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Prevalence and Echocardiographic Predictors of Left Atrial Appendage Inactivity in Patients of Mitral Stenosis

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Abstract

Background: Mitral stenosis (MS) is a common valvular heart disease. Thromboembolism is one of the most serious consequences of mitral stenosis, particularly when it is accompanied with atrial fibrillation (AF). When linked with Left atrial appendage inactivity (LAAI), patients with sinus rhythm (SR) are also at risk for this condition. In mitral stenosis, LAA inactivity determined by S-wave is an independent predictor of thromboembolism. The aim of the study was to evaluate the Prevalence and Echocardiographic Predictors of Left Atrial Appendage inactivity in patients of Mitral Stenosis. **Material & Methods:** Sixty MS patients were evaluated by transthoracic echocardiography (TTE) and all patients underwent transesophageal echocardiography (TEE). The annular systolic (S-wave) and diastolic (Em- and Am-waves) velocities were recorded by tissue Doppler imaging (TDI). LAA inactivity was defined as LAA emptying velocity <25 cm/second determined by pulse wave Doppler at the junction of LA & LAA (TEE). Patients were divided into three groups; group A I (n = 18). Sinus rhythm (SR) and LAA emptying velocity ≥25 cm/sec, group A II (n -22): SR and LAA emptying velocity <25cm/sec and group B (n = 20): atrial fibrillation. **Results:** Thrombus was detected in 14 patients and spontaneous echo contrast (SEC) was detected in 43 patients. Both S-wave and peak LAA emptying velocities were decreasing, while SEC frequency and density were increasing from group A to group B. There was a positive correlation between LAA emptying vs. S-wave and LAA emptying vs. Am velocities ($p < 0.001$, $r= 0.708$ and $p<0.001$, $r=0.495$). Multivariate regression analysis showed that only S-wave is the independent predictor of inactive LAA ($p = 0.001$, odds ratio = 0.133, 95% Cl =0.032-0.556). In patients with SR, the cutoff value of S-wave was 10 cm/sec for the prediction of the presence of inactive LAA (sensitivity: 92.3%, specificity: 95.3%). **Conclusions:** In individuals with severe mitral stenosis in sinus rhythm, there is a significant prevalence of left atrial appendage inactivity. The mean pressure gradient across the mitral valve, as well as S-wave are independent predictors of left atrial appendage inactivity. Inactivity of the left atrial appendage is an independent predictor of left atrial/left atrial appendage smoke and associated thrombus.

Keywords:- Mitral stenosis (MS), Left atrial appendage (LAA) function, annular systolic velocity (S-wave).

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INTRODUCTION

Systemic thromboembolism is a major cause of morbidity and mortality in patients of mitral stenosis (MS).[1,2] Although thromboembolic events are common in patients of MS with atrial fibrillation (AF), it has also been reported in 5-15% of patients in sinus rhythm (SR).[2,3,4] Left atrial appendage (LAA) is the commonest site for thrombus formation and impairment of its contractility leading to stasis is an independent predictor of thromboembolic events in patients of MS.[5,6] Serken S et al,[4] in an interesting study have shown that in patients of severe MS (Mitral valve area [MVA] <1.5 cm2) there is an impairment of LAA contractility to a similar extent irrespective of whether a patient is in SR or AF. However, no data is available about the prevalence of LAA hypocontractility/inactivity (defined as LAA peak emptying velocity [LAAEV] <25cm/sec) in patients of severe MS in SR that promotes spontaneous echo contrast (SEC) formation(a precursor of thrombus) and is an independent predictor of thromboembolic events.[7,8,9,10] So, the primary aim of this study was to assess the incidence of LAA inactivity (LAAI) in patients of severe MS in sinus rhythm. The assessment of LAAEV to detect LAAI requires transesophageal echocardiography (TEE) which is invasive, requires expertise and is not readily available. The secondary aim was to assess clinical and transthoracic echocardiographic variables that can predict presence of LAA inactivity. Sample size: As the proportion of active and inactive LAA in patients of severe MS in SR is not known in our population, we considered inactive LAA to be present in 50% patients. Considering 50% with 10% regression on either side with 95% confidence interval (CI), we needed 60 patients to attain an adequately powered study.

MATERIAL AND METHODS

Sixty MS patients were evaluated by transthoracic echocardiography and all patients underwent transesophageal echocardiography. The annular systolic (S-wave) and diastolic (Em- and Am-waves) velocities were recorded. Inactive LAA was defined as LAA emptying velocity <25 cm/sec. Patients were divided into three groups; group AI (n =18) Sinus rhythm (SR) and LAA emptying velocity ≥25 cm/sec, group AII (n - 22): SR and LAA emptying velocity <25cm/sec and group B (n = 20): atrial fibrillation.

RESULTS

[Table 1] shows that the mean age was higher in patients with atrial fibrillation (32.5±8.3) than that of sinus rhythm (28.8±8.1), but the mean difference was not statistically significant (p >0.05). Regarding sex distribution, mean difference between the groups was not significant (p >0.05) also. The mean mitral valve area was lower in atrial fibrillation (0.77±0.15) than that of sinus rhythm (1.07±0.21) and the mean difference was highly significant (P<0.01). But, mean left atrial dimension was higher in atrial fibrillation (54.2±7.5) than that of sinus rhythm (47.6-10.0) and the mean difference was significant (p<0.05). The mean difference between the ejection fractions was not significant p>0.05). The transmitral mean gradient was higher in sinus rhythm (15.3±5.9) than that of atrial fibrillation (11.1±2.1) and the mean difference is highly significant (P<0.01).Whereas, transmitral peak gradient showed no significant difference (p>0.05). [Table 2] shows

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that among age and sex there was no significant scinereio (p=0.05). Mitral valve area was higher in patients in MS with normal LAA function (12.6±01.5) than that of sinus rhythm with LAA dysfunction (0.91-0.07). Similany, MVA was higher in patients of sinus rhythm with LAA dysfunction than that or atrial fibrillation group (0.77±0.15). The mean differences between the three groups were highly significant (p<0.01). Thus, there was progressive decrease of mitral valve area among the three groups. But, LA dimensions in patients with normal LAA function (40.4±3.5), sinus rhythm with LAA dysfunction (53.4+9.8) and atrial fibrillation (54.2±7.5) were increasing progressively. The mean difference between normal LAA function and SR with LAA dysfunction was highly significant, as the difference between normal LAA function and atrial fibrillation was. But, the mean difference between SR with LAA dysfunction and atrial fibrillation was not significant (p>0.05). The ejection fraction between the three groups showed no significant difference. The transmitral mean gradient was highest in SR with LAA dysfunction (19.9±2.7) than those with normal LAA function (9.8±3.4) and atrial fibrillation (11.1±2.1). The mean difference between normal LAA function and SR with LAA dysfuncton was highly significant (p<0.01), as the difference between SR with LAA dysfunction and atrial fibrillation. But the difference between normal LAA function and atrial fibrillation showed no significant difference. The transmitral peak gradient was also highest in patients of sinus rhythm with LAA dysfunction (29.9±4.6) than those of normal LAA function (15.4±3.9) and atrial fibrillation (21.2±3.9). The mean difference among three groups were highly significant (p <0.01) to each other.

Table 1: Baseline demographic and clinical functional class of patients.

	GroupA (n=40)	**Group B (n=20)**	**p-value**
	Mean±SD	**Mean±SD**	
Age	28.8±8.1	32.5±8.3	0.100NS
Sex(M/F)	13/27	6/14	0.844NS
MVA(cm^2)	1.07±0.21	0.77±0.15	0.0001
LAD(mm)	47.6±10.0	54.2±7.5	0.012
EF%	60.2±5.9	58.1±5.1	0.187
MG(mmHg)	15.3±5.9	58.1±5.1	0.187NS
PG(mmHg)	22.9±8.1	21.2±3.9	0.364NS
S wave(cm/sec)	17.5±3.8	12.0±1.1	0.001
Em(cm/sec)	14.4±3.1	13.3±3.1	0.194NS
Am(cm/sec)	14.5±2.7	-	-
Laaev(cm/sec)	21.6±8.4	3.5±5.8	0.001
Mean SEC density	2.1±1.4	4.6±0.9	0.001
SEC%	23(57.5)	20(100)	0.001
Thrombus%	2(5.0)	12(60.0)	0.001

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Table 2: Demographic and Transthoracic Echocardiographic Characteristics in groups: (N=60).

	Group A(I) (n=18)	**Group(II) (n=22)**	**Group B (n=20)**	**ρ**	**ρ2**	**ρ3**
	Mean±SD	**Mean±SD**	**Mean±SD**			
Age(year)	30.6±8.0	27.3±8.1	32.5±8.3	0.203^{NS}	0.473^{NS}	0.05^{NS}
Sex(M/F)	5/13	8/14	6/14	0.564^{NS}	0.880^{NS}	0.662^{NS}
MVA(mm^2)	1.26±0.15	0.91±0.07	0.77±0.15	0.001	0.001	0.001
LAD(mm)	40.4±3.5	53.4±9.8	54.2±7.5	0.001	0.001	0.787^{NS}
EF%	60.4±5.5	59.8±6.3	58.1±5.1	0.775^{NS}	0.180^{NS}	0.312^{NS}
MG(mmHg)	9.8±3.4	19.9±2.7	11.1±2.1	0.001	0.172^{NS}	0.001
PG9mmHg)	15.4±3.9	29.9±4.6	21.2±3.9	0.001	0.001	0.001

p value was reached from unpaired Student's t test.

Table 3: Doppler tissue imaging and transoesophageal echocardiograpnic Variables in Groups (N=60)

	Group A(I) (n=18)	**Group A(II) (n=22)**	**Group B (n=20)**	**ρ1**	**ρ2**	**ρ3**
	Mean±SD	**Mean±SD**	**Mean±SD**			
S wave(cm/sec)	19.6±2.7	15.8±3.8	12.0±1.1	0.001	0.001	0.000
Em(cm/sec)	14.3±2.7	14.5±3.3	13.3±3.1	0.807	0.317	0.234
Am(cm/sec)	15.8±1.2	13.4±3.2		0.006		
Laaev(cm/sec)	29.5±5.8	15.1±2.7		0.001		
Mean SEC	1.5±1.1	2.6±1.5	4.6±0.9	0.009	0.001	0.001
density						
SEC%	3(16.7)	20(90.9)	20(100)	0.001	0.001	0.268
Thrombus		2(9.1)	12(60.0)	0.296	0.003	0.002

P value was reached from unpaired Student's t test.

The mean lateral mitral annular systolic velocity (S-wave) in patients of normal LAA function (19.6±2.7) was highest. Patients of SR with LAA dysfunction (15.8±3.8) showed higher S-wave than those of atrial fibrillation (12.0±1.1).Among the groups, they were decreasing progressively. The mean difference between patients of normal LAA function and SR with LAA dysfunction was highly significant, as the difference between normal LAA function and atrial fibrillation was. But, the mean difference between SR with LAA dysfunction and atrial fibrillation was very highly significant. Among the three groups lateral mitral annular early diastolic velocities (Em) showed no significant difference. Lateral mitral annular late diastolic velocity (Am) in patients of normal LAA function (15.8±1.2) was higher than that of SR with LAA dysfunction (13.4±3.2) and the difference was highly significant. But, No definite Am could be detected in group B. Left atrial appendage emptying velocity (LAAEV) was higher in patients with Normal LAA function (29.5±5.8) than those of SR with LAA dysfunction (15.1±2.7). The mean difference was highly

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Page no- 40-47 | Section- Research Article (Cardiology)

significant. Patient's fibrillation showed no definite LAAE. The mean SEC density was highest in atrial fibrillation group (4.6±0.9) and lowest in patients with normal LAA function (1.5±1.1). The mean difference was highly significant between the groups to each other. It was increasing progressively among the three groups. SEC was present in all of the patients of atrial fibrillation, most of the patients of SR with LAA dysfunction (91.9%), but in a few (17%) of normal LAA function. The mean difference was highly significant between normal LAA function and SR with LAA dysfunction, as the difference between normal LAA function and atria fibrillation was. But, the difference between SR with LAA dysfunction and atrial fibrillation was not significant. The SEC frequency was also increasing progressively among the three groups like density. Thrombus was absent in patients with normal LAA function, 2 (9%) in SR with LAA dysfunction and 12 (60%) in atrial fibrillation. The mean difference between patients with normal LAA function and SR with LAA dysfunction was not significant. But, the difference between SR with LAA dysfunction and AF was significant ($p<0.05$), whereas the difference between patients with normal LAA function and AF was highly significant.

DISCUSSION

This is the prospective study that systematically assessed the frequency of LAAI (defined by peak LAA emptying velocity <25cm/sec) in patients of severe isolated rheumatic MS (MVA<1.5cm2) in sinus rhythm.[11,12,13,14] In our study 73% patient had inactive LAA of which 53% had very severe MS (MVA <1 cm2) and 20% had severe MS (MVA >1 but <1.5cm2). On multivariable regression analysis, mean gradient across mitral valve and lateral mitral annulus systolic velocity were found to be independent predictors of LAAI.[15] MVA assessed by planimetry failed to achieve statistical significance as an independent predictor of LAAI in our study. Hoit et al,[16] and Bilge et al,[17,18,19,20] have shown that elevation of LA pressure causes reduction in LAA emptying velocity. The degree of obstruction to outflow across mitral valve is a predictor of LA pressure. In spite of similar mitral valve areas, patients have variable LA pressure due to variable resistance to flow across the mitral valve apparatus determined by the degree of pliability of the valves and sub-valvular obstruction. These aspects of obstruction across mitral valve apparatus are better reflected by the mean transmitral gradient across MV than the MVA determined by 2D. Hence, in our study, mean transmitral gradient was found to be an independent predictor of LAAI over MVA assessed by planimetry. Mitral annulus has an important role for LA and left ventricular (LV) function by moving throughout cardiac cycle along the LV long axis.[21,22,23] The excursion of the mitral annulus is responsible for approximately 20% of total LV filling and emptying in healthy subjects.[16] It also contributes to LA filling by creating a suction effect during systole and contributes to LA emptying by decreasing LA blood volume during diastole.[16,17,18] In patients of MS LV, LA and LAA function are impaired and the excursion of the mitral annulus is reduced due to scaring and inflammatory processes. In our study, we found a strong positive correlation between Sa-wave and LAA peak emptying

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Page no- 40-47 | Section- Research Article (Cardiology)

velocity. The cut off value of Sa-wave to predict LAAI in our study was 6.8 cm/sec which was lower then cut off value reported by Cayle et al,[7] of 13.5 cm/sec and higher than the cut off value of 5.5 cm/sec reported by Arava et al.[24] This is due to the fact Cayle et al (7) had enrolled patients with MVA <1.5 cm2 whereas Arava et al 24 had enrolled patients of critical MS with MVA <1 cm2. The mean Wilkins score in our study was 7.3+-0.8 which is less compared to the mean Wilkins score of 7.9+-0.9 by Arava et al.[24] The degree of damage to the MV apparatus in our study was lesser than patients recruited by Arava et al (24) and more than patients studied by Cayle et al.[7] Accordingly, the cut-off value of S-wave obtained in our study was lower than that by Cayle et al. and higher than that of Arava et al. In our study, two echocardiographic parameters assessed by TTE- mean transmitral pressure gradient and lateral mitral annulus systolic velocity were found to be independent predictors of LAAI. As TEE is an invasive procedure requiring skill and has limited availability, determination of mean transmitral gradient and lateral annulus systolic velocity can help to predict LAAI by a non-invasive modality like TTE. To the best of our knowledge, this is the first study that has analysed and reported about two echocardiographic variables that can predict the presence of LAAI with combined positive predictive value of around 80%.

In our study, LAAI was the only variable found to be an independent predictor of LA/LAA smoke and associated thrombus. Ninety percent patients with LAAI had evidence of LA/LAA smoke (SEC) which is a risk factor for thromboembolism. It has already been shown by Serkan et a,[14] that in patients of severe MS, there is similar degree of impairment of LAA contractility, irrespective of whether the patients are in AF or sinus rhythm. So we feel that just as the presence of AF in patients of MS is considered an indication for initiating oral anticoagulant therapy [OAC],[25] presence of LAAI in patients of severe MS in sinus rhythm should also be considered as an indication for initiating OAC. Therapy with OAC should be continued till LAA afterload imposed by the high transmitral gradient can be significantly reduced by mitral valvuloplasty which have been shown to improve LAA contractility.[24,26]

Limitations of the study

It is a single center study. Undiagnosed intermittent AF could not be ruled out in our patient population.

CONCLUSIONS

There is a high prevalence of LAAI in patients of severe MS in sinus rhythm. Mean transmitral pressure gradient and lateral annular systolic velocity are independent predictors of LAAI. LAAI is also an independent predictor of LA/LAA smoke and associated thrombus.

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Page no- 40-47 | Section- Research Article (Cardiology)

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Page no- 40-47 | Section- Research Article (Cardiology)

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