Inflammation Is Associated With Platelet Coagulation Function Rather Than Enzymatic Coagulation Function in Patients With Takayasu Arteritis

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Summary

The integral changes of coagulation and fibrinolysis, and their relationships with inflammation in patients with Takayasu arteritis (TA) remain undetermined. The purpose of this study was to analyze the changes of coagulation and fibrinolysis process in patients with TA by thrombelastography (TEG).

A total of 127 patients with TA and 55 healthy controls were enrolled. Patients with TA were grouped according to disease activity. The routine hematological parameters, traditional coagulation assays, and TEG parameters were summarized retrospectively.

A shorter K time, larger alpha angle, and higher levels of MA, MA(A), G, and TPI were found in patients with TA, especially in those at the active stage. The R time, EPL, LY30, and CL30 were similar between patients with TA and healthy controls, as well as TA patients with different disease activity. Spearman’s correlation showed that ESR was correlated with PLT ($r = 0.206, P = 0.020$), $K (r = -0.353, P < 0.001)$, alpha angle ($r = 0.328, P < 0.001$), MA ($r = 0.474, P < 0.001$), MA (A) ($r = 0.623, P < 0.001$), G ($r = 0.475, P < 0.001$), and TPI ($r = 0.458, P < 0.001$).

In conclusion, inflammation was associated with platelet coagulation function rather than enzymatic coagulation function in patients with TA. Physicians should focus on antiplatelet treatment for improving the prognosis of patients with TA. (Int Heart J 2017; 58: 589-592)

Key words: Inflammation, Disease activity, Thrombelastography

Inflammation-induced thrombosis is well known in many rheumatic diseases.1,2 Takayasu arteritis (TA) is a chronic non-specific vasculitis which may result in stenosis, occlusion, dilation, or aneurysm in the aorta and its main branches.3,4

A thrombotic tendency also exists in patients with TA. Numano, et al6 reported that when compared to healthy subjects, levels of platelet P-selectin and plasma thromboxane B2 were higher, while plasma cyclic adenosine monophosphate levels were lower in patients with TA, which indicated that increased platelet activity existed in patients with TA. Whether hypercoagulability contributes to thrombosis development in patients with TA is undetermined. Girona, et al7 reported that there were only minor abnormalities in coagulation in a few patients with TA, and no clinical relevance was found in the findings. However, the study of Akazawa, et al8 showed β-thromboglobulin, thrombin/AT-III complex, fibrinopeptide A, and D-dimer were found to be significantly higher in TA patients than in normal controls, which indicated hypercoagulability may exist in patients with TA. A retrospective study9 in 48 patients with TA showed only antiplatelet agents had a protective effect against acute ischemic events. Although no difference concerning ischemic events was observed in patients on anticoagulant therapy in the study, only 6 patients who used anticoagulant agents were included and so the limited sample size may have influenced the validity of the results. Thus, the changes in coagulation and whether anticoagulant agents are needed for preventing thrombus formation are still to be determined.

In addition, the coagulation and fibrinolysis function may vary depending on the intensity of systemic inflammation.10,11 For example, increased mean platelet volume (MPV) is found in low-grade inflammation, whereas decreased MPV is associated with high-grade inflammation.11 However, whether the coagulation and fibrinolysis process is also altered in TA patients with different disease activity remains unknown.

Thrombelastography (TEG) provides a global assessment of haemostatic function, beginning with initial platelet-fibrin
interaction, to platelet aggregation, clot strengthening, and fibrin cross-linkage, and eventually clot lysis.\textsuperscript{12,16} The purpose of the present study was to compare by TEG the coagulation and fibrinolysis process between patients with TA and healthy controls, as well as TA patients with different disease activity.

**METHODS**

**Patients:** A total of 127 patients with TA and 55 healthy controls in Fuwai Hospital between January 2009 and December 2015 were enrolled and received TEG assessment. All patients with TA fulfilled the criteria for diagnosis of TA according to the 1990 American College of Rheumatology\textsuperscript{15} and were grouped depending on disease activity. Disease activity was assessed according to the criteria of the National Institute of Health;\textsuperscript{16} the active stage of TA was diagnosed if a patient had more than two new or worsening of the following features: 1) systemic symptoms not attributable to other clinical conditions; 2) characteristics of vascular insufficiency, such as claudication, vascular pain, bruit, or asymmetry in pulses or blood pressure; 3) elevated ESR without infection or malignancy; and 4) typical angiographic characteristics. Individuals with severe liver or kidney insufficiency, a hematological disease, or who accepted anticoagulation drugs were excluded. The clinical features, laboratory data, TEG parameters, and medication during pre-admission were summarized retrospectively. The study protocol was approved by the Institutional Ethics Committee of Fuwai Hospital.

**Measurements:** Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were evaluated by immunoturbidimetry (Beckmann Assay 360, Bera, CA, USA). Routine hematological parameters were analyzed using an XE 2100 Sysmex\textsuperscript{TM} automated hematology analyzer (Sysmex, Kobe, Japan). Traditional coagulation assays were assessed using a STAGO Coagulation analyzer (Diagnostica Stago, Asnières, France). The hematological test parameters determined included platelet count (PLT), thrombocytocrit (PCT), MPV, platelet volume distribution width (PDW), platelet–large cell ratio (P–LCT), platelet count (PLT), thrombocrit (PCT), MPV, and fibrinogen degradation products (FDP).

**TEG assessment:** The blood samples were collected and analyzed using a Thromboelastograph Analyzer 5000 (Haemoscope Corp., IL, USA). The coagulation process is initiated by kaolin, and the parameters of the process are not influenced by antiplatelet drugs. All parameters were recorded and described as follows. The R value (reaction time) is the most representative parameter of enzymatic clotting factors with a normal range of 4-9 minutes. On the TEG tracing, it is the time taken from the beginning of the trace until it reaches an amplitude of 2 mm. The K value (coagulation time) and the alpha angle depend on fibrinogen and platelets. K is the time taken for elevation of the amplitude from 2 to 20 mm (normal range, 1-3 minutes). The alpha angle (normal range: 46-76 degrees) is the slope of the tracing that represents the rate of clot formation. The MA and G reflect clot strength. MA is the greatest amplitude of the tracing with a normal range of 50-71 mm, which mainly depends on platelet contribution. High MA values correspond with platelet hypercoagulability. G (total clot strength), which is calculated by amplitude, is inclusive of both platelet and enzymatic contributions to overall clot strength. TMA represents the time to MA, and TPI is the thrombodynamic potential index (normal range, 5-90). EPL, CL30, and LY30 are parameters that reflect the fibrinolysis process. EPL is estimated lysis at 30 minutes after MA, while CL30 is surplus clot at 30 minutes after MA. LY30 represents the velocity of lysis in the 30 minutes after MA.

**Statistical analyses:** Continuous variables are presented as the mean with standard deviation or median (interquartile range) according to the normality of variables. Comparisons between groups were performed by the independent t-test or Mann-Whitney U test. Categorical variables are presented as the count (proportion), and comparisons between groups were performed using the chi-square test. The relationships between ESR and thrombosis-related parameters were assessed by the Spearman correlation. Statistical analyses were carried out using SPSS software (version 21.0). P values of less than 0.05 were considered statistically significant.

**RESULTS**

Thrombosis-related parameters between patients with TA and healthy controls: In routine hematological parameters (Supplemental Table I), MPV (10.40 [9.90, 11.15] versus 10.70 [10.20, 11.33], \(P = 0.035\) and PDW (12.00 [10.70, 13.60] versus 12.55 [11.50, 14.03], \(P = 0.046\)) were lower in the patients with TA compared with healthy controls. A slight increase in PLT (235.00 [191.00, 284.00] versus 216.00 [187.50, 250.50]*10^9/L, \(P = 0.085\)), PCT (0.25 [0.20, 0.29] versus 0.24 [0.21, 0.27], \(P = 0.161\)) and a slight decrease in P-LCT (27.90 [23.20, 34.60] versus 30.05 [26.10, 35.53], \(P = 0.054\)) were found in patients with TA. No significant differences were found in PT, aPTT, or the level of FDP.

**TEG assessment:** A shorter K time (1.60 [1.30, 2.00] versus 1.80 [1.60, 2.20], \(P = 0.009\)), larger alpha angle (66.30 [60.30, 70.20] versus 63.30 [58.90, 67.10], \(P = 0.019\)), higher level of MA (60.50 ± 6.76 versus 56.40 ± 6.21, \(P < 0.001\)), G (7.60 [6.40, 9.30] versus 6.40 [5.60, 7.60], \(P < 0.001\)), TPI (47.70 [31.60, 64.70] versus 36.60 [27.50, 46.80], \(P = 0.001\)), and MA(A) (9.80 [7.20, 13.55] versus 6.90 [5.55, 8.25], \(P = 0.001\)) were found in the patients with TA in comparison with healthy controls. The R time, TMA, EPL, LY30, and CL30 were similar between the two groups.

**Clinical characteristics between TA patients at stable and active stages:** The clinical characteristics of 80 TA patients at stable stage and 47 TA patients at active stage are summarized in Supplemental Table II. No differences in the clinical characteristics existed except for a higher female proportion (97.9% versus 76.3%, \(P = 0.001\)) and higher level of inflammation biomarker in the active group. Hypertension was the most common comorbidity, followed by hyperlipidemia, stroke, and diabetes mellitus in both groups. No significant differences were found in the pre-admission usage of prednisone, antiplatelet agents, and statins between the two groups.

Thrombosis-related parameters between TA patients at active and stable stages: Among routine hematological parameters (Supplemental Table III), PLT (245.00 [207.00, 308.00] versus 223.00 [181.00, 276.00]*10^9/L, \(P = 0.027\)) and PCT (0.26 [0.22, 0.31] versus 0.23 [0.19, 0.28], \(P = 0.026\)) were significantly higher in the active group compared with the stable group, whereas only slight decreases in MPV (10.30 [9.78,
were similar between the two groups. The results while, TPI and MA(A), which reflect the function of platelets and fibrinogen, were higher in patients with TA. Mean-

enhanced function of platelets and fibrinogen were associated with inflammation. Previous studies\(^{17,19}\) reported thrombopoi-

eisis was enhanced in the inflammation state, while large amounts of highly reactive large-sized platelets migrate to inflam-

atory sites and are consumed intensely. Similarly, our study found slight increases in PLT in patients with TA. Mean-

while, MPV was decreased, and a slight decrease in P-LCT was also observed in patients with TA. Thus, the results of our study depended on the balance of thrombopoiesis, accumula-

tion, and consumption of large-sized platelets in vessels in pa-


tients with TA. Moreover, all the above parameters were correlated with ESR, which indicated the en-

hanced function of platelets and fibrinogen were associated with inflammation. Although fibrinogen was not measured in our study, higher MA (A) demonstrated that the function of fibrinogen was enhanced in patients with TA, especially in those at the active stage.

The present study showed aPTT was longer in the active group than that in the stable group, while no difference in PT was found between the two groups. In addition, the time of R, which reflects enzymatic coagulation function, was not different between the two groups. There may be several reasons for this phenomenon. First, the coagulation reaction involves multiple approaches; prolongation in one approach cannot influence the integrity of the coagulation process. Second, the two tests were initiated with a different activator, and based on different mechanisms, one reflected the partial approach of coagulation, and the other reflected the integral process of coagulation and fibrinolysis. Third, the specificity and sensitivity of the two tests were different.

Some studies\(^{22,23}\) have reported that fibrinolysis may be associated with inflammation. However, in accordance with the previous study by Girona,\(^7\) our study showed no correlations between FDP, EPL, LY30, CL30, and ESR, which indicated inflammation may not play a role in fibrinolysis in patients with TA. A limitation of the study should be considered. Due to the cross-sectional design of the study, we could not determine the definite causality between inflammation and changes in hemostatic function and fibrinolysis in TA. Further longitudinal intervention studies are needed to confirm the results of our study.

In conclusion, inflammation was associated with platelet coagulation function rather than enzymatic coagulation function in patients with TA, and therefore, physicians should focus on antiplatelet treatment for improving the prognosis of patients with TA.
DISCLOSURE

There is no conflict of interest.

REFERENCES


SUPPLEMENTAL FILES

Supplemental Tables I, II, III, IV
Supplemental Figures 1, 2
Please find supplemental files; https://www.jstage.jst.co.jp/article/ihj/58/4/58_16-533/_article/supplement