30	5.6 ± 1.0[b]	101 ± 17[b]	5.1 ± 2.3	7.3 ± 2.2[b]	0.70[a]
12 h	30	4.0 ± 0.5[b]	149 ± 18[b]	6.2 ± 2.4	8.8 ± 2.4[a]	0.70[a]
1 d	30	4.2 ± 0.6[b]	155 ± 19[a]	6.3 ± 2.3	9.0 ± 3.3[a]	0.70[a]
3 d	30	1.7 ± 0.5	257 ± 25	7.3 ± 3.2	10.0 ± 3.6	0.73[a]
7 d	30	3.9 ± 0.3[a]	159 ± 20[a]	9.1 ± 3.0[a]	11.7 ± 4.2	0.78[a]
14 d	30	4.3 ± 0.4[a]	132 ± 18[a]	11.0 ± 4.0[b]	14.3 ± 5.1	0.78[a]
21 d	30	1.6 ± 0.3	201 ± 20	7.3 ± 3.0	16.3 ± 5.1	0.45

Note: Compared with the control group, [a]$P < 0.05$, [b]$P < 0.01$. AT: anticoagulant enzyme, PAI: plasminogen activin inhibitor, TAT: blood coagulation enzyme-AT complex, T/P: ratio of tPA to PAI-1, tPA: tissue plasminogen activator.
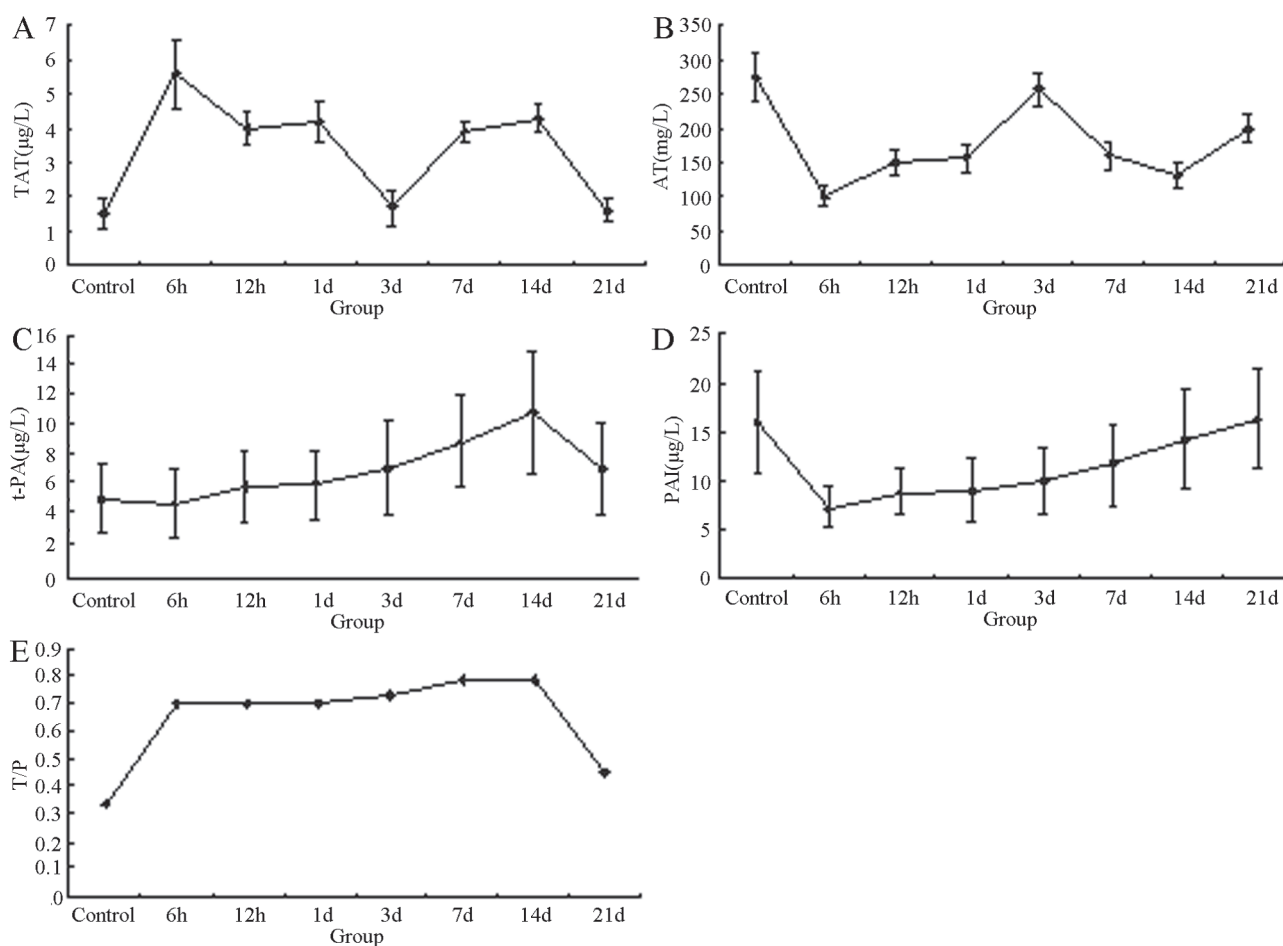

Fig. 1 Dynamic change of blood coagulation, fibrinolysis index. A: TAT (μg/L), B: AT (mg/L), C: tPA (μg/L), D: PAI (μg/L), E: T/P. AT: anticoagulant enzyme, CVS: cerebral vasospasm, PAI: plasminogen activin inhibitor, SAH: subarachnoid hemorrhage, TAT: blood coagulation enzyme-AT complex, tPA: tissue plasminogen activator.

Discussion

When the cerebral vessel bleeds, the balance between blood coagulation and the fibrinolytic system is broken. The body responds by a series of blood coagulation and fibrinolytic changes to regain the balance.[12] In clinical practice, testing for blood coagulation disorders involves the determination

Table 2 Plasma TAT, AT, tPA, and PAI-1 activity in the SAH patients without CVS and with CVS ($x \pm s$)

Group		Cases	TAT (μg/L)	AT (mg/L)	tPA (μg/L)	PAI (μg/L)
SAH with CVS	6 h	5	6.0 ± 0.9[a]	91 ± 14[a]	6.8 ± 2.7	4.0 ± 1.1
	12 h	5	5.9 ± 0.4[a]	110 ± 18[a]	7.9 ± 3.0	6.3 ± 2.1
	1 d	7	6.1 ± 0.5[a]	117 ± 20[a]	8.3 ± 3.2	7.4 ± 2.7
	3 d	9	1.6 ± 0.4	250 ± 24	8.8 ± 3.5	9.1 ± 3.0
	7 d	18	4.4 ± 0.3[a]	120 ± 18[a]	10.5 ± 3.6	21.6 ± 4.1[a]
	14 d	16	3.0 ± 0.4[a]	130 ± 18[a]	11.2 ± 4.0	23.3 ± 5.8[a]
	21 d	5	1.5 ± 0.3	200 ± 21	7.3 ± 3.3	16.2 ± 4.0
SAH not CVS	6 h	25	3.0 ± 0.9	120 ± 18	6.0 ± 2.5	4.3 ± 1.5
	12 h	25	3.8 ± 0.4	184 ± 20	7.4 ± 2.8	6.6 ± 2.3
	1 d	23	4.0 ± 0.6	198 ± 19	7.8 ± 2.9	7.5 ± 2.8
	3 d	21	1.5 ± 0.3	271 ± 33	8.0 ± 3.1	9.5 ± 3.1
	7 d	12	3.5 ± 0.2	190 ± 21	9.0 ± 3.1	11.8 ± 4.3
	14 d	14	4.2 ± 0.3	218 ± 20	10.0 ± 3.5	16.0 ± 5.1
	21 d	25	1.4 ± 0.3	254 ± 30	7.1 ± 2.7	15.9 ± 5.1

Note: Compared with the corresponding time point of SAH not with CVS, [a]$P < 0.05$. AT: anticoagulant enzyme, CVS: cerebral vasospasm, PAI: plasminogen activin inhibitor, SAH: subarachnoid hemorrhage, TAT: blood coagulation enzyme-AT complex, tPA: tissue plasminogen activator.
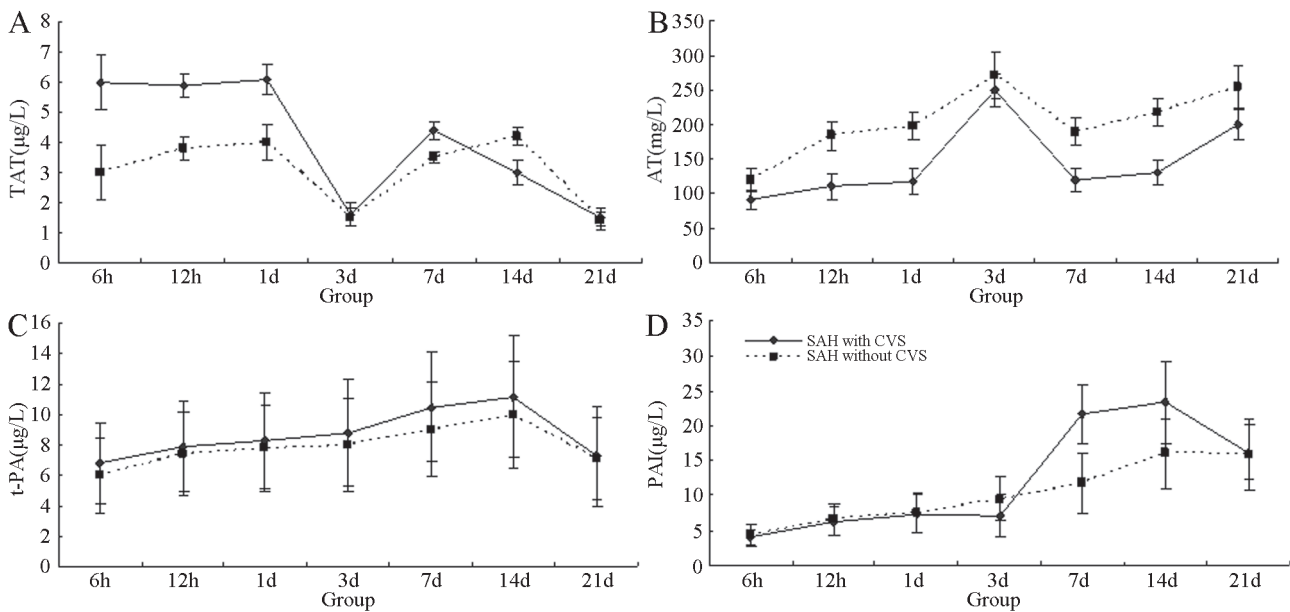

Fig. 2 Plasma TAT, AT, tPA, PAI-1 activity in the SAH patients not with CVS and with CVS. A: TAT (μg/L), B: AT (mg/L), C: tPA (μg/L), D: PAI (μg/L). AT: anticoagulant enzyme, CVS: cerebral vasospasm, PAI: plasminogen activin inhibitor, SAH: subarachnoid hemorrhage, TAT: blood coagulation enzyme-AT complex, tPA: tissue plasminogen activator.

of TAT. The duration of the hypercoagulative stage is very short and difficult to determine because of few clinical symptoms. Once thrombin is produced, it rapidly binds AT to form TAT. This appearance of TAT in early-stage bleeding renders it as a highly sensitive molecular marker of early blood coagulation activation.[13] In the current study, blood coagulation was in a hyperfunctional state 6 h after SAH and TAT increased sharply. Consequently, the clinical use of hemostatic drugs early after SAH has no obvious clinical value.[14] AT is a major adult plasma anticoagulation factor. Brain tissue is rich in thrombokinase, which is released into the blood after intracerebral hemorrhage and forms clumps at

Table 3 TAT, AT, tPA, and PAI-1 changes in the groups classified by Fisher CT (x ± s)

Group		Cases	TAT (µg/L)	AT (mg/L)	tPA (µg/L)	PAI (µg/L)
Fisher I-II	6 h	15	4.4 ± 1.0	121 ± 17	6.0 ± 2.3	6.7 ± 2.5
	12 h	15	2.0 ± 0.4	181 ± 21	6.1 ± 2.4	7.3 ± 2.5
	1 d	15	2.3 ± 0.5	185 ± 20	6.4 ± 2.2	8.8 ± 2.6
	3 d	15	1.0 ± 0.4	277 ± 26	6.6 ± 2.4	9.0 ± 2.6
	7 d	15	3.1 ± 0.3	179 ± 21	6.8 ± 2.9	9.1 ± 3.1
	14 d	15	4.0 ± 0.3	192 ± 20	10.7 ± 3.6	12.4 ± 4.0
	21 d	15	1.6 ± 0.3	221 ± 21	6.8 ± 2.7	15.0 ± 5.0
Fisher III-IV	6 h	15	6.4 ± 1.0[a]	81 ± 16[a]	9.0 ± 3.0[a]	16.0 ± 5.1[a]
	12 h	15	5.0 ± 0.4[a]	91 ± 13[a]	9.4 ± 3.3[a]	17.9 ± 5.4[a]
	1 d	15	5.2 ± 0.7[a]	105 ± 19[a]	10.0 ± 3.5[a]	20.0 ± 5.6[a]
	3 d	15	2.7 ± 0.5	237 ± 23	7.1 ± 2.5	10.2 ± 3.4
	7 d	15	6.9 ± 0.3[a]	129 ± 19[a]	10.8 ± 3.7[a]	23.2 ± 5.5[a]
	14 d	15	6.3 ± 0.4[a]	122 ± 18[a]	12.7 ± 4.7[a]	22.7 ± 5.3[a]
	21 d	15	2.6 ± 0.2	200 ± 19	7.9 ± 3.1	17.9 ± 5.7

Note: Compared with the corresponding time point of Fisher I-II, [a]$P < 0.05$. AT: anticoagulant enzyme, CVS: cerebral vasospasm, PAI: plasminogen activin inhibitor, TAT: blood coagulation enzyme-AT complex, tPA: tissue plasminogen activator.
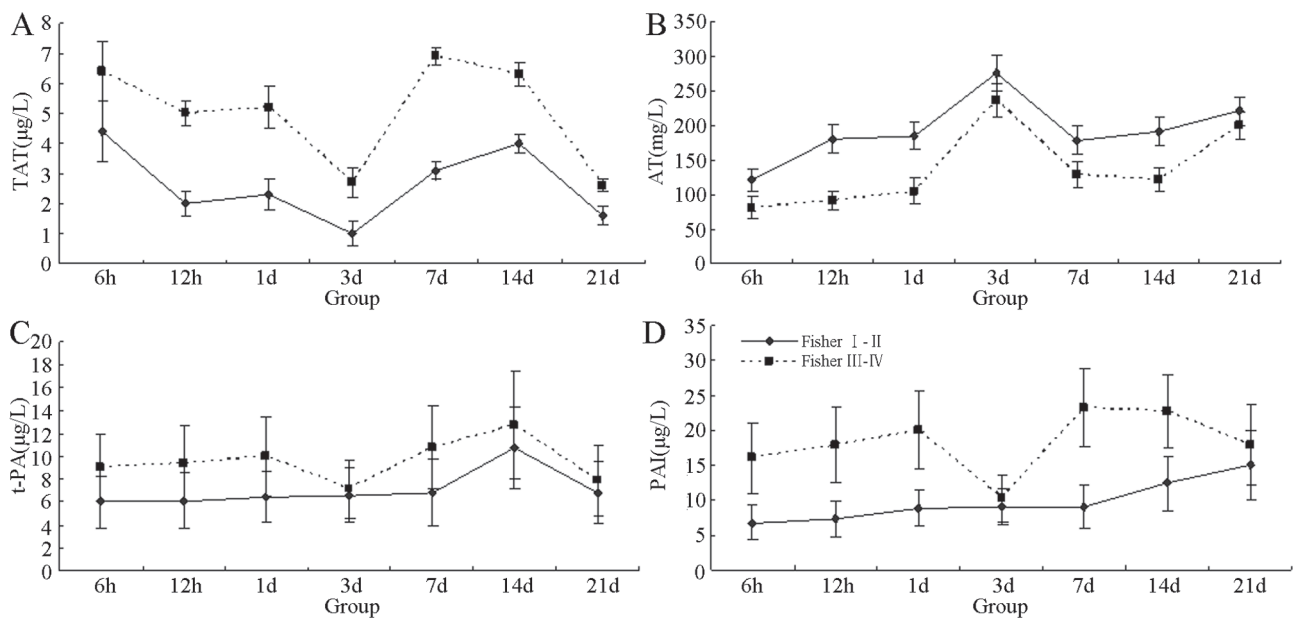

Fig. 3 TAT, AT, tPA, and PAI-1 changes in the groups classified by Fisher CT. A: TAT (µg/L), B: AT (mg/L), C: tPA (µg/L), D: PAI (µg/L). AT: anticoagulant enzyme, CT: computed tomography, PAI: plasminogen activin inhibitor, TAT: blood coagulation enzyme-AT complex, tPA: tissue plasminogen activator.

the site of angiorrhexis. As the main anticoagulation factor, AT quickly neutralizes many kinds of active blood coagulation factors by deactivating them to avoid concomitant systemic coagulation. In the present study, TAT increased sharply 6 h after SAH, and AT was significantly lower than in the control group. This result is mainly due to consumption caused by the blood coagulation process.

Blood coagulation function is at a hyperfunctional state early after SAH, and results in secondary fibrinolytic activity changes.[15] In the current work, fibrinolytic activity became relatively slow after SAH, reflecting the absorption process of the hematoma. Plasma tPA activity within 24 h of SAH gradually

Table 4 TAT, AT, tPA, and PAI-1 changes in the groups classified by Hunt ($x \pm s$)

Group		Cases	TAT (µg/L)	AT (mg/L)	tPA (µg/L)	PAI (µg/L)
Hunt I-II	6 h	18	3.4±1.0	121±17	6.0±2.3	6.7 ± 2.4
	12 h	18	3.0±0.4	181±21	6.1±2.4	7.4 ± 2.5
	1 d	18	3.2 ± 0.5	185 ± 20	6.3 ± 2.2	8.7 ± 2.6
	3 d	18	1.1 ± 0.4	277 ± 26	6.4 ± 2.6	8.8 ± 2.6
	7 d	18	3.1 ± 0.3	159 ± 21	6.6 ± 2.9	9.3 ± 3.0
	14 d	18	3.1 ± 0.3	152 ± 20	8.7 ± 3.1	12.4 ± 3.8
	21 d	18	1.5 ± 0.3	220 ± 21	6.8 ± 2.7	14.8 ± 4.1
Hunt III	6 h	7	6.4 ± 1.1[a]	81 ± 16[a]	9.0 ± 3.1[a]	11.4 ± 5.0[a]
	12 h	7	6.0 ± 0.4[a]	101 ± 19[a]	9.3 ± 3.2[a]	13.0 ± 5.4[a]
	1 d	7	6.1 ± 0.7[a]	115 ± 19[a]	9.9 ± 3.5[a]	15.1 ± 5.6[a]
	3 d	7	2.7 ± 0.5	237 ± 23	10.2 ± 3.5	8.2 ± 2.4
	7 d	7	5.9 ± 0.5[a]	109 ± 19[a]	10.7 ± 3.7[a]	12.2 ± 5.5[a]
	14 d	7	5.9 ± 0.4[a]	112 ± 18[a]	14.5 ± 4.6[a]	13.2 ± 5.0[a]
	21 d	7	2.5 ± 0.2	200 ± 19	7.9 ± 3.1	16.9 ± 5.6
Hunt IV-V	6 h	5	7.4 ± 1.2[a]	70 ± 15[a]	9.1 ± 3.1[a]	18.2 ± 5.1[b]
	12 h	5	6.1 ± 0.4[a]	109 ± 18[a]	9.3 ± 3.4[a]	19.7 ± 5.6[b]
	1 d	5	7.5 ± 0.7[a]	108 ± 19[a]	11.9 ± 3.5[a]	22.2 ± 5.7[b]
	3 d	5	3.7 ± 0.6	227 ± 22	12.2 ± 3.6	10.1 ± 3.6
	7 d	5	7.8 ± 0.5[a]	99 ± 18[a]	12.7 ± 3.7[a]	26.2 ± 5.7[b]
	14 d	5	8.0 ± 0.5[a]	102 ± 18[a]	15.5 ± 4.6[a]	25.2 ± 5.1[b]
	21 d	5	3.5 ± 0.3	190 ± 18	8.8 ± 3.2	17.9 ± 5.7

Note: Compared with the corresponding time point of Hunt I-II, [a]$P < 0.05$, [b]$P < 0.01$. AT: anticoagulant enzyme, CVS: cerebral vasospasm, PAI: plasminogen activin inhibitor, TAT: blood coagulation enzyme-AT complex, tPA: tissue plasminogen activator.
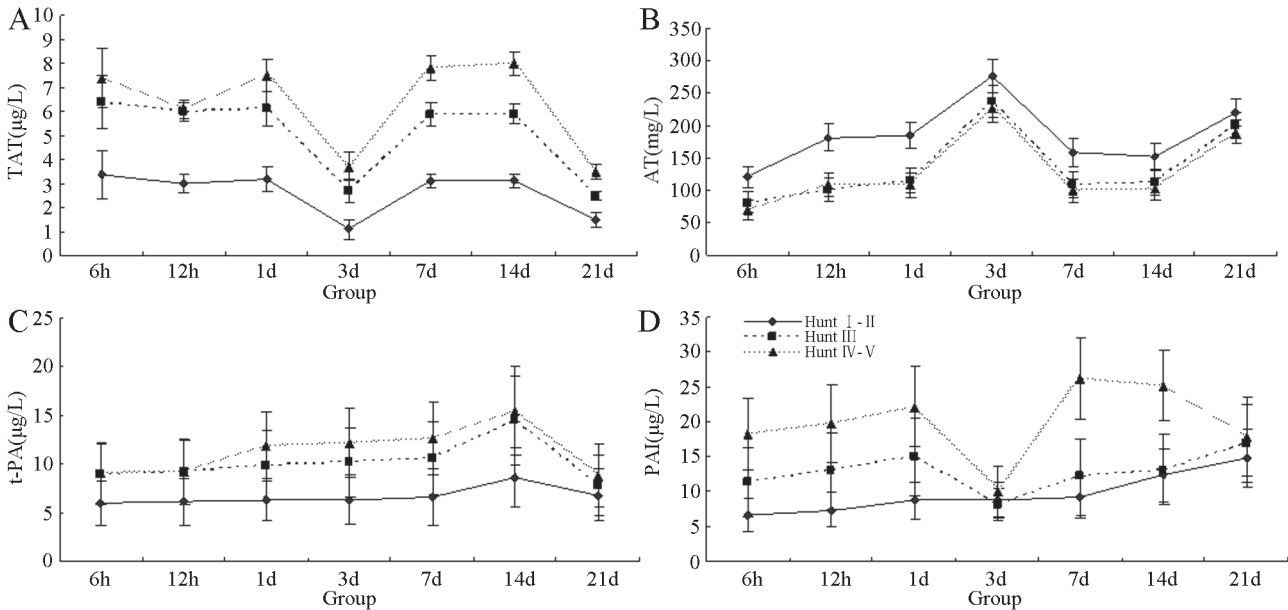

Fig. 4 TAT, AT, tPA, and PAI-1 changes in the groups classified by Hunt. A: TAT (µg/L), B: AT (mg/L), C: tPA (µg/L), D: PAI (µg/L). AT: anticoagulant enzyme, PAI: plasminogen activin inhibitor, TAT: blood coagulation enzyme-AT complex, tPA: tissue plasminogen activator.

increased and peaked until 14 d to dissolve fibrin deposits in and out of blood vessels as well as maintain blood flow. PAI-1 plays an important role in the regulation of the balance of the fibrinolytic system. After SAH, PAI-1 activity also gradually increased with increased tPA activity, reflecting the dynamic adjustment process of fibrinolysis. Free plasma tPA is also bound by the rapid inhibition and deactivation PAI-1. Thus, the tPA antigen level actually indicates the combination of PAI-1 with the already inactivated tPA. Hence, a higher tPA antigen level may in fact reflect decreased, not increased, endogenous fibrinolytic activity.[16] In clinical settings, the implications of dynamic changes in blood coagulation and the fibrinolytic system must be taken seriously.

The relative balance between plasma tPA and PAI-1 activities is the most important component that influences blood coagulation and the fibrinolytic system. This balance is one of the most important factors that maintain the normal operation of blood circulation.

The current study showed that the T/P (the ratio of tPA to PAI-1) change was consistent with that of tPA and indicated the existence of serious endothelial function injuries. The fibrinolytic activity significantly increased compared with the control, providing theoretical basis for the clinical use of fibrinolytic agents to prevent the dissolution of blood coagulation and re-bleeding. T/P significantly increased from 1 d to 14 d after SAH, indicating that increased fibrinolytic activity participated in the early stage to the metaphase of SAH development.

The results also showed the correlation of TAT and AT changes after SAH with CVS. The index changes in the CVS group were more significant than those in the control group at the same time point. The discrepancy is attributed to the fact that thrombin can mediate the occurrence of inflammation as well as initiate arachidonic acid synthesis and thromboxane A2 formation to induce endothelial cells to release endothelin. The cytotoxicity of endothelin causes blood capillary contraction, increased cell gap, increased brain barrier permeability, brain edema formation, increased intracranial pressure, etc. All these phenomena can lead to CVS.[7] AT can induce the contraction of basal arteries pretreated by fibrinolytic enzyme, cause thrombin relaxation, and alleviate CVS after SAH.[17]

The plasma PAI-1 activities of the patients after SAH with concurrent CVS were higher than those of the control at 7 d to 14 d. The changes in tPA activity had no statistical significance. These results were similar to those of Ikeda et al.,[18] suggesting the close relationship between CVS and PAI-1

after SAH. Once CVS occurs, drugs can be used to increase fibrinolytic activity.

The results also showed that higher Fisher CT and Hunt levels resulted in greater blood coagulation and fibrinolytic activity changes. This finding can be attributed to the fact that massive ischemia and severe hypoxia in patients affect more brain microvessels and tissues, produce more active substances, and induce endothelial cells to produce more substances involved in blood coagulation and fibrinolysis.[19]

Conflicts of Interest Disclosure

The authors report no conflicts of interest.

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