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ORIGINAL RESEARCH

Analysis of Variables Associated with Positive Micro-Embolic Signals Detected by Transcranial Doppler in Patients with Atrial Fibrillation and Their Predictive Value for Embolic Risk

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Objective: This study examined the factors associated with positive micro-embolic signals (MES) on transcranial Doppler monitoring in patients with atrial fibrillation (AF), as well as the predictive value of MES for the risk of embolism in AF.

Methods: Sixty-six patients who had micro emboli with AF were included in the positive group, and 75 patients who did not have micro emboli with AF served as the control group. The clinical data, congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65–74, female (CHA2DS2-VASc) score, D-dimer (D-d) level, echocardiography results, and brain magnetic resonance imaging (MRI) findings were compared between the two groups. Logistic regression models were used to analyze the relationship between positive micro emboli with CHA2DS2-VASc score, D-d, left atrial anteroposterior diameter (LAD), and silent cerebral ischemia (SCI) occurrence.

Results: The CHA2DS2-VASc score, D-d level, and LAD were significantly higher in the positive group than in the control group ($P < 0.05$) and were accompanied by a higher detection rate of SCI by brain MRI ($P < 0.01$). Elevated D-d levels, increased LAD, and the detection rate of SCI were all highly positively correlated with positive micro emboli. Also, CHA2DS2-VASc score ≥ 2 showed a significant positive correlation with positive micro emboli, and the higher CHA2DS2-VASc score was associated with a stronger correlation. The multivariate regression analysis demonstrated that positive micro-embolic was independently associated with SCI and a CHA2DS2-VASc score of ≥ 4.

Conclusion: Positive micro emboli in patients with persistent AF are consistent with an increased risk of embolism, and are independently associated with a higher CHA2DS2-VASc score and SCI, which can be used as an indicator of individual embolic risk in patients with AF.

Keywords: atrial fibrillation, AF, CHA2DS2-VASc score, D-dimer, left atrial anteroposterior diameter, micro-embolic signal, MES, silent cerebral ischemia

Introduction

Atrial fibrillation (AF) is the most prevalent persistent arrhythmia in the clinic, and its prevalence dramatically increases with age. One of the primary dangers of AF is the formation of intra-atrial thrombus, which can lead to arterial embolism, including stroke, and has a high rate of mortality and disability, resulting in a significant increase in the burden on families and society.[1,2] Currently, the congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65–74, female (CHA2DS2-VASc) scoring system is widely recognized and used clinically to assess the risk of embolism in patients with non-valvular AF. In particular, this system is used to calculate scores for relevant factors, thereby stratifying patients with AF according to their risk. The increased score is associated with a high risk of embolism, based on which patients with a low to moderate risk and high risk of thromboembolism can be distinguished for prophylactic anticoagulant therapy.[3,4]

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According to prior studies, both plasma D-dimer (D-d) levels and left atrial anteroposterior diameter (LAD) are independent predictors of the risk of embolism in patients with AF.[5–7] In this study, we observed the correlation between the positive result of transcranial Doppler (TCD) monitoring of micro-embolic signals (MES) and CHA2DS2-VASc score, D-d levels, and LAD in patients with persistent AF. We also directly analyzed its relationship with the incidence of silent cerebral ischemia (SCI) to reveal the potential predictive value of positive MES for the risk of embolism in patients with AF.

Participants and Methods

Participants

In this study, we included a total of 66 consecutive patients with MES who were first diagnosed with non-valvular persistent AF and underwent TCD monitoring of MES signals from February 2020 to November 2022 in our outpatients and wards as the experiment group, and 75 patients with persistent AF whose continuous MES monitoring from May 2022 to October 2022 was negative as the control group. This study was approved by the Ethics Committee of Suzhou Wuzhong People's Hospital (No. KY2019006-BC), and informed consent was waived. 1. The inclusion criteria of cases were as follows: (1) patients were diagnosed with AF by 12-lead electrocardiography, with symptoms lasting more than 7 days; (2) patients receiving TCD and MES monitoring; (3) patients with detailed routine examinations, including hematological tests, transthoracic electrocardiography and brain magnetic resonance imaging (MRI). 2. The exclusion criteria of cases were listed below: (1) patients with various valvular AF, including rheumatic heart disease, or undergoing mechanical or biological valve replacement; (2) patients with previous application of anticoagulant drugs; (3) patients combined with hyperthyroidism, malignancies, hematologic diseases, severe liver or kidney dysfunction, and other systemic diseases; (4) patients with a history of deep vein thrombosis and pulmonary embolism.

Methods

(1). Micro emboli were monitored using EMS-9PB TCD from Delica. MES were identified using the following criteria:[8] unidirectional signals appearing in the blood flow spectrum for a brief period (< 300 ms) with an intensity of 3 dB higher than the background signal, accompanied by sharp birdsong or whistle sounds. In detail, (i) each intracranial and extracranial vessel was routinely examined with a 4 MHz probe, followed by detection of micro emboli in bilateral middle cerebral arteries; (ii) after the middle cerebral artery was probed in the temporal window, the probe was fixed with a fixed frame for monitoring in the beginning segment of the middle cerebral artery; (iii) All spectral changes were saved, and the number of micro emboli was automatically calculated. The monitoring lasted for 30 minutes. Following the monitoring, the same experienced TCD physician then replayed for analysis and confirmation. The result was positive when MES were monitored (Figure 1), otherwise, it was negative. All patients were monitored within 24 hours of the initial diagnosis.

(2). CHA2DS2-VASc scoring was conducted as previously reported:[3,4] Patients were scored on clinical characteristics such as age 75 years (2 points), diabetes mellitus (2 points), ischemic stroke/transient ischemic attack (2 points), age 65–74 years (1 point), hypertension (1 point), congestive heart failure (1 point), vascular disease (1 point), and female (1 point) with a maximum score of 9. The scoring was completed by an attending physician in cardiology or above.

(3). Diagnosis of SCI through MRI findings within 24 hours of a patient's visit, combined with symptoms, were consistent with the diagnostic basis described in previous studies:[9,10] (i) The absence of any cerebral ischemic symptoms and abnormal neurological signs; (ii) single or multiple spotted or small patch-like lesions (2–8 mm) in brain MRI performed on the GE1.5T MRI system, with a scan layer width of 2.5 mm, low signal in T1-weighted image (T1WI) and high signal in T2WI, evaluated by a senior attending radiologist or above; (iii) exclusion of patients with a clear previous history of cerebral infarction.

(4). Data were collected: The general and clinical information of patients were collected using an outpatient and inpatient electronic medical record system, such as age, gender, disease duration, comorbid diseases, antiplatelet drugs, B-type natriuretic peptide (BNP), plasma D-d levels, and echocardiographic LAD.

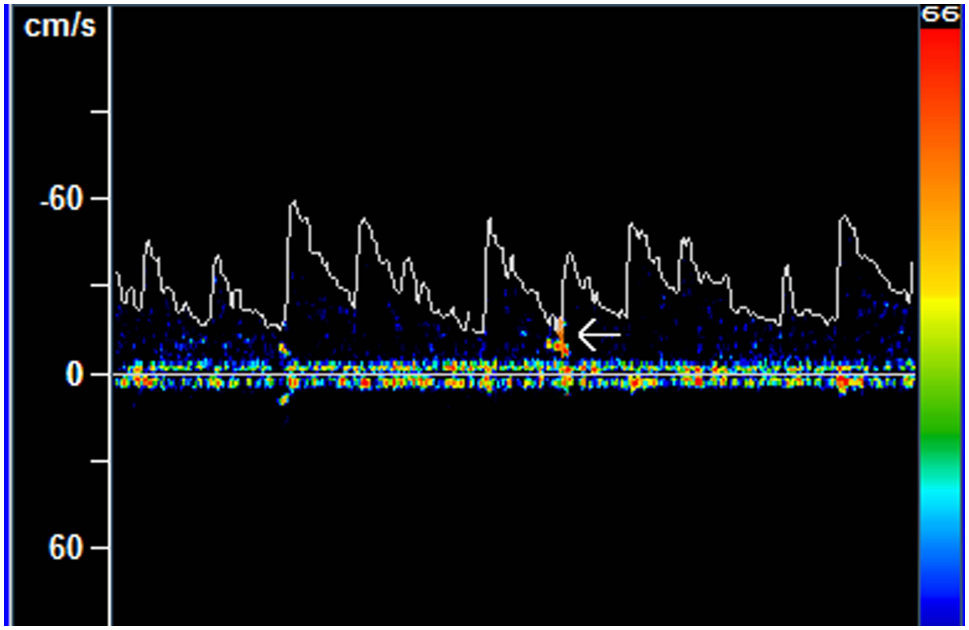

Figure 1 A graphical representation of the monitoring process of a patient with micro embolus. The color bar on the right of the image from blue at the bottom to red at the top indicates the intensity of the echo signal from low to high. The yellow high-intensity single-direction signal indicated by the white arrow, combined with the audio emitted by the instrument, was determined to be a micro-embolic signal.

Statistical Analysis

SPSS25.0 software was used for statistical analysis. The measurement data with a normal distribution were expressed as x ± s, while those with a skewed distribution were expressed as M (Q1, Q3), and the independent sample *t*-test or *U*-test were used to compare the two groups. Count data were expressed as cases, and the $\chi 2$ test was used for comparison between the two groups. Logistic regression models were used to examine and compare the factors associated with positive micro emboli in patients with AF and to compare the strength of the association. A difference was considered statistically significant at $P < 0.05$ (two-sided test).

Results

Comparison of General Information

The 141 patients included in the study had a mean age of 60.5 ± 10.8 years, with 88 males. There were no statistically significant differences in terms of age, gender, or duration of AF between the positive and control groups (Table 1).

Comparison of Clinical Data Between the Two Groups

The proportion of patients combined with hypertension, diabetes, and cerebral infarction in the positive group was statistically insignificantly higher than in the control group. The differences were not statistically significant in the proportion of patients taking antiplatelet drugs and BNP levels between the two groups. The CHA2DS2-VASc score, D-d levels, LAD ($P < 0.05$), and detection rate of micro emboli ($P < 0.01$) by brain MRI were significantly higher in the positive group than in the control group (Table 2).

Table 1 Comparison of General Information Between the Two Patient Groups

Items	Positive Group (n = 66)	Negative Group (n = 75)	$t/\chi^2/z$	P
Age (years)	62.1±11.4	61.0±12.3	0.832	0.286
Male (cases, %)	42(63.6%)	46(61.3%)	1.023	0.272
Duration of atrial fibrillation (years)	2.5(0.1,5.0)	2.8(0.1–6.2)	0.237	0.681

Table 2 A Comparison of Clinical Data of Patients with Atrial Fibrillation Between Two Groups

Items	Positive Group (n = 66)	Negative Group (n = 75)	t/χ^2	P
CHA2DS2-VASc Score	2.8±0.2	1.6±0.3	1.689	0.018
Comorbid diseases				
Hypertension	44(66.6%)	40(53.3%)	2.061	0.150
Diabetes mellitus	10(15.1%)	8(10.6%)	0.295	0.586
Cerebral infarction	8(12.1%)	6(8.0%)	0.285	0.593
Antiplatelet drugs				
Aspirin	22	20	0.461	0.497
Clopidogrel	8	9	0.041	0.838
BNP (pg/mL)	450±89.2	434±66.1	0.718	0.472
D-d (ng/mL)	252±18.1	128±22.5	2.980	<0.001
LAD (mm)	44.8±5.5	38.2±6.0	3.614	<0.001
SCI (cases,%)	43(65.1%)	11(14.6%)	5.718	<0.001

Abbreviations: BNP, B-type natriuretic peptide; D-d, D-dimer; LAD, left atrial anteroposterior diameter; SCI, silent cerebral ischemia.

3. Logistic regression analysis of factors associated with positive microemboli on TCD monitoring in patients with persistent AF

Each index was grouped and transformed into dichotomous variables: D-d levels greater than or equal to 500 ng/mL as 1 and D-d levels less than as 0; LAD greater than or equal to 38 mm as 1 and LAD within the normal range as 0; SCI detection as 1 and no detection of SCI as 0; CHA2DS2-VASc scores greater than or equal to the corresponding score as 1 and CHA2DS2-VASc scores less than the corresponding score as 0 (CHA2DS2-VASc scores were grouped with different scores of 2, 3, and 4). Each dichotomous variable was analyzed using univariate regression with the group as the dependent variable. The results revealed that elevated D-d levels, increased LAD, and CHA2DS2-VASc score ≥ 2 were all significantly positively correlated with positive micro emboli. The higher the CHA2DS2-VASc score, the stronger the correlation. Also, SCI detection was highly positively correlated with positive micro emboli; Then, the factors with P<0.05 were included in the multivariate logistic regression model analysis, which showed that the only independent factors significantly associated with positive micro-emboli were a CHA2DS2-VASc score of ≥ 4 and SCI. (Table 3).

Discussion

The CHA2DS2-VASc score is widely recognized and used in clinics to assess the risk of embolism in patients with AF.[3,4] This score focuses on the presence of clinical factors such as age, gender, hypertension, heart failure, diabetes mellitus,

Table 3 Logistic Regression Model Analysis of Micro-Embolus Positive Correlation Factors

Variable	Univariate Regression Analysis		Multivariate Regression Analysis	
	OR (95% CI) Value	P	OR (95% CI) Value	P
CHA2DS2-VASc score				
≥2	1.83(1.01–3.80)	0.043	1.18(0.76–2.01)	0.162
≥3	3.97(1.38–9.25)	0.011	1.98(0.91–4.12)	0.134
≥4	6.62(2.78–11.53)	<0.001	3.86(1.18–6.95)	0.008
D-d	4.17(2.13–11.22)	<0.001	2.16(0.92–6.56)	0.069
LAD	4.83(1.88–11.83)	0.003	2.25(0.95–7.01)	0.072
SCI	6.64(2.81–15.82)	<0.001	4.01(1.68–8.94)	0.005

Abbreviations: D-d, D-dimer; LAD, left atrial anteroposterior diameter; SCI, silent cerebral ischemia; CI, confidence interval.

and a history of stroke in patients with AF and emphasizes the possibility of embolism in different risk groups. There are still patients who are at high-risk in the low-risk group who develop embolism every year, and patients in the high-risk group who have been free of embolism for a long time, and anticoagulation therapy is invariably accompanied by an increased risk of hemorrhage.[11] As a result, it is critical to develop simple and objective testing indexes to aid and enrich stratification of the risk of embolism in AF, particularly in identifying high-risk individuals and guiding the individualized application of anticoagulation therapy for patients with AF.

The mechanism of routine micro embolism formation in patients with AF is thought to be related to the constant formation and dislodgement of microthrombi in the left atrium, particularly in the left auricle, caused by blood flow stasis and abnormal coagulation. Transesophageal ultrasonography is the most accurate method for detecting thrombus in the left auricle. However, this method is technically demanding and difficult to implement.[7] According to reports, we have found that TCD is the only method for monitoring micro emboli in cerebral blood flow, and simultaneous monitoring of MES in bilateral middle cerebral arteries is strongly suggestive of cardio embolism.[12] Several studies have analyzed the number of micro emboli during ablation procedures for AF and compared the difference between different surgical approaches.[13,14] Also, other studies have confirmed the presence of asymptomatic embolic events after AF ablation using brain MRI,[15] as well as the association of AF with dementia and cognitive dysfunction, which may be explained by a mechanism, and an increase in brain micro emboli.[16,17]

Few domestic and international studies have been conducted in patients with persistent AF to assess the risk of embolism.[18–20] Previous research has suggested that D-d and LAD are both independent predictors of embolic risk in patients with AF.[5–7] According to our study, the CHA2DS2-VASc score, D-d level, and LAD were significantly higher in the positive group than in the control group. In the univariate logistic regression analysis, as the CHA2DS2-VASc score increased, the correlation with positive micro emboli was gradually enhanced and positive micro emboli were clearly positively correlated with D-d and LAD. These results demonstrate that positive micro emboli are associated with an increased risk of embolism in patients with AF. The rate of MRI-confirmed SCI was significantly higher in the positive group than in the control group, and SCI was highly positively correlated with positive micro emboli, both CHA2DS2-VASc score ≥ 4 and SCI were associated with a higher risk of embolism. Multivariate regression analysis suggested that positive micro-emboli was only independently associated with the above factors. It is suggested that positive micro-embolus may directly identify high-risk individuals in patients with atrial fibrillation.

This study has several limitations, including cross-sectional observational study, failure to follow up on the occurrence of clinical thromboembolism events in patients, long investigation time, and a small sample size are all limitations of this study. More prospective cohort studies are expected to look at the frequency of clinical embolic events in patients who are diagnosed with micro emboli with AF, as well as the value of micro emboli monitoring methods in predicting the risk of embolism in AF.

Conclusion

The transcranial TCD monitoring method for micro emboli is simple and easy to use, with widely available and low-cost instrumentation. As a result, it can be applied multiple times. This study reveals that, positive micro embolus monitoring has a clear value for predicting and confirming embolic risk in patients with persistent AF, and it is clinically essential for identifying patients with AF at high risk of embolism, so it is expected to be widely used as an important complement to the CHA2DS2-VASc score for predicting embolic risk.

Ethical Statement

The studies were reviewed and approved by Ethics Committee of Suzhou Wuzhong People's Hospital (KY2019006-BC). This study did not cause harm to patients, the Ethics Committee of Suzhou Wuzhong People's Hospital has granted a waiver for patient consent. Patient data confidentiality was ensured, and the study complied with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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