

A Study on the Role of Platelet Function in Patients with Chronic Pulmonary Thromboembolism

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There has been no study on platelet function in the patient with chronic pulmonary thromboembolism (CPTE). We speculate that platelet function may be elevated in these patients.

Purpose: 1. Platelet functions were compared among CPTE patients before surgery, patients with deep vein thrombosis (DVT) and normal adults. 2. The severity of CPTE in clinical grading to platelet functions were compared. 3. Platelet function were compared before and after pulmonary thromboendarterectomy.

Methods: Pre-operative CPTE group (n=16), post-operative CPTE group (n=11), DVT group (n=9) and control group (normal adults: n=33) were investigated on the platelet functions defined as platelet adhesion (AD) and platelet aggregation (AG) test in this study.

Results: 1. No activation of platelet functions was observed in the pre-operative CPTE patients. 2. There was no apparent relationship between the severity of disease and platelet functions. 3. Significant elevation of AG was obtained in the patients who underwent pulmonary thromboendarterectomy.

Conclusion: In consideration of the findings in the postoperative study, the administration of anti-platelet drug will help to prevent re-thrombosis of the pulmonary arteries after surgery. (*Ann Thorac Cardiovasc Surg* 2001; 7: 133–7)

Key words: chronic pulmonary thromboembolism, platelet function, platelet adhesion, platelet aggregation, pulmonary thromboendarterectomy

Introduction

Chronic pulmonary thromboembolism (CPTE) associated with pulmonary hypertension usually presents with a symptom of exertional dyspnea. It has also a self progressive nature manifesting as right heart failure induced by elevated pulmonary arterial pressure as well as hypoxia and is refractory to medical treatment.¹⁾ The only effective treatment under these circumstances at present is surgical treatment by means of pulmonary thromboendarterectomy.²⁾

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Received August 21, 2000; accepted for publication December 25, 2000.

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The etiology of this disease has not been well established yet, although it is considered that the chronic type is not a simple extension of acute pulmonary thromboembolism.³⁾ The widely accepted theory in relation to the etiology is the recurrence of embolism from the deep venous thrombosis (DVT). The pathology of the thrombus originating in the pulmonary artery is organized thrombus which firmly adhere to the inner surface of pulmonary arteries and it is considered to be the result of recurrent embolization.⁴⁾ On the other hand, Moser et al. speculate that, due to the abnormality of fibrinolytic function in the pulmonary artery, initially embolized thrombus is not resolved and results in organization.⁵⁾ To the contrary, over half of the patients do not have a history of DVT nor episodes of acute pulmonary thromboembolism. And one third of patients exhibit some type of coagulopathy such as anti-cardiolipin antibodies or protein C deficiency.⁶⁾

Until now, we could not find any study on platelet function in patients with CPTE. Because the fundamental pathology is the presence of a thrombus in the pulmonary artery, we speculate that the elevated platelet function or hypercoagulopathy may contribute to the development of CPTE which prompted us to investigate a platelet function study in patients with CPTE.

Methods

Purpose of study

Platelet functions were investigated in the following protocol.

- 1) Platelet functions were compared in patients with CPTE before surgery, DVT and in normal adults.
- 2) The relationship between clinical grading of CPTE and platelet functions were analyzed. The clinical grading of the disease was defined as the value of pulmonary vascular resistance and the functional classification of right heart failure (New York Heart Association, NYHA) as well as PaO₂ at rest on room air.
- 3) The platelet functions before and after surgery were compared in patients who underwent pulmonary thromboendarterectomy.

Patients profile

The pre-operative CPTE group consisted of 16 patients, ranging in age from 34 to 74 years old with a mean age of 52.8±10.6. The male and female ratio was 5:11 in this group. Eleven patients were categorized as the post-operative CPTE group, their age ranged from 32 to 74 years old with a mean age of 52.5±9.3 years and the male to female ratio was 3:8. Nine patients were in the DVT group ranging in age from 16 to 66 years old (mean: 47.9±16.6) and the male to female ratio was 4:5. The control group consisted of 33 normal adults, ranging in age from 25 to 72 years old with a mean age of 36.9±13.7 years and the male to female ratio was 17:16.

Method of platelet function study

In the process of thrombus formation, platelets play a role of a series of reactions in the adhesion, aggregation and release of platelet granules. Among these reactions, the platelet adhesion (AD) and the platelet aggregation (AG) test were employed in this study.

For the platelet adhesion test, the collagen coat bead method was applied. Using a constant speed pump (1.5 ml/minute, ISK company), the blood was passed through the collagen coat bead column and the difference in num-

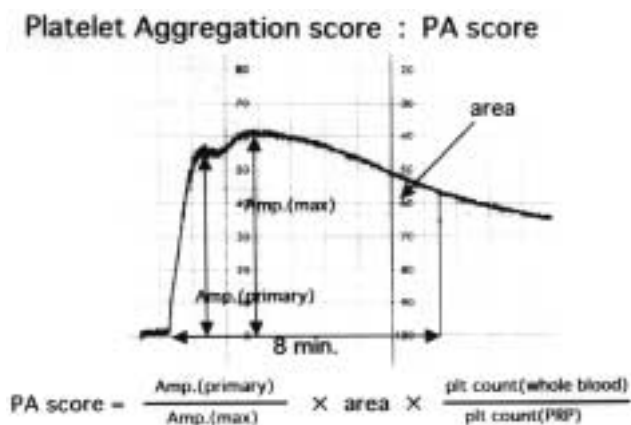


Fig. 1. Platelet aggregation curve and formula of calculation of platelet aggregation score (PA score).

ber of platelets was represented as a percentage. The collagen coat bead column was designed with a 2 mm inner diameter in which 0.2 g of 5600 sphere shape plastic bead coated with type 1 collagen was contained and made a total area of 28 cm² (ISK company).

The platelet aggregation test was performed in the following process. Blood mixed with citric acid was centrifuged with a speed of 800 rpm for 10 minutes and supernate was isolated which was considered as the platelet rich plasma (PRP). The rest of blood was re-centrifuged again with a speed of 3000 rpm for 15 minutes this time and this supernate was designated as the platelet poor plasma (PPP). Adenosine diphosphate of 2.5 μmol/l was used as an aggregating trigger material and aggregation was measured for 8 minutes according to Born's method) (Hematracer 1: Nikon Bioscience model PAT-2M) (Fig. 1). The platelet aggregation score was calculated according to the formula illustrated in Fig. 1. The process was completed within 45 to 90 minutes of drawing the blood sample.

The blood samples from the post-operative group were taken in a one to 12 month period after the surgery and those from the DVT group were taken in the chronic phase, more than 6 months after the onset of the disease. On the contrary in the control group, the blood samples were obtained from normal adults on a fast so as not to be affected by the intake of food.

Statistical analysis

Simple regression analysis was applied for the correlation. The measurement value was showed by the mean ± standard deviation. Homogeneity of variance for each group was confirmed by the Bartlett test, and then each group was compared for equality with one-way analysis

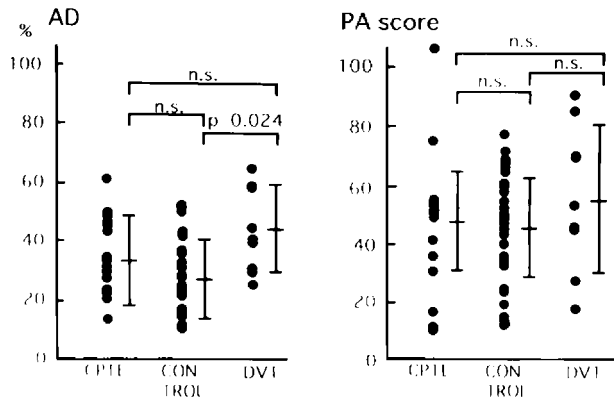


Fig. 2. platelet function among CPTE, DVT and control group. AD: platelet adhesion, PA score: platelet aggregation score.

of variance (ANOVA). Statistical significance was defined as $p < 0.05$.

Results

1) The comparison of platelet function among the pre-operative CPTE, DVT and control group
There was no significant difference on the platelet adhesion function between the CPTE and control group ($35.3 \pm 13.7\%$ vs. $27.9 \pm 12.4\%$) nor CPTE and DVT group (35.3 ± 13.7 vs. $43.7 \pm 14.8\%$). However, a significant difference was observed between the control and DVT group ($27.9 \pm 12.4\%$ vs. $43.7 \pm 14.8\%$) (Fig. 2).

The platelet aggregation function did not show any significant differences among three groups (CPTE: 46.7 ± 18.3 , DVT: 55.9 ± 28.0 , control: 46.3 ± 18.4) (Fig. 2).

2) The relationship between the clinical grading of CPTE and the platelet functions

No significant relationship was obtained between the pre-operative value of pulmonary vascular resistance and each platelet function test. Also no significant correlation was obtained between the NYHA functional classification, PaO₂ at rest on room air and each platelet function (Figs. 3 and 4).

3) The platelet function in the post-operative CPTE group

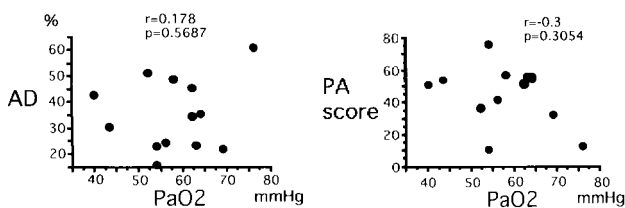


Fig. 4. Severity of CPTE (respiratory function) and platelet functions.

PaO₂: preoperative PaO₂ at rest on room air.

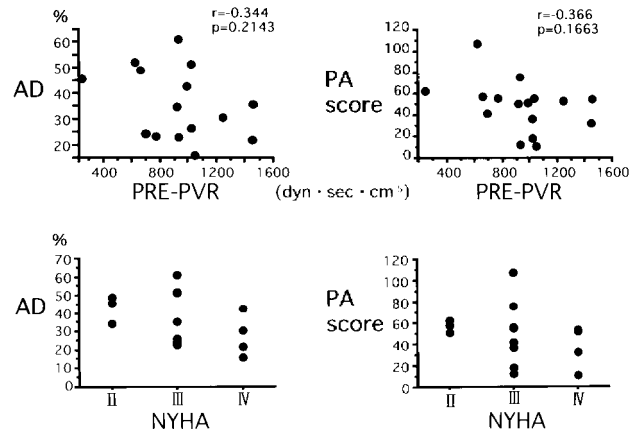


Fig. 3. Severity of CPTE (hemodynamics) and platelet functions. PRE-PVR: pre-operative pulmonary vascular resistance.

The platelet adhesion function in the post-operative CPTE group ($35.5 \pm 13.7\%$) did not prove to have any significant differences to the control group, however, a significant difference was observed between the two groups in the platelet aggregation function (62.7 ± 26.2 vs. 46.7 ± 18.3). However, no significant difference was obtained in both of the platelet functions between the pre-operative and post-operative group (Fig. 5).

The above results are interpreted as follows. 1: No activation of the platelet functions in term of adhesion and aggregation test was observed in pre-operative CPTE patients. 2: There was no apparent relationship between the clinical grading of disease (pulmonary vascular resistance, NYHA functional classification and PaO₂ value on room air) and the platelet functions. 3: Significant elevation of the platelet aggregation function was obtained in the patients who underwent pulmonary thromboendarterectomy.

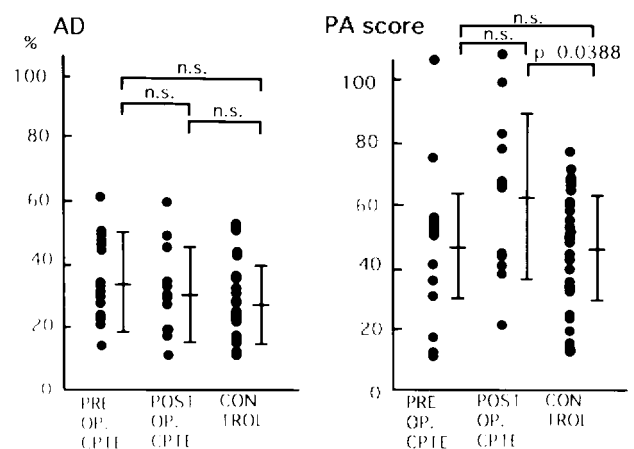


Fig. 5. Comparison of platelet function before and after pulmonary thromboendarterectomy.

Discussion

Chronic pulmonary thromboembolism combined with advanced pulmonary hypertension is a grave disease with poor prognosis which is refractory to medical treatment,⁷⁾ is of a self progressive nature and results in severe right heart failure. Recently, the effectiveness of surgical treatment for this disorder has been firmly established and a satisfactory prognosis for patients after pulmonary thromboendarterectomy has been reported,⁸⁾ as a consequence, the differential diagnosis between the primary pulmonary hypertension and this disorder is important in considering the approach for treatment.

Until now, to our knowledge, no study has undertaken to investigate the platelet functions in CPTE patients. One explanation for the lack of reports on this issue is assumably based on the consideration that CPTE is closely related to DVT and that the characteristics of thrombus is venous origin. A venous thrombus is different from an arterial one, the former contains less platelets but a higher amount of fibrin. With these characteristics, it is considered that the coagulation cascade plays a major role in the formation of venous thrombus rather than the role of platelets.⁹⁾ However, the report from the Antiplatelet Trialists Collaboration Study¹⁰⁾ in 1994 predicted the efficacy of the antiplatelet agent for the prevention of venous thrombosis. We considered the possibility that the platelets played a certain role in the formation of thrombus in CPTE patients which led us to investigate platelet functions in this particular disorder.

However, our results showed that no significant difference was observed in platelet adhesion and the aggregation function in patients with CPTE in comparison to the control normal adults. On the other hand in DVT patients, no significant difference was obtained in the platelet aggregation function, however, the platelet adhesion function had a significant difference in comparison to that of the control group. The reason for this positive finding is not well understood and further research would be desirable. From these findings, it will be suggested that the role of platelets as an etiological factor contributing to the development of thrombus formation in CPTE patients is negligible.

Nakochnicov et al. studied the platelet aggregation function in patients with primary pulmonary hypertension and found that the platelet aggregation function was elevated in this disorder. They also noted that this acceleration of function was in accordance to the severity of disease presented by the NYHA functional classification

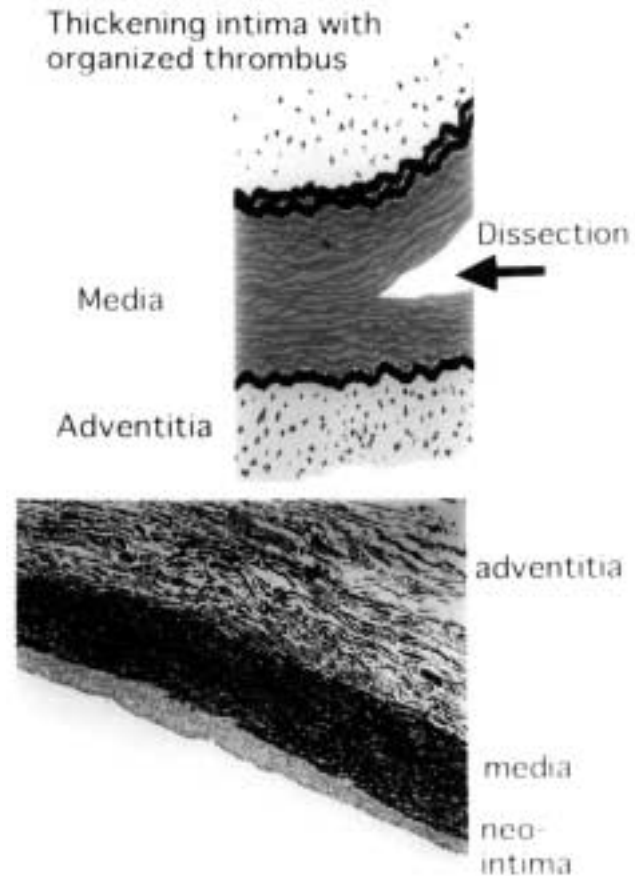


Fig. 6. Upper: schematic drawing of endarterectomy and dissecting plane. Bottom: autopsy specimen of 13 days after thromboendarterectomy. Neo-intima containing of α -smooth muscle actin was already covered over the exposed medial layer.

and the prognosis was influenced by the degree of elevation of the platelet aggregation function.¹¹⁾ We repeated a similar study in patients with CPTE to see whether the severity of preoperative clinical condition was influenced by platelet function. In CPTE, the graveness of the illness is expressed by several modalities such as pulmonary vascular resistance, NYHA functional classification for right heart failure, PaO₂ in resting condition and so on. However in our present study, we could not detect any correlation on these parameters to the platelet function. Both of the above lesions are similarly manifested as advanced pulmonary hypertension, however as far as the platelet function is concerned, the equivalent result could not be obtained.

The surgical treatment for CPTE consists solely of thromboendarterectomy of the pulmonary arteries. The precise surgical technique of this procedure is to endarterectomize the organized thrombus through a certain plane of the medial layer of the pulmonary arterial wall as is illustrated in Fig. 6. As a consequence, the

medial layer is directly exposed to the blood flow surface immediately following surgery. As seen in our study of autopsy cases,¹²⁾ these rough surfaces are repaired by regeneration of neointima in the early post-operative period. Although anti-thrombogenicity of this newly formed neointima is not contained, it is speculated that the platelet function may accelerate at this stage. The platelet functions which were compared before and after surgery did not show any significant difference, although some tendency in acceleration of the platelet aggregation function was observed. Therefore, the administration of anti-platelet drug in the postoperative period may help to prevent re-thrombosis of the pulmonary arteries after thromboendarterectomy surgery.

Conclusion

In patients with CPTE, the acceleration of platelet functions presented as the platelet adhesion and aggregation was not observed. Also, there was no correlation between the severity of the disease and platelet function. However, as the platelet aggregation appeared to be accelerated after pulmonary thromboendarterectomy surgery, the administration of anti-platelet drugs will help to prevent re-thrombosis of the pulmonary arteries.

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