Predictive Factors of Systemic Embolism in Patients with Mitral Stenosis in Sinus Rhythm

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Background: *Systemic embolism is one of the major complications in patients with mitral stenosis (MS) who are in atrial fibrillation; however, this serious complication can also occur in patients with MS in sinus rhythm.*

Objective: *The purpose of the present study was to identify the predictive factors of systemic emboli in patients with MS in sinus rhythm.*

Material and Method: *Twenty patients with MS in sinus rhythm with recent cerebral embolism and 32 with MS in sinus rhythm without any history of systemic embolism were studied between January 2004 and May 2006. Clinical and echocardiographic data were assessed using stepwise logistic regression for prediction of systemic embolism.*

Results: *Age (odds ratio [OR], 1.14; 95% confidence interval [CI] 1.04 -1.26) and left atrial spontaneous echo contrast (LASEC) grade 3+ and 4+ (OR, 46.42; 95% CI, 5.00-436.49) were associated with, and predictive of, systemic emboli, whereas left atrial appendage contraction flow velocities, left atrial size and mitral valve area were not.*

Conclusion: *The present study demonstrates that age and LASEC are the major predictive factors of systemic embolism in patients with MS in sinus rhythm. It would therefore be prudent to give anticoagulants to patients in atrial fibrillation as well as to those in sinus rhythm at risk of systemic embolism.*

Keywords: *Systemic embolism, Mitral stenosis, Sinus rhythm*

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Systemic embolism is one of the major complications in patients with mitral stenosis (MS)[1,2]. Before the advent of surgical therapy, this serious complication occurred in 10-20% of patients with MS[3]. Since there is no correlation between the frequency of embolic events and the severity of MS[3,4], the simple occurrence of an embolic event may be the first manifestation of MS and may occur in patients with mild MS even before the development of heart failure. The majority of patients with MS suffering from systemic emboli are usually in atrial fibrillation; however, Coulshed et al, showed that systemic embolism can occur in 8% of patients in sinus rhythm[2].

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Anticoagulation therapy is strongly recommended in patients with MS and atrial fibrillation[5]; notwithstanding, no firm evidence indicates that oral anticoagulation reduces the incidence of systemic embolism in patients with MS in sinus rhythm. Current guidelines do not recommend anticoagulation for patients without atrial fibrillation, who may be at risk of systemic embolism[6,7]. Therefore, identification of risk factors for systemic embolism is crucial for the prevention of this event. The purpose of the present study was to identify the risk factors of systemic embolism in patients with MS in sinus rhythm.

Material and Method

Patients

The present study was conducted at Khon Kaen University Hospital between January 2004 and

May 2006. The authors included adult patients (age $\geq$ 18) with MS in sinus rhythm who presented with cerebral embolism. The authors excluded patients who had intracranial hemorrhage, atrial fibrillation, received anticoagulation therapy more than 3 months ago, or significant mitral regurgitation. Patients with MS in sinus rhythm who had no previous systemic emboli served as the control group. All patients underwent a full physical examination, 12-lead electrocardiogram, transthoracic and transesophageal echocardiography. Computerized tomographic scanning was performed for the diagnosis of cerebral emboli in patients who presented with neurological deficit.

Echocardiography

Transthoracic and transesophageal echocardiography (TTE and TEE, respectively) were performed in all patients. TTE was performed using a 2.5- or 3.5-MHz phase array transducer (Sonos 5500, Hewlett-Packard, Andover, Massachusetts). The measurements were obtained according to the standard of the American Society of Echocardiography[8]. The authors measured left atrial diameter at the end of systole (from the parasternal view), mitral valve area (by both planimetry from two-dimensional echocardiography and the continuous wave Doppler pressure halftime method) and the mitral valve echocardiographic score[9].

TEE studies were performed with a 5-MHz multi-plane transducer (Hewlett-Packard Sonos 5500). After standard examination of the cardiac chambers and valves, the left atrial appendage (LAA) was visualized in both the basal short axis and two chamber views. LAA contraction velocities were assessed with pulse Doppler velocity by positioning the sample volume just inside (the proximal third) of the appendage[10]. Flow velocities were averaged over three cardiac cycles.

Left atrial thrombus was diagnosed according to the presence of an intracavitary echogenic mass clearly distinct from the left atrial endocardium and the pectinate muscles, and visualized on at least two different planes. Left atrial spontaneous echo-contrast (LASEC) was characterized by dynamic clouds of echoes within the left atrial cavity. The severity of LASEC was graded from 0 to 4+, as described by Fatkin et al[11]. The observation of LASEC was standardized by varying both the gain and compress settings throughout their full range during each study. For analysis purposes, the authors defined the presence of LASEC as a predictor of systemic embolism in patients with grade 3+ and 4+. All studies were recorded on a VHS videotape.

Written informed consent was obtained from each patient, and the research protocol was approved by the present institutional ethics committee.

Statistical analysis

Continuous variables are presented as means $\pm$ SD, and categorical variables are described with frequencies and percentages. The comparison of continuous variables was performed using the *t*-test, as appropriate. The categorical variables were compared using the Chi-square test or Fisher exact test where appropriate.

A univariate logistic regression model was used to examine the individual relationship between each variable and systemic embolism. Candidate variables were selected from clinical variables based on the results from others studies and on clinical expert opinion. Six clinical and echocardiographic variables including age, mitral valve area, left atrial appendage contraction flow velocity, left atrial size and LASEC were examined in this prospective case control study. After each variable was tested independently in a univariate regression model, those that achieved a p-value < 0.25 were selected for testing in a multivariable logistic regression. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to illustrate the association between potential risk factors and systemic embolism. A two-sided p-value < 0.05 was considered statistically significant. All the analyses were performed using SPSS version 11.0 (SPSS Inc., Chicago, Illinois, USA).

Results

A total of 52 patients (34 women; 18 men) with MS in sinus rhythm were included. Age ranged between 18 and 65 years (mean: 42.3 $\pm$ 9.3). There were twenty patients with cerebral embolism (Group I) and 32 without recent systemic embolism (Group II). The patients in Group I were older than those in Group II (mean age 45.6 $\pm$ 9.3 *vs.* 40.1 $\pm$ 8.8, p < 0.05).

Four patients had been receiving anticoagulation therapy for a short time (< 3 months). Five patients had undergone percutaneous transvenous mitral commissurotomy (PTMC). Approximately 65% of patients in Group I had LASEC grade 3+ to 4+, compared to 15.6% of the patients in Group II. LA thrombi were observed in three patients (5.8%); in all of whom, this finding was associated with thrombus within the LAA. Ten percent of patients in Group I had LA thrombus

compared to 3.1% of those in Group II. Notably, LA diameter was slightly but not significantly larger in Group I compared with Group II (48.6 ± 3.4 mm vs. 45.7 ± 6.9 mm). No significant differences in LAA contraction flow velocities were found between those with and without systemic embolism. The clinical and echocardiographic variables are shown in Table 1.

Univariate analysis

Univariate analyses of the clinical and echocardiographic variables are shown in Table 2. Two predictors were identified: Age (p = 0.046) and LASEC

Table 1. Clinical and echocardiographic variables in patients with mitral stenosis in sinus rhythm

Variable	All patients n = 52	Group I n = 20	Group II n = 32
Clinical variables			
Age (y), mean ± SD	42.3 ± 9.3	45.6 ± 9.3*	40.1 ± 8.8
Female, n (%)	34 (65.4)	15 (75.0)	19 (59.4)
Hypertension, n (%)	3 (5.8)	2 (10.0)	1 (3.1)
Smoking, n (%)	3 (5.8)	2 (10.0)	1 (3.1)
Anticoagulation, n (%)	4 (7.7)	1 (5.0)	3 (9.3)
PTMC, n (%)	5 (9.6)	3 (15.0)	2 (6.3)
NYHA class III-VI, n (%)	7 (13.5)	1 (5.0)*	6 (18.8)
Echocardiographic variables			
LA size (mm), mean ± SD	46.7 ± 6.8	48.3 ± 6.4	45.7 ± 6.9
LAA contraction flow velocity (cm/s), mean ± SD	23.4 ± 10.6	21.4 ± 9.5	24.6 ± 11.2
LASEC grade 3-4+, n (%)	18 (34.60)	13 (65.0)*	5 (15.6)
LA thrombus, n (%)	3 (5.8)	2 (10.0)	1 (3.1)
MVA (cm^2), mean ± SD	1.1 ± 0.3	1.1 ± 0.4	1.1 ± 0.3
mPG (mmHg), mean ± SD	14.5 ± 6.9	11.8 ± 5.9*	16.3 ± 7.1
MV score, mean ± SD	8.1 ± 0.7	8.3 ± 0.7	7.9 ± 0.7
LVEF (%), mean ± SD	63.1 ± 8.2	63.8 ± 7.0	62.7 ± 8.8

LA = left atrium; LAA = left atrial appendage; LASEC = left atrial spontaneous echo; MVA = mitral valve area; mPG = mean pressure across mitral valve; LVEF = left ventricular ejection fraction
* $p < 0.05$

Table 2. Univariate relationship between baseline characteristics and systemic embolism in patients with mitral stenosis in sinus rhythm

Characteristics	Odds ratio	95% CI	p-value
Age (year)	1.07	1.00-1.15	0.046
MVA ($cm^{2)}$	1.07	0.21-5.59	0.934
LA size (mm)	1.06	0.97-1.16	0.185
LAA contraction flow (cm/s)	0.97	0.91-1.03	0.276
LASEC grade 3+, 4+	10.03	2.67-37.72	0.001
LA thrombus	5.47	0.52-56.74	0.154

Table 3. Multivariate relationship between baseline characteristics and systemic embolism in patients with mitral stenosis in sinus rhythm

Characteristics	Odds ratio	95% CI	p-value
Age (year)	1.14	1.04-1.26	0.008
LA size (mm)	0.95	0.84-1.07	0.406
LASEC grade 3+, 4+	46.42	5.00-436.49	0.001
LA thrombus	4.83	0.30-81.10	0.273

($p < 0.000$), while LA size, mitral valve area, LA thrombus and LAA contraction flow velocity were not.

Multivariate analysis

Age and LASEC were predictive of systemic embolism in multivariate analysis (Table 3) with an odds ratio of 1.14 (95% CI 1.04-1.26, $p = 0.008$) and 46.42 (95% CI 5.01-436.49, $p = 0.001$). The predictive values of LASEC and LA thrombus are, however, likely exaggerated because of the small number of patients.

Discussion

Increased embolic events in MS are associated with older patients. Casella noted a mean age of 45.4 years in the population with emboli over against 40.5 years for those without emboli ($p < 0.001$)[12]. Coulshed et al[2] also showed that age was an independent predictor of systemic embolism in MS patients without atrial fibrillation: 5 and 11 percent, respectively, for those < 35 and > 35 years of age. In the present study, univariate and multivariate analyses showed that age was significantly associated with systemic embolism (Tables 2, 3).

The development of LASEC has been attributed to low flow states and is associated with the aggregation of red blood cells[13,14]. The pathogenesis of LASEC, therefore, includes the stasis of blood flow in the left atrium and the abnormalities of blood coagulation[15]. Some investigators have reported that the presence of LASEC leads to thrombus formation and systemic embolism in patients with mitral stenosis in atrial fibrillation[16,17]. Kasliwal et al demonstrated that 57.3% of patients with MS in sinus rhythm had LASEC on TEE examination[18]. Among patients with LASEC in that study, 31% had either left atrial thrombus or a history of systemic embolism. The present study confirms that LASEC is a strong predictor of systemic embolism in patients with MS in sinus rhythm, suggesting that LASEC is an important precursor of LA thrombus and systemic embolism.

LAA flow velocity was the most significant correlate of spontaneous echo contrast in the study by Fatkin et al[11] Few data are available on the association between LAA function and thrombus formation in MS with normal sinus rhythm. Daimee et al[19] reported a subgroup of patients with MS in sinus rhythm at risk of thromboembolism. In that study; the incidence of systemic embolism was increased in patients with low biphasic velocity (< 25 cm/s). In contrast to previous studies, the authors found that LAA flow velocities were not associated with systemic embolism in patients with MS in sinus rhythm.

Correlation between LA thrombus and systemic embolism has been demonstrated in patients with MS. Chiang et al[20] found that the presence of a left atrial thrombus was a positive predictor of systemic embolism (relative risk 37.1; 95% CI 2.82-487.8) for patients with MS in sinus rhythm. No relationship was evident between LA thrombus and embolic events in the present study, but the number of patients with LA thrombus was relatively small. The authors speculate that the dislodgement of LA thrombus was the reason why the authors could not demonstrate LA thrombus in most patients who experienced an embolic event.

Conclusion

The present study demonstrates that age and severity of LASEC are associated with systemic embolism in patients with MS in sinus rhythm. Generally, patients with mitral stenosis in atrial fibrillation are given anticoagulants but their use in patients with mitral stenosis in sinus rhythm is uncertain. The present findings suggest that anticoagulation may be indicated in patients at risk of systemic embolism; however, more studies are needed to demonstrate the beneficial effect of this treatment strategy.

Study limitations

Paroxysmal atrial fibrillation could not be completely excluded by 12-lead ECG. All of the limitations of a cross-sectional study apply to the present study. Finally, because the authors' institute is a referral center, the study may contain a referral bias compounded by a greater severity of disease.

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ปัจจัยเสี่ยงของการเกิดภาวะลิ่มเลือดหลุดอุดหลอดเลือดในผู้ป่วยลิ้นไมทรัลตีบที่มีจังหวะการเต้นหัวใจปกติ

ทรงศักดิ์ เกียรติชูสกุล, ไชยสิทธิ์ วงศ์วิภาพร, ทรงขวัญ ศิลารักษ์, ปิยทัศน์ ทัศนาวิวัฒน์

***ภูมิหลัง**: ภาวะลิ่มเลือดหลุดอุดหลอดเลือด เป็นภาวะแทรกซ้อนที่สำคัญของโรคลิ้นไมทรัลตีบ ปัจจัยเสี่ยงที่สำคัญคือภาวะหัวใจเต้นผิดจังหวะชนิด atrial fibrillation อย่างไรก็ตามผู้ป่วยลิ้นไมทรัลตีบที่มีการเต้นของหัวใจปกติ มีโอกาสที่จะเกิดลิ่มเลือดหลุดอุดหลอดเลือดได้มากกว่าคนปกติ*

***วัตถุประสงค์**: เพื่อหาปัจจัยเสี่ยงของการเกิดภาวะลิ่มเลือดหลุดอุดหลอดเลือดในผู้ป่วยลิ้นไมทรัลตีบที่มีการเต้นของหัวใจปกติ*

***วัสดุและวิธีการ**: ทำการศึกษาในผู้ป่วยลิ้นไมทรัลตีบที่มีการเต้นของหัวใจปกติและมีประวัติของการเกิดลิ่มเลือดหลุดอุดหลอดเลือดสมองจำนวน 20 ราย และผู้ป่วยลิ้นไมทรัลตีบที่มีการเต้นของหัวใจปกติ และไม่เคยเกิดภาวะลิ่มเลือดหลุดอุดหลอดเลือดจำนวน 32 ราย โดยเก็บข้อมูลลักษณะทางคลินิก และการตรวจคลื่นเสียงสะท้อน หัวใจ ทำการทดสอบปัจจัยที่มีผลต่อการเกิดภาวะลิ่มเลือดหลุดอุดหลอดเลือดโดยใช้สถิติแบบ logistic regression*

***ผลการศึกษา**: พบว่าปัจจัยเสี่ยงต่อการเกิดลิ่มเลือดหลุดอุดหลอดเลือดในผู้ป่วยลิ้นไมทรัลตีบที่จังหวะการเต้นหัวใจปกติ ได้แก่ อายุ (odds ratio [OR], 1.14; 95% confidence interval [CI] 1.04 -1.26) และ การไหลวนของเลือดในเอเตรียมซ้าย (OR, 46.42; 95% CI, 5.00-436.49) ในขณะที่ ขนาดของเอเตรียมซ้าย ขนาดพื้นที่ของลิ้นหัวใจไมทรัล และการบีบตัวของเอเตรียมซ้าย ไม่มีผลต่อการเกิดลิ่มเลือดอุดหลอดเลือด*

***สรุป**: การศึกษานี้แสดงให้เห็นว่า อายุ และ การไหลวนของของเลือดในเอเตรียมซ้าย เป็นปัจจัยเสี่ยงของเกิดภาวะลิ่มเลือดหลุดอุดหลอดเลือดในผู้ป่วยลิ้นไมทรัลตีบที่มีการเต้นของหัวใจปกติ และอาจจะมีความจำเป็นที่ต้องให้ยาต้านการแข็งตัวของเลือดในผู้ป่วยกลุ่มที่มีความเสี่ยงสูง*