Changes in Hematologic Markers in Patients with Mitral Stenosis after Successful Percutaneous Balloon Mitral Valvuloplasty

Rewat Phankingthongkum MD*, Visanu Thamlikitkul MD*,
Decho Jakrapanichakul MD*, Sutiphol Udompanthurak MSc**

** Department of Medicine, Faculty of Medicine, Siriraj Hospital*
*** Office of Research Promotion, Faculty of Medicine, Siriraj Hospital, Mahidol University*

Systemic embolism is a major complication of mitral stenosis which is usually related to a presence of left atrial thrombus. Percutaneous balloon mitral valvuloplasty (PBMV) was previously reported to reduce the incidence of this complication. However, the mechanisms of this beneficial procedure was under investigated. The aim of this study was to investigate the changes in coagulation activity, platelet activity and endocardial function in 29 patients with mitral stenosis after successful PBMV. All subjects had good left ventricular systolic function and 48.3% had atrial fibrillation. There was a significant reduction in thrombin-antithrombin complex (TAT) after a successful procedure and the level of thrombomodulin was also significantly higher one month after successful procedure. However, the level of platelet factor 4 (PF_4) and beta-thromboglobulin (-TG) were increased after this procedure but not achieved the statistical significance.

In conclusion, successful PBMV can reduce the prethrombotic state in patients with mitral stenosis. In addition, it may improve endocardial function of the left atrium in those without atrial fibrillation.

Keywords : *Mitral stenosis, Balloon mitral valvuloplasty, Left atrial thrombus*

J Med Assoc Thai 2004; 87(6): 594-9

A serious complication of mitral stenosis is systemic embolism. Risk factors for systemic embolism in mitral stenosis patients are old age, atrial fibrillation, the presence of left atrial thrombus, large left atrial size, previous history of embolism and small mitral valve area[1-5]. The consequence of mitral valve obstruction is stasis of blood in the left atrium which may contribute to a local pre-thrombotic state due to abnormal activation of platelet activity and accumulation of circulating pre-thrombotic substances as reflected by the increased concentration of thrombin-anti-thrombin complex (TAT), Prothrombin activation F_{1+2} and D-dimer in the left atrium of these patients[6-10]. If this abnormal physiology persists and gradually increases, it may overwhelm the ability of the fibrinolytic system to maintain hemostasis, and thrombus formation may occur in the left atrium. Abnormal fibrinolysis has been found in patients with mitral stenosis as demonstrated by an increased level of PAI-I (plasminogen activator inhibitor-I) in the peripheral blood[11]. In addition, the level of thrombomodulin, reflecting the function of the endocardium of the left atrium was found to be decreased as a result of injury from high left atrial pressure which may predispose the patient to left atrial thrombus formation. One study reported that the patients who had previous percutaneous balloon mitral valvuloplasty (PBMV) had a lower incidence of thromboembolism[3]. However, there is little data concerning the effects of balloon mitral valvuloplasty on coagulation and platelet activity in these patients.

The objective of the present study was to determine the changes in coagulation activity, platelet activity and endocardial function of the left atrium in patients with mitral stenosis after successful balloon mitral valvuloplasty.

Correspondence to : Phankingthongkum R, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand. Phone: 0-2419-7745, Fax: 0-2412-7412

Patients and Method

The study was conducted in 29 patients with moderate to severe symptomatic mitral stenosis who had successful balloon mitral valvuloplasty at Siriraj Hospital between March and November 2002. Exclusion criteria included continuing use of aspirin or anticoagulant, stopping antiplatelet drugs or anticoagulant drugs less than 2 weeks before the study, having a history of renal or liver disease, pulmonary embolism, deep vein thrombosis, malignancy or connective tissue disorder. Antiplatelet drugs (aspirin, dipyridamole and clopidogrel), warfarin and hemorheologically active drugs such as NSAIDs or estrogen containing drug were discontinued in all patients 10 days before the procedure. Transthoracic and transesophageal echocardiography were performed the day before the mitral valvuloplasty procedure to assess the presence or absence of left atrial thrombi, interatrial septum, mitral valve score, spontaneous echo contrast (SEC), mitral valve area, transmitral valve gradient and the severity of mitral regurgitation.

Percutaneous balloon mitral valvuloplasty procedure

Right and left heart catheterization were performed by a percutaneous approach with the right femoral vein and artery to obtain hemodynamic data before the process of dilatation. Subsequently, transeptal puncture was performed using the standard technique[12] and the Inoue balloon catheter was carefully inserted over a spring-coil wire into the left atrium and further manipulated into the left ventricle for mitral valve dilatation. A left ventriculogram was also performed before and after PBMV to assess left ventricular function and the degree of mitral regurgitation. A successful outcome was defined as a final mitral valve area, (determined by Gorlin's formulation) of more than 1.5 cm^2 without mitral regurgitation of more than grade 2 by Seller's Classification[13] with no major complications.

Blood sample collection and Assay procedure

A blood sample was collected from the patients on 2 occasions. The first blood collection was done by cautiously withdrawing 4.5 ml of blood from the vascular sheath placed in the femoral vein before heparin was administered. The second specimen was collected 1 month after the PBMV after discontinuing anti-platelet and anticoagulant drugs for at least 10 days. All blood samples were then analyzed for hematologic markers including platelet count, PT, aPTT, F1+2, thrombin-antithrombin III complex (TAT), plasminogen activator inhibitors-1 (PAI-1), platelet factor 4 (PF_4), beta-thromboglobulin (-TG), thrombomodulin, von Willebrand factor (vWF) and fibrinogen.

Plasma concentration of F1+2 and TAT were measured using enzyme immunoassay kits from DADE BEHRING (E' NOST F1+2, E' NOST TAT). Plasma concentration of -TG, PF_4 and PAI-1 was determined by enzyme immunoassay kits from Diagnostic Stage, France (ASSERACHROM -TG, ASSERACHROM PF_4, and ASSERACHROM PAI-1). D-dimer was measured by a latex-enhanced, turbidimetric test from DADE BEHRING (BC D-dimer). Monoclonal antibodies specific to each detected parameter were used in all of the test systems.

Statistical analysis

Continuous variables are expressed as mean $\pm$ SD and categorical variables as percent. A paired t-test was used to compare the hematologic markers pre-and post- mitral valvuloplasty if the data was normally distributed and a Wilcoxon Ranged test if the data were not normally distributed. A P value $\leq$ 0.05 was considered significant.

Results

Out of 29 patients who had a successful procedure, 72.4% were female and 27.6% were male. The mean age was 40 years and 48.3% of the patients had atrial fibrillation. A previous history of stroke was found in 6.9% of the patients. All of them had good left ventricular systolic function with a mean left ventricular ejection fraction of 65%. The mean mitral valve area and transmitral valve gradient before the dilatation procedure were 0.97 cm^2 and 12.35 mmHg respectively. After PBMV, the mean mitral valve area increased to 2.05 cm^2 and the mean transmitral valve gradient was reduced to 5.07 mmHg as shown in Table 1.

The hematologic markers before and after PBMV are shown in Table 1. There was a significant reduction in TAT after a successful procedure. In addition, the level of F_{1+2} also decreased but this was not statistically significant. Thrombomodulin was significantly higher one month after a successful procedure. The concentration of PF_4 and TG were increased after successful dilatation but the differences were not significant. Finally, the level of PAI-1 was not significantly lowered after the valvuloplasty procedure.

Table 1. Hemodynamic data and hematologic markers pre-and post-PBMV in 29 patients

Hemodynamic data	Pre-PBMV	Post-PBMV	P
Mean ± SD of Mitral valve area (cm^2)	0.97 ± 0.28	2.05 ± 0.54	< 0.001
Mean ± SD of LA-LV gradient (mmHg)	12.35 ± 4.07	5.07 ± 2.22	< 0.001
Mean ± SD of Pulmonary artery pressure (mmHg)	33.31 ±11.42	31.93 ± 8.78	0.302
Mean ± SD of Cardiac output ($l/min/M^2$)	3.95 ± 0.84	4.70 ± 0.92	< 0.001
Mitral regurgitation			
Grade 0	55.2%	44.8%	
Grade 1	41.4%	48.3%	
Grade 2	3.4%	6.9%	
Hematologic markers			
Mean ± SD of PT (sec)	12.81 ± 2.34	15.86 ± 7.23	0.03
Mean ± SD of PTT (sec)	31.42 ± 5.78	34.67 ± 7.94	0.06
Mean ± SD of F1+2 (nmol/L)	0.91 ± 0.53	0.75 ± 0.78	0.3
Mean ± SD of TAT (ug/L)	12.84 ± 17.52	2.70 ± 1.89	0.01
Mean ± SD of PAI-I (ng/ml)	13.15 ± 12.55	11.60 ± 9.05	0.45
Mean ± SD of D-Dimer (ug/L)	233.72 ± 135.60	255.45 ± 169.01	0.21
Mean ± SD of Platelet ($x10^3$)	235.76 ± 57.83	225.34 ± 60.84	0.23
Mean ± SD of PF4 (IU/ml)	49.00 ± 34.44	56.38 ± 29.11	0.31
Mean ± SD of -TG (IU/ml)	121.10 ± 64.77	137.32 ± 52.62	0.33
Mean ± SD of Thrombomodulin(ng/ml)	6.43 ± 1.25	8.01 ± 2.07	0.001
Mean ± SD of VWF (IU/ml)	100.68 ± 27.64	108.91 ± 22.41	0.05
Mean ± SD of Fibrinogen (mg/dl)	393.45 ± 129.67	414.31 ± 115.90	0.27

NB: PT = Prothrombin time
PTT = Partial thromboplastin time
F1+2 = Prothrombin activation fragment 1+2
TAT = Thrombin-antithrombin complex
PAI-1 = Plaminogen activation inhibitor-1
-TG = Beta-thromboglobulin
PF_4 = Platelet factor-4
vWF = Von Willebran factor

Discussion

Thromboembolic events in patients with mitral stenosis are associated with left atrial thrombus formation which is related to various potential mechanisms such as the accumulation of pre-thrombotic substances, an abnormality of endocardial function, increased platelet activation, decreased fibrinolysis and rhythm abnormality (atrial fibrillation)[6-11]. All of these abnormalities may be reduced by PBMV as shown in previous studies[14-16].

In the present study, the authors demonstrated that the level of thrombin-antithrombin complex (TAT), a marker of thrombus formation, was significantly lower one month after successful balloon mitral valvuloplasty. In addition, the level of PAI-1 and F_{1+2} were also decreased but this did not achieve statistical significance. These results confirm those of Zaki A et al who also reported that balloon mitral valvuloplasty caused a significant reduction of TAT in the right atrium 30 minutes after the procedure in a subgroup with a left atrial pressure of less than 10 mmHg[16]. The beneficial effect of PBMV on the level of TAT was demonstrated significantly in the subgroup with atrial fibrillation as shown in Table 2. However, no significant changes of F_{1+2} were observed in the present study. One reason may in part be explained by the different stage of the formation of TAT and F1+2 which gives different information about coagulation activity. Considering the level of D-dimer as shown in Table 1, the present study could not demonstrate a significant change of this marker after successful PBMV. The reason might be related to the method of measuring the level of this marker which is a latex-enhanced, turbidimetric method that is probably not as good as an ELISA technique. Another reason might be related to the small sample size.

Looking at the levels of vWF and thrombomodulin, which reflect endocardial function in the left atrium, these were also increased after a successful procedure especially in patients without atrial fibrillation as shown in Table 3. This was a new finding that has never previously been reported. It may indicate that successful PBMV can improve

Table 2. Hemodynamic data and hematologic markers pre-and post-PBMV in 14 patients with atrial fibrillation (AF)

Hemodynamic data	Patients with AF		
	Pre-PBMV	Post-PBMV	P
Mean ± SD of Mitral valve area (cm^2)	0.91 ± 0.33	1.97 ± 0.62	< 0.001
Mean ± SD of LA-LV gradient (mmHg)	11.29 ± 4.45	5.00 ± 2.80	< 0.001
Mean ± SD of Pulmonary artery pressure (mmHg)	35.29 ± 13.21	33.43 ± 8.80	0.385
Mean ± SD of Cardiac output (l/min/M^2)	3.47 ± 0.61	4.17 ± 0.66	< 0.001
Hematologic markers			
Mean ± SD of PT (sec)	13.36 ± 3.09	19.43 ± 8.35	0.02
Mean ± SD of PTT (sec)	32.69 ± 7.55	38.73 ± 6.32	0.07
Mean ± SD of F1±2 (nmol/L)	0.96 ± 0.68	0.75 ± 1.02	0.46
Mean ± SD of TAT (ug/L)	15.54 ± 21.02	2.46 ± 1.46	0.04
Mean ± SD of PAI-I (ng/ml)	17.62 ± 15.80	13.86 ± 11.51	0.37
Mean ± SD of D-Dimer (ug/L)	223.43 ± 83.90	235.00 ± 160.80	0.69
Mean ± SD of Platelet ($x10^3$)	257.21 ± 69.32	229.21 ± 73.93	0.05
Mean ± SD of PF4 (IU/ml)	49.97 ± 34.78	46.56 ± 26.95	0.74
Mean ± SD of -TG (IU/ml)	134.00 ± 69.37	119.67 ± 49.37	0.58
Mean ± SD of Thrombomodulin(ng/ml)	6.52 ± 1.42	7.28 ± 1.46	0.18
Mean ± SD of VWF (IU/ml)	110.66 ± 21.86	114.53 ± 18.63	0.6
Mean ± SD of Fibrinogen (mg/dl)	403.08 ± 124.41	445.17 ± 93.02	0.08

NB: PT = Prothrombin time
PTT = Partial thromboplastin time
F1+2 = Prothrombin activation fragment 1+2
TAT = Thrombin-antithrombin complex
PAI-1 = Plaminogen activation inhibitor-1
-TG = Beta-thromboglobulin
PF_4 = Platelet factor-4
vWF = Von Willebran factor

Table 3. Hemodynamic data and hematologic markers pre-and post-PBMV in 15 patients without atrial fibrillation (AF)

Hemodynamic data	Patients with AF		
	PrePBMV	PostPBMV	P
Mean ± SD of Mitral valve area (cm^2)	1.03 ± 0.22	2.13 ± 0.46	< 0.001
Mean ± SD of LA-LV gradient (mmHg)	13.33 ± 3.56	5.13 ± 1.60	< 0.001
Mean ± SD of Pulmonary artery pressure (mmHg)	31.47 ± 9.57	30.53 ± 8.81	0.593
Mean ± SD of Cardiac output (l/min/M^2)	4.39 ± 0.80	5.21 ± 0.87	< 0.001
Hematologic markers			
Mean ± SD of PT (sec)	12.29 ± 1.24	12.53 ± 3.87	0.8
Mean ± SD of PTT (sec)	30.23 ± 3.27	30.88 ± 5.22	0.57
Mean ± SD of F1±2 (nmol/L)	0.85 ± 0.36	0.75 ± 0.51	0.43
Mean ± SD of TAT (ug/L)	10.33 ± 13.76	2.93 ± 2.25	0.07
Mean ± SD of PAI-I (ng/ml)	8.98 ± 6.69	9.48 ± 5.56	0.66
Mean ± SD of D-Dimer (ug/L)	243.33 ± 173.31	274.53 ± 179.75	0.13
Mean ± SD of Platelet ($x10^3$)	215.73 ± 36.58	221.73 ± 47.96	0.54
Mean ± SD of PF4 (IU/ml)	48.10 ± 35.31	65.93 ± 28.75	0.11
Mean ± SD of -TG (IU/ml)	109.06 ± 60.01	153.79 ± 51.68	0.03
Mean ± SD of Thrombomodulin(ng/ml)	6.34 ± 1.12	8.70 ± 2.35	0.001
Mean ± SD of VWF (IU/ml)	91.36 ± 29.86	103.67 ± 24.91	0.010
Mean ± SD of Fibrinogen (mg/dl)	384.47 ± 138.12	385.51 ± 130.34	0.97

NB: PT = Prothrombin time
PTT = Partial thromboplastin time
F1+2 = Prothrombin activation fragment 1+2
TAT = Thrombin-antithrombin complex
PAI-1 = Plaminogen activation inhibitor-1
-TG = Beta-thromboglobulin
PF_4 = Platelet factor-4
vWF = Von Willebran factor

endocardial function in these patients. Thus, the possibility of left atrial thrombus formation can be reduced. Regarding platelet activity, in contrast to a previous study[14], the present study found that platelet activity, reflected by the level of -TG and PF_4, was not significantly decreased after successful PBMV. Moreover, when the authors analyzed only the subgroup without atrial fibrillation, it was noted that the level of -TG was significantly higher after successful PBMV (Table 3). Therefore, it is plausible that in patients with mitral stenosis and no atrial fibrillation, this procedure might provoke thromboembolic events one month after a successful procedure via the mechanism of increased platelet activity. However, this finding should be further investigated in the future with a larger sample size. It should be mentioned that there are some limitations to the present study. First, the authors included only patients with moderate to severe mitral stenosis, thus, it may not be appropriate to apply the present results to those with mild mitral stenosis. Second, from the present study, the impact is not known of PBMV on patients with adequate mitral valve dilatation who develop mitral regurgitation of greater than grade 3 (by Seller's Classification) because of the small size of this subgroup. Third, knowledge of TAT regarding to the level which is prone to thrombosis is still lacking.

In summary, successful PBMV can reduce the pre-thrombotic state in patients with severe mitral stenosis as demonstrated by the decreased level of TAT after a successful procedure. In addition, PBMV may improve the endocardial function of the left atrium in those without atrial fibrillation as shown by the increased level of vWF and thrombomodulin.

Acknowledgement

The authors wish to thank the Faculty of Medicine Siriraj Hospital and the Thailand Research Fund for supporting the study.

References

1. Cerebral Embolism Task Force. Cardiogenic brain embolism. Arch Neurol 1986; 43: 71-84.
2. Casella L, Abelmann WH. Patients with mitral stenosis and systemic emboli. Arch Intern Med 1964; 114: 773-81.
3. Chiang CW, Lo SK, Ko YS, Cheng NJ, Lin PJ, Chang CH. Predictors of systemic embolism in patients with mitral stenosis: a prospective study. Ann Intern Med 1998; 128: 885-9.
4. Coulshed N, Epstein EJ, Mekendrick CS. Systemic embolism in mitral valve disease. Br Heart J 1970; 32: 26-34.
5. Fleming HA, Bailey SM. Mitral valve disease, systemic embolism and anticoagulants. Postgrad Med J 1995; 47: 599-604.
6. Jafri SM, Caceres L, Rosman HS, Ozawa T, Mammen E, Sesch M, et al. Activation of the coagulation in women with mitral stenosis and sinus rhythm. Am J Cardiol 1992; 70: 1217-9.
7. Ileri M, Buyukasik Y, Ileri NS, Haznedaroglu IC, Goksel S, Kirazli S, et al. Activation of blood coagulation in mitral stenosis and sinus rhythm. Am J Cardiol 1998; 81: 795-7.
8. Yamamoto K, Ikeda U, Sino Y, Mito H, Fujikawa H, Sekiguchi H, et al. Coagulation activity is increased in the left atrium of patients with mitral stenosis. J Am Coll Cardiol 1995; 25: 107-12.
9. Yasaka M, Miyatake K, Mitani M, Beppu S, Nagata S, Yamaguchi T, et al. Intracardiac mobile thrombus and D-dimer fragment of fibrin in patients with mitral stenosis. Br Heart J 1991; 66: 22-5.
10. Li-Saw-Hee FL, Blann AD, Goldsmith I, Lip GYH. Indexes of hypercoagubility measured in peripheral blood levels in intracardiac blood in patients with atrial fibrillation secondary to mitral stenosis. Am J Cardiol 1999; 83: 1206-9.
11. Marin F, Roldan V, Monmeneu JV, Bodi V, Fernandez C, Burgos FGD, et al. Prothrombotic state and elevated levels of plasminogen activator inhibitor-1 in mitral stenosis with and without atrial fibrillation. Am J Cardiol 1999; 84: 862-4.
12. Brockenbrough EC, Braunwald E, Ross J Jr. Transeptal left heart catheterization. A review of 450 cases studies and description of an improved technique. Circulation 1962; 25: 15-21.
13. Sellers Rd, Levy MJ, Amplatz K, et al. Left retrograde cardioangiography in acquired cardiac disease: technique, indications and interpretation of 700 cases. Am J Cardiol 1964; 14: 437-47.
14. Kataoka H, Yano S, Tamura A, Mikuriya Y. Hemostatic changes induced by percutaneous mitral valvuloplasty. Am Heart J 1993; 125: 777-82.
15. Yamamoto K, Ikeda U, Minezaki KK, Fukazawa H, Mizuno O, Kim S, et al. Effect of mitral valvuloplasty in mitral stenosis on coagulation activity. Am J Cardiol 1997; 79: 1131-5.
16. Zaki A, Salama M, Masry ME, Abou-Freikha M, Abou-Ammo D, Sweelum M, Mashhour E, et al. Immediate effect of balloon valvuloplasty on hemostatic changes in mitral stenosis. Am J Cardiol 2000; 85: 370-5.

การเปลี่ยนแปลงของปัจจัยการเกิดลิ่มเลือดในห้องหัวใจเอเตรียมซ้ายในผู้ป่วยลิ้นไมตรัลตีบหลังได้รับการขยายลิ้นหัวใจด้วยบอลลูน

เรวัตร พันธุ์กิ่งทองคำ, วิษณุ ธรรมลิขิตกุล, เดโช จักราพานิชกุล, สุทธิพล อุดมพันธุรัก

ภาวะแทรกซ้อนที่สำคัญของโรคลิ้นหัวใจไมตรัลตีบคือการที่มีลิ่มเลือดจากหัวใจกระจายไปอุดตามหลอดเลือดต่าง ๆ ในร่างกายโดยเฉพาะที่ระบบประสาทส่วนกลางทำให้ผู้ป่วยเกิดอัมพาต ลิ่มเลือดดังกล่าวมักเกิดขึ้นในห้องหัวใจเอเตรียมซ้าย มีรายงานว่าการขยายลิ้นไมตรัลตีบด้วยบอลลูนสามารถลดอุบัติการณ์ของภาวะแทรกซ้อนดังกล่าวได้ อย่างไรก็ตามกลไกที่ช่วยลดอุบัติการณ์ดังกล่าวยังไม่ทราบแน่ชัด วัตถุประสงค์ของการวิจัยนี้คือเพื่อทราบการเปลี่ยนแปลงของการแข็งตัวของเลือด การทำงานของเกร็ดเลือด รวมทั้งการทำงานของเยื่อบุห้องหัวใจเอเตรียมซ้ายในผู้ป่วยโรคลิ้นหัวใจไมตรัลตีบจำนวน 29 คนที่ได้รับการขยายลิ้นไมตรัลตีบด้วยบอลลูนและประสบความสำเร็จพบว่าระดับของทรอมบิน-แอนติทรอมบิน คอมเพล็กที่หนึ่งเดือนลดลงอย่างมีนัยสำคัญทางสถิติและระดับของทรอมโบมอดูลินก็เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติด้วย ส่วนระดับของเพล็ดเล็ดแฟคเตอร์สี่และเบต้าทรอมโบกลอบบูลินมีแนวโน้มจะเพิ่มขึ้นแต่การเปลี่ยนแปลงดังกล่าวไม่มีความแตกต่างอย่างมีนัยสำคัญ

การศึกษานี้สรุปได้ว่าการขยายลิ้นไมตรัลตีบทำให้ปริมาณสารที่ก่อให้เกิดลิ่มเลือดลดลง และอาจทำให้การทำงานของเยื่อบุหัวใจเอเตรียมซ้ายดีขึ้นในผู้ป่วยลิ้นไมตรัลตีบที่มีจังหวะการเต้นของหัวใจเป็นปกติ