

Prevalence of Interatrial Block in Mitral Stenosis and Its Association With Systemic Embolism in Patients With Sinus Rhythm: A Cross-Sectional Study

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Abstract

Objectives: To investigate the prevalence of interatrial block (IAB) among mitral stenosis (MS) patients and its association with the development of systemic embolism.

Setting: Tabriz, Iran.

Participants: This cross-sectional observational study was conducted on 159 patients with (n=18) or without (n=141) systemic thromboembolism.

Outcome Measures: Prevalence of systemic thromboembolism, partial/advanced IAB, and P-wave dispersion.

Results: IAB was detected in 99 patients (62.26%), of whom 16.35% had advanced block, and 45.91% had partial block. The mitral valve area was comparable between the groups ($P=0.639$). The multivariate regression analysis demonstrated that the appearance of IAB in the electrocardiogram was independently associated with the occurrence of systemic thromboembolism in patients with MS. In addition, the appearance of advanced IAB in patients increased the odds of systemic thromboembolism about 5-fold compared with those without IAB (OR: 5.21; 95% CI: 1.23–22.07) and more than 3-fold higher compared to those with partial IAB (OR: 3.73; 95% CI: 1.04–13.37).

Conclusions: It was revealed that advanced IAB in patients with MS and sinus rhythm is an independent risk factor for systemic thromboembolic events. Therefore, future studies can evaluate the feasibility and efficiency of preventing thromboembolic treatment to reduce mortality and morbidity in these patients.

Keywords: Heart block, Atrial fibrillation, Mitral stenosis, Thromboembolism

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Introduction

Although the prevalence of rheumatic mitral stenosis (MS) has declined among developed countries, it is one of the main concerns of healthcare systems in developing countries. Furthermore, calcific MS, largely resulting from mitral annulus calcification, has become increasingly prevalent in both developing and developed countries.¹ Medical interventions for increasing valve areas in these patients (e.g., surgery) can decrease mortality.² However, systemic thromboembolism remains one of the severe complications in MS patients, particularly in those with atrial fibrillation (AF).³ The optimal anticoagulation strategy for systemic thromboembolism prevention in MS patients is yet to be determined. Thus, the investigation for elaborating on the risk factors of systemic thromboembolism is a topic of interest in recent research.³

MS brings about morphological and atrial functional changes, predisposing affected patients to a higher risk of systemic thromboembolism. It causes the enlargement of the left atrium following volume overload and constant pressure, resulting in a high prevalence of AF.^{4,5} AF can be a major risk factor for thromboembolic events, such as stroke; hence, the prediction/early detection of AF in susceptible individuals is of prominent importance.⁶

Bachmann et al described a phenomenon called interatrial conduction delay, which can lead to AF.⁷ The interatrial block (IAB) is defined as the delay or blockage of the impulse between the right and left atrium, which is mainly through the Bachmann bundle. In this condition, the duration of the P wave increases to more than 120 ms.⁸ The IAB can be partial (P-IAB) or advanced (A-IAB) depending on the severity and degree of conduction



delay in the Bachmann bundle.⁹ IAB can cause structural changes in the left atrium that predispose the patient to thromboembolism.¹⁰ Some studies have shown that the prevalence of IAB in patients with embolic events is more than 80%, which is extremely higher than in the general population.^{11,12} The link between A-IAB and AF was described in 1988 when the disorder was later referred to as Bayes' syndrome.¹³ Moreover, cases of transient ischemic attack and stroke have been reported in cohort studies in patients with A-IAB with or without AF.¹⁴⁻¹⁷

Whether the development of IAB can also increase the risk of systemic thromboembolism in MS patients, even in the absence of AF rhythm, is yet to be determined. Therefore, this study aims to investigate the prevalence of IAB in patients with MS having sinus rhythm in their electrocardiogram (ECG) and its association with systemic thromboembolism.

Methods

Study Design

All patients with MS and sinus rhythm who met the inclusion criteria were included in this cross-sectional study. The study protocol was approved by the Institutional Review Board and the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1395.725).

Study Population and Inclusion Criteria

Patients were consecutively included from all patients admitted with a definite diagnosis of MS or systemic thromboembolism for the first time (e.g., stroke, myocardial infarction, or limb embolism or other vascular events) due to MS from several tertiary care teaching hospitals covering almost all referred patients in an area of northwest Iran (over four million inhabitants), including Imam Reza, Shahid Madani, and Razi Hospitals affiliated to Tabriz University of Medical Sciences, Iran, from April 2017 to March 2021. The inclusion criteria were an established diagnosis of MS confirmed by two attending cardiologists, MVA less than 2 cm², and sinus rhythm on admission ECG. However, patients with a history of previous cerebrovascular events, non-ischemic (hemorrhagic) stroke or non-embolic ischemic events, peripheral vascular diseases, abnormal heart rhythms, including AF, atrial flutter, and atrial pacemaker, myocardial infarction, or heart failure were excluded from the study.

Then, the included patients were categorized into two groups: (1) MS with sinus rhythm and without acute systemic or cerebral thromboembolism and (2) MS with sinus rhythm and with acute systemic or cerebral embolism.

Electrocardiogram: Twelve-lead electrocardiography was conducted using a mitral annulus calcification 500 ECG machine (GE Medical System, USA) with a paper speed of 25 mm/s and standard voltage. Moreover, ECG analyses were performed by two attending cardiologists who were blinded to the patients' clinical history, using

digital calipers on a 12-lead ECG and magnified to 200% of normal size. Additionally, the discrepancies between them were resolved by consultation with the third cardiologist in order to mitigate intra-observer variability.

Based on P-wave duration, patients were divided into three groups, which were defined as follows:

1. Advanced Interatrial Block: P-wave length of 120 ms or more and biphasic P-wave form in inferior leads (II, III, avf) [- / +]
2. Partial Interatrial Block: P wavelength of 120 ms or more and bimodal (notched) P waveform in inferior leads
3. Lack of IAB

P wave dispersion was defined as the difference between the widest and the narrowest P-wave duration recorded from the 12 ECG leads.

Echocardiography Findings

Different echocardiographic parameters were recorded for all patients in a pre-prepared checklist, including left ventricular ejection fraction (LVEF), patent foramen ovale, left atrial appendage (LAA), outflow velocity index, left atrial volume (LAV), MVA, left atrial spontaneous echo contrast, and pulmonary arterial systolic pressure. The other related parameters were left atrial enlargement (LAE; defined as left atrial diameter [LAD] \geq 4.1 cm in men or \geq 3.9 cm in women), mean mitral valve gradient (MG), maximum mitral gradient (mxGra), Wilkins score, aortic stenosis, and mitral valve calcification.

The echocardiography of the patients was performed by experienced board-certified attending cardiologists using the VIVID 7 cardiac ultrasound system (GE Healthcare, Horten, Norway). In addition, Doppler studies were conducted using 2.5-MHz to 3.5-MHz transducers. Furthermore, chamber dimensions and MVA by planimetry were measured according to standard techniques.¹⁸ Moreover, LVEF was calculated by the area-length method using combined orthogonal apical four-chamber and two-chamber views. Additionally, other echocardiographic assessments were performed according to standard techniques.¹⁸

Other Evaluations

The clinical files of all patients were reviewed, and demographic data were embedded in a pre-prepared checklist, including age, gender, and medical history, including hypertension, diabetes mellitus, coronary artery disease, percutaneous transvenous mitral commissurotomy, stenosis, percutaneous coronary intervention, and coronary artery bypass grafting. In addition, other demographic data were chronic obstructive pulmonary disease, heart failure, hypothyroidism and hyperthyroidism, hypercholesterolemia, hypertriglyceridemia, and chronic renal failure, as well as a history of smoking, medication history, heart rate, and systolic blood pressure.

Statistical Analysis

Data were analyzed using SPSS software, version 20. All the statistical analyses were performed using R software 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Mean ± standard deviation (SD), as well as frequencies and percentages, were reported for non-categorical and categorical data, respectively. In addition, the Shapiro–Wilk test was used to test for normal distribution of data. Moreover, an independent t-test or Mann-Whitney U test was utilized for continuous variables with normally or non-normally distributed data, respectively. Further, the chi-square test or Fisher’s exact test was employed for categorical data. Furthermore, univariate and multivariable regression analyses were applied to assess the association between IAB or P wave dispersion and the occurrence of systemic thromboembolism. LAD and LAV were compared within three subgroups of IAB using a two-way analysis of variance and post hoc Tukey’s test. Statistical significance level was considered at a P-value of less than 0.05. The sample size was estimated according to the study by Acartürk et al.¹⁹

The Wilkins scoring system was evaluated by using echocardiography, leaflet thickening, mobility, calcification, and subvalvular involvement on a scale of 0–4

Results

Overall, 159 patients were investigated, including 18 cases

with systemic thromboembolism (11.3%) and 141 cases without systemic thromboembolism (88.7%). IAB was detected in 99 patients (62.26%) among all included MS patients. Based on the results, 16.35% and 45.91% had A-IAB and P-IAB, respectively.

The mean age was significantly higher in patients with systemic thromboembolism than in those without systemic thromboembolism (51.89 ± 11.94 vs. 42.46 ± 12.63 years, respectively; P=0.005). Moreover, the heart rate was higher in patients with systemic thromboembolism than in those without systemic thromboembolism (79.56 ± 18.58 vs. 81.94 ± 8.43 per min, respectively; P=0.049). Nevertheless, the two groups of patients with and without systemic thromboembolism demonstrated no significant differences in terms of gender, LVEF, medical history, drug history, systolic blood pressure, or smoking (Table 1).

The Wilkins score was calculated to be 9.2 (± 2.24) in those with systemic thromboembolism, which was significantly higher than that in patients without systemic thromboembolism (8.47 ± 1.36; P=0.003; Table 2). The MVA was comparable between the groups (P=0.639). However, the MR grade displayed no significant difference between the two groups (P=0.664).

P wave dispersion was higher in those with systemic thromboembolism in comparison with those without systemic thromboembolism, but the difference was not

Table 1. Baseline Characteristics of Included Patients With Mitral Stenosis

| | | All Patients | MS With Systemic Embolism (n=18) | MS Without Systemic Embolism (n=141) | P-Value |
|------------------------|-------------------|---------------|----------------------------------|--------------------------------------|---------|
| Gender, n (%) | Female | 126 (79.25) | 14 (77.78) | 112 (79.43) | 1.000 |
| | Male | 33 (20.75) | 4 (22.22) | 29 (20.57) | |
| Age, mean (SD) | | 43.53 (12.87) | 51.89 (11.94) | 42.46 (12.63) | 0.005 |
| NYHA class, mean (SD) | | 1.94 (0.94) | 1.22 (1.17) | 2.04 (0.87) | 0.004 |
| Medical history, n (%) | PTMC | 8 (5.03) | 1 (5.56) | 7 (4.96) | 1.000 |
| | Stenosis | 7 (4.4) | NA | 7 (4.96) | 0.721 |
| | PCI/CABG | 3 (1.89) | NA | 3 (2.13) | 1.000 |
| | HTN | 37 (23.27) | 7 (38.89) | 30 (21.28) | 0.171 |
| | DM | 11 (6.92) | 2 (11.11) | 9 (6.38) | 0.802 |
| | High cholesterol | 7 (4.4) | 1 (5.56) | 6 (4.26) | 1.000 |
| | High triglyceride | 7 (4.4) | 1 (5.56) | 6 (4.26) | 1.000 |
| | COPD | 1 (0.63) | NA | 1 (0.71) | 1.000 |
| | Hypothyroidism | 4 (2.52) | NA | 4 (2.84) | 1.000 |
| | CRF | 1 (0.63) | 1 (5.56) | NA | 0.221 |
| Smoking, n (%) | | 7 (4.4) | 1 (5.56) | 7 (4.96) | 0.721 |
| HR, mean (SD) | | 79.56 (18.58) | 81.94 (8.43) | 79.26 (19.49) | 0.049 |
| SBP, mean (SD) | | 127.3 (15.28) | 128 (15.06) | 127.2 (15.36) | 0.407 |
| Medication history | B-blocker | 103 (64.78) | 14 (77.78) | 89 (63.12) | 0.335 |
| | CCB | 17 (10.69) | 4 (22.22) | 13 (9.22) | 0.202 |
| | Anti-platelet | 57 (35.85) | 5 (27.78) | 52 (36.88) | 0.619 |
| | Diuretic | 37 (23.27) | 2 (11.11) | 35 (24.82) | 0.311 |

Note. SD: Standard deviation; HR: Heart rate; SBP: Systolic blood pressure; PTMC: Percutaneous trans-mitral commissurotomy; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft surgery; HTN: Hypertension; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease; GFR: Glomerular filtration rate; CCB: Calcium channel blocker; CKD, Chronic renal failure; MS: Mitral stenosis; NYHA: The New York Heart Association.

Table 2. Echocardiography and Electrocardiography Findings of Included Patients With Mitral Stenosis

| | All Patients | MS With Systemic Embolism (n = 18) | MS Without Systemic Embolism (n = 141) | P-Value | |
|---------------------------|-------------------------------|---------------------------------------|---|---------------|-------|
| Echocardiography findings | LVEF, mean (SD) | 53.57 (4.05) | 54.44 (2.91) | 53.45 (4.16) | 0.419 |
| | PFO, n (%) | 3 (1.89) | NA | 3 (2.13) | 1.000 |
| | LAA velocity index, mean (SD) | 29.57 (13.28) | 34.62 (16.73) | 28.92 (12.78) | 0.477 |
| | LAE | 107 (67.3) | 7 (38.89) | 100 (70.92) | 0.104 |
| | LAV, mean (SD) | 75.79 (24.44) | 69.09 (30.25) | 76.53 (23.79) | 0.550 |
| | MVA, mean (SD) | 1.01 (0.3) | 1.03 (0.4) | 1 (0.28) | 0.639 |
| | MG, mean (SD) | 10.22 (4.67) | 10.54 (4.45) | 10.19 (4.72) | 0.705 |
| | mxGra, mean (SD) | 20.07 (7.55) | 20 (6.82) | 20.08 (7.67) | 0.821 |
| | PASP, mean (SD) | 42.28 (17.53) | 43.5 (15.57) | 42.14 (17.78) | 0.564 |
| | MR grade, n (%): Mild | 62 (38.99) | 6 (33.33) | 56 (39.72) | 0.664 |
| | Moderate | 22 (13.84) | 1 (5.56) | 21 (14.89) | |
| | Normal | 61 (38.36) | 8 (44.44) | 53 (37.59) | |
| | Severe | 2 (1.26) | NA | 2 (1.42) | |
| | Wilkins score | 8.54 (1.48) | 9.2 (2.24) | 8.47 (1.36) | 0.003 |
| | AS | 4 (2.52) | NA | 4 (2.84) | 1.000 |
| | MV calcification | 5 (3.14) | 2 (11.11) | 3 (2.13) | 0.154 |
| | SEC | 6 (3.77) | 2 (11.11) | 4 (2.84) | 0.246 |
| ECG findings | P wave dispersion | 53.02 (25.95) | 68.39 (38.34) | 51.06 (23.39) | 0.112 |
| | IAB: A-IAB | 26 (16.35) | 7 (38.89) | 19 (13.48) | 0.020 |
| | P-IAB | 73 (45.91) | 7 (38.89) | 66 (46.81) | |
| | No-IAB | 60 (37.74) | 4 (22.22) | 56 (39.72) | |

Note. LAD: Left atrial diameter; LAV: Left atrial volume; MVA: Mitral valve area; SEC: Spontaneous echo contrast; PASP: Pulmonary arterial systolic pressure; LAA: Left atrial appendage; LAE: Left atrial enlargement; ECG: Electrocardiogram; LVEF: Left ventricular ejection fraction; SD: Standard deviation; PFO: Patent foramen ovale; MG: Mean mitral valve gradient; mxGra: Maximum mitral gradient; AS: Aortic stenosis; MV: Mitral valve; IAB: Interatrial block; A-IAB: Advanced interatrial block; P-IAB: Partial interatrial block.

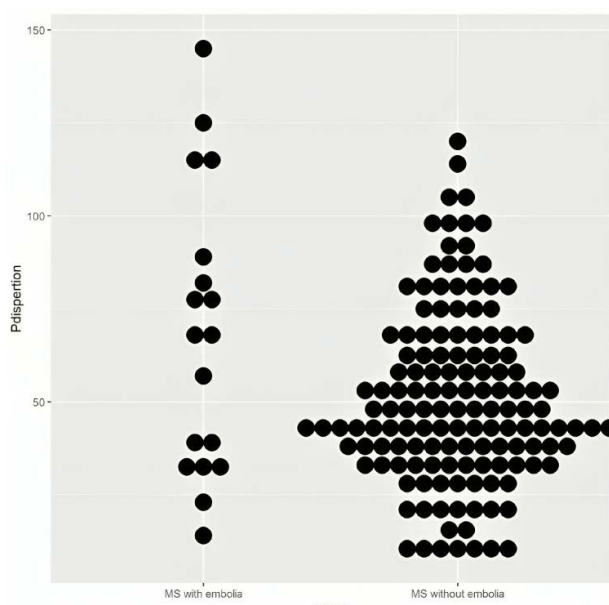


Figure 1. The Distribution of P Wave Dispersion in MS Patients With or Without Systemic Thromboembolism
Note. MS: Mitral stenosis

statistically significant (68.39 ± 38.34 vs. 51.06 ± 23.39 ms, respectively; $P=0.112$; [Figure 1](#)). Among those with systemic thromboembolism, 7 patients (38.89%) developed A-IAB, and 7 patients (38.89%) developed

P-IAB. However, among those without systemic thromboembolism, 19 patients (13.48%) developed A-IAB, and 66 patients (46.81%) developed P-IAB. The number of patients with normal P wave duration (no IAB) was 4 (22.22%) in those with systemic thromboembolism and 56 (39.72%) in those without systemic thromboembolism ($P=0.020$; [Figure 2](#)).

The multivariate regression analysis demonstrated that the appearance of IAB in ECG is independently associated with the occurrence of systemic thromboembolism in patients with MS. Particularly, the appearance of A-IAB could increase the odds of systemic thromboembolism about 5-fold higher than those without IAB (OR, 5.21; 95% CI: 1.23–22.07) and more than 3-fold higher than those with P-IAB (OR: 3.73; 95% CI: 1.04–13.37; [Table 3](#)).

Further multivariate analysis revealed a significant association between P wave dispersion and the occurrence of systemic thromboembolism in patients with MS (OR: 0.98; 95% CI: 0.96–1.00; $P=0.027$; [Table 4](#)).

There was a significant difference in LAD among the three levels of IAB ($P=0.041$; [Figure 3-A](#)). Nevertheless, there was no statistically significant difference in the three levels of IAB in terms of LAV ($P=0.251$; [Figure 3-B](#)). Univariate regression analysis of the association between studied parameters and occurrence of systemic thromboembolism in patients with mitral stenosis is

Table 3. Multivariate Regression Analysis of the Association Between IAB and Occurrence of Systemic Thromboembolism in Patients With Mitral Stenosis

| | OR | 95% CI | | P Value |
|-------------------|------|--------|-------|---------|
| A-IAB vs. No-IAB | 5.21 | 1.23 | 22.07 | 0.025 |
| A-IAB vs. P-IAB | 3.73 | 1.04 | 13.37 | 0.043 |
| Age | 0.95 | 0.90 | 0.99 | 0.026 |
| Male vs. female | 1.37 | 0.37 | 5.03 | 0.639 |
| HTN | 0.78 | 0.22 | 2.77 | 0.698 |
| DM | 1.41 | 0.20 | 9.90 | 0.729 |
| High cholesterol | 2.49 | 0.24 | 26.02 | 0.445 |
| Anti-platelet use | 1.89 | 0.59 | 6.04 | 0.282 |

Note. IAB: Interatrial block; HTN: Hypertension; DM: Diabetes mellitus; OR: Odds ratio; CI: Confidence interval.

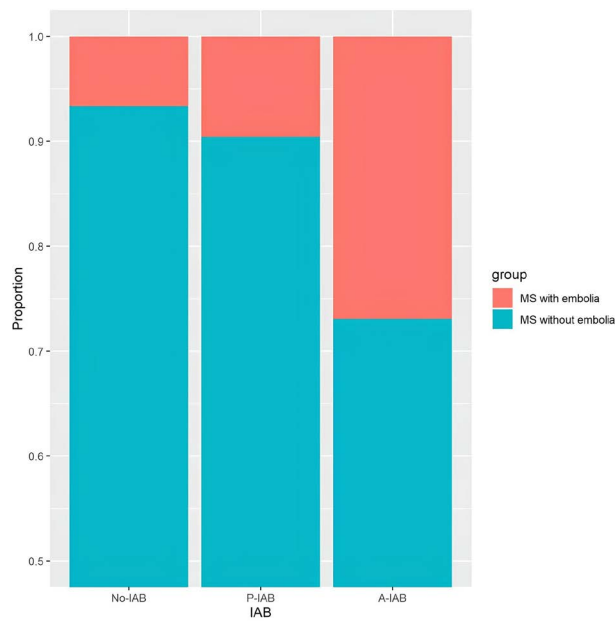


Figure 2. The Proportion of MS Patients With or Without Systemic Thromboembolism in Three Subgroups of Interatrial Block
Note. MS: Mitral stenosis; IAB: Interatrial block

presented in supplementary file 1.

Discussion

Among 159 patients with MS, IAB was detected in 99 patients (62.26 %), of whom 16.35% had an advanced block, and 45.91% had a partial block. The MVA was comparable between the groups ($P=0.639$). The multivariate regression analysis confirmed that the appearance of IAB in ECG was independently associated with the occurrence of systemic thromboembolism in patients with MS.

It is estimated that 40–75% of patients with MS have an AF rhythm in their ECG, and these patients have an increased risk of thromboembolic events.²⁰ Notably, systemic thromboembolism is one of the major complications of MS, and it has also been shown to occur in 8% of patients with MS with sinus rhythm.²¹ In addition, IAB can cause a weak and enlarged left atrium, which is prone to thrombosis and subsequent thromboembolism.²²

Accordingly, our results demonstrated that the

Table 4. Multivariate Regression Analysis of the Association Between P Wave Dispersion and Occurrence of Systemic Thromboembolism in Patients With Mitral Stenosis

| | OR | 95% CI | | P Value |
|-------------------|------|--------|-------|---------|
| P wave dispersion | 0.98 | 0.96 | 1.00 | 0.027 |
| Age | 0.95 | 0.90 | 0.99 | 0.022 |
| Male vs. female | 1.31 | 0.35 | 4.88 | 0.683 |
| HTN | 0.90 | 0.25 | 3.27 | 0.877 |
| DM | 1.50 | 0.22 | 10.52 | 0.681 |
| High cholesterol | 1.48 | 0.14 | 15.77 | 0.744 |
| Anti-platelet use | 1.78 | 0.56 | 5.59 | 0.326 |

Note. OR: Odds ratio; CI: Confidence interval; HTN: Hypertension; DM: Diabetes mellitus.

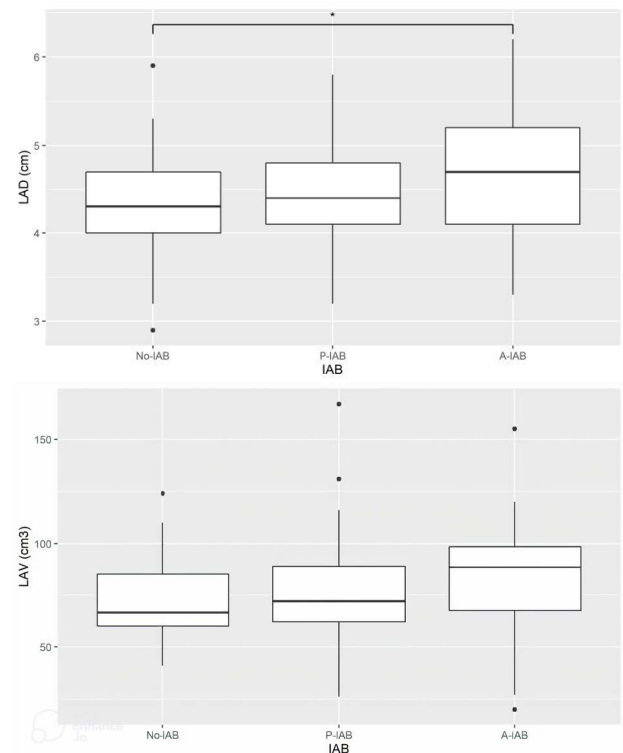


Figure 3. Left Atrial Size Among Three Subgroups of Interatrial Block: (A) Left Atrial Diameter and (B) Left Atrial Volume
Note. LAV: Left atrial volume; IAB: Interatrial block; A-IAB: Advanced interatrial block; P-IAB: Partial interatrial block

prevalence of A-IAB and P-IAB was significantly higher among MS patients with systemic thromboembolism even in the absence of AF rhythm. Likewise, Lorbar et al found that 80% of patients with embolic stroke and sinus rhythm had IAB.¹² Moreover, two other studies^{23,24}, reported a 40–50% prevalence of IAB in the general hospital population with sinus rhythm.

The prevalence of MS was generally higher in women. Approximately 80% of the patients in our study were female. Similarly, Movahed et al observed a higher prevalence of MS in women.²⁵ This 15-year echocardiographic study of patients showed that the prevalence of MS in women was significantly higher than in men (1.6% vs. 0.4%, $P<0.001$).²⁵

A-IAB was independently related to the occurrence of

systemic thromboembolism in MS patients. Accordingly, P wave dispersion was also independently associated with systemic thromboembolism.

Moreover, LAD was greater in patients with A-IAB and P-IAB in our study, and the severity of IAB was positively related to the increase in LAD. Additionally, LAE was reported as a common finding in patients with IAB in another study.²⁶ LAE changes the left atrial systolic indices over time following electrical delays caused by IAB.⁶ Due to LAE in patients with IAB and subsequent weakness of contraction, the volume of blood output is decreased in the left atrium during contraction. In addition, blood stasis resulting from these disorders inside the left atrium is a risk factor for thromboembolism.

IAB is recognized as a risk factor for AF.²⁷ In a study by Conde et al⁹, the incidence of atrial arrhythmias in patients with A-IAB was higher than in P-IAB. Disruption of the electrical performance of the atrium due to IAB, as well as other consequences of IAB, including increased atrial pressure, LAE, and atrial fibrosis, causes endothelial dysfunction and increases the risk of local thrombosis, resulting in systemic thromboembolic events.²⁸

One of the limitations of this study was the low quality of ECGs in some patients, which led to the exclusion of these patients from the study. Further, the cross-sectional design of our study prevented us from analyzing the dependent outcome in a time-dependent manner and estimating the hazard ratio and its confidence interval. Furthermore, there was a low rate of outcome (the occurrence of systemic thromboembolism) in our sample size. It should be noted that it was impossible to add more confounding variables to the model in order to avoid overfitting in multivariable regression analysis.

Conclusions

A-IAB in patients with MS and sinus rhythm is an independent risk factor for systemic thromboembolic events. Therefore, future researchers can investigate the feasibility and effectiveness of preventing thromboembolic treatment for reducing morbidity and mortality in these patients.

Statement of Artificial Intelligence Use

AI was not used in this work.

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Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical approval

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences (ethical code IR.TBZMED.REC.1395.725).

Consent for publication

Not applicable.

Conflict of interests

The authors declare that they have no competing interests.

Supplementary File

Supplementary file contains Table S1.

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