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Usefulness of the uric acid and CHA_2DS_2-VASc score in prediction of left atrial thrombosis in patients with mitral stenosis and sinus rhythm

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Abstract

Background: *The risk of thrombus formation in the left atrium is known to be very high in patients with both mitral stenosis (MS) and atrial fibrillation (AF). However, that risk should not be ignored in patients with MS in sinus rhythm (SR). The aim of this study was to determine the clinical, echocardiographic, and biochemical factors that could have a determining role in the formation of a left atrial (LA) thrombus in patients with MS in SR.*

Method: *A total of 207 consecutive patients with MS who underwent both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) for diagnosis or to investigate the presence of a thrombus in the LA and appendage were enrolled in this study.*

Results: *LA thrombus was detected in 21 of 207 patients. CHA_2DS_2-VASc score was not found to be a predictor of LA thrombosis in patients with MS in SR, despite the higher CHA_2DS_2-VASc scores observed in those patients. The mitral valve area and mitral valve gradient were not predictive of LA thrombus development; however, LA anteroposterior diameter (LAAPD) was found to be a predictor of LA thrombosis. Levels of high sensitivity-C-reactive protein and uric acid were higher in the patients with LA thrombosis, but only uric acid was found to be a predictor of LA thrombosis in multivariate analysis.*

Conclusions: *A larger LAAPD and an elevated serum uric acid level were found to be independent predictors of LA thrombosis in patients with MS in SR.* (Cardiol J 2015; 22, 3: 336–342)

Key words: mitral stenosis, sinus rhythm, left atrial thrombosis, uric acid, CHA_2DS_2-VASc score

Introduction

A thrombus within the left atrium (LA) is a common source of thromboemboli and it is frequently seen in atrial fibrillation (AF) [1], valve disease [2, 3], and severe left ventricular systolic and diastolic dysfunction [4, 5]. The risk of thrombus formation in the LA is known to be very high in patients with both mitral stenosis (MS) and AF. However, the risk should not be ignored in patients with MS in sinus rhythm (SR). The prevalence of LA clots in patients with MS in SR was reported

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as ranging from 2.4% to 13.5% in previous studies [6–10]. The pathophysiology of LA thrombosis in patients with MS includes mechanisms such as hypercoagulable conditions, blood stasis, inflammation, and abnormal platelet size and activation [11–13].

Serum uric acid (SUA), which is the final product of purine metabolism, has been associated with the pathophysiology of several diseases, including hypertension [14], chronic kidney disease [15], congestive heart failure [16], metabolic syndrome [17], type 2 diabetes mellitus [18], atherosclerosis with or without cardiovascular events [19–21], and stroke [22–23]. In addition, a correlation was recently detected between hyperuricemia and the development of new-onset AF and increased risk of ischemic stroke in patients with AF [24–27]. Previous studies suggested associations between hyperuricemia and endothelial dysfunction [28], local oxidant generation, and elevated circulating levels of systemic inflammatory mediators [29, 30].

The aim of the present study was to determine the clinical, echocardiographic, and biochemical factors that could play determining roles in the formation of LA thrombosis, and to investigate the relationship between SUA level and frequency of LA thrombosis in patients with MS in SR.

Methods

Patient selection

A total of 207 consecutive patients with MS (mitral valve area [MVA] < 1.5 cm^2), who underwent both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) for diagnosis or to investigate the presence of a thrombus in the LA and appendage, were enrolled in this study. All patients had attended regular hospital appointments for at least 6 months and were in SR, as documented via electrocardiogram (ECG), at every control appointment and during TEE examination. Exclusion criteria included AF, no TEE, not presenting at regular visits for least 6 months, renal failure, acute rheumatic fever, acute infection, inflammatory disease, malignancy, and a history of anti-inflammatory, anticoagulant drug use.

Informed consent was obtained from all patients. This study complies with the Declaration of Helsinki, and the trial protocol was approved by the local Ethics Committee.

Blood sample

Blood samples were drawn from the antecubital vein for determination of biochemical and hemostatic parameters after overnight fasting. EDTA tubes were used for automatic blood count. The blood counts were measured using an auto hematology analyzer (Mindray BC 5800, China, Mainland) per the manufacturer's instructions. High-sensitivity C-reactive protein (hs-CRP) levels were immunologically determined using the immunoturbidimetric method (Abbott Aeroset 1600 Autoanalyzer, Abbott Reagents, Germany). SUA levels were measured using an enzymatic colorimetric test on a Roche/Hitachi analyzer.

Echocardiographic assessment

Transthoracic 2-dimensional (2D) and Doppler echocardiographic assessments were performed using a Vivid S6 with a 3.5 MHz phased array transducer (GE Medical System, Horten, Norway). 2D and pulsed wave Doppler echocardiographic studies were performed in the left lateral decubitus position with the conventional views (parasternal long- and short-axis, apical 4-chamber views). LA diameter, left ventricle (LV) end-diastolic diameter, and LV end-systolic diameter were measured by M-mode echocardiography. The LV ejection fraction (LVEF) was assessed from apical 2- and 4-chamber views, using the modified Simpson method. The MVA was measured using the planimetric method. The maximum velocity of tricuspid regurgitation was measured, and the pressure gradient was calculated. To estimate systolic pulmonary artery pressure, assumed right atrial pressure (10 mm Hg) was added to the gradient. M-mode measurements and conventional Doppler echocardiographic examinations were performed based on the criteria specified in the American and European Society of Echocardiography guidelines [31].

TEE was performed using a commercially available echocardiography machine (VIVID 6, GE Medical) with the use of a multiplane TEE probe and a 5 MHz phased array transducer. After administering topical anesthesia using lidocaine, the TEE probe was advanced and echocardiographic images were obtained. LA thrombus was diagnosed by the presence of a clearly defined echogenic intracavitary mass with an echo texture different from that of the underlying endocardium and not due to the pectinate muscle. The presence or absence of a LA thrombus was evaluated independently by 2 observers, and any discrepancy was resolved by consensus.

Statistical analysis

All analyses were performed using SPSS V 16.0 software for Windows (SPSS, Chicago,

Table 1. Demographic, clinical, echocardiographic and laboratory parameters of the study population.

Variable	Thrombus (+)	Thrombus (–)	P
Age [years]	49.9 ± 9.7	41 ± 8.7	< 0.001
Female gender	11 (55%)	153 (81.8%)	0.009
Diabetes mellitus	9 (45%)	42 (22.5%)	0.036
Hypertension	6 (30%)	54 (28.9%)	0.916
Ischemic stroke	3	3	0.015
LVEF	55.7 ± 7.6	61.4 ± 3.5	< 0.001
Left atrial diameter [cm]	5.2 ± 0.3	4.4 ± 0.4	< 0.001
Mitral valve area [cm^2]	1 ± 0.1	1.1 ± 0.1	0.070
Mitral valve gradient [mm Hg]	14.9 ± 4.4	10.9 ± 4.6	< 0.001
Left atrial appendage velocity [cm/s]	16.3 ± 7.7	37.5 ± 12.1	< 0.001
Mean platelet volume [fL]	9.7 ± 1	8.5 ± 1.1	<0.001
Neutrophil/lymphocyte ratio	3.4 ± 0.8	2.1 ± 0.9	< 0.001
Uric acid [mg/dL]	9.1 ± 1.4	4.2 ± 1.8	< 0.001
Hs-CRP [mg/L]	2.6 ± 0.8	1.4 ± 0.5	< 0.001
Creatinine [mg/dL]	0.9 ± 1	0.9 ± 1.1	0.918
CHA_2DS_2-VASc	2.5 ± 1.5	1.4 ± 1.1	0.006

Hs-CRP — high sensitivity C-reactive protein; LVEF — left ventricular ejection fraction; CHA_2DS_2-VASc — Congestive heart failure, Hypertension, diabetes mellitus, age > 75 years, prior stroke or transient ischemic attack, vascular disease, age 65–74, female gender

Illinois). All data are presented as mean ± standard deviation unless otherwise stated. Comparison of parametric values between the two groups was performed by means of an independent sample t-test. Comparisons of nonparametric values between the two groups were performed by means of a Mann-Whitney U test. Categorical variables were compared by means of the χ^2 test. Pearson's test was used to test the correlation of parametric variables, and Spearman's test was used to test the nonparametric variables. Logistic regression analysis was used to assess the predictors of LA thrombosis. Those variables with $p < 0.1$ by univariate analysis were included in the multivariate logistic regression analysis model and the respective odds ratios (OR) with 95% confidence intervals (CI) were calculated. All statistical tests were 2-sided and significance was determined at $p < 0.05$.

Results

The baseline characteristics of the study population are shown in Table 1. LA thrombus was found in 21 of the 207 patients. Patients with LA thrombosis were older than those without (49.9 ± 9.7 vs. 41 ± 8.7 years, respectively; $p <$ < 0.001). Of the patients with LA thrombus, 55% were female compared to 81.8% of the patients without a thrombus ($p = 0.009$). The patients with LA thrombosis were more likely to have diabetes mellitus and a history of ischemic stroke ($p = 0.03$ and $p = 0.01$, respectively). On investigation of clinical parameters, CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Diabetes mellitus, age > 75 years; prior stroke or transient ischemic attack, Vascular disease, Age 65–74, female gender) score was found to be significantly higher in patients with LA thrombosis (2.5 ± 1.5) than in the patients without a thrombus (1.4 ± 1.1; $p =$ = 0.006). CHA_2DS_2-VASc score appeared to predict LA thrombosis on univariate analysis, but not on multivariate analysis (Tables 2, 3).

In terms of echocardiographic parameters, the LVEF values were lower in the patients with LA thrombosis compared to the patients without it (55.7 ± 7.6% vs. 61.4 ± 3.5%, respectively; $p < 0.001$). The LA anteroposterior dimension (LAAPD) values were greater in the patients with LA thrombosis compared to the patients without a thrombosis (5.2 ± 0.3 vs. 4.4 ± 0.4 cm, respectively; $p < 0.001$). There was no significant difference in MVA between the thrombotic and non-thrombotic patients (1 ± 0.1 vs. 1.1 ± 0.1 cm^2, respectively; $p = 0.07$). However, mitral valve gradient values were higher in the patients with LA thrombosis compared to the non-thrombotic patients (14.9 ± ± 4.4 vs. 10.9 ± 4.6 mm Hg, respectively; $p < 0.001$). The mean LA appendage filling velocities were

Table 2. Odds ratio in univariate analysis.

Variable	Odds ratio	Confidence interval	P
Mitra valve gradient	2.126	0.746–6.763	0.638
LVEF	0.809	0.786–0.889	< 0.001
CHA_2DS_2-VASc	1.901	1.331–2.716	< 0.001
Mean platelet volume	2.606	1.668–4.073	< 0.001
Left atrial diameter	22.911	6.990–75.101	< 0.001
Left atrial appendage velocity [cm/s]	0,847	0.795–0.903	< 0.001
Uric acid	3.440	2.082–5.682	< 0.001
Hs-CRP	15.290	5.799–40.713	< 0.001
Mitral valve area	0.102	0.009–1.110	0.061
Diabetes mellitus	2.825	1.097–7271	0.031
Hypertension	0.985	0.363–2.673	0.977
Age	1.105	1.047–1.167	< 0.001
Female gender	3.375	1.317–8647	0.011

Abbreviations as in Table 1.

Table 3. Multivariate regression analysis for the investigation of independent correlates of left atrial thrombosis in the study population.

Variable	Odds ratio	Confidence interval	P
LVEF	0.913	0.759–1.098	0.332
Uric acid	2.497	1.132–5.510	0.023
Age	1.119	0.988–1.267	0.076
Female gender	5.665	0.453–70.796	0.178
Mean platelet volume	2.135	0.910–5.010	0.081
Hs-CRP	4.973	0.681–36.337	0.114
CHA_2DS_2-VASc	0.800	0.273–2.341	0.683
Left atrial diameter	7.209	1.073–48.452	0.042
Left atrial appendage velocity [cm/s]	0.906	0.792–1.036	0.148
Diabetes mellitus	0.089	0.006–1.383	0.084

Abbreviations as in Table 1.

16.3 ± 7.7 cm/s in patients with thrombosis compared to 37.5 ± 12.1 cm/s in those without a thrombus ($p < 0.001$). On univariate analysis, LAAPD and mean LA appendage filling velocities were found to be statistically significant predictors of thrombus development in SR. Nevertheless, on multivariate analysis, LAAPD was the only echocardiographic parameter that was found to be an independent predictor of LA thrombosis in the patients with MS in SR (OR 7.209, CI 1.073–48,452; $p = 0.04$) (Tables 2, 3).

On evaluation of the biochemical and hemostatic parameters, mean platelet volume (MPV) was found to be significantly higher in the patients with LA thrombosis than in the patients without a thrombus (9.7 ± 1 vs. 8.5 ± 1.1 fL, respectively; $p < 0.001$). The hs-CRP levels were higher in the patients with a thrombus compared to those without a thrombus (2.6 ± 0.8 vs. 1.4 ± 0.5 mg/L, respectively; $p < 0.001$). SUA levels were also significantly higher in patients with LA thrombosis than without (9.1 ± 1.4 vs. 4.2 ± 1.8 mg/dL, respectively; $p < 0.001$) (Fig. 1). In addition, there was a positive correlation between SUA and hs-CRP ($r = 0.674$; $p < 0.001$) (Fig. 2). In univariate analysis, the parameters that appeared to predict development of thrombosis were hs-CRP, MPV, and uric acid. However, in multivariate analysis, only uric

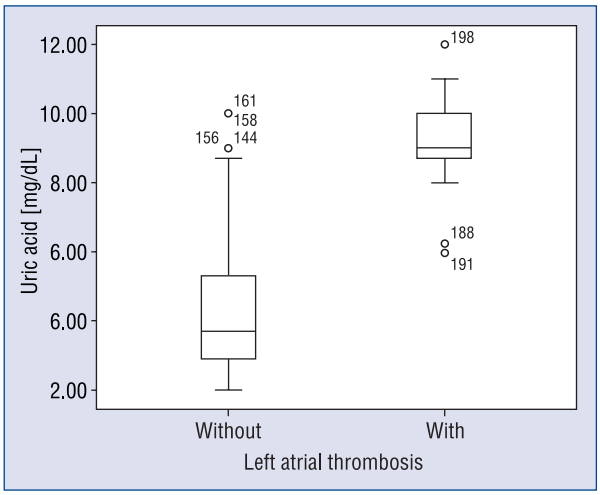

Figure 1. Serum uric acid levels of patients with and without left atrial thrombosis.

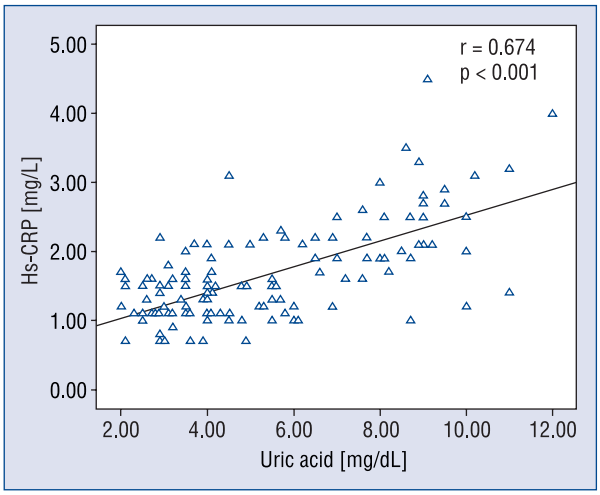

Figure 2. Correlation graph of high sensitivity C-reactive protein (Hs-CRP) with uric acid.

acid was found to be a predictor of LA thrombosis development in the patients with MS in SR (OR 2.497, CI 1.132–5.510; p = 0.02).

Discussion

In the present study, the predictors of LA thrombosis and the relationship between uric acid and LA thrombosis were investigated in patients with MS in SR. LAAPD and uric acid were found to be independent predictors of LA thrombosis in the patients with MS in SR.

Patients with AF are known to have a high incidence of LA thrombi. However, the incidence of LA thrombosis in patients with normal SR is not negligible. In a past study that assessed more than 20,000 patients in SR using TEE, the prevalence of LA thrombosis was approximately 0.1% [32]. However, in the same study, patients who had high-risk factors, such as valve disease, LV systolic and diastolic dysfunction, or a history of AF, had a higher incidence of LA thrombosis. AF patients with severe MS have been shown to be at high risk for thromboemboli [33]. However, various studies have demonstrated that the risk of LA thrombosis in patients with MS in SR is still high. The prevalence of LA clots in patients with MS in SR was found to range from 2.4% to 13.5% in various studies [6–10]. The prevalence of LA clots was 13.5% in a study performed by Saidi et al. [8]. In another study that included 848 patients with MS in SR, the prevalence of LA clots was 6.6% [34]. In the present study, the prevalence of LA thrombosis was 10.1%. Similar to the findings from a previous study [34], in the present study the patients with thrombi were older. Diabetes mellitus was more common in the patients with thrombi, but age and diabetes mellitus were not predictive of LA thrombosis development on multivariate analysis. Patients with MS in AF are known to have a high risk of thromboemboli, and there is no need to use CHA_2DS_2-VASc scores for risk evaluation in that patient population. However, no studies have been performed to evaluate the ability of the CHA_2DS_2-VASc score to predict LA thrombosis in patients with MS in SR. On evaluation of clinical parameters, CHA_2DS_2-VASc score was not found to be a predictor of LA thrombosis in patients with MS in SR, despite the higher CHA_2DS_2-VASc scores observed in patients with LA thrombi. Potentially, the lack of significance was due to the low CHA_2DS_2-VASc scores in our patient population.

Various studies with conflicting results have been performed to evaluate echocardiographic parameters in patients in SR. Some of the studies identified only the MVA as a predictor of LA thrombus formation [35, 36]. Kasliwal et al. [9] investigated the predictors of spontaneous echo contrast (SEC) in patients with MS and SR, and they demonstrated an association between SEC and smaller MVA, larger LA, and higher mean diastolic mitral pressure gradient. Nevertheless, in the study by Saidi et al. [8], which evaluated the relationship between echocardiographic parameters and LA thrombosis in patients with MS in SR, none of the parameters was found to be predictive of LA thrombosis. A recent study by Manjunath et al. [34], which included a larger patient group than

previous studies, reported a relationship between LA thrombosis and increasing age, anterosuperior LA dimension, and mean mitral valve gradient. In the present study, LA thrombus formation seemed to be associated with higher mean mitral valve gradient, smaller MVA, greater LAAPD, and decreased LA appendage filling velocity, but LAAPD was the only echocardiographic parameter found to be an independent predictor of LA thrombosis on multivariate analysis.

Previous studies have reported that patients with MS, with or without AF, have a hypercoagulable condition [37]. Although intra-atrial stasis and low blood velocity are the major factors in LA thrombus formation, the pathophysiology of LA thrombosis and SEC occurring in patients with MS exhibits some other mechanisms, such as inflammation, abnormal platelet size and activation [1–13]. Some previous studies have shown that inflammation plays an important role in the formation of SEC and thromboemboli, and some inflammatory markers could be used as independent predictors for SEC and LA thrombosis in patients with MS. Karthikeyan et al. [38] demonstrated an association between LA thrombosis and elevated hs-CRP levels, independent of the severity of MS. Similarly, Kaya et al. [39] found increased hs-CRP level to be an independent risk factor of LA SEC in patients with MS. In the present study, hs-CRP level was also higher in patients with LA thrombosis and, in univariate analysis, hs-CRP levels appeared to predict the development of thrombi. However, in multivariate analysis, hs-CRP levels were not predictive of LA thrombus formation in the patients with MS in SR. The difference in the predictive quality of the hs-CRP levels in the present study may be related to the patient population. While the above-mentioned studies included patients with MS in both AF and SR, the patient population in our study consisted only of patients with MS in SR.

Whether or not gout is present, elevated SUA level is associated with cardiovascular diseases such as hypertension [14], coronary heart disease [19–21], AF [24, 26], and stroke [22, 23]. Previous studies have suggested that this correlation could be due to endothelial dysfunction, local oxidant generation, elevated vascular smooth cell proliferation, and reduced vascular nitric oxide production induced by SUA [28–30]. Furthermore, a positive correlation has been demonstrated between SUA and elevated circulating levels of systemic inflammatory mediators, such as monocyte chemoattractant protein-1, nuclear factor-κB, interleukin-1β, interleukin-6, and tumor necrosis factor-α. Similarly [28–30], in the present study, a positive correlation between SUA and hs-CRP was also detected. Several studies have detected a correlation between SUA and ischemic stroke [22, 23, 25]. Studies have suggested that SUA may have harmful effects on platelet function [40] and it may cause endothelial dysfunction [41], thereby explaining the relationship. In addition, hyperuricemia was found to be correlated with LA dimension and a significant risk factor of new-onset AF [42]. In a recent study, hyperuricemia was associated with higher stroke rate in patients with AF, and even after CHA_2DS_2-VASc score adjustment, hyperuricemia was found to be a significant risk factor for ischemic stroke [25]. No data on the association between SUA and LA thrombus in SR was found in the literature, and the present study was the first to investigate the relationship between SUA level and LA thrombosis in patients with MS in SR. The SUA level was higher in patients with LA thrombosis, and the SUA level was found to be an independent predictor of the presence of LA thrombi.

As a limitation of this study, the possibility of intermittent AF, cannot be eliminated with 24 h of undergoing an ECG; however, the patients in this study were regularly evaluated with the standard 12 lead ECG for at least 6 months.

Conclusions

In summary, patients in SR still have considerable risk for thromboemboli, and clinical, echocardiographic, and biochemical predictors are required when evaluating patients for risk stratification. In the present study, none of the clinical parameters were predictive of LA thrombus formation. However, larger LAAPD and elevated SUA levels were found to be independent predictors of LA thrombosis in patients with MS in SR.

Conflict of interest: None declared

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