

Original Research Article

Altered left atrial appendage function associated with cardioembolic stroke in patients with rheumatic heart disease

Zeeshan H. Mansuri¹, Jit H. Brahmbhatt^{1*}, Roopesh R. Singhal¹, Karthik Natarajan²

¹Department of Cardiology, SBKSMIRC, Waghodia, Vadodara, Gujarat, India

²Department of Cardiology, UNMICRC, BJMC, Ahmedabad, Gujarat, India

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*Correspondence:

Dr. Jit H. Brahmbhatt,

E-mail: jit.brahmbhatt1@gmail.com

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ABSTRACT

Background: Left atrial appendage (LAA) is usually the first site for thrombus formation in rheumatic heart disease (RHD). LAA function is altered in RHD which may predispose it to thrombus formation. The aim of this study was to determine an association between function of LAA and cardioembolic stroke.

Methods: Total 132 patients with RHD were studied by means of transthoracic echocardiography and/or transesophageal echocardiography and left atrial (LA) size, LAA ejection fraction (EF) and peak flow velocities were measured. These patients were followed up for 18 months with reference to development of cardioembolic stroke.

Results: Seventy nine patients had atrial fibrillation (AF), of which 34 had thrombus in LAA. Out of 53 patients with sinus rhythm, 5 had LAA thrombus. Mean LAA EF was significantly lower in patients with thrombus in LAA, so was the peak flow velocity (both variables $p < 0.0001$). Saw tooth LAA outflow velocity pattern was visible in 30 (80%) patients with LAA thrombus versus 20 (28%) patients without LAA thrombus. Total 14 patients experienced cardioembolic stroke. Patients with cardioembolic stroke had lower mean LAA EF and peak flow velocity as compared to patients without cardioembolic stroke.

Conclusions: Increased LAA size, reduced LAA EF and reduced peak flow velocity are associated with increased risk of cardioembolic stroke. LAA evaluation should be mandatory in deciding treatment strategies in patients with RHD and AF.

Keywords: Left atrial appendage, Cardioembolic stroke, Atrial fibrillation, Rheumatic heart disease

INTRODUCTION

Atrial systole plays an important role in ventricular filling by means of pushing extra blood into ventricles at the end of diastole. Mechanical activity of LAA is considered an important factor in atrial systole as well as in A type natriuretic peptide production, which stabilizes blood volume and pressure in the LA and may indirectly affect cardiac output.¹ LAA may harbour blood clots or thrombus in patients with AF.²⁻⁴ LAA flow velocity has been studied

to assess the propensity for thrombus formation.⁵ LAA is also an important structure in cardiac hemodynamics. Assessment of LAA structure and function should be routinely done in making therapeutic decisions.⁶

AF is an independent risk factor for stroke and peripheral emboli, contributing close to 40% of overall neurologic events.¹ LAA is a common site of thrombus formation in atrial fibrillation. Anticoagulation in AF patients is complex and needs a lot of supervision.⁷ Structural and

functional assessment of LAA is useful in risk prediction and prognostication.⁶

Echocardiography, particularly transesophageal echocardiography (TEE), is the modality of choice for evaluation of LAA. It is safe, inexpensive and allows detailed study of the LAA anatomy and function.⁶

The objective of this study was to determine an association between LAA structure and function with respect to LAA thrombus formation and development of cardioembolic stroke.

METHODS

This was a prospective, observational, single-center study, carried out in the department of cardiology of at Smt. B. K. Shah medical institute and research center in Gujarat, India from April 2018 to April 2020. A total of 132 patients with RHD were included. Patients with comorbidities, history of hypercoagulability and with genetic risk factors for stroke were excluded.

Institutional ethics committee approval was taken prior to beginning of the stud. This study was performed in compliance with the world medical association declaration of Helsinki. The clinical and demographic data of the patients were recorded. Patients underwent clinical examination, laboratory investigations, electrocardiography (ECG), two-dimensional (2D) transthoracic echocardiography (TTE) and 2D and three-dimensional TEE. The principal investigations included hemoglobin, serum creatinine, prothrombin time with INR and random blood sugar.

Patients were evaluated with 2D ECG and LA, left ventricular (LV) end-systolic and LV end-diastolic dimensions and EF were stressed upon. The LAA appendage was assessed in detail and looked for the presence of spontaneous echocardiographic contrast (SEC) or thrombus. LAA function was assessed by peak flow velocity, pattern of waveforms and the presence of SEC or thrombus. Patients were evaluated on an outpatient as well as an inpatient basis. All patients were followed up for 18 months for the development of cardioembolic stroke. All patients received guideline directed medical therapy during the period of follow up.

LAA EF was measured by measuring LAA maximum and minimum diameters.

$$\text{LAA EF} = \frac{\text{LAA}_{\text{max}} - \text{LAA}_{\text{min}}}{\text{LAA}_{\text{max}}}$$

Peak Doppler flow velocity was recorded with TDI.

The statistical analysis was done with the help of IBM SPSS software version 20.0 (Chicago, IL, USA).

Quantitative data expressed as mean±standard deviation and qualitative data were expressed in terms of number and percentage. Multivariate logistic regression analysis was performed to find out the correlation between rhythm types and presence of thrombus. Differences with $p < 0.05$ were found to be significant statistically.

RESULTS

Demographics, type of stroke (confirmed by imaging evidence), rhythm (sinus rhythm or AF), TTE findings and TEE findings were used for the analysis. There were 56 (42.42%) male and 76 (57.57%) female patients and the mean age was 46.47 ± 10.55 years. A total of 53 (40%) patients were in sinus rhythm of which five patients had LAA thrombus. In 79 (60%) patients with AF, 34 (53.4%) patients had LAA thrombus. In patients with AF, LAA_{max} was measured independent of the ECG. Fourteen patients went on to have cardioembolic stroke during the follow up period despite being on optimal medical treatment (Table 1).

Mean LAA EF of 42.89 ± 11.90 was seen in patients without LAA thrombus. Mean LAA EF of 23.63 ± 8.09 was found in patients having LAA thrombus which showed a strong correlation between thrombus and LAA EF ($p < 0.0001$). LAA size in patients without thrombus was average 42.30 ± 15.01 mm which was significantly lower than that seen in patients with LAA thrombus (67.92 ± 12.08 mm, $p = 0.002$). The mean peak flow velocity in sinus rhythm and AF patients was 39.23 ± 8.69 and 15.21 ± 2.09 cm/s, respectively. Peak flow velocity and AF had significant correlation ($p < 0.0001$). Peak flow velocity (15.32 ± 4.47 m/s) in patients with LAA thrombus was less than that in patients without LAA thrombus (28.74 ± 15.9 m/s). Sawtooth peak flow wave pattern was seen in 30 of 39 (80%) patients with LAA thrombus versus 20 of 93 (28.1%) patients without LAA thrombus ($p < 0.0001$) (Table 2).

Patients without cardioembolic stroke had mean LAA EF of 45.41 ± 12.10 . Patients with cardioembolic stroke had a mean LAA EF of 25.07 ± 11.09 and there was statistically significant association between cardioembolic stroke and LAA EF ($p < 0.0001$). LAA_{peak} flow velocity (17.89 ± 2.58 m/s) in patients with cardioembolic stroke was less than that in patients without cardioembolic stroke (35.32 ± 3.44 m/s) (Table 3).

Subgroup variables were studied by means of binary logistic regression. LA_{size}=0.03 (95% confidence interval CI: 0.94-0.99; $p = 0.005$) and LAA EF=0.18 (95% CI: 0.74-0.94; $p = 0.002$) were found to inversely correlate to rhythm types so that higher LA size and lower LAA EF were seen in atrial fibrillation. Higher LA dimension was the strongest predictor of thrombus (0.18; 95% CI: 1.05-1.36; $p = 0.009$).

Table 1: Nascent variables of patients in sinus rhythm versus AF.

| Variables | Sinus rhythm (N=53) | Atrial fibrillation (N=79) | P value |
|---------------------|---------------------|----------------------------|---------|
| Mean age (in years) | 46.01±12.78 | 46.98±11.90 | 0.56 |
| Men | 25 (44.64) | 31 (55.36) | 0.24 |
| Women | 28 (36.84) | 48 (63.16) | 0.09 |
| LA size | 43.94±15.02 | 52.98±15.45 | 0.006 |
| LAA EF | 49.56±10.94 | 31.62±11.05 | 0.004 |
| Peak flow velocity | 39.23±8.69 | 15.21±2.09 | <0.0001 |
| Thrombus | 5 (10.02) | 34 (53.41) | 0.001 |
| Raised echogenicity | 21 (39.02) | 53 (67.08) | 0.001 |

Table 2: Nascent variables of patients with versus without LAA thrombus.

| Variables | No thrombus (N=93) | Thrombus (N=39) | P value |
|---------------------|--------------------|-----------------|---------|
| Mean age (in years) | 50.61±13.89 | 43.27±15.92 | 0.16 |
| Men | 43 (76.79) | 13 (23.21) | 0.07 |
| Women | 50 (65.8) | 26 (34.2) | 0.06 |
| LA size | 42.30±15.01 | 67.92±12.08 | 0.002 |
| LAA EF | 42.89±11.90 | 23.63±8.04 | <0.0001 |
| Peak flow velocity | 28.74±15.9 | 15.32±4.47 | 0.002 |

Table 3: Comparison of variables of patients who had cardioembolic stroke versus no stroke.

| Variables | Stroke (N=14) | No stroke (N=118) | P value |
|---------------------|---------------|-------------------|---------|
| Mean age (in years) | 50.34±9.34 | 43.27±10.48 | 0.31 |
| Men | 5 (8.93) | 51 (91.07) | 0.49 |
| Women | 9 (11.84) | 67 (88.16) | 0.15 |
| LA size | 58.38±15.22 | 42.93±14.32 | 0.008 |
| LAA EF | 25.07±11.09 | 45.41±12.18 | <0.0001 |
| Peak flow velocity | 17.89±2.58 | 35.32±3.44 | <0.0001 |
| Thrombus | 12 (85.45) | 28 (26.16) | 0.0001 |
| Raised echogenicity | 14 (100) | 37 (34.57) | 0.004 |

DISCUSSION

Objective of this study was to establish an association between LAA function, LAA thrombus formation and its impact on development of cardioembolic stroke.⁸⁻¹¹

AF was present in 60% patients, whereas in the study by Kurzawski et al it was seen in 68%.¹² AF can contribute to LAA dysfunction. Patients with AF showed saw tooth pattern, lower emptying velocities and increased presence of SEC. Tamura et al marked a first in the history to study the peak flow velocity. Peak flow velocity was studied on TTE using TDI. LAA WV <8.7 cm/s was found to be a predictor of stroke in patients with AF.^{13,14}

The study by Kurzawski et al had male preponderance (61.25% of males and 38.75% of females), whereas Omran et al reported 58% of males and 42% of females.¹² In our study, 42.42% were male and 57.58% were female. The predominant lesion in our study was mitral stenosis (106, 88.3%).¹⁵ Similar predominant lesion was present in studies by Uretsky et al and Gölbaşı et al.^{16,17}

The mean LA size in patients with AF was higher than in patients with sinus rhythm ($p=0.002$), which was similar to other studies in which mean LA area was increased. The mean LA area in the study by Kurzawski et al was 32 cm², whereas in the study by Uretsky et al the mean LA area was 41 cm².^{12,16}

LAA peak flow velocity was another echocardiographic parameter in the assessment of LAA function. It was recorded even in patients with AF, but it was very low. Biase et al demonstrated that LAA morphology may precipitate thrombus formation.¹⁸

LAA peak flow velocity in patients with AF was several times (15.21±2.09) lower than that in patients with sinus rhythm (39.23±8.69). Kurzawski et al showed an average velocity of 15±1.8 cm/s in their study. SEC was present in 27 (58%) patients in their study.¹²

We reported that 29.54% (N=39) patients had LAA thrombus and 56% (N=74) had SEC. Both these were significant independent predictors of results ($p=0.02$). Presence of SEC was found higher in patients with LAA

thrombus as compared to patients without thrombus ($p=0.02$) which made the presence of SEC as a predictor of thrombus formation in LAA. In a study by Fatkin et al there were 61% of patients with SEC and 15% with thrombus. Kurzawski et al showed the presence of SEC or thrombus in 75% of patients. In their study, Black et al reported left atrial thrombus in 59% of patients.^{12,19}

Successful BMV causes improvement in the appendage function within 24-72 hours and may also led to resolution of the stroke risk. A study published by Reddy et al reported the effect of BMV on LAA function in patients with symptomatic mitral stenosis in sinus rhythm.²⁰

In our study 14 patients developed cardioembolic stroke during the follow up period. All these patients were on oral anticoagulant therapy with their prothrombin time within target range. All patients with cardioembolic stroke had LAA SEC on baseline evaluation. Twelve out of fourteen had LAA thrombus on baseline evaluation. Patients who developed cardioembolic stroke had lower LAA EF and LAA peak flow velocity as compared to patients without cardioembolic stroke. Patients with stroke had higher LAA size as compared with patients without stroke. LAA peak flow velocity and LAA EF were strongly associated with development of cardioembolic stroke.

Limitations

This was a prospective observational study done at a single centre hence very small number of participants. Large scale studies were required to include a greater number of participants before we can generalize the results to whole population.

CONCLUSION

We conclude that LAA enlargement, LAA dilatation, reduced LAA EF and reduced LAA peak flow velocity are all associated with LAA thrombus formation and development of cardioembolic stroke. LAA size, LAA EF and LAA peak flow velocity are more often neglected at the time of cardiovascular imaging, however these tools can help identify patients at high risk of developing thrombus and cardioembolic stroke. Hence this study highlights the need of monitoring LAA structure and function while deciding anticoagulation strategy in patients with RHD to predict and prevent cardioembolic stroke.

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