An Abnormal Systemic and Regional Hypercoagulable State in Patients with Mitral Stenosis

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Abstract

Mitral stenosis still remains a major problem in Southeast Asia including Thailand. It contributes to the morbidity and mortality related to thromboembolism which was associated with the left atrial thrombus. However, the pathogenesis of left atrial thrombus in these patients is not completely understood. Therefore, the objective of this study was to investigate the coagulation and platelet activity including the function of the endocardium in the left atrium and peripheral circulation in patients with mitral stenosis who were free of left atrial thrombus and to compare those hematologic markers activity in the peripheral venous blood between the patients with mitral stenosis and the control.

Thirty-six patients with moderate to severe mitral stenosis were included in the study. Most of the patients were in functional class II and 50 per cent had atrial fibrillation. Blood was obtained from the femoral vein, femoral artery, pulmonary artery and left atrium of these patients before heparin was administered to determine the value of various hematologic markers. In the control group, blood for determining the hematologic markers was collected only from the antecubital vein. The results of this study demonstrated that the levels of prothrombin activation fragment 1+2 (F1+2), thrombin-antithrombin III complex (TAT) and Beta-thromboglobulin (β-TG) in the left atrium of the patients with mitral stenosis were significantly higher than those in the femoral vein and femoral artery, whereas the level of thrombomodulin was significantly lower in the left atrium compared with the femoral artery and vein. When comparing with the control group, the levels of TAT, plasminogen activator inhibitors-1 (PAI-1) from the peripheral vein were significantly higher and the level of thrombomodulin was also significantly lower in the patients with mitral stenosis.

In conclusion, the present study demonstrated an abnormal hypercoagulable state of the left atrium and systemic circulation related to the abnormalities of coagulation, platelets and the endocardium which may cause the formation of left atrial thrombus in patients with mitral stenosis.

Key word : Mitral stenosis, Coagulation, Platelet, Thrombus, Hypercoagulable State

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One of the major causes of morbidity and mortality in mitral stenosis is thromboembolism that occurs 10-12 times more often than in the normal population[1-3]. Thromboembolism in mitral stenosis is usually related to left atrial thrombus especially in patients with atrial fibrillation. Predisposing factors which increase the risk of thromboembolism include atrial fibrillation (AF), increased age, a prior thromboembolic event, left atrial spontaneous echo contrast (LASEC), left atrial enlargement and left ventricular dysfunction[1-5]. However, the pathogenesis of the left atrial thrombus formation in these patients has not clearly been defined. In the past, some studies reported the abnormalities of coagulation activity both in the left atrium and systemic circulation in patients with mitral stenosis[6-12]. This information included the increased level of fibrinopeptide A, thrombin-antithrombin III complex (TAT), prothrombin activation fragment 1+2 (F1+2), D-dimer, Beta-thromboglobulin (β-TG) and platelet factor 4 (PF_4). However, these results have been conflicting. In addition, there have been a few studies concerning platelet activity in these patients[6,8,14]. Therefore, the objective of the present study was separated into two parts. The first objective was to assess coagulation and platelet activity including the function of the endocardium in the left atrium and peripheral circulation in patients with mitral stenosis who were free of left atrial thrombus. The second was to compare those hematologic markers activity in the peripheral venous blood between the patients with mitral stenosis and the control group.

MATERIAL AND METHOD

From June 2001 to February 2002, 36 patients with symptomatic moderate to severe mitral stenosis confirmed by echocardiography and suitable for balloon mitral valvuloplasty seen in the outpatient department and heart clinic were prospectively recruited to the present study. The exclusion criteria were as follows:- left atrial thrombus, mitral regurgitation > 2+, inability to perform transeptal puncture, severe concomitant valvular lesions, concurrent aspirin or anticoagulant therapy, a history of renal or liver disease, pulmonary embolism, deep vein thrombosis, malignancy or a connective tissue disorder.

The control group consisted of 33 healthy subjects who were age and sex-matched recruited from normal volunteers and staff. All control subjects were in normal sinus rhythm and had no history of various disorders that could interfere with the hematologic markers in the present study as stated above.

The study was conducted following permission from the Siriraj Ethical Committee. Written informed consent was obtained from all patients and control subjects before blood was sampled.

Valvuloplasty and blood sampling procedure

Warfarin and aspirin were discontinued in all patients 10 days before the procedure. The mean INR in 10 patients who were previously given warfarin was 1.05 on the day of the procedure. In addition of clinical assessment, the transthoracic and transesophageal echocardiography were performed in patients the day before valvuloplasty procedure to assess if left atrial thrombi was present, the interatrial septum, mitral valve score, left atrial size, left atrial spontaneous echo contrast (LASEC), mitral valve area, transmitral valve gradient, the severity of mitral regurgitation, other concomitant valvular lesions, the severity of pulmonary hypertension and the left ventricular ejection fraction (LVEF).

After the vascular sheaths were placed in the right femoral artery and vein, 4.5 ml of blood from the artery and vein was cautiously drawn. After that, the Swan-Ganz catheter was inserted through the venous vascular sheath and placed in the pulmonary artery to determine the cardiac output and 4.5 ml of blood was taken for analysis. Subsequently, the transeptal puncture was performed using standard technique[13] and 4.5 ml of blood was collected from the left atrium. Then, the balloon mitral valvuloplasty procedure was further done. All blood samples had been collected before heparin was administered. For the control subjects, the blood sample was collected only from the antecubital vein.

Assay procedure

The hematologic markers determined from the blood samples included platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), prothrombin activation fragment 1+2 (F1+2), thrombin-antithrombin III complex (TAT), plasminogen activator inhibitors-1 (PAI-1), platelet factor 4 (PF_4), beta-thromboglobulin (β-TG), thrombomodulin, von Willebrand factor (vWF) and fibrinogen.

F1+2 and TAT were used as the markers of thrombin activity, whereas D-dimer and PAI-1 gave the information about the fibrinolytic system. PF_4 and β-TG were measured to assess the platelet activity. Finally, the endocardial function of the left atrium was assessed by the measurement of vWF and thrombomodulin.

The plasma concentration of F1+2 and TAT were measured with the use of enzyme immunoassay kits from Dade Behring (E' NOST F1+2, E' NOST TAT). The plasma concentration of β-TG, PF_4, PAI-1 and thrombomodulin were determined using enzyme immunoassay kits from Diagnostic Stage, France (ASSERACHROM β-TG, ASSERACHROM PF_4, ASSERACHROM PAI-1 and ASSERACHROM thrombomodulin). D-dimer was measured using a latex-enhanced, turbidimetric test from Dade Behring (BC D-dimer). Fibrinogen was measured using immunoassay kits from Dade Behring (Thromborel S on Sysmex CA-500, Clauss assay). Monoclonal antibodies specific for each detected parameter were used in all of the test systems. Intra-assay coefficients of variation for all assays were less than 10 per cent.

Statistic analysis

Continuous variables were expressed as mean ± SD and categorical variables as per cent. A paired *t*-test was used for comparison of the hematologic markers between various sample sites and the left atrium if the data was normally distributed and Wilcoxon Signed Rank test if abnormally distributed. An unpaired *t*-test was carried out to compare the hematologic markers from the peripheral circulation between the normal control and the patients with mitral stenosis if the data was normally distributed, and a Mann-Whitney U test was used if the data wasn't normally distributed. ANOVA-Dunnett was used to compare the hematologic markers between the control and the mitral stenosis patients with and without atrial fibrillation.

RESULTS

The authors studied 36 patients with moderate to severe mitral stenosis. The mean age of the patients was 40 and the ratio of female to male was 2 : 1. Most of the patients were in functional class II. Fifty per cent of the patients had atrial fibrillation and 8.3 per cent had a history of prior stroke. The severity and the hemodynamic data recorded before the mitral valvuloplasty procedure are shown in Table 1. Coagulation activity, fibrinolytic activity, platelet activity and the endocardial function were analyzed respectively.

In patients with mitral stenosis, it was demonstrated that the level of TAT and F1+2, markers of thrombin activity, was significantly higher in the left atrium than in the femoral vein, femoral artery and pulmonary artery as shown in Table 2. In addition, the fibrinogen level was lower in the left atrium compared with the pulmonary artery and femoral artery but no

Table 1. Demographic data.

	%
N	36
Age (yr)	40.14 ± 9.64
Sex	
Male	33.3
Female	66.7
NYHA Functional Class.	
Class I	11.1
Class II	80.6
Class III	5.6
Class IV	2.8
Prior history of stroke	8.3
LA size (mm)	53.61 ± 14.21
LVEF (%)	65.31 ± 8.30
Atrial fibrillation	50
Mitral valve area (cm^2)	0.99 ± 0.31
Mean LA-LV gradient (mmHg)	12.89 ± 4.27
Mean pulmonary artery pressure (mmHg)	34.61 ± 12.62
Cardiac output ($l/min/M^2$)	3.86 ± 0.82
Mitral regurgitation	
Grade 0	58.3
Grade 1	38.9
Grade 2	2.8

significant difference was found when compared with the sample from the femoral vein. The level of PAI-1 in the left atrium was also higher than in the other sites but this did not reach statistical significance. Nevertheless, the level of D-dimer in the left atrium was not significantly different from that in the peripheral circulation.

The concentration of PF_4, the index of platelet activation, was shown to be significantly higher in the left atrium compared with the pulmonary and femoral arteries. In addition, there was also significant difference in the level of β-TG, another marker of platelet activation, between the left atrium and the femoral vein and femoral artery.

Regarding the markers of endocardial function, it was found that the level of thrombomodulin was significantly lower in the left atrium than in the femoral vein and femoral artery. However, there was no significant difference in the level vWF between the left atrium and the other sites.

When the authors compared the plasma concentration of the hematologic markers in the peripheral vein between the patients with mitral stenosis and controls, it was demonstrated that the levels of PT, aPTT, TAT and PAI-1 in the patients with mitral stenosis were significantly higher than the control group as shown in Table 3. Additionally, the level of thrombomodulin was significantly lower in the patients compared with the controls. The levels of fibrinogen, PF_4 and β-TG were also higher in the patients but this didn't achieve statistical significance.

This study also showed that the plasma levels of PT, aPTT, F1+2, TAT and PAI-1 in the patients with mitral stenosis and atrial fibrillation were higher than those in the controls; in addition, the levels of thrombomodulin were also lower in the patient group as shown in Table 4. In the patients without atrial

Table 2. Comparison of the level of hematologic markers between the femoral vein, pulmonary artery, femoral artery and left atrium.

	FV	FA	PA	LA
PT (sec)	12.90 ± 2.30$^{\pi}$	13.00 ± 2.00	13.80 ± 4.50$^{\#}$	12.90 ± 2.10
PTT (sec)	31.10 ± 5.30$^{\pi}$	31.70 ± 4.60	35.50 ± 11.30$^{\#}$	30.90 ± 6.40
F1+2 (nmol/L)	0.83 ± 0.52$^{*\,\Omega}$	0.60 ± 0.29^{SS}	0.69 ± 0.35$^{\#}$	1.60 ± 1.12
TAT (μg/L)	11.34 ± 16.05$^{*\,\Omega\,\pi}$	3.47 ± 1.82^{SS}	5.90 ± 5.73$^{\#}$	35.71 ± 25.33
PAI-1 (ng/ml)	16.59 ± 17.47$^{\Omega}$	15.11 ± 16.54	15.23 ± 15.61	17.17 ± 16.30
D-Dimer (μg/L)	223.30 ± 136.60	222.60 ± 146.00	220.3 ± 143.50	238.40 ± 158.50
Platelet (x10^3)	243.60 ± 63.00$^{*\,\pi}$	242.70 ± 67.30^{o}	229.80 ± 63.20	234.50 ± 63.5
PF4 (IU/ml)	46.41 ± 32.89$^{\pi\,\Omega}$	23.95 ± 21.50^{SS}	31.34 ± 27.60$^{\#}$	46.18 ± 28.41
β-TG (IU/ml)	123.24 ± 63.57$^{*\,\Omega}$	101.06 ± 60.8^{SS}	141.21 ± 60.13	141.85 ± 50.78
Thrombomodulin (ng/ml)	6.50 ± 1.35*	6.41 ± 1.29$^{\Phi}$	6.21 ± 1.29	5.98 ± 1.06
VWF (IU/ml)	100.90 ± 27.80	104.20 ± 31.00	102.3 ± 26.90	104.90 ± 29.20
Fibrinogen (mg/dl)	406.40 ± 130.70$^{\pi}$	411.70 ± 138.90$^{SS\,o}$	422.50 ± 136.20$^{\#}$	402.40 ± 137.40

FV = Femoral vein, PA = Pulmonary artery, FA = Femoral artery, LA = Left atrium.
* $p < 0.01$; FV compared with LA, $^{\pi}$ $p < 0.05$; FV compared with PA
^{SS} $p < 0.01$; FA compared with LA, ^{o} $p < 0.05$; FA compared with PA,
$^{\Phi}$ $p < 0.05$; FA compared with LA, $^{\Omega}$ $p < 0.05$; FV compared with FA, $^{\#}$ $p < 0.01$; PA compared with LA.

fibrillation, the level of thrombomodulin was significantly lower than the controls but the other hematologic indices were not significantly different.

DISCUSSION

Because mitral stenosis is a disease of mechanical obstruction of LV inflow, the consequences of this obstruction may produce the stasis of blood in the left atrium which may contribute to a local prethrombotic state due to accumulation of circulating prothrombotic substances. From the present study the authors found that there was an increase in TAT and F1+2, reflecting the status of thrombin activity, in the left atrium of patients with mitral stenosis compared with levels in the femoral vein, pulmonary artery and femoral artery as shown in Table 2. These results are similar to a previous study by Yamamoto et al[6] and Peverill et al[7]. In addition, it was found that the level of fibrinogen was significantly lower in the left atrium compared with the pulmonary and femoral arteries. These findings might indicate that there was a process of increased consumption of coagulation factors in the left atrium.

Another factor that predisposes to thrombus formation is local fibrinolytic activity in the left atrium of a patient with mitral stenosis which can be demonstrated by measuring the levels of PAI-1 and D-dimer. In the present study, the authors couldn't show that

Table 3. Comparison of hematologic markers from the peripheral vein between patients with mitral stenosis and normal controls.

	Controls (n = 33)	Mitral stenosis (n = 36)	P
PT (sec)	11.30 ± 0.60	12.90 ± 2.30	0.000
PTT (sec)	28.20 ± 2.20	31.10 ± 5.30	0.004
F1+2 (nmol/L)	0.80 ± 0.29	0.83 ± 0.52	0.805
TAT (ug/L)	2.01 ± 0.80	11.34 ± 16.05	0.000
PAI-1 (ng/ml)	7.26 ± 5.54	16.59 ± 17.47	0.004
D-Dimer (ug/L)	242.90 ± 187.00	223.30 ± 136.60	0.618
Platelet ($x10^3$)	290.70 ± 78.20	243.60 ± 63.00	0.007
PF4 (IU/ml)	31.71 ± 27.30	46.41 ± 32.89	0.053
β-TG (IU/ml)	97.96 ± 63.49	123.24 ± 63.57	0.103
Thrombomodulin (ng/ml)	8.55 ± 2.50	6.50 ± 1.35	0.000
VWF (IU/ml)	107.60 ± 26.70	100.90 ± 27.80	0.326
Fibrinogen (mg/dl)	350.80 ± 118.80	406.40 ± 130.70	0.069

Table 4. Comparison of hematologic markers from the peripheral vein between mitral stenosis patients with and without atrial fibrillation and normal controls.

	Controls (n = 33)	MS with AF (n = 18)	MS without AF (n = 18)
PT (sec)	11.30 ± 0.60	13.46 ± 2.86*	12.31 ± 1.32
PTT (sec)	28.20 ± 2.20	32.59 ± 6.77*	29.70 ± 3.25
F1+2 (nmol/L)	0.80 ± 0.29	0.84 ± 0.65*	0.82 ± 0.37
TAT (ug/L)	2.01 ± 0.80	13.01 ± 19.04*	9.67 ± 12.72
PAI-1 (ng/ml)	7.26 ± 5.54	23.16 ± 22.19*	10.23 ± 6.71
D-Dimer (μg/L)	242.90 ± 187.00	209.50 ± 87.33	237.06 ± 174.35
Platelet ($x10^3$)	290.70 ± 78.20	256.22 ± 62.48	230.94 ± 62.74#
PF4 (IU/ml)	31.71 ± 27.30	45.36 ± 33.59	47.46 ± 33.17
β-TG (IU/ml)	97.96 ± 63.49	127.02 ± 68.40	119.45 ± 60.10
Thrombomodulin (ng/ml)	8.55 ± 2.50	6.73 ± 1.59*	6.27 ± 1.05#
VWF (IU/ml)	107.60 ± 26.70	107.03 ± 24.89	95.14 ± 29.27
Fibrinogen (mg/dl)	350.80 ± 118.80	403.19 ± 114.25	409.59 ± 148.59

* $p < 0.05$; mitral stenosis with AF compared with control.
# $p < 0.05$; mitral stenosis without AF compared with control.

there was a significant difference in levels of PAI-1 and D-dimer in the left atrium of the patient with mitral stenosis compared with a peripheral blood sample. These results are similar to the study of Li-Saw-Hee FL et al[8] and Yamamoto K et al[6].

Regarding the role of platelet in the formation of left atrial thrombus, the authors found that the level of PF_4 in the left atrium of the patients with mitral stenosis was significantly higher than those in pulmonary artery and femoral artery. Similarly, there was a difference in the level of β-TG between the left atrium and the femoral vein and femoral artery as shown in Table 2. Additionally, the number of platelets in the left atrium was significantly lower than the femoral vein. This finding, similar to the previous study[14], supports the hypothesis of an increased consumption of platelets by small thrombus or the greater adherence of platelets to the left atrial wall surface probably occurs. However, the present results were different from the study of Yamamoto et al[6] and Li-Saw-Hee FL et al[8] which reported no difference of PF_4 and β-TG between left atrium and the other sites. This might partly be explained by the small sample size of both studies and the accuracy of blood sample collection because if this is not carefully performed, the platelets might be activated and release PF_4 and β-TG.

Looking at endocardial function of the left atrium, the results of the present study have shown that the level of thrombomodulin in the left atrium was significantly lower when compared with the femoral vein and femoral artery, whereas the level of vWF didn't differ significantly between the left atrium and the other sites sampled. The present results were different from the study reported by Li-Saw-Hee FL et al [8] who didn't demonstrate a difference in thrombomodulin level between the left atrium and femoral vein and right atrium despite the fact that the reagent used in both studies came from the same company. The explanation for the disconcordant results might be related to various factors including the different baseline characteristics of the study population, the different numbers of the study population and the process of blood collection including the accuracy of measurement. However, the present study confirmed the previous study[8] that the level of vWF in patients with mitral stenosis was not different between the left atrium and the peripheral circulation. The different results for thrombomodulin and vWF in the previous studies and the present study are probably explained by the different aspects of vascular physiology of both markers.

Another interesting question is whether there is a systemic hypercoagulable state in mitral stenosis. In the present study, the authors tried to answer this question by comparing the hematologic markers from the peripheral vein between patients with mitral stenosis and normal controls who were age and sex matched. The present study showed that the level of PAI-1 and TAT was significantly higher in the patients with mitral stenosis than the controls. These findings, similar to the studies of Marin F et al[10] and Zaki A et al[14], possibly indicated that prethrombotic state in the peripheral circulation might also occur in these patients. However, it can't be explained why there was no difference of F1+2 and D-dimer between these patients and the controls. One reason may in partly be explained by the different stage of the formation of TAT and F1+2 which gives different information about coagulation activity. Further studies are needed to answer this question.

In conclusion, the present study demonstrated that there is a hypercoagulable state of the left atrium and systemic circulation related to the abnormalities of coagulation, platelets and the endocardium which may subsequently cause the formation of left atrial thrombus and thromboembolic events in patients with mitral stenosis.

Limitations of the study

There are some limitations to the present study. Firstly, only patients with moderate to severe mitral stenosis were included, therefore, the authors could not apply the result of study to patients with mild mitral stenosis. Secondly, the technique for D-dimer detection in the present study was a latex-enhanced, turbidimetric method which is probably not as good as the ELISA technique; therefore, it can cause the results of D-dimer in the present study to differ from the previous study. Finally, the duration of stopping warfarin for 10 days might not be long enough in some patients with hepatic congestion, therefore, it is possible that the level of D-dimer and F1+2 may be partially suppressed enough to demonstrate no difference of these markers from the normal controls.

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ความผิดปกติของระบบการแข็งตัวของเลือด การทำงานของเกร็ดเลือดและเยื่อบุของเอเตรียมซ้ายในผู้ป่วยลิ้นไมตรัลตีบ

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ในประเทศไทยและประเทศในแถบเอเชียอาคเนย์ พบว่าโรคลิ้นหัวใจไมตรัลตีบ ยังคงเป็นปัญหาสำคัญที่พบได้บ่อย และก่อให้เกิดภาวะแทรกซ้อนที่สำคัญ คือการเกิดลิ่มเลือดในหัวใจซึ่งสามารถทำให้เกิดพยาธิสภาพในตำแหน่งที่ลิ่มเลือดนี้หลุดไปอุดโดยเฉพาะที่ระบบประสาทส่วนกลาง มีผลทำให้ผู้ป่วยเกิดอัมพาต หรืออัมพฤกษ์ได้ตั้งแต่อายุน้อย จากการศึกษาในอดีตพบว่ากลไกที่ทำให้เกิดลิ่มเลือดนี้ยังไม่เป็นที่เข้าใจแน่ชัด ผู้วิจัยจึงได้ทำการศึกษาความผิดปกติของระบบการแข็งตัวของเลือด การทำงานของเกร็ดเลือดและเยื่อบุหัวใจของเอเตรียมซ้าย ในผู้ป่วยลิ้นหัวใจไมตรัลตีบที่มารับการรักษาด้วยวิธีการขยายลิ้นหัวใจด้วยบอลลูน จำนวน 37 ราย โดยทำการดูดเลือดจากตำแหน่งต่าง ๆ ได้แก่หลอดเลือดดำ femoral หลอดเลือดแดง femoral หลอดเลือดแดง pulmonary และเอเตรียมซ้าย เพื่อนำไปตรวจหาสารต่าง ๆ ที่เกี่ยวข้องกับระบบการแข็งตัวของเลือด การทำงานของเกร็ดเลือดและเยื่อบุหัวใจของเอเตรียมซ้าย ในการศึกษานี้ได้เจาะเลือดดำจากแขนของคนปกติ 33 ราย ที่อายุและเพศใกล้เคียงกับกลุ่มผู้ป่วย เพื่อใช้เป็นกลุ่มเปรียบเทียบ

จากการศึกษาพบว่าในผู้ป่วยโรคลิ้นหัวใจไมตรัลตีบ จะมีระดับของ F1+ 2, TAT และ β-TG ในเอเตรียมซ้ายสูงกว่าตำแหน่งอื่น และระดับของ thrombomodulin ในเอเตรียมซ้าย จะมีค่าต่ำกว่าตำแหน่งอื่นเมื่อวัดในคนเดียวกัน นอกจากนี้เมื่อเปรียบเทียบระหว่างผู้ป่วยลิ้นไมตรัลตีบและคนปกติ จะพบว่าระดับ TAT และ PAI-I ในเลือดดำที่เจาะจากหลอดเลือดส่วนปลายของผู้ป่วยลิ้นไมตรัลตีบมีค่าสูงกว่าคนปกติ

โดยสรุป การศึกษานี้พบว่าในผู้ป่วยลิ้นไมตรัลตีบ จะมีความผิดปกติของระบบการแข็งตัวของเลือด การทำงานของเกร็ดเลือด รวมทั้งความผิดปกติของเยื่อบุหัวใจของเอเตรียมซ้ายและในระบบไหลเวียนโลหิต ซึ่งความผิดปกติดังกล่าวอาจเป็นปัจจัยสำคัญของการเกิดลิ่มเลือด รวมทั้งการเกิดภาวะก้อนเลือดอุดตัน

คำสำคัญ : ลิ้นหัวใจไมตรัลตีบ, การแข็งตัวของเลือด, เกร็ดเลือด, ลิ่มเลือด

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