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## Case report

## Relationship between spontaneous echo contrast and hematological markers in patients with rheumatic mitral stenosis

Nermin Bayar<sup>a,\*</sup>, Zehra Erkal<sup>a</sup>, Selcuk Küçükseymen<sup>a</sup>, Ramazan Güven<sup>b</sup>, Şakir Arslan<sup>a</sup><sup>a</sup> Antalya Education and Research Hospital, Cardiology Department, Antalya, Turkey<sup>b</sup> Bitlis State Hospital, Emergency Medicine Department, Antalya, Turkey

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## ABSTRACT

**Introduction:** Systemic thromboembolism is a serious morbidity and mortality cause for patients with rheumatic mitral stenosis (RMS). Previously conducted researches showed that spontaneous echo contrast (SEC) found in the left atrium can constitute a risk factor for thrombus formation. The aim of this study is to evaluate the role of echocardiographic and hematologic parameters in anticipating the presence of SEC in the left atrium of patients with moderate–severe RMS.

**Methods:** This retrospective study includes all patients who were diagnosed with moderate–severe RMS and underwent a transesophageal echocardiography between 2011 and 2014. They were then divided in two groups depending on SEC presence; a SEC negative group and a SEC positive group.

**Results:** There were 33 patients (32%) in the SEC negative group and 71 patients (68%) in the SEC positive group. The mean platelet volume was found to be significantly higher in the SEC positive group ( $10.0 \pm 1.3$  vs.  $11.6 \pm 1.4$ ,  $p < 0.001$ ). To identify the factors affecting the presence of SEC, a multivariate analysis of the hematologic parameters was conducted and the mean platelet volume was found to be an independent predictor (odds ratio 1.913, 95% confidence interval 1.300–2.814;  $p = 0.001$ ). In the receiver operating characteristics curve analysis, a mean platelet volume  $> 11.8$  fl had a 55% sensitivity and 92% specificity in predicting SEC in patients with mitral stenosis.

**Conclusion:** Mean platelet volume constitutes an independent risk factor for the presence of left atrial SEC in patients with moderate–severe mitral valve stenosis.

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## Introduction

Especially in developing countries, rheumatic mitral stenosis (RMS) is still a major health concern.<sup>1</sup> Patients with RMS show an elevated risk for systemic thromboembolism, which becomes a primary mortality and morbidity cause.<sup>2</sup> Among the suggested mechanisms leading to the disease are autoimmunity, inflammation and increased thrombotic activity.<sup>3–5</sup>

Spontaneous echo contrast (SEC) is the presence of smoke – like echoes with a characteristic swirling motion of blood found during echocardiography.<sup>6</sup> Previously conducted researches showed that presence of SEC in the left atrium can constitute a risk factor for thrombus formation.<sup>7</sup> In patients with RMS the risk of thrombosis and left atrial SEC development is eventually higher.<sup>8</sup> The aim of this study is

to investigate the relationship between the presence of SEC and related hematologic parameters in patients with moderate–severe RMS.

## Methods

In this retrospective study all moderate–severe RMS patients, who had a percutaneous mitral balloon valvuloplasty between 2011 and 2014 in our clinic were included (mitral valve area  $< 1.5$  cm<sup>2</sup>). Their respective electrocardiograms were inspected and the rhythm defined.

The exclusion criteria for the present study were left atrial thrombus formation, significant mitral regurgitation (grade  $> 1$ ), other moderate or severe valve disease, history of malignancy, history of inflammatory disease, current therapy with corticosteroids, connective tissue disease, thyroid disease, other hematological disease and acute infectious disease. A medical history was recorded from patient anamnesis form.

Transesophageal echocardiography (TEE) and transthoracic echocardiography (TTE) records were also investigated (EPIQ 7 Ultrasound System, Philips, Heide, Netherlands). All the echocardiographic findings were carefully evaluated by two separate cardiologists. All measurements were taken according to the recommendations of the American Society of Echocardiography.<sup>9</sup> The mean value of 3 measurements was

\* Corresponding author at: Antalya Education and Research Hospital, Cardiology Department, Muratpasa, 07100 Antalya, Turkey. Tel.: +90 505 400 7509; fax: +90 242 244 4900.

E-mail address: [dr.nermin@mynet.com](mailto:dr.nermin@mynet.com) (N. Bayar).

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taken from patients with sinus rhythm and the mean value of 7 measurements from patients with atrial fibrillation. Routine echocardiographic measurements were also recorded. The planimetric measurements of the mitral valve area were also conducted. The mitral valve was assessed by TEE. The Wilkins score was determined by rating the severity of leaflet mobility, leaflet thickening, leaflet calcification and subvalvular thickening with a score of 0–4 and then adding the results together.<sup>10</sup> Left atrial SEC presence and degree was assessed by TEE according to the criteria laid down by Fatkin et al.<sup>11</sup> The patients were then divided into two groups; a SEC positive group and a SEC negative one.

On the TEE day, the patients had blood drawn from the antecubital vein and underwent routine biochemistry and complete blood count (CBC) tests, after a 12 hour fast. CBC including white blood cell (WBC), neutrophil and lymphocyte counts, mean platelet volume (MPV, normal range: 7.4–10.4 fl) were done using an automatized CBC count device (Abott Cell Dyn, Illinois USA). The C-reactive protein (CRP) levels (normal range: 0–5 mg/L) were analyzed with a Beckman Coulter Inc. (Image 800, California, USA).

### Statistical analysis

Data were analyzed with the SPSS software version 21.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean  $\pm$  SD, and categorical variables are expressed as percent. The  $\chi^2$  test and Fisher's exact test were used to compare categorical variables. The Shapiro–Wilk test was used to assess the distribution of continuous variables. Student's t-test was used for variables with normal distribution and the values were presented as mean  $\pm$  SD. Continuous variables without normal distribution were analyzed using Mann–Whitney U test. Receiver operating characteristic (ROC) curve analysis was performed to identify optimal cutoff values for MPV. The effects of different variables on SEC were calculated in univariate analysis for each. The variables for which the unadjusted P-value was 0.10 in logistic regression analysis were identified as potential risk markers and included in the full model. The odds ratios (OR) and 95% confidence intervals (CI) were calculated. A two-tailed p-value of  $<0.05$  was considered statistically significant.

### Results

104 patients were included in this study of which 80 (77%) were female. 33 of them (32%) were in the SEC negative group (mean age 43.6  $\pm$  14.5) and 71 (68%) in the SEC positive group (mean age 47.0  $\pm$  11.3). Mean age, diabetes mellitus, hypertension, hyperlipidemia presence and aspirin or warfarin usage was similar among the groups. Atrial fibrillation (AF) was detected in 11 (33%) of the SEC negative group patients and 28 (40%) in the SEC positive one ( $p = 0.634$ ). Also, in 31 of the 39 patients who had AF (79%) and in 48 of the 65 patients who did not have AF (73%), SEC presence was detected ( $p = 0.632$ ). The groups' baseline characteristics are shown in Table 1.

The Wilkins score (9.6  $\pm$  2.8 vs. 7.0  $\pm$  2.2,  $p < 0.001$ ) and the left atrial diameter (46.3  $\pm$  2.7 mm vs. 44.7  $\pm$  2.2 mm,  $p = 0.010$ ) were found to be significantly higher in the SEC positive group. There was no significant difference among groups with regard to the mitral valve area (1.0  $\pm$  0.2 vs. 1.1  $\pm$  0.2,  $p = 0.423$ ). TTE and TEE findings are shown in Table 2.

There was no significant difference among the groups with respect to some hematologic parameters like WBC count, platelet count, red cell distribution width and CRP (Table 3). However, MPV (11.6  $\pm$  1.4 vs 10.0  $\pm$  1.3,  $p < 0.001$ ) was found to be significantly higher in the SEC positive group (Fig. 1). A univariate logistic regression analysis was performed in order to determine the factors leading to SEC presence and MPV (OR = 1.972, 95% CI: 1.411–2.758;  $p < 0.001$ ), Wilkins score (OR = 1.409, 95% CI: 1.172–1.693,  $p < 0.001$ ) and left atrial diameter (OR = 1.265, 95% CI: 1.051–1.522;  $p = 0.013$ ) were

**Table 1**  
Demographic characteristics of the groups according to the SEC presence.

Variable	SEC negative (n = 33)	SEC positive (n = 71)	P value
Age, years	43.6 $\pm$ 14.5	47.0 $\pm$ 11.3	0.286
Female, n (%)	28 (84%)	52 (73%)	0.062
DM, n (%)	3 (11.5%)	13 (16.7%)	0.755
Hypertension, n (%)	11 (42.3%)	37 (47.4%)	0.650
TC, mg/dl	189.0 $\pm$ 42.9	184.3 $\pm$ 36.5	0.417
LDL, mg/dl	125.5 $\pm$ 34.5	115.0 $\pm$ 34.6	0.106
HDL, mg/dl	45.0 $\pm$ 9.3	42.2 $\pm$ 8.3	0.119
Trygliceride, mg/dl	98.9 $\pm$ 43.3	122.2 $\pm$ 59.1	0.072
AF, n (%)	11 (33%)	28 (40%)	0.634
Aspirin, n (%)	17 (51%)	38 (53%)	0.248
Warfarin, n (%)	12 (38%)	29 (41%)	0.228
Beta blocker, n (%)	16 (48%)	36 (51%)	0.728

(Data are expressed as mean  $\pm$  standard deviation for normally distributed data and percentage for categorical variables).

(AF: atrial fibrillation, DM: diabetes mellitus, HDL: high density lipoprotein, LDL: low density lipoprotein, TC: total cholesterol).

shown to be risk factors. Also, a multivariate logistic regression analysis was performed in order to determine the factors leading to SEC presence and MPV value was found to be an independent predictor (OR = 1.913, 95% CI: 1.300–2.814,  $p = 0.001$ ) (Table 4). In the ROC curve analysis, a MPV  $> 11.8$  fl had a 55% sensitivity and 92% specificity in predicting SEC in patients with mitral stenosis (area under the curve 0.780,  $p < 0.001$ ) (Fig. 2).

### Discussion

Patients with moderate–severe RMS were included in this study and 23% of them were found to have SEC presence in their left atrium. Univariate and multivariate analysis showed that Wilkins echo score, MPV and left atrium diameter were risk factors related to left atrial SEC presence. In addition to that, MPV  $> 11.8$  fl was found to have a 55% sensitivity and 92% specificity in predicting SEC presence in patients with mitral stenosis.

SEC is a dynamic smoke-like echo with a characteristic swirling motion of blood detected by echocardiography.<sup>12</sup> In RMS patients there is an increase in general inflammatory and prothrombotic state and therefore the risk of stasis in the left atrium that will eventually lead to left atrial SEC or thrombus, is significantly higher than the normal population.<sup>13,14</sup> In previous studies SEC was found to have a frequency of 21–67% in RMS patients and systemic thromboembolism was reported as an independent predictor of SEC presence.<sup>6,15,16</sup> Some

**Table 2**  
Echocardiographic characteristics of the groups according to the SEC presence (variables with normal distribution were expressed as mean  $\pm$  SD).

Variable	SEC negative (n = 33)	SEC positive (n = 71)	P value
LVEF, %	62.1 $\pm$ 4.2	62.0 $\pm$ 4.4	0.682
LA diameter, mm	44.7 $\pm$ 2.2	46.3 $\pm$ 2.7	0.010
LAVI, ml/m <sup>2</sup>	32.1 $\pm$ 8.2	33.4 $\pm$ 7.2	0.378
LVEDD, mm	44.0 $\pm$ 4.0	46.1 $\pm$ 5.0	0.128
LVESD, mm	28.3 $\pm$ 4.4	30.1 $\pm$ 5.0	0.090
MVA, cm <sup>2</sup>	1.1 $\pm$ 0.2	1.0 $\pm$ 0.2	0.423
Peak gradient, mm Hg	24.5 $\pm$ 9.2	21.9 $\pm$ 7.7	0.679
Mean gradient, mm Hg	14.5 $\pm$ 6.2	13.1 $\pm$ 6.2	0.317
WS	7.0 $\pm$ 2.2	9.6 $\pm$ 2.8	$<0.001$
Valve mobility	1.7 $\pm$ 0.6	2.4 $\pm$ 0.7	$<0.001$
Subvalvular	1.6 $\pm$ 0.6	2.4 $\pm$ 0.9	$<0.001$
Valve thickness	1.9 $\pm$ 0.7	2.5 $\pm$ 0.8	0.004
Calcification	1.7 $\pm$ 0.9	2.3 $\pm$ 0.9	0.010
sPAP, mm Hg	43.9 $\pm$ 13.4	40.7 $\pm$ 8.7	0.365

(LA: left atrium, LAVI: left atrial volume index, LVEF: left ventricular ejection fraction, LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter, MVA: mitral valve area, SEC: spontaneous echo contrast, WS: Wilkins score).

**Table 3**

Common hemogram and inflammatory parameters of the groups according to the SEC presence.

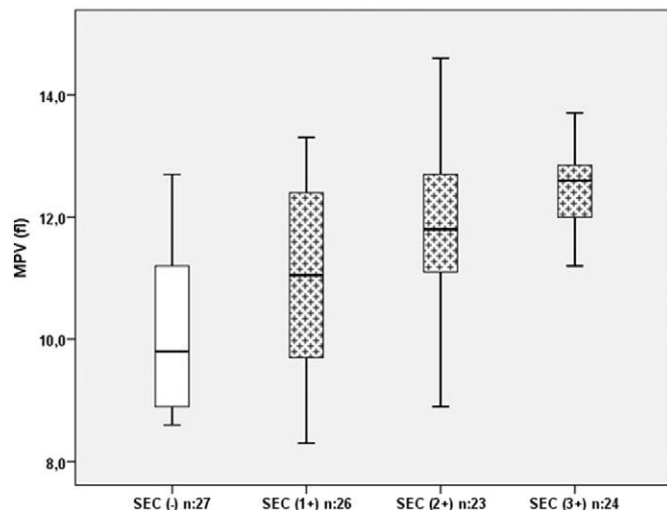
Variable	SEC negative	SEC positive	P value
	(n = 33)	(n = 71)	
Hemoglobin, g/dl	12.2 ± 1.2	13.0 ± 1.3	0.023
WBC, (× 10 <sup>3</sup> /μL)	7.8 ± 2.0	7.9 ± 2.3	0.892
Platelet count, (× 10 <sup>3</sup> /μL)	221.2 ± 69.3	236.6 ± 59.9	0.276
MPV, fl	10.0 ± 1.3	11.6 ± 1.4	<0.001
RDW, %	15.2 ± 2.2	14.4 ± 1.9	0.073
CRP, mg/l	6.1 ± 5.5	6.1 ± 5.2	0.703

Variables with normal distribution were expressed as mean ± SD. CRP: C-reactive protein, MPV: mean platelet volume, RDW: red blood cell distribution width, WBC: white blood cells count.

of the reported clinic and echocardiographic risk factor of SEC in RMS patients are atrial fibrillation, high Wilkins score, small mitral valve area, increased mitral gradient, left atrial dilation without severe mitral insufficiency.<sup>4,17</sup> In a similar way, our study found that Wilkins score was significantly higher in the SEC positive group, but couldn't find a significant association with mitral valve area and mitral gradient.

The pathophysiological mechanism of RMS is related to the antigenic similarity of the streptococcal M protein with cardiac tissue and to the related autoimmune response that follows. In the chronic state of the disease, inflammation is persistent even without the presence of an infectious agent.<sup>3,18</sup> According to previous studies, inflammatory predictors were found to be elevated in RMS patients.<sup>4,19</sup> Kaya et al. studied the systemic inflammatory state predictors in RMS patients with SEC presence and reported significantly elevated values of high sensitive CRP and neutrophil/lymphocyte ratio. Also, a neutrophil/lymphocyte ratio >3.1 was found to have a specificity of 72% and a sensitivity of 80% in detecting left atrial SEC presence in this study.<sup>20</sup>

Increased prothrombotic state has also been reported, alongside increased inflammation, in RMS patients. Previous studies have reported increased MPV, P-selectin, fibrinogen and D-dimer levels as conditions related to the increased prothrombotic state in these patients.<sup>5,21,22</sup> It has also been shown that MPV values, in RMS patients, tend to decrease after percutaneous mitral balloon valvuloplasty.<sup>22</sup> MPV is one of the indicators of platelet function. Bigger platelets are hemostatically more reactive than smaller ones and an increase in MPV values, reflect an increase in platelet function.<sup>23–25</sup> Akpek et al. included 232 RMS patients in their study and found that MPV values were correlated to left atrial SEC presence and SEC degree.<sup>14</sup> In a study conducted by İleri et al., examined 84 patients with RMS, severe MR and left atrium SEC presence have been shown to be associated with increased in MPV.<sup>26</sup>



**Fig. 1.** MPV levels in the SEC negative and SEC positive patients.

**Table 4**

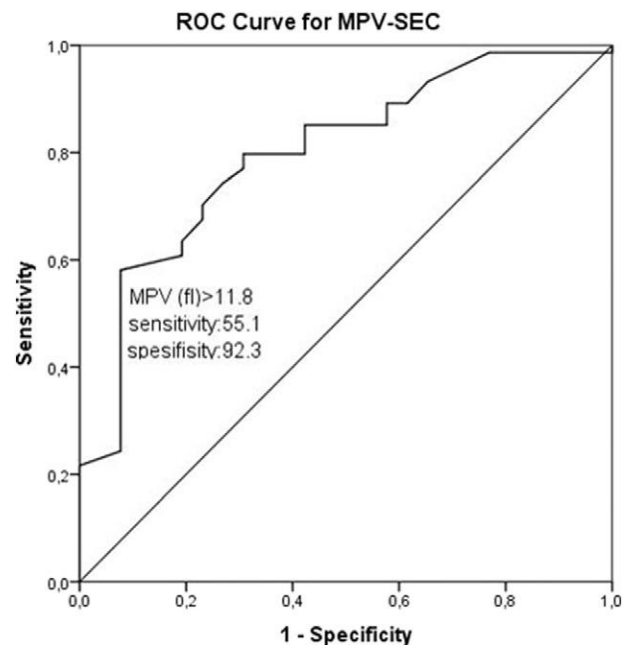
Evaluation of the factors affecting the presence of the SEC by univariate and multivariate logistic regression analysis.

Variable	Univariate	P value	Multivariate	
	OR (95% CI)		Adjusted OR (95%CI)	P value
Sex	0.123 (0.016–0.959)	0.046		
Hemoglobin	1.552 (1.072–2.246)	0.020	1.424 (0.950–2.134)	0.087
MPV	1.972 (1.411–2.758)	<0.001	1.913 (1.300–2.814)	0.001
RDW	0.835 (0.677–1.031)	0.093		
CRP	0.996 (0.919–1.079)	0.926		
Trygliceride	1.009 (0.999–1.019)	0.072		
LA diameter	1.265 (1.051–1.522)	0.013	1.007 (0.997–1.017)	0.026
WS	1.409 (1.172–1.693)	<0.001	1.345 (1.092–1.657)	0.005
LVEF	9.992 (0.894–1.100)	0.876		
LVESD	1.126 (1.018–1.246)	0.022		
Mean gradient	0.967 (0.903–1.036)	0.335		
MVA	0.418 (0.050–3.476)	0.420		

CRP: C-reactive protein, LA: left atrium, LVEF: left ventricle ejection fraction, MPV: mean platelet volume, MVA: mitral valve area, RDW: red blood cell distribution width, WS: Wilkins score.

In a similar way, our study found that MPV values were higher in SEC positive patients, compared to SEC negative patients. In addition to this, our study found that a MPV > 11.8 fl value was an independent predictor of SEC presence.

Atrial fibrillation is an important risk factor for the development of left atrial SEC or thrombus.<sup>7</sup> In addition to patients with AF, previous studies have reported an increased hypercoagulable state in RMS patients with sinus rhythm too.<sup>27</sup> Risk factors associated with left atrial thrombus are advanced age, atrial fibrillation, small mitral valve area, dilated left atrium and SEC presence.<sup>17,28</sup> Munjunath et al. studied 848 RMS patients with sinus rhythm and reported that left atrial thrombus did not form without a SEC presence.<sup>27</sup> Therefore it is important to detect SEC positive patients. Our study did not detect any significant difference among the groups with respect to atrial fibrillation but reported increased MPV values as independent predictors of SEC presence. Despite being on sinus rhythm, patients with MPV > 11.8 fl had a higher probability of developing SEC and therefore should be regularly monitored with TEE. To investigate the need and effectiveness of



**Fig. 2.** ROC curve analysis for MPV in prediction of SEC (area under the curve 0.780, p < 0.001).

anti-inflammatory, antiplatelet and anticoagulant therapy in these patients, large randomized trials results are needed.

### Study limitations

This study was a retrospective one. The possible limitations of the present study include that it was a single-center experience and included a small number of patients. Possibility of intermittent atrial fibrillation cannot be ruled out. Measures of thromboembolic risk like left atrial appendage size, and filling and emptying velocities were not studied. Because the majority of the included patients were expecting a percutaneous mitral balloon valvuloplasty, those with severe mitral insufficiency were not included. Therefore these results may not represent patients with severe mitral insufficiency.

### Conclusion

Independently from cardiac rhythm, MPV value was found to be independently related to left atrial SEC presence in RMS patients.

### Conflict of interest

None declared.

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