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RELATIONSHIP BETWEEN LEFT ATRIAL SPONTANEOUS ECHO CONTRAST (SEC) IN MITRAL STENOSIS WITH PLATELET INDICES

Pathology

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ABSTRACT

Objective: The accurate underlying pathogenic mechanism behind spontaneous echo contrast (SEC) is complex and poorly understood. The aim of this study was to characterize the relationship between platelet indices and left atrium SEC in patients with mitral stenosis (M.S).

Material and Methods: A total of 102 consecutive patients with M.S were enrolled to the study. Transthoracic echocardiography (TTE) and transoesophageal echocardiography (TEE) were performed for each patient to rule out the thrombus formation in the left atrium (LA). The study population were divided into two groups according to the formation of SEC in the LA: Group 1 (SEC-): M.S without SEC; Group II (SEC +): M.S complicated with SEC. Group I included 60 patients, and group II included 42 patients.

Results: Mean platelet volume (MPV) levels (10.15 ± 0.60 vs. 9.6 ± 1.4, $p<0.001$) and plateletcrit levels (0.238 ± 0.02 vs. 0.222 ± 0.05, $p = 0.007$) were significantly higher in the SEC (+) group. There was significant increase in MPV values with increase in severity of SEC ($p<0.001$).

Conclusion: In patients with M.S, platelet indices including MPV and PCT levels were associated with the presence of SEC and were independent risk factors of SEC. MPV levels correlated with severity of SEC.

KEYWORDS

Spontaneous echo contrast, Platelet indices, Mitral stenosis

INTRODUCTION

Rheumatic valve diseases are an important cause of morbidity and mortality, particularly in developing and undeveloped countries. The stasis of blood flow in the left atrium associated with rheumatic mitral valve stenosis causes the formation of spontaneous echo contrast (SEC).

SEC appears as smoke-like echoes with a characteristic swirling motion of blood in echocardiography. It results from aggregation in cellular components of blood in the situations with blood stasis and low velocity of bloodflow.[1] SEC is commonly seen in the left atrium (LA) and particularly caused by mitral stenosis (M.S)[2] and non-valvular atrial fibrillation (AF).[3] Previous studies have shown that SEC is a risk factor for LA thrombus formation and an important marker of systemic embolism originating from the heart.[1,4,5] Patients with rheumatic M.S may have thromboembolic events, even though on oral anticoagulants treatment, suggesting the role of platelets in the development of thromboembolic events in patients with M.S. Platelet indices, including platelet count, platelet distributing width (PDW), mean platelet volume (MPV), and plateletcrit (PCT), are easily measurable parameters in complete blood count (CBC).Mean platelet volume (MPV) which is a simple measure of platelet activation, has recently become an interesting topic in cardiovascular research. When platelets become activated, MPV increases and change from quiescent discs to swollen spheres. The relationship between platelet indices and SEC in patients with M.S has not been studied in detail. In this study, we aim to determine the relationship of platelet indices with SEC in patients with M.S.

MATERIAL AND METHODS

Study population

The present study was conducted in the department of Cardiology, NEIGRIHMS, Shillong, Meghalaya, India, from a period of January 2014 to November 2015.

A total of 102 consecutive patients with symptomatic M.S, planned for mitral balloon valvuloplasty were enrolled to the study. Transthoracic echocardiography (TTE) and transoesophageal echocardiography (TEE) were performed for each patient to rule out the thrombus formation in the LA. The SEC was evaluated by TEE for all patients. The study population were divided into two groups according to the formation of SEC in the LA: Group 1 (SEC-): M.S without SEC; Group II (SEC +) : M.S complicated with SEC. Group I included 60 patients, and group II included 42 patients. Exclusion criteria for the study were presence of LA thrombus, history of malignancy, presence of connective tissue disease, thyroid disease or other haematological disease. AF was determined by electrocar diogram. Blood pressure was measured and heart rate was recorded.

Written consents were taken from all the subjects. This study has been approved by institutional review committee and institute medical ethical committee. The study was conducted according to the recommendations of the Declaration of Helsinki on biomedical research involving human subjects.

Laboratory measurements:

In all patients, venous blood samples for the laboratory analysis were taken immediately after TEE. Tripotassium EDTA-based anticoa gulated blood samples for CBC were measured by a Beckman Coulter UH 750 analyser within 5 min of sampling. The samples were studied immediately in order to avoid platelet swelling. Also, all routine biochemical tests were carried out on an autoanalyser (Beckman Coulter AU 2700 analyser).

Platelet indices, hemoglobin and hematocrit parameters of subjects were recorded using an automatic blood counter. Also, routine biochemical tests including glucose, creatinine, and lipid profiles were recorded.

Echocardiography examination:

Two-dimensional echocardiography was performed by using a commercially available machine (Vivid GE9) with a 3.5 MHz transducer for TTE and 5 MHz for TEE, during at least three (for sinus rhythm) or seven (for atrial fibrillation) consecutive cardiac cycles. TTE and TEE were performed in the same session. Simpson's method was used to assess the left ventricular ejection fraction (LVEF) as recommended by American Society of Echocardiography guidelines.6 Mitral valve area(MVA) was measured with the planimetric method.

The maximum velocity of tricuspid regurgitation jet was measured, and the pressure gradient was calculated. This gradient was added to an assumed right atrial pressure (10 mmHg) to give an estimate of systolic pulmonary artery pressure (PAP). For TEE, after patient's pharyngeal local anaesthesia with lidocaine spray, the probe was initially carried forward to a depth of 25–35 cm and then manipulated to optimum imaging. All images were archived and evaluated by two independent echocardiographer cardiologists. The degree of the LA SEC was graded as previously defined criteria.[7] The absence of echogenicity was defined as 0; 1+ (mild), minimal echogenicity in the LA appendage or sparsely distributed in the LA which was detected only transiently during the cardiac cycles; 2+ (mild to moderate), more dense than 1+ but similar distribution and detectable without increased gain settings; 3+ (moderate), more dense swirling pattern distributed to both LA appendage and LA which could change in intensity but was detectable throughout the cardiac cycle; 4+ (severe), very intense echo density and slow swirling motion distribution as for 3+.

Statistical analysis:

Continuous variables were tested for normal distribution by the Kolmogorov–Smirnov test. Since almost all the variable were not normally distributed, we report continuous data as median ± interquartile range (IQR). Categorical variables were summarized as number and percentages where appropriate. Continuous variables were compared by Mann–Whitney U-test and categorical variables with Chisquare test. The platelet indices in the SEC (+) group were compared with Kruskal- Wallis test. Multiple logistic regression analyses were performed to identify independent factors associated with presence of SEC. A two tailed P-value of < 0.05 was considered significant within a 95% confidence interval (CI). All statistical analyses were performed with the SPSS version 17.

RESULTS

A total of 102 consecutive patients were enrolled to the study. Patients were divided into two groups according to the presence of SEC. Group I (SEC-) included 60 patients, and group II (SEC +) included 42 patients.

Patient characteristics

Baseline characteristics are as shown in Table 1. There were no significant differences in the presence of hypertension, diabetes mellitus, smoking status, or any other basal demographic feature between the groups. With respect to the rhythm status of patients, 21 (35 %) of patients in the SEC (-) group were in AF, whereas 20 (47.6%) of patients in the SEC (+) group were in AF (p=0.223). Previous thromboembolic events were higher in the SEC (+) group, however it was not statistically significant (p= 0.714).

Table 1.Baseline characteristics of all patients.

Variable	Group I (SEC-) (n = 60)	Group II (SEC+) (n = 42)	p value
Age (years)	34 ± 4	35 ± 3.25	0.061
Female, n, (%)	44 (73.3%)	28 (66.7%)	0.512
BMI (kg/m2)	20.3 ± 2.1	20.75 ± 1.2	0.273
Hypertension, n, (%)	13 (21.7%)	9 (21.4%)	1.000
Diabetes, n, (%)	6 (10%)	4 (9.5%)	1.000
Smoking	5 (8.3%)	3 (7.1%)	0.999
Creatinine (mg/dl)	1.07 ± 0.05	1.08 ± 0.06	0.085
Total cholesterol(mg/dl)	134 ± 34	133 ± 53	0.956
Triglyceride (mg/dl)	98.5 ± 43	110.5 ± 64	0.603
LDL (mg/dl)	87.5 ± 33	74.5 ± 41	0.353
HDL (mg/dl)	38 ± 10	39.5 ± 12	0.206
SBP (mm Hg)	108 ± 10	106 ± 10	0.223
DBP (mm HG)	70 ± 11	68 ± 8.5	0.091
Heart rate (bpm)	73.5 ± 30.7	87.5 ± 28.5	0.793
Atrial fibrillation, n,(%)	21 (35%)	20 (47.6%)	0.223
Warfarin, n,(%)	21 (35%)	20 (47.6%)	0.221
Thromboembolicevents n,(%)	4 (6.7%)	4 (9.5%)	0.714

Numerical data are expressed as median±interquartile range. BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density ; SBP,systolic blood pressure; DBP,diastolic blood pressure.

CBC parameters

Table 2 summarizes the complete blood picture of both the groups. No significant difference was observed between the two groups in terms of haemoglobin, haematocrit, mean corpuscular volume, red cell distributed width, white blood count, neutrophil count, and lymphocyte count. With respect to platelet indices, there was no significant difference in the platelet count and platelet distribution width between the groups. However, MPV levels (10.15 ± 0.60 vs. 9.6 ± 1.4, p <0.001) and plateletcrit levels (0.238 ± 0.02 vs. 0.222 ± 0.05, p = 0.007) were significantly higher in the SEC (+) group.

Table 2.Complete blood counts of both groups.

Parameters	Group I (SEC-) (n = 60)	Group II (SEC+) (n = 42)	p value
Haemoglobin, (g/dL)	12.7 ± 1.1	12.8 ± 1.0	0.505
Hematocrit, (%)	37 ± 5	38 ± 5	0.718
Mean corpuscular volume (fL)	91 ± 20.5	88 ± 11	0.360
Red cell distributed width (%)	14 ± 0.67	14 ± 0.60	0.731
White blood cell, (103µL)	6750 ± 2100	7000 ± 2275	0.406
Neutrophil, (103µL)	4332 ± 660	4315 ± 500	0.304
Lymphocyte (103µL)	1800 ± 200	1800 ± 200	0.551
Platelet count, (103µL)	245 ± 79	234 ± 74	0.967
Mean platelet volume, (fL)	9.6 ± 1.4	10.15 ± 0.60	< 0.001*
Plateletcrit, (%)	0.222 ± 0.05	0.238 ± 0.02	0.007*
Platelet distribution width, (%)	13.75 ± 1.2	13.85 ± 0.7	0.074

Data expressed as median±interquartile range. *P value < 0.05 was considered significant.

Echocardiographic parameters

The echocardiographic parameters are listed in table 3.There were no significant differences in terms of LVEF, and PAP. Mean gradient was significantly higher in SEC (+) group (11±2 vs.10.35±1.5, p=0.0195), while planimetric MVA was significantly higher in the SEC(-) group than in the SEC(+) group (1.08±0.3 vs.0.96±0.17, p=0.0015). In addition, LA volume was significantly higher in SEC (+) group when compared with SEC (-) group (74±4 vs.71±5, p=0.0007).

Table 3. Comparison of echocardiographic findings between two groups

Parameters	Group I (SEC-) (n = 60)	Group II (SEC+) (n = 42)	p value
LVEF, (%)	60 ± 2.75	60 ± 3.25	0.558
Mean gradient (mmHg)	10.35 ± 1.5	11± 2	0.0195*
Mitral valve area (cm2)	1.08 ± 0.3	0.96 ± 0.17	0.0015*
LA volume(ml)	71 ± 5	74 ± 4	0.0007*
PAP (mmHg)	52 ± 10.75	53.5 ± 9	0.1782
SEC,n,(%)			
No sec	60 (100%)		
1 (+)	0	12 (28.5%)	
2 (+)	0	16 (38.1%)	
3 (+)	0	8 (19 %)	
4 (+)	0	4 (14.3%)	

Data are expressed as median±interquartile range. LVEF, left ventricular ejection fraction; LA, left atrium; PAP, pulmonary arterial pressure; SEC, spontaneous echo contrast.

Subgroup analysis on the basis of degree of SEC

None of the patients in group I had any evidence of SEC on echocardiographic examination (table 3). In group II, 12 (28.5%)

patients had 1+ (mild), 16 (38.1%) patients had 2+ (mild to moderate), 8 (19 %) patients had 3+(moderate),and 4 (14.3%) patients had 4+ (severe) degree of SEC(table 3).

Also, there was significant increase in MPV values with increase in severity of SEC($p<0.001$) (figure 1).

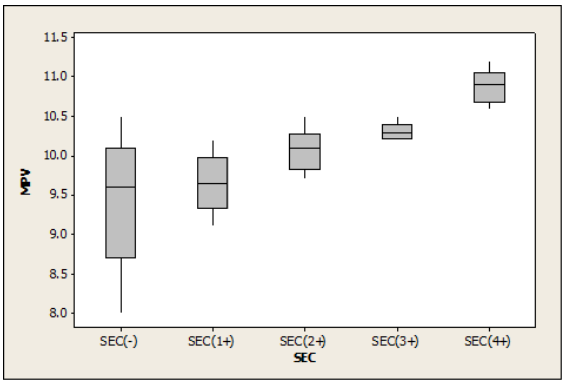

Figure 1. Median platelet volume levels in the spontaneous echo contrast-negative group and in the subgroup of spontaneous echo contrast-positive patients.

Association between SEC and other potential variables

In order to establish the independent association between SEC and other potential variables, we computed a multiple logistic regression analysis. In multiple logistic regression analysis, MPV, MVA, mean gradient, and LA volume were found to be independently associated with presence of SEC (table 4).

Table 4. Effect of potential variables on spontaneous echo contrast in multivariate regression analysis

Variables	Odds ratio	95% Confidence interval	p value
MPV(fl)	7.30	2.47 - 21.59	<0.001
MVA(cm2)	0.00	0.00 – 0.12	0.002
Mean gradient(mmHg)	1.56	1.00 – 2.42	0.049
LA volume(ml)	1.20	1.05 – 1.38	0.009
Plateletcrit	1.94	0.23 – 16.27	0.540

MPV, mean platelet volume; MVA,mitral valve area; LA, left atrium.

DISCUSSION

In this study, we found that MS patients with left atrial SEC had significantly higher MPV values and PCT than MS patients without left atrial SEC, and there was a positive correlation between MPV levels and the severity of SEC.

Systemic thromboembolism is an important complication in patients with M.S. Stasis of blood in LA plays an important role in thromboembolism. Also, patients with rheumatic M.S may have thromboembolic events, although on oral anticoagulant treatment. Therefore, in addition to the coagulation system, platelets may play an important role in the development of thromboembolic events in patients with M.S.

The SEC has been described as smoke-like echoes with a characteristic swirling motion of blood flow resulting from the accentuated ultrasonic backscatter of the aggregation of the blood cellular components in the situations of blood stasis or low peak flow velocity of LA appendage.[8] The phenomenon of SEC has always been the focus of attention since it was reported in 1981 by Sigel et al.[8] Although it can develop in any cardiac chamber during any rhythm, the presence of SEC is commonly seen in the left atrium and LA appendage, especially in patients with AF. Left atrial SEC provides a semi-quantitative assessment of left atrial blood stasis and has been detected in various pathologies of the cardiovascular system.[9] Nevertheless, several clinical and epidemiological studies showed that left atrial SEC is associated with a hypercoagulable state associated with previous or future thromboembolism, and death in patients with AF during follow up.[9,10] The incidence of LA thrombus is 60% in patients with obvious SEC, while it is only 9% in those without SEC.[11] Nevermore, left atrial SEC is considered as an important predictor of systemic embolization independent from the presence of thrombus in the LA and the frequency of thromboembolic complications tend to increase with the higher degree of left atrial SEC.[12] For all these reasons, left atrial SEC may be considered as a potential early warning indicator of thromboembolic complications, which may occur in the future.

Several mechanisms have been implicated in pathophysiology of SEC. It occurs from aggregation of blood components in the situations with blood stasis and low velocity of bloodflow.[1] Otherwise, Sigel et al8 reported that echogenicity of blood in SEC occurred with erythrocytes aggregation in plasma. Erbel et al[13] found evidence of increased platelet aggregation in nine patients with SEC and resolution of SEC after antiplatelet therapy. These data suggest that SEC may reflect not only stasis of blood in LA, but also associated with blood characteristics including erythrocytes and platelets. Disappearance of SEC after antiplatelet therapy suggests that patients with M.S complicated with SEC who have high MPV levels might gain advantage from antiplatelet therapy and decrease the risk of thromboembolic events. However, role of antiplatelet therapy in the treatment of SEC is still controversial. So, further prospective studies should be planned to determine the effect of aspirin on SEC.

MPV is an easily measurable index for platelet function.[14,15] It has been demonstrated that a higher MPV is correlated with a greater platelet activation.[16] Larger platelets contain more prothrombotic materials including thromboxane A2 and B2 and also have more glycoprotein IIb–IIIa receptor expression on the surface of platelets.[17,18] Jakubowski et al[19] reported that the presence of a greater platelet decreases the inhibitory effectiveness of PGI2 on both platelet aggregation and the release reaction. Thus, larger platelets tends to be more aggregable metabolically and enzymatically more reactive compared to smaller ones. PCT is the percentage of blood volume occupied by platelets.[20] According to the current literature, PCT is an indicator of platelet mass in the blood and is physiologically superior to the platelet count to estimate the platelet status.[21]

In the present study, PDW, platelet count, and other haematological parameters including haemoglobin, haematocrit, red cell distribution width, mean corpuscular volume, and white blood cell count were not associated with SEC in patients with M.S. However, MPV, a sign of platelet activation, was significantly higher in the SEC (+) group. In the subgroup of SEC, MPV levels also correlated with the degree of SEC. In addition, MPV levels were the independent risk factor for SEC in patients with M.S. Although PCT levels were statistically independently associated with SEC in patients with M.S, PCT did not increase in a graded fashion with SEC intensity as did MPV. Because PCT represents the percentage of whole blood occupied by platelets, PCT and MPV are different descriptive parameters of the platelet fraction of blood. Although MPV tends to be higher in patients with left atrial SEC in our study, it is uncertain whether it is a cause or a consequence of left atrial SEC. Long term follow-up studies of patients with left atrial SEC are needed to establish this relationship. This study has some limitations. First, the number of patients were relatively small and a larger study is needed to reach a major conclusion. Second, use of EDTA for blood sampling, may lead to platelet swelling, thereby increasing MPV values.

CONCLUSION

In conclusion, in patients with M.S, cheap and easily measurable platelet indices including MPV and PCT levels are associated with the presence of SEC and are independent risk factors of SEC. The findings of this study also suggest that left atrial SEC may point out not only blood stasis, but also associated with elevated MPV level, which shows the contribution of increased platelet activation. Thus, we suggest that SEC (+) patients with high MPV and PCT levels might gain advantage from intensive antiplatelet therapy and decrease the risk of thromboembolic events. However, further prospective studies are needed in order to determine the effects of antiplatelet therapy on SEC in patients with M.S.

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