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# Relationship between Tissue Plasminogen Activator, Plasminogen Activator Inhibitor and CT Image in Chronic Subdural Hematoma

Dong-Jun Lim, M.D., Yong-Gu Chung, M.D., Youn-Kwan Park, M.D., Jun-Hyuk Song, M.D., Hoon-Kap Lee, M.D., Ki-Chan Lee, M.D., Jeong-Wha Chu, M.D., Yong-Son Yang, M.D.*

*Department of Neurosurgery, Department of Clinical Pathology,* College of Medicine, Korea University, Seoul, Korea*

*The present study was performed to investigate the relationship between the concentrations of tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor (PAI) and the CT images in 23 cases of chronic subdural hematomas (SDHs). The concentrations of t-PA and PAI-1 were quantified by enzyme-linked immunosorbent assay (ELISA). Chronic SDHs were divided into five groups according to their appearance on computed tomography : high-density (n=4), isodensity (n=8), low-density (n=5), mixed-density (n=3), layering (n=3) types. The volume of hematoma was measured with an image analyzing software program. The concentrations of t-PA were higher in layering (41.2 ± 0.3 ng / ml, mean ± standard error of the mean) and high-density (40.0 ± 1.1 ng / ml) types compared to those of low-density (23.3 ± 4.1 ng / ml) and iso-density (25.1 ± 3.7 ng / ml) types. The concentrations of PAI-1 were lower in layering (95.9 ± 1.0 ng / ml) and high-density (103.4 ± 34.5 ng / ml) types compared to that of low-density (192.5 ± 2.6 ng / ml) type. So the ratio between t-PA and PAI-1 (t-PA / PAI) was greater in layering and high-density types. The volume of hematoma was larger in mixed-density and layering types but statistically insignificant. These results presumably suggest that the ratio between t-PA and PAI concentration may contribute to the pathogenesis of the chronic SDH.*

Key Words : *Chronic subdural hematoma, Tissue-type plasminogen activator (t-PA), Plasminogen activator inhibitor (PAI)*

## INTRODUCTION

The etiology of chronic subdural hematoma (SDH) is not yet fully understood. Inflammation of the dural membrane, osmotic pressure of hematoma (Gardner, 1932 ; Zollinger and Gross, 1934), or intermittent hemorrhage due to hyperfibrinolysis (Ito, 1975) have all been raised as its etiology. Tissue-type plasminogen activator is a key enzyme of this system, and endothelial cells lining the vascular wall synthesize and secrete t-PA (Loskutoff and Mussoni, 1983). The plasminogen activator is serine protease with approximately 60,000 molecular weight composed of two disulfide-linked polypeptide chains (Collen, 1980). Hu-

Address for correspondence : *Yong-Gu Chung, Department of Neurosurgery, Korea University Anam Hospital, 5-ka Anam-dong, Sungbuk-gu, Seoul, 136-701, Korea. Tel : 920-5729.*

man endothelial cells produce an inhibitor of t-PA (PAI) (Philips et al., 1984) as well as t-PA, and plasminogen activator activity depends on a balance between the two.

The incidence of chronic SDH is 1 to 2 per 100,000 people per year (Fogelholm and Waltimo, 1975). Although the symptoms and signs are variable and are not pathognomic, impaired consciousness and hemiparesis are common. The diagnostic procedure of choice is the CT scan. The most frequently employed treatment for chronic SDH is evacuation through burrholes at the site of maximum hematoma thickness, and the mortality following treatment is less than 10 percent.

In this study, t-PA and PAI contained in the hematoma were quantified by means of enzyme-linked immunosorbent assay (ELISA) and their relationship with CT findings was investigated.

## MATERIALS AND METHODS

Twenty-three chronic SDHs were studied in 19 patients between 19 and 79 years of age, with a mean age of 60 years. There were 13 men and 6 women. Chronic SDH was confirmed by CT scan preoperatively. CT studies were performed with parameters of 10 mm slice thickness from foramen magnum to vertex before and after infusion of iodine contrast media. Chronic SDHs were classified into five types according to their appearance on CT : high-density (four cases) ; isodensity (eight cases) ; low-density (five cases) ; mixed-density (three cases) ; layering (three cases) (Fig. 1).

The volume of hematoma was measured using a scanner (Umax) and commercial image analyzing software (ImagePro plus) (Fig. 2). After measuring the hematoma volumes in each 2-dimensional axial brain CT scans, the total heamtoma volumes were calculated using software program by adding the respective volumes in each CT slice. Hematomas were evacuated through burr-hole drainage.

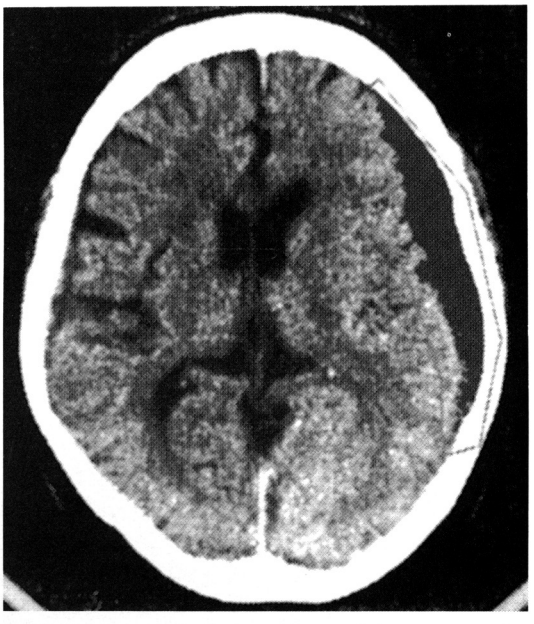
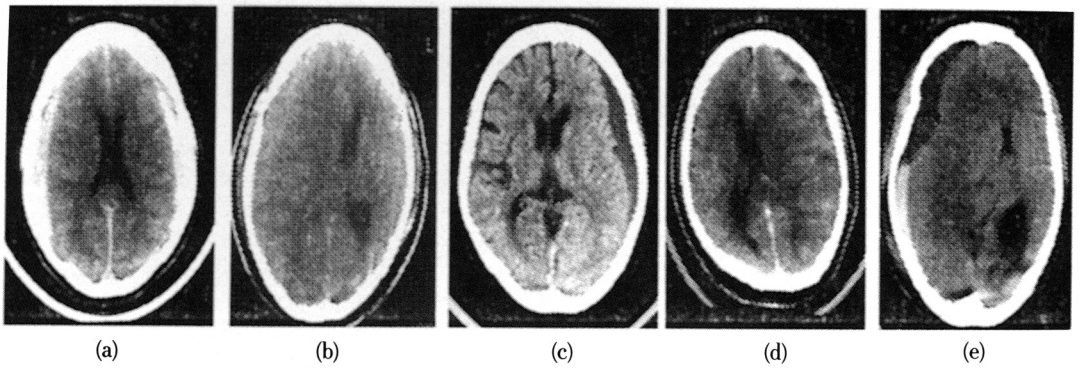


**Fig. 2.** Measurement of the volume of hematoma using scanner (Umax) and image analyzing software (Ima gePro Plus).



(a) (b) (c) (d) (e)

**Fig. 1.** Computerized tomography scans demonstrating five types of chronic subdural hematoma : high-density(a), isodensity(b), low-density(c), mixed density(d), layering(e).

Hematoma samples were collected in tubes containing strong sodium citrate in the operation room. The samples were centrifuged at 3,000 G for 10 min within 2 hours after sampling. And then, the supernatant was prepared and stored at -70℃. Quantitative determination of t-PA and PAI was done using commercial mouse anti-PAI-1 antibody (TintElize PAI-1), and goat anti-tPA IgG (TintElize tPA) by ELISA.

## RESULTS

The average volume of hematoma was 65.9 ± 31.0 cc (mean ± standard error of the mean). The values in mixed-density (99.7 ± 35.1 cc) and layering (74.3 ± 16.2 cc) types were higher than average but had no statistical significance compared to other types ($p<0.05$)(Fig. 3). There was no statistical relationship between the volume of hematoma and concentrations of t-PA and PAI (Fig. 4).

The average concentration of t-PA in the supernatant fluid of chronic SDHs was 30.2 ± 2.2 ng/ml (mean ± standard error of the mean), which was much higher than normal value of the peripheral blood (4.0 - 5.5 ng/ml). The values in layering (41.2 ± 0.3 ng/ml) type, which was possibly related to recent hemorrhage, and high-density (40.0 ± 1.1 ng/ml) types were significantly higher than those in low-density (23.3 ± 4.1 ng/ml) and iso-density (25.1 ± 3.7 ng/ml) types ($p<0.05$) (Fig. 5).

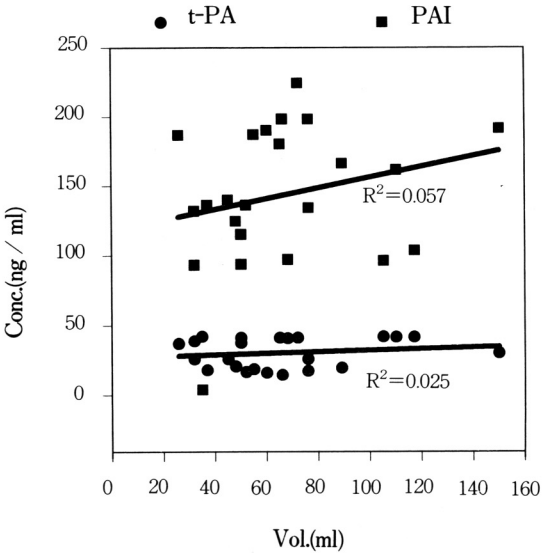



Fig. 4. Relationship between the amount of hematoma and the concentrations of t-PA and PAI is not significant(-line : regression line)($R^2$ : correlation correlation coefficient).

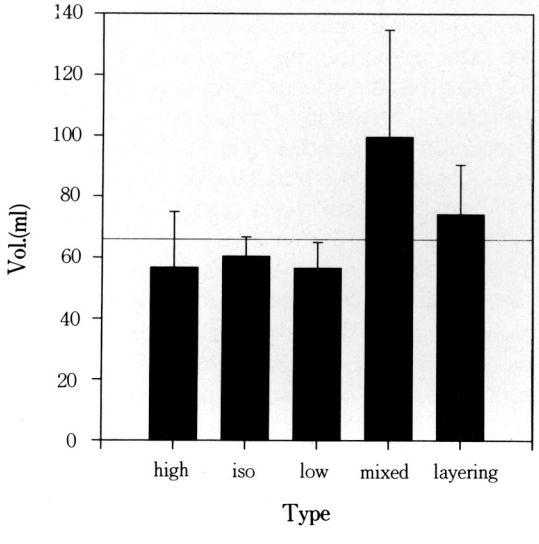



Fig. 3. The volume of hematoma is larger in mixed-density and layering types than other types(-line : average volume).

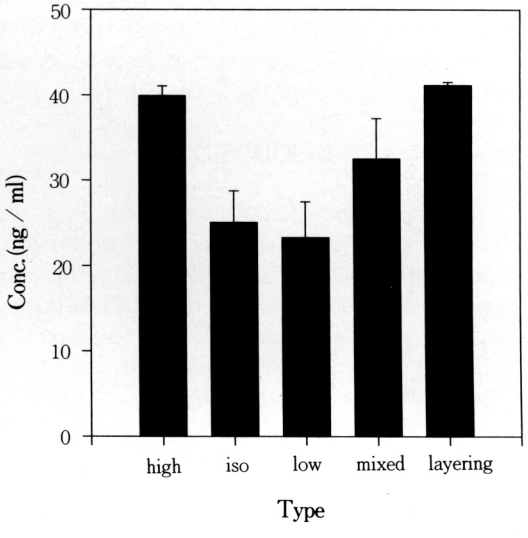



Fig. 5. The concentrations of t-PA are higher in layering and high-density types than in low-density and iso-density types(paired t-Test, $p<0.05$).

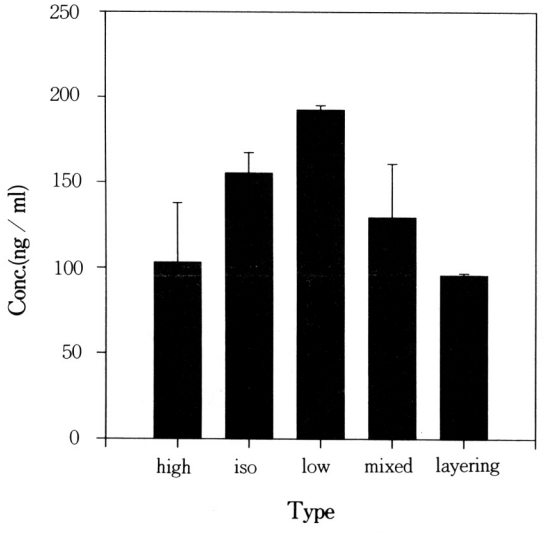



**Fig. 6.** The concentrations of PAI are lower in layering type than in low-density and iso-density types(paired t-Test, $p < 0.05$).

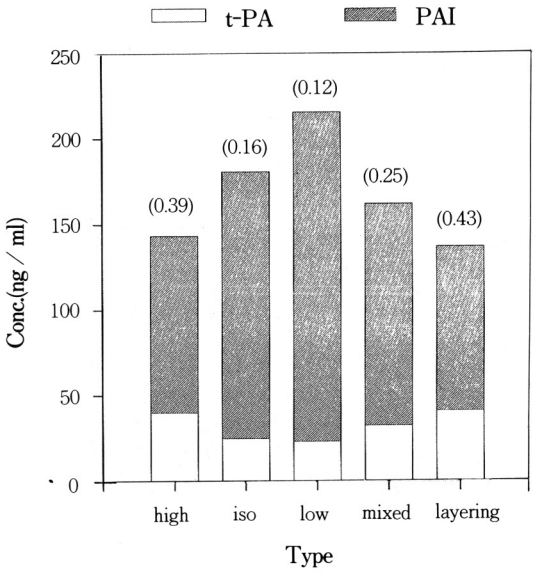



**Fig. 7.** Ratio between t-PA and PAI.
( ) value=t-PA/PAI

The average concentration of PAI was 143.4 ± 10.4 ng/ml, which was higher than normal value in the peripheral blood (4 - 43 ng/ml). The values in layering (95.9 ± 1.0 ng/ml) and high-density (103.4 ± 34.5 ng/ml) types were significantly lower than those in low-density (192.5 ± 2.6 ng/ml) type ($p < 0.05$) (Fig. 6). Fibrinolytic activity (t-PA vs PAI-1 ratio) was greater in layering (0.43, t-PA/PAI-1) and high-density (0.39) types compared to those of low-density (0.12) and isodensity (0.16) types (Fig. 7).

## DISCUSSION

Although chronic subdural hematoma is a well known clinical entity, its etiology and mechanism of evolution are still under debate. Ito, et al.(1976) stated that local hyperfibrinolysis prevents complete hemostasis and causes rebleeding into the hematoma cavity. The fibrinolytic system basically consists of fibrinogen, fibrin, plasminogen, plasmin, and plasminogen activators. The high level of t-PA in the hematoma fluid and hyperfibrinolysis in chronic SDH are chiefly due to oversecretion of t-PA from the sinusoidal and capillary endothelial cells in the outer membrane (Fujisawa et al., 1991). The activity of t-PA is enhanced by fibrin(ogen) degradation product (FDP) (Nieuwenhuizen et al., 1983) : FDP has an antithrombin effect (Fletcher et al., 1962), it inhibits platelet aggregation (Kowalski et al., 1964) and fibrin polymerization (Alkjaersig et al., 1962), it produces a structurally defective fibrin polymer (Bang et al., 1962), and the plasmin converts from plasminogen by t-PA degrades factor V, VIII, and XI (Kwaan, 1972). So hemostatic balance is impaired in the hematoma cavity. Therefore, hemorrhages from the capillaries of the outer membrane may recur. Hyperfibrinolysis in the outer membrane leads to a vicious cycle, that is, fibrinolysis, hemostatic impairment, hemorrhage, coagulation, and fibrinolysis (Fig. 8). In chronic SDH, it is suggested that overproduction and oversecretion of t-PA from the sinusoidal and capillary endothelial cells in the outer membrane causes hyperfibrinolysis, which in turn impairs normal hemostasis, and repeated hemorrhage from the capillaries results in enlargement of the hematoma (Fujisawa et al., 1991). Most of the patients with chronic subdural hematoma can be cured by surgical irrigation. This procedure may break the vicious cycle mentioned above and restore normal hemostatic balance. An inhibitor of t-PA may play a part in slowing the growth of a hematoma or its gradual disappearance.

The relationship between the appearance of the hematoma on CT and the concentrations of t-PA and PAI was examined. In the layering and high-density

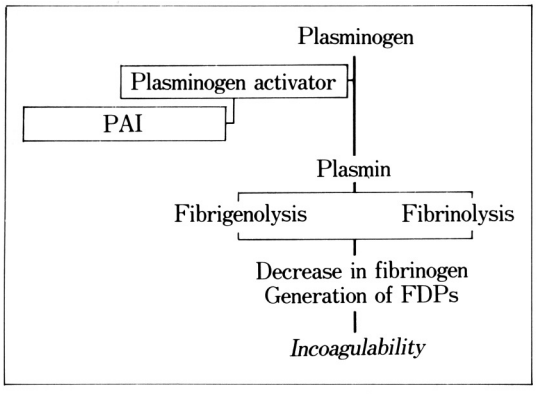



Fig. 8. Sequence of hyperfibrinolysis.

types of chronic SDH, concentration of t-PA was higher and that of PAI was lower than other types (especially low-density type), that indicates relative imbalance between concentration of t-PA and PAI. Kao reported that the layering type of hematoma may be remarkable for a significant amount of rebleeding and may herald acute clinical deterioration (Kao, 1983). Saito, et al., stated that, in layering hematomas, the plasmin-$\alpha_2$-plasmin inhibitor complex was higher than any other types of chronic SDH (Saito et al., 1989). Nomura, et al., stated that a large amount of recent rebleeding ocurred and coagulative and fibrinolytic activities were high in layering hematoma (Nomura et al., 1994). Ito et al.(1987) suggested that high-density hematoma indicated recent rebleeding, because clots or sediments obtained from the hematomas included many $^{51}$Cr-labeled erythrocytes administered intravenously. These results agree with ours, in that the hyperfibrinolytic activity seems to cause frequent, copious rebleeding that causes severe signs and symptoms.

The hematoma volume was not related to the concentrations of t-PA and PAI in our study even though t-PA and the ratio between them play an important role in hyperfibrinolysis. Other factors such as osmotic pressure, exudation and absorption after hemorrhage may also contribute to the expansion of hematoma in chronic SDH (Ito et al., 1987).

We speculate that high t-PA and the ratio between t-PA and PAI may play a major role in the pathogenesis of chronic SDH. Concentrations of t-PA and PAI may be useful parameters for progression of the disease. Our preliminary study was too limited in number of cases to reach any conclusion, and further study is needed in the future.

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