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Left Atrial Appendage Function in Patients with Left Ventricular Dysfunction and Thrombotic Potential in Nonvalvular Atrial Fibrillation

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Abstract

Background: Left atrial appendage has a significant role in cardiac hemodynamics. In dysfunction this appendage forms as a substrate for thrombus formation leading to potentially destructive embolic problems. *Aim:* To assess the effects of left ventricular diastolic dysfunction on left atrial appendage functions, spontaneous echo contrast and development of thrombus in patients having non-valvular atrial fibrillation. *Materials and Methods:* We carried our study on 80 subjects suffering from chronic nonvalvular atrial fibrilation at Prathima Institute of Medical Education, Karimnagar, Telangana, from January 1, 2015 to December 31, 2017. Patients were divided in two groups: Group D (n=40): subjects with diastolic dysfunction, Group N (n=40): subjects without diastolic dysfunction. Left atrial appendage functions, left atrial spontaneous echo contrast grading and left ventricular diastolic functions were assessed using transoesophageal and transthoracic echocardiograms. *Results:* In Group D, pulmonary vein D level was significantly higher than group N ($p<0.001$) whereas, LAA filling velocity, LAA lateral wall velocity and pulmonary vein S/D levels were significantly lower than Group N ($p<0.001$). *Conclusion:* In patients with left ventricular diastolic dysfunction, left atrial appendage functions was reduced and therefore it may signify a probable risk for formation of thrombus and stroke.

Keywords: Atrial Appendage Function; Atrial Fibrillation; Diastolic Dysfunction; Thrombus Formation.

Introduction

Earlier it was thought that, Left atrial appendage (LAA) was a vestigial structure. Nevertheless, with the introduction of echocardiographic techniques, currently it become clear that it is an actively contracting structure that probably play an significant part in cardiac hemodynamics. More notably, LAA dysfunction acts as a substrate for formation of thrombus that may lead to potentially distressing embolic complications [1,2].

Echocardiography, principally transesophageal echocardiography (TEE), at present is the used in preference for evaluating the LAA. It permits comprehensive description of its anatomy and at the same time also allows a thorough evaluation of its function. The LAA flow velocities by pulsed-wave Doppler can be attained from any of the normal imaging planes on TEE, if the blood flow direction is parallel to the ultrasound beam [3,4].

TEE thus can be used to assess LAA function like finding out the cause of thrombus formation. In patients with Atrial Fibrillation (AF) and sinus rhythm, TEE can reveal various flow patterns and thrombus formation in LAA. Apart from demarcation of thrombus, TEE is also useful in finding of LAA Spontaneous Echo Contrast (SEC), which is a smoke-like swirling pattern observed on two-dimensional imaging and is believed to be due to rouleaux formation resultant from blood stasis. SEC was supposed to be the harbinger of thrombus formation and hence, a predictor of thromboembolic risk. In AF, the flow pattern and amplitude is relatively variable. In most of the cases, saw-tooth waves of differing amplitude and regularity, due to active LAA contraction appear [4,5].

We did this study to appraise the left ventricular diastolic dysfunction effects on LAA functions, SEC and thrombus formation in patients having non-valvular AF.

Materials and Methods

After obtaining institutional ethical committee clearance, an observational study was carried out by retrieving information from medical records of consecutive 80 patients with nonrheumatic, paroxysmals or persistent AF at Prathima Institute of Medical Education, Karimnagar, Telangana, from January 1 2015 and December 31, 2017. Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) was done on all the patients, after obtaining informed consent. The presence of AF was confirmed by ≥1 AF episode recognized with electrocardiography.

Exclusion Criteria

1. Patients with valvular stenosis or previous valve surgery.
2. Patients with pacemaker
3. Patients with other arrhythmia were excluded (e.g. SVT, VT).
4. Patients on anticoagulant drugs
5. Patients whose LV ejection fraction (EF) was below 50%

If multiple transthoracic or transesophageal echocardiographic examinations were carried out, the first study results were chosen. The subjects were considered to have diastolic dysfunction, if in TTE the ratio of mitral early diastolic (E) velocity attained from mitral valve tips with pulsed wave Doppler using apical four-cavity imaging to Ea velocity measured from lateral mitral annulus with tissue Doppler, was over 11 and if in TEE pulmonary systolic/diastolic (S/D) ratio was less than 1, measurements averaged over 5 to 10 cardiac cycles. TEE was used to measure LAA area, and LAA emptying and filling velocities. LAA velocity values were attained by placing pulsed wave Doppler to the orifice of LAA. Grading of the LA and LAA SEC were given based on the scale mentioned below:

A. 0: No echogenity detected.

B. +1 Mild SEC: It cannot be found out without increasing gain. Minimal echogenity determined temporarily during cardiac cycle.

C. +2 Mild-Moderate SEC: A turbulence like form more intensive than +1, but location is the same as +1. It can be found out without increasing gain.

D. +3 Moderate SEC: Intensive turbulance like movement arise all through the cardiac cycle. It is less intense in LA than LAA.

E. +4 Severe SEC: In LAA and LA cavity, intensive echo density and very slow turbulent flow is seen.

Statistical Analysis

Statistical Package for Social Science (SPSS) for Windows 19 was used for analyzing the data. Descriptive statistics were shown as mean and standard deviation for continuous variables (assessed by Mann-Whitney U test or Student's t test) and as the number of cases and percentages for categorical variables (Pearson's chi-square or Fisher's exact test). The significance of the linear correlation among the degree of SEC and clinical measurements was estimated by Spearman's Correlation analysis. A P value of <0.05 was deemed as statistically significant.

Results

A. Baseline characteristics

Both the groups D and N were matched in relation to baseline characteristics like age, body mass index (BMI), hypertension, diabetes, coronary artery disease, hyperlipidemia, cerebrovascular event history and CHADS2 score (Table 1) and the difference was insignificant (P> 0.05).

Table 1: Baseline Characteristics.

Variables	Group N (n=40)	Group D (n=40)	P value
Age, year	62.6±11.8	66.9±9.6	0.0777
Body mass index, kg/m2	26.8±4.2	27.4±3.8	0.5048
Hypertension, n, %	23 (50%)	24 (60%)	0.3717
Diabetes, n, %	5 (7.5%)	6 (10%)	0.6942
CAD, n, %	7 (15%)	6 (15%)	1.000
Hyperlipidemia, n, %	3 (5%)	4 (10%)	0.3989
CVE, n, %	2 (2.5%)	0	0.3173
CHADS2 score	1.6±0.9	1.6±1.1	0.9646

*Mann-Whitney U test, Student t-test

CAD - coronary artery disease; CVE - cerebrovascular event; Group D - patients with diastolic dysfunction; Group N - patients without diastolic dysfunction

B. Correlation between TEE parameters and SEC, Thrombus

On the other hand, in Group D, pulmonary vein D level was significantly higher than group N

(p<0.001) while, LAA filling velocity, LAA lateral wall velocity and pulmonary vein S/D levels were significantly lower than Group N (p<0.001) (Table 2).

Table 2: Correlation between TEE parameters and SEC, Thrombus.

Variables	Group N (n=40)	Group D (n=40)	P value
LA size, cm2	4.54±0.85	4.62±0.61	0.6300
LVED diameter, cm	4.79±0.64	4.68±0.53	0.4050
LVES diameter, cm	3.18±0.59	2.93±0.62	0.0685
EF, %	59.87±7.02	64.62±7.34	0,0041*
RA maximum size, cm2	5.51±1.01	5.63±0.92	0.5801
LAA, cm2	3.61±1.53	3.76±1.41	0.6497
LAA emptying velocity, cm/s	0.31±0.12	0.24±0.14	0.7004
LAA filling velocity, cm/s	0.38±0.11	0.22±0.14	<0.001*
LAA lateral wall velocity, cm/s	9.09±3.87	6.05±3.03	<0.001*
Pulmonary vein S wave, cm/s	0.54±0.21	0.35±0.11	<0.001*
Pulmonary vein D wave, cm/s	0.42±0.15	0.55±0.2	<0.001*
Pulmonary vein S/D	1.49±0.53	0.80±0.53	<0.001*
Mitral E velocity, cm/s	0.93±0.15	1.12±0.15	<0.001*
Mitral Ea, m/s	0.14±0.11	0.69±0.03	<0.001*
Mitral E/Ea	7.02±1.49	13.53±4.02	<0.001*

*Pearson's chi-square, Fisher's exact test

D - diastolic; E - pulsed Doppler E velocity; Ea - tissue Doppler E velocity; EF - ejection fraction; Group D - patients with diastolic dysfunction; Group N - patients without diastolic dysfunction; LA - left atrium; LAA - left atrium appendix; LVED - left ventricle end-diastolic; LVES - left ventricle end-systolic; RA - right atrium; S - systolic

Thrombus in group D was higher than group N (p=0.003) (Table 3).

Table 3: Distribution of cases according to SEC level in left atrium and frequency of thrombus.

Variables	Group N (n=40)	Group D (n=40)	P value
Absent	31 (77.5%)	3 (7.5%)	<0.0001*
Grade 1	2 (5%)	9 (22.5%)	0.0239
Grade 2	3 (7.5%)	12 (30%)	0.0104
Grade 3	2 (5%)	4 (10%)	0.3989
Grade 4	2 (5%)	4 (10%)	0.3989
Thrombus in left atrium	0	8 (20%)	0.003*

*Student -t test, Mann-Whitney U testi

Group D - patients with diastolic dysfunction; Group N - patients without diastolic dysfunction; NS - not significant

We did not notice any significant association between SEC in left atrium and age, BMI, left and right atrium size, LAA area (p > 0.05). Nevertheless, negative correlation was observed between SEC in LA and respectively, LAA emptying, filling, pulmonary vein S/D levels and lateral wall velocities (r=-0.438, r=-0.328, r=-0.233, r=-0.447 respectively) (Table 4).

Table 4: Variables of left atrium and SEC grading.

Variables of Left atrium	SEC grading	
	R	P
Age	0.224	0.02
Body mass index	0.072	0.54
LA Size	0.218	0.096
RA maximum size	0.063	0.663
LAA	0.021	0.863
LAA emptying velocity	-0.429	<0.001
LAA filling velocity	-0.321	0.015
LAA lateral wall velocity	-0.462	<0.001
Pulmonary vein S	-0.252	0.068
Pulmonary vein D	-0.191	0.172
Pulmonary vein S/D	-0.228	0.081

*Spearman's correlation analysis

D - diastolic; E - pulsed Doppler E velocity; Ea - tissue Doppler E velocity; LA - left atrium; LAA - left atrium appendix; LVED - left ventricle end-diastolic; LVES - left ventricle end-systolic; RA - right atrium; S - systolic

In LA, we did not observed any significant difference between grade 1 SEC group and grade 2-3-4 SEC groups in relation to mean age, MI, hypertension, heart failure, LA size, maximum size of right atrium (p>0.05). Whereas there was significant difference between groups with regard to LAA emptying, filling and lateral wall velocity, which was significantly lower in SEC 2-3-4 group than SEC 1 groups respectively (Table 5).

Table 5: Echocardiographic measurements in SEC 1 and SEC 2-3-4 groups.

Variables	Group SEC 1	Group SEC 2-3-4	P value
LAA emptying velocity, cm/s	0.36±0.15	0.24±0.14	0.0004*
LAA filling velocity, cm/s	0.39±0.17	0.18±0.12	<0.001*
LAA lateral wall velocity, cm/s	8.7±2.91	5.7±2.84	<0.001*
Pulmonary vein S/D	1.4±0.39	0.84±0.31	<0.001*

*Student t-test, Mann-Whitney U test

D - diastolic; LAA - left atrium appendix; S - systolic

Discussion

Atrial fibrillation (AF) is a chronic arrhythmia seen most often in clinical practice and presents a 5-fold risk of stroke. Impairment in left ventricular (LV) systolic functions results in increased LV and left atrium (LA) filling pressures besides loss of function in LAA (LAA), blood stasis and therefore to SEC and thrombus formation. Similarly, in individuals with disturbed diastolic function, increased LV end-

diastolic pressure and LA pressure leads to a reduction in filling and emptying velocities of LAA. Therefore as blood stasis and SEC formation will be increased LAA, thereby facilitating the formation of thrombus. Hence assessment of LAA function by TEE is suggested in patients with diastolic dysfunction [6-8].

In our study we observed decreased LAA velocities in patients with diastolic dysfunction, thus acting as a marker for LAA SEC formation by TEE. Our findings are similar to Demirçelik et al (2014) [9].

Few authors believe that the main source of cardioembolic ischemic stroke happening in AF patients is the thrombus formation in LAA. This was shown by serial TEE investigation in LA and in LAA during conversion of AF to sinus rhythm, where slowing of conduction velocity of LAA is seen as a result of the organised mechanic contraction loss during AF [10,11].

Studies have shown that in AF, there is a reduction of flow in LA and LAA which is related with SEC, formation of thrombus and embolic events [12,13].

Particularly under low flow situations, TTE or TEE imaging might identify SEC or smoke in the form of turbulent pus at altering intensity. SEC can be a sign of stasis related to AF [14,15].

In patients with non-valvular AF and LV systolic dysfunction, LAA velocity was found to be lower. But still the impact of LV diastolic dysfunction on LAA velocity and diastolic dysfunction as a possible risk factor for stroke has not been scientifically recognized. In order to determine the functioning of LAA, the values of LAA velocity and LAA EF are considered as major determinants. But in AF patients, LAA EF measurements is not likely as there is no contraction in LAA [2].

We found that LAA filling and emptying velocities were significantly lower in LV diastolic dysfunction group than those who do not have it. Lateral wall velocity of LAA was also low in the patient group with diastolic dysfunction. Our findings are similar to Demirçelik et al (2014) [9]. We suggest that measuring LAA lateral wall velocity by TEE will be useful in indicating the functions of LAA.

LAA emptying velocity increases in the beginning stages of heart failure, so as to maintain LA hemodynamic function. However if there is a progression in failure, there will be an impairment in LAA emptying velocity as a result of the drop in LAA compliance. Reduced LAA function increases the incidence of LA thrombus formation and is an significant forecaster of cardiac mortality. In patients with LV systolic dysfunction, augmented pulmonary capillary wedge pressure (PCWP) reduces LAA flow velocity. Increased diastolic filling pressure is related with a higher rate of LAA thrombus in AF, partially through blood stasis or impaired LAA function.[16, 17]

Kamp et al found that LAA peak emptying velocity of less than 20 cm/sec as an independent predictor for thromboembolic event in nonvalvular AF cases [18].

Ozer et al reported that in patients with stroke, LAA flow velocities were lesser than normal in both patients with AF and sinus rhythm. We also found LAA peak emptying velocity to be lower in patients with diastolic dysfunction, and also, in patients with high grade SEC [19]. Likewise Ito et al on found lower LAA flow velocity in patients with stage 3 diastolic dysfunction than stage 2 diastolic dysfunction [20]. We suggest that diastolic dysfunction may act as a risk predictor for SEC and stroke in patients with nonvalvular AF and preserved LV ejection fraction.

Limitations of Study

1. Lower sample size
2. Lack of homogeneity in the SEC's groups.

Conclusion

In patients with nonvalvular AF, LAA functions decrease and SEC grading increases with preserved LVEF and diastolic dysfunction. Reduced LAA flow velocities can be helpful in predicting embolic complications in these patients. Thus, diastolic dysfunction has a role in identification of subgroups having risk for embolic events in a disease that can influence public health significantly such as AF. We believe that assessment of diastolic dysfunction in patients with nonvalvular AF will reveal the approach to anticoagulants in clinical practice. In contrast to earlier thought, LAA is now considered to play a vital role in normal cardiac hemodynamics.

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