

# Association of Left Atrial Spontaneous Echocardiographic Contrast with Inflammatory Markers in Mitral Stenosis Patients

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## Abstract:

**Keywords:**  
Spontaneous echocardiographic contrast (SEC), Mitral stenosis, hs-CRP

**Background:** Spontaneous echocardiographic contrast (SEC) is a risk factor for left atrial thrombus formation and an important indicator of potential systemic embolism originated from heart. An established relation exists between the inflammatory status and the prothrombotic state. The present study was conducted to evaluate the association between left atrial spontaneous echocardiographic contrast with inflammatory markers in mitral stenosis patients.

**Methods:** This observational analytical study was undertaken in the department of Cardiology, National Institute of Cardiovascular diseases (NICVD), Dhaka. A total of 70 patients with mitral stenosis were categorized into two groups: group I with left atrial SEC and group II without left atrial SEC. All patients underwent transthoracic as well as transoesophageal echocardiography. Complete blood count with ESR was done and neutrophil lymphocyte ratio was calculated. The high sensitive C-reactive protein (hs-CRP) was assayed.

**Results:** The hs-CRP levels were significantly greater in the SEC-positive group ( $5.6 \pm 2.1$  vs  $1.5 \pm 0.7$ ,  $p=0.001$ ). The mean ESR level was significantly greater in the SEC-positive group ( $32.6 \pm 15.5$  mmvs  $15.8 \pm 4.7$  mm). The neutrophil levels ( $76.1 \pm 1.9$  vs  $63.7 \pm 3.3$ ) were significantly greater in the SEC-positive group, and the lymphocyte levels ( $33.3 \pm 3.0$  vs  $21.5 \pm 1.3$ ) were significantly greater in the SEC-negative group ( $p=0.001$  for each). The neutrophil/lymphocyte (N/L) ratio was also significantly greater in the SEC-positive group ( $3.4 \pm 0.4$  vs  $2.1 \pm 0.6$ ,  $p=0.001$ ). On multivariate analysis hs-CRP, neutrophil/lymphocyte ratio, raised ESR, mitral valve area and left atrial diameter were independent risk factors for SEC in patients with mitral stenosis.

**Conclusion:** From this study it may be concluded that left atrial SEC is associated with raised inflammatory markers in majority of patients with mitral stenosis. So, SEC may be considered as a reflection of ongoing inflammatory process in patients with mitral stenosis.

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## Introduction:

Spontaneous echocardiographic contrast (SEC) is the presence of smoke-like echoes with a characteristic swirling motion of blood found during echocardiography. SEC is commonly seen in the left atrium and is caused in particular by mitral stenosis (MS) and nonvalvular atrial fibrillation.<sup>1,2</sup> Previous clinical studies have demonstrated that SEC is a risk factor for left atrial thrombus formation and an important indicator of potential systemic embolism originated from heart.<sup>3,4</sup> In the Pathophysiology of SEC, several mechanisms have been previously reported. It occurs from aggregation in the cellular component of the blood in situations with

blood stasis and low velocity of the blood stream.<sup>3</sup> Sigel, et al. reported that the echogenicity of blood in SEC occurred with erythrocyte aggregation in the plasma. Another recent study demonstrated that plateletcrit and mean platelet volume also plays important role in the pathophysiology of SEC.<sup>6</sup>

An established relation exists between inflammatory status and prothrombotic state in the published data.<sup>7</sup> In addition it has been demonstrated that the inflammatory status is associated with the prothrombotic state and SEC formation in patients with atrial fibrillation with mitral stenosis.<sup>8</sup>

As SEC has close relation to thrombus formation in the left atrial cavity, it may be prudent to require early, intensive follow up examinations to diagnose left atrial thrombus whenever the SEC is observed, even if no thrombus can be detected. By measuring the inflammatory markers like hs-CRP, ESR and Neutrophil/lymphocyte (N/L) ratio, we can assess the prothrombotic state and this can predict the risk of formation of thrombus from SEC. So, the present study was planned and carried out.

### Materials and Methods:

This observational, analytical study conducted in the department of Cardiology, NICVD, from January, 2013 to October, 2013. A total of 70 patients were divided into two groups according to the presence of Spontaneous Echocardiographic contrast (SEC) in the left atrium. Group I comprised of the patients with left atrial SEC (n=35) and Group II comprised of the patients without left atrial SEC (n=35). The study protocol was approved by the ethical review board.

The exclusion criteria for the present study were presence of left atrial thrombus, mitral regurgitation (>Gr-II), prior PTMC, CMC or mitral valve replacement, a history of malignancy, a history of inflammatory disease, current therapy with corticosteroids and nonsteroidal anti-inflammatory drugs, connective tissue disease, thyroid disease, and other hematologic disease. A medical history was recorded from patient anamnesis.

Both transthoracic and transoesophageal echocardiography was performed in both group of patients. Transthoracic echocardiography was performed using vivid 5 system with a 3.5 MHZ phased array transducer. All patients were evaluated independently by two cardiologist experts in echocardiography. Standard echocardiographic measurements with left ventricular ejection fraction (LVEF) were taken; valves were examined for morphology and gradient. For TEE, after patients had been administered pharyngeal local anesthesia with a lidocaine spray, the probe was initially carried forward to a depth of 25 to 35 cm and then manipulated for optimum imaging. All images were archived and evaluated by 2 independent

expert cardiologists. Left atrial cavity and appendage were searched for spontaneous echo contrast and thrombus. SEC was defined as a pattern of slowly swirling intracavity echocardiographic densities imaged with gain settings adjusted to distinguished background noise.<sup>9</sup> SEC is classified as-

- Mild: When localized to LA or LA appendage
- Moderate: When seen intermittently with adjustment of gain settings
- Severe: When present continuously at normal gain settings.<sup>10</sup>

Peripheral blood samples for measurement of hs-CRP were taken. hs-CRP was assayed by Nephelometric system. Complete blood count with ESR was done. Neutrophil/Lymphocyte ratio was calculated.

### Statistical Methods

The numerical data obtained from the study were analyzed and significance of differences was estimated by using statistical methods. Data were presented as frequency and percentage for categorical variables and as mean with standard deviation for quantitative variables. Categorical variables were analyzed by chi-square test. Quantitative variables were analyzed by t-test or ANOVA.

Correlations between severity of SEC, hs-CRP and N/L ratio was measured by Pearson's and Spearman – s correlation test. Multiple logistic regression analysis was performed to establish the independent predictive value of C-reactive protein. A p-value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS, version 16.0 (SPSSInc).

### Results:

The main objective of the study was to evaluate the association between left atrial spontaneous echocardiographic contrast and raised inflammatory markers in patients with mitral stenosis. Group I comprised of the patients with left atrial SEC (n=35) and Group II comprised of the patients without left atrial SEC (n=35). The mean age of the patients were 31.5± 9.8 years and 31.7± 7.8 years in group I and group II respectively. Female sex predominated in both groups with a male female ratio of 1:5.

In this study, baseline parameters like age, sex, body mass index, baseline drug intake showed no statistically significant differences among the study subjects of two groups (Table I).

**Table-I**  
*Baseline parameters of the study patients (n=70)*

Variables	Group I (n= 35)	Group II (n =35)	p value
Age (years)	31.5±9.8	31.7±7.8	0.91 <sup>ns</sup>
Women	31(88.6%)	28(80%)	0.51 <sup>ns</sup>
Body Mass Index (kg/m <sup>2</sup> )	21.6±1.3	21.8±1.3	0.39 <sup>ns</sup>
Drug history			0.45 <sup>ns</sup>
Aspirin	9(25.7%)	6(17.1%)	
Penicillin	6(17.1%)	4(11.4%)	

Clinical presentation was almost same in both groups but NYHA functional class II and III was significantly greater in group I (Table II).

Regarding echocardiographic parameters, left atrial diameter was significantly greater in group I (48.7± 8 vs 44.2± 4.9 mm) and mitral valve area was significantly higher in group II (0.9± 0.3 vs 0.7± 0.3 cm<sup>2</sup> ). LV ejection fraction was significantly higher in group II (Table III).

Table IV shows the hematologic and biochemical parameters of the study patients. The mean ESR level was 32.6±15.5 mm in 1<sup>st</sup> hour in group I and 15.8±4.7 mm in 1<sup>st</sup> hour in group II. The difference was statistically significant (p=0.001). The mean lymphocyte levels were significantly greater in group II (33.3±3.0 vs 21.5±1.3, p<0.05), the neutrophil levels were significantly greater

in group I (76.1±1.9 vs 63.7±3.3) and no significant difference was found in the monocyte count between the two groups (p>0.05). The mean neutrophil/lymphocyte ratio was observed 3.4±0.4 in group I and 2.1±0.6 in group II with statistical significant difference (p<0.05). The mean hs-CRP was 5.6±2.1 mg/L in group I and 1.5±0.7 mg/L in group II. Mean difference of hs-CRP level was statistically significant in two groups (p<0.05).

Table V shows level of hematologic and biochemical parameters among study patients. ESR within 21-40 (mm in 1<sup>st</sup> hour) was observed significantly higher in group I than group II patients (51.4% vs 25.7%, p<0.05). Neutrophil/Lymphocyte ratio >3.1 was observed significantly greater in group I than group II patients (74.2% vs 20%, p=0.001). hs-CRP (>3 mg/L) was also observed significantly higher in group I than group II patients (68.5% vs 17.2%, p<0.05).

The association between the degree of SEC and the levels of hs-CRP was studied. The levels of hs-CRP in mild, moderate and severe degree of SEC were 4.2, 5.9 and 7.1 mg/L respectively (Table VI).

In this study, the correlation between SEC and other variables have been studied. There is a strong positive correlation between hs-CRP and severity of SEC (r=0.71) and a fair positive correlation between neutrophil/lymphocyte ratio and ESR (mm in 1<sup>st</sup> hour) (r=0.55) (figure 1 and 2).

**Table-II**  
*Distribution of the study patients by NYHA functional class (n=70)*

NYHA functional class	Group I (n= 35)		Group II (n =35)		p value
	Number	%	Number	%	
Class I	3	8.6	19	54.3	0.001 <sup>s</sup>
Class II	25	71.4	15	42.9	0.01 <sup>s</sup>
Class III	7	20.0	1	2.9	0.03 <sup>s</sup>
Class IV	0	0.0	0	0.0	

**Table-III**  
*Echocardiographic parameters of the study patients (n = 70)*

Variables	Group I (n= 35)	Group II (n =35)	p value
	Mean ± SD	Mean ± SD	
Left ventricular ejection fraction (%)	58.6±6.9	63.0±5.6	0.005 <sup>s</sup>
Trans-mitral peak pressure gradient (mmHg)	24.3±7.8	22.4±7.0	0.27 <sup>ns</sup>
Mitral valve area (cm <sup>2</sup> )	0.7±0.3	0.9±0.3	0.001 <sup>s</sup>
Systolic pulmonary arterial pressure (mmHg)	63.3±18.1	55.5±16.2	0.06 <sup>ns</sup>
Left atrial diameter (mm)	48.7±8.0	44.2±4.9	0.007 <sup>s</sup>

**Table-IV**  
*Hematologic and biochemical parameters of the study subjects (n = 70)*

Parameters	Group I (n= 35)	Group II (n =35)	p value
	Mean ± SD	Mean ± SD	
ESR (mm in 1 <sup>st</sup> hour)	32.6±15.5	15.8±4.7	0.001 <sup>s</sup>
White blood cell distribution (%)			
Lymphocyte	21.5±1.3	33.3±3.0	0.001 <sup>s</sup>
Neutrophil	76.1±1.9	63.7±3.3	0.001 <sup>s</sup>
Monocyte	2.1±0.9	2.3±1.2	0.38 <sup>ns</sup>
Neutrophil/lymphocyte ratio	3.4±0.4	2.1±0.6	0.001 <sup>s</sup>
hs-CRP mg/L	5.6±2.1	1.5±0.7	0.001 <sup>s</sup>

**Table-V**  
*Level of hematologic and biochemical parameters among study patients (n=70)*

Parameters	Group I (n= 35)		Group II (n =35)		p value
	Number	%	Number	%	
ESR (mm in 1 <sup>st</sup> hour)					
0 – 20	10	28.6	26	74.3	0.001 <sup>s</sup>
21 – 40	18	51.4	9	25.7	0.03 <sup>s</sup>
> 40	7	20.0	0	0.0	0.005 <sup>s</sup>
Neutrophil/Lymphocyte ratio					
> 3.1	26	74.2	7	20	0.001 <sup>s</sup>
≤3.1	9	25.8	28	80	
hs-CRP (mg/L)					
> 3 mg/L	24	68.5	6	17.2	0.001 <sup>s</sup>
≤3 mg/L	11	31.5	29	82.8	

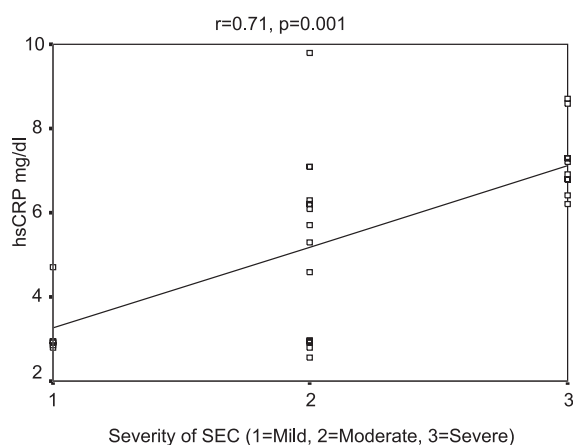
**Table-VI**  
*Severity of SEC with level ofhs-CRP (n=35)*

Severity of SEC	hs-CRP		p value
	Mean	SD	
Mild (n=6)	4.2	0.3	0.001 <sup>s</sup>
Moderate (n=15)	5.9	1.4	
Severe (n=14)	7.1	0.7	

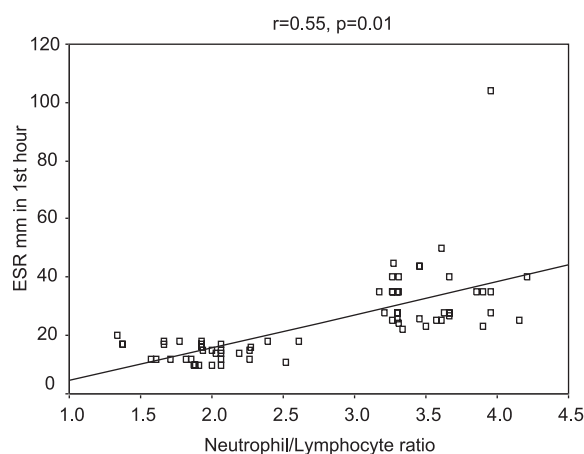
The effects of multiple variables on SEC were analyzed using univariate and multivariate logistic regression analyses. The variables for which the p value was <0.05 on univariate analysis were identified as potential risk markers for SEC and included in the full model. On univariate analysis hs-CRP, N/L ratio, raised ESR, mitral valve area and left atrial diameter

were independent risk factors for SEC in mitral stenosis patients with ORs being 1.27, 1.82, 1.24, 1.18 and 1.19 respectively (Table VII).

On multivariate analysis hs-CRP, N/L ratio, raised ESR, mitral valve area and left atrial diameter were independent risk factors for SEC patients with ORs being 1.51, 1.69, 1.38, 1.13 and 1.17 respectively.



**Fig.-1:** Correlation between severity of SEC and hs-CRP



**Fig.-2:** Correlation between neutrophil/lymphocyte ratio and ESR (mm in 1st hour)

**Table-VII:**

*Effect of various variables on spontaneous echocardiographic contrast (SEC) on univariate logistic regression analysis.*

Variables of interest	Unadjusted OR	95% CI of OR	p value
Atrial fibrillation	1.21	0.347-3.212	0.21 <sup>ns</sup>
High-sensitive CRP	1.27	0.102-1.314	0.03 <sup>s</sup>
Neutrophil/lymphocyte ratio	1.82	0.924-2.397	0.003 <sup>S</sup>
Raised ESR	1.24	0.235-3.110	0.02 <sup>S</sup>
Mitral valve area	1.18	0.160 – 1.494	0.04 <sup>s</sup>
Left atrial diameter	1.19	0.104 – 1.534	0.04 <sup>s</sup>

**Table-VIII**

*Effect of various variables on spontaneous echocardiographic contrast (SEC) on multivariate logistic regression analysis.*

Variables of interest	AdjustedOR	95% CI of OR	p value
Atrial fibrillation	1.68	0.657-4.451	0.16 <sup>ns</sup>
High-sensitive CRP	1.51	1.054-1.684	0.02 <sup>s</sup>
Neutrophil/lymphocyte ratio	1.69	1.064-2.287	0.03 <sup>S</sup>
Raised ESR	1.38	1.044-3.340	0.03 <sup>S</sup>
Mitral valve area	1.13	1.015 – 1.369	0.04 <sup>s</sup>
Left atrial diameter	1.17	1.019 – 1.334	0.04 <sup>s</sup>

**Discussion:**

The mean age of the studied patients were  $31.6 \pm 8.8$  years ranging from 17 to 62 years. The mean age difference of group I and group II were found statistically insignificant ( $p > 0.05$ ). In a similar study done by Kaya, et al., the mean age was  $45 \pm 12$  years in SEC positive group and  $45 \pm 11$  years in SEC negative group. The low mean age of our study population may be due to high rate of recurrent attack of rheumatic fever in our country resulting in early age of presentation.

In this study, baseline parameters like age, sex, body mass index, baseline biochemical parameters showed no statistically significant differences among the study subjects of two groups. Clinical presentation was almost same in both groups but NYHA functional class II and III was significantly greater in group I. This is more or less comparable with the findings of other authors.<sup>12,13</sup>

In the present study, electrocardiographic parameters of study patients revealed highest percentage had atrial fibrillation in group I (57.1% vs 31.4%). Kaya, et al. showed that atrial fibrillation was present in 53% of patients with spontaneous echo contrast. Regarding echocardiographic parameters, left atrial diameter was significantly greater in group I ( $48.7 \pm 8$  vs  $44.2 \pm 4.9$  mm) and mitral valve area was significantly higher in group II ( $0.9 \pm 0.3$  vs  $0.7 \pm 0.3$  cm<sup>2</sup>). Black, et al. showed that mitral valve area was  $1.1 \pm 0.3$  cm<sup>2</sup> in the SEC positive group compared with  $1.4 \pm 0.3$  cm<sup>2</sup> in patients without SEC ( $p < 0.05$ ).

The mean ESR level was  $32.6 \pm 15.5$  mm in 1<sup>st</sup> hour in group I and  $15.8 \pm 4.7$  mm in 1<sup>st</sup> hour in group II. The difference was statistically significant ( $p < 0.05$ ). The mean lymphocyte levels were significantly greater in group II ( $33.3 \pm 3.0$  vs  $21.5 \pm 1.3$ ,  $p < 0.05$ ) and the neutrophil levels were significantly greater in group I ( $76.1 \pm 1.9$  vs  $63.7 \pm 3.3$ ,  $p < 0.05$ ). Kaya, et al. in a similar study showed that neutrophil level was significantly higher in SEC positive group ( $73 \pm 9$  vs  $65 \pm 9$ ,  $p < 0.05$ ).

The mean hs-CRP was  $5.6 \pm 2.1$  mg/L in group I and  $1.5 \pm 0.7$  mg/L in group II. Mean difference of hs-CRP level was statistically significant in two groups ( $p < 0.05$ ). In a similar study done by Kaya,

et al., hs-CRP levels were significantly greater in SEC positive group than in the SEC negative group ( $10.6 \pm 6.3$  vs  $3.9 \pm 2.2$ ,  $p < 0.05$ ).

The neutrophil/lymphocyte ratio as an indicator of systemic inflammation has been studied in numerous epidemiological studies.<sup>14,15</sup> In the present study, the mean neutrophil/lymphocyte ratio was observed  $3.4 \pm 0.4$  in group I and  $2.1 \pm 0.6$  in group II with statistical significant difference ( $p < 0.05$ ). According to Kaya, et al., the neutrophil/lymphocyte ratio was significantly greater in the SEC positive group ( $4.5 \pm 1.8$  vs  $3.0 \pm 1.8$ ,  $p < 0.05$ ).

In this study there was a significant ( $p < 0.05$ ) positive correlation between hs-CRP and severity of SEC ( $r = 0.71$ ) and a fair positive correlation between neutrophil/lymphocyte ratio and ESR (mm in 1<sup>st</sup> hour) ( $r = 0.55$ ). On multivariate analysis hs-CRP, neutrophil/lymphocyte ratio, raised ESR, mitral valve area and left atrial diameter were independent risk factors for SEC patients with ORs being 1.51, 1.69, 1.38, 1.13 and 1.17 respectively. The findings are similar to the studies done by Kaya, et al.

**Conclusion:**

From this study it may be concluded that left atrial spontaneous echocardiographic contrast is associated with raised inflammatory markers such as high sensitive C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR) and neutrophil/lymphocyte ratio in majority of patients with mitral stenosis. So, spontaneous echocardiographic contrast may be considered as a reflection of ongoing inflammatory process in patients with mitral stenosis.

**Study limitation:**

The possible limitations of the present study include that it was a single-center experience and included a small number of patients. However, our population contained homogenous unselected patients with MS, mirroring the real world scenario.

**Conflict of Interest - None.****References:**

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