[原著] Changes of fibrinolytic activityin the circulating blood of patients after open heart surgery

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Changes of fibrinolytic activity in the circulating blood of patients after open heart surgery

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Abstract

Following surgical operations, it has been reported that the fibrinolytic activity may be increased in the circulating bloold. In this study, we attempted to clarify the mechanism of enhanced fibrinolytic activity related to open heart surgery. Immediately after the operation, the t-PA concentration increased gradually, and this increase in t -PA concentration continued until 24 hours after the operation. On the other hand, the FDP concentration began to increase at 2 days after the operation, and thereafter the FDP concentration increase gradually. From the above results, it is concluded that the enhanced fibrinolytic activity was based on an increased concentration of t-PA in the circulating blood. Furthermore, the increase in t-PA may have been favorable for excluding excess thrombus such as hemostatic plugs.

Introduction

It has been shown that the fibrinolytic activity in the circulating blood was increased after operations[1]. Spontaneous activity of fibrinolysis may be associated with surgical operations. Furthermore, it has been suggested that increased fibrinolytic activity following surgical operations could be related to stress and to increased release of adrenalin into the circulatory blood. On the other hand, in animal experiments employing perfused dog leg, administration of vasoactive drug into the blood vessels increased the release of plasminogen activator from the endothelial cells[2),3)]. In addition, in animal experiments on rats, administration of vasoactive drug to the animals enhanced the fibrinolytic activity in the euglobulin fraction of the plasma, and elevation of blood pressure was observed at the same time[4]. It has also been found that neuroactive drugs can produce enhanced fibrinolytic activity[5]. In the case of open heart surgery, we expected that the stress would be larger than that of operations involving local anesthesia and the change of fibrinolytic activity in the circulating blood after the operation would be outstanding. In this study, three parameters of the fibrinolytic system (the concentra-

tion of tissue plasminogen activsator(t-PA), the α_2-plasmin inhibitor (α_2-PI) activity and the level of fibrin degradation product(FDP)) were estimated and the significance of fibrinolytic activity in open heart surgery was assessed.

Materials and methods

The patients were divided into two groups. That is to say, determinations were made of the fibrinolytic activity of the circulating blood in patients with congenital heart disease (group I) and with acquired heart disease(group A). The times of blood sampling from the cubital vein were as follows: before the operation, during the operation (at the time of administration of heparin), immediately after the operation, at 3, 6, 12 and 24 hours, and at 2, 3, 4, 5, 6 and 7 days after the operation. Citric acid(3.8%) was used as an anticoagulant. The plasma was obtained after centrifuging the blood at 3,000 r.p.m. for 15 min.

Determinations of t-PA and FDP concentration

The t-PA concentration was estimated with the ELISA kit produced by Bio-Pool Corporation[6),7)]. That is, antibody to tissue plasminogen activator derived from human uterus was employed in the determination. The concentration of FDP was estimated with the Testzym FDP kit produced by Daiichi Chemical Co., Ltd. [8),9)]. The activity of α_2-PI was determined using the synthetic substrated, S-2251[10)].

Results

1) *Changes of t-PA concentration*

In group A, in comparison with the preoperative value, the level of t-PA in the circulating blood immediately after the operation, and at 3, 6, 12 and 24 hours after the operation, was significantly increased ($P<0.05$). However, at 2 days after the operation, the level was decreased and the differnce from the preoperative level was not significant. In group I, the change in t -PA concentration was similar to that found in group A (Fig. 1).

2) *Changes of FDP concentration*

In group A, in comparison with the preoperative value, the level of FDP from 2 days to 7 days after the operation was significantly increased ($P<0.05$). Furthermore, the change of FDP concentration in group I followed almost the same level as that in group A. At 24 hours after the operation, in comparison with the preoperative value, the level of FDP was significantly increased ($P<0.05$). In addition, from 2 days to 7 days after the operation, a gradual increase in FDP concentration was observed (Fig.2).

3) *Changes of α_2-PI activity*

In group A, in comparison with the preoperative value, the α_2-PI activity at 3 hours after the operation showed a significant increase ($P<0.05$), and a grdadual increase was then observed up to 3 days after the operation. In group I, the α_2-PI activity gradually increased up to 3 days after the operation (Fig.3).

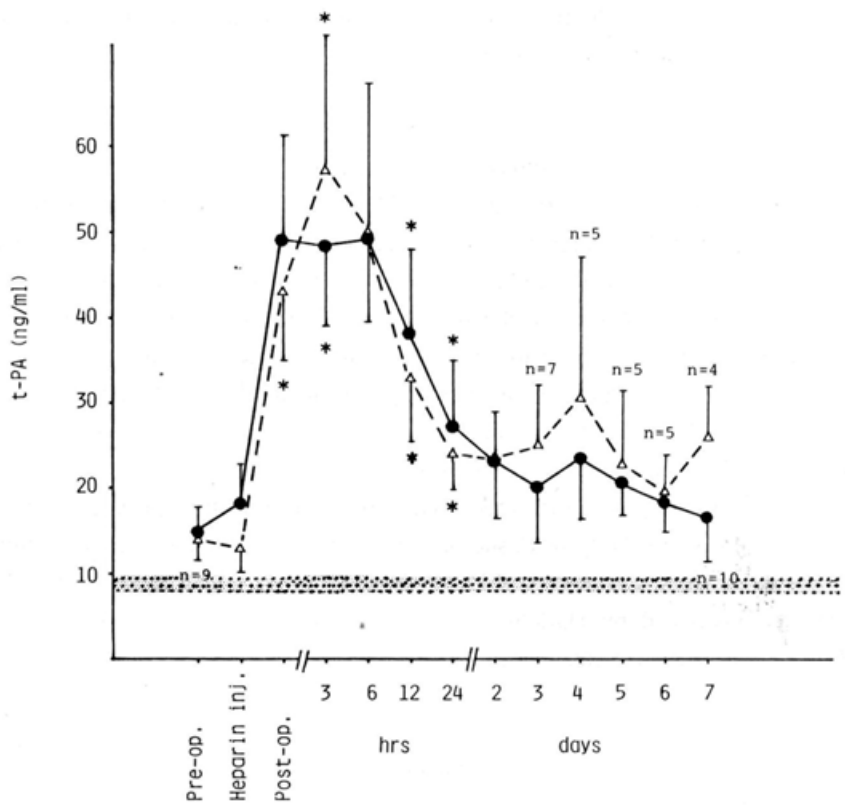

Fig.1. Changes of t-PA concentration in the circulatory blood before, during and after open heart surgery.

Ordinate, concentration of t-PA(mean ± S.E.).

Abscissa, times at which the t-PA concentration in the plasma was determined.

Pre-op.: before the operation.

Heparin inj.: time of heparin injection during the operation.

●—● : group of patients with acquired heart disease(group A)

△···△ : group of patients with congenital heart disease(group I)

▨: range of t-PA concentration in healthy adults

* : significantly different compared to the value before operation in the same group

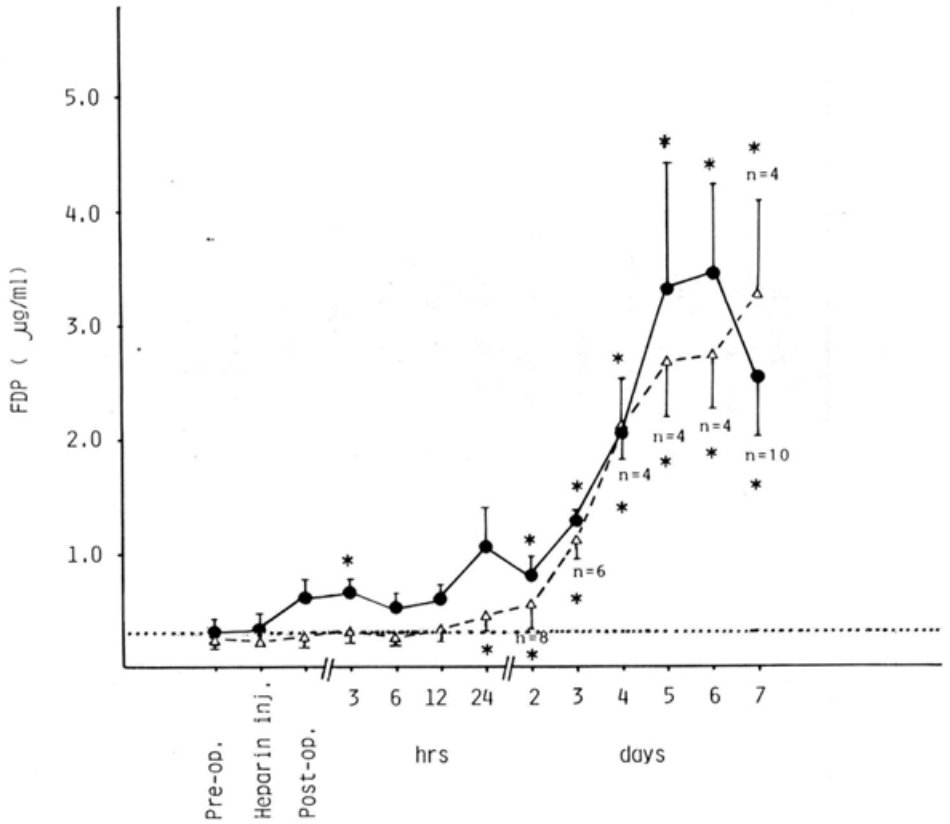

Fig.2. Changes of FDP concentration in the ciuculatory blood before, during and after open heart surgery.
Ordinate, concentration of FDP (mean ± S.E.).
Abscissa, times at which the FDP concentration in the plasma was determined.
Other details as in Fig.1.

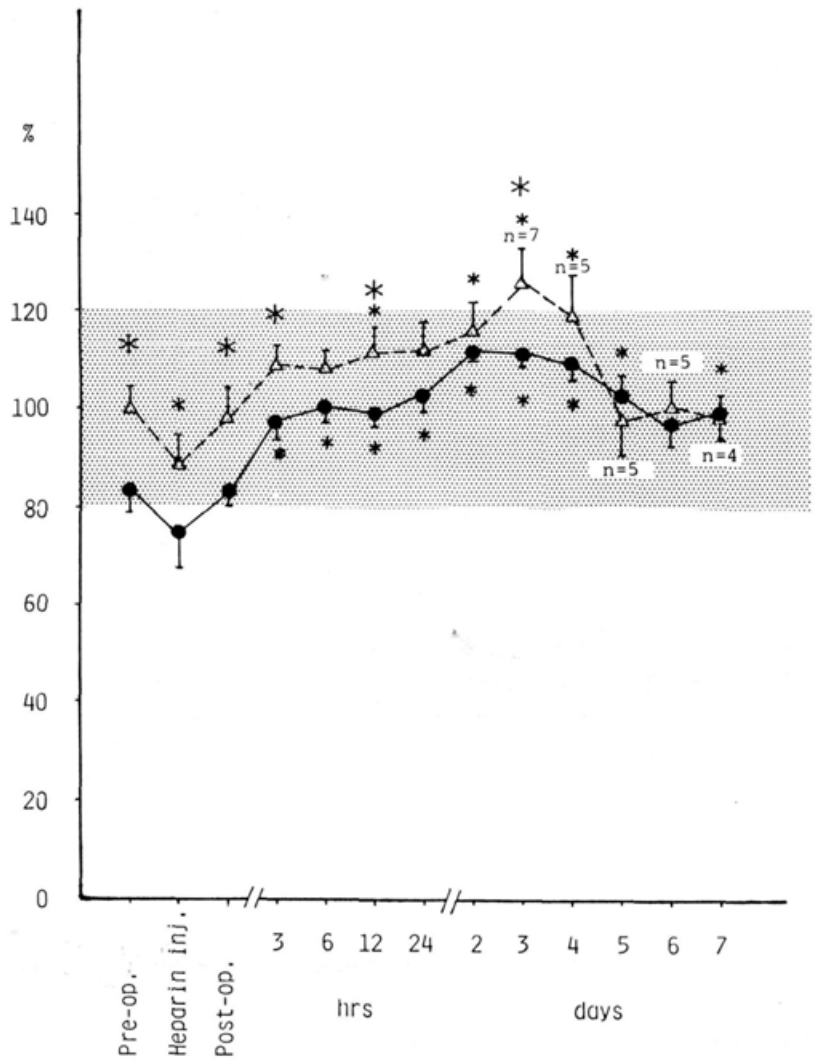

Fig.3. Changes of α_2-PI activity in the circulatory blood before, during and after open heart surgery.
Ordinate, α_2-PI acstivity (mean ± S.E.).
Abscissa, times at which the α_2-PI acstivity in the plasma was determined.
* : Significantly different($p<0.05$) compared to the activity in both groups.
Other details as in Fig.1.

Discussion

It has been reported previously that fibrinolytic activity following operations was increased[1]. Furthermore, exercise or administration of adrenalin has been found to evoke fibrinolysis[11]. What kind of mechanism can be expected to give rise to increased fibrinolytic activity after an operation? We found that the euglobulin lysis time was shortened in the case of sinectomy and tonsillectomy using local anesthesia[12),13]. It has been reported that plasminogen activator (PA) was contained in the euglobulin fraction of plasma. On the other hand, PA in the circulating blood has been shown to originate from the endothelial cells of blood vessels. In the present study, the t-PA concentration in the circulating blood was determined by means of ELISA. During operations, an increased concentration of t-PA was observed, and after the operation the concentration of t-PA gradually decreased. It is suggested that this decreased concentration of t-PA was based on the consumption of t-PA. That is, to exclude thrombi previously formed to protect against bleeding, t-PA was consumed in the ciuculating blood and a decreased level of t -PA was observed in spite of continuous release from the endothelial cells. Furthermore, the results for FDP concentration indicated that the increased FDP level after the operation reflected enhancement of thrombolysis in the circulating blood via production of plasmin activated by means of the plasminogen activator derived from the endothelialcells of the blood vessels. In the circulating blood of patients following open heart surgery, it was found that fibrinogenolysis did not occur but fibrinolysis appeared. The changes in t-PA and FDP concentration demonstrated that thrombolysis progressed in the circulating blood. However, it could be said that this phenomenon of thrombolysis indicated physiological acceptance. If such thrombolysis represented a pathological condition, a hyperplasminic condition should have appeared in the circulating blood. However, the activity of a α_2-PI remained within the normal range in this study. Although we were not able to determine the activity of t-PA inhibitor in the circulating blood, it is suggested that the activity of this inhibitor would be changeable after the operation. On the other hand, the increase of t-PA was apparently based on in creased release from the endothelial cells of the blood vessels. It has been reported that catecholamine [13),14),15)], strong exercise[16),17)], venous occlusion[18)], 1-desamine-8-D-arginine vasopressin (DDAVP)[19)], and platelet-activating factor (PAF)[20)] stimulated t-PA release from the endothelial cells of blood vessels. Hypoxia in the circulating blood was also found to stimulate release of t-PA from endothelial cells[21)]. From the above-mentioned observations, it was expected in this study that the underlying mechanism of the increased concentration of t-PA involved enhanced catecholamine and hypoxia. In the case of open heart surgery, administration of dopamine hydrochloride was frequently given and it was expected that the concentration of catecholamine was enhanced in the circulating blood. Furthermore, hypoxia in the peripheral circulating blood was thought to appear during manipulation of the artificial heart-lung machine. However, an increase of PAF was not considered to occur in the circulating heart-lung machine since in this study during the operation it was observed that the platelet function induced by ADP and collagen decreased (data not shown).

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