Original Article

Prevalence of Paroxysmal Atrial Fibrillation in Patients Presenting with Embolic Stroke of Undetermined Source

Emad Effat Fakhry, Mohamed Mostafa El Nwagy, Hayam Mohamed Eldamnhoury, Maha Mohamed Mohamed Khalifa

Cardiology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

ORCID:

Emad Effat Fakhry: https://orcid.org/0000-0002-8993-4250
Mohamed Mostafa El Nwagy: https://orcid.org/0000-0002-6192-2434
Hayam Mohamed Eldamnhoury: https://orcid.org/0000-0002-2871-3139
Maha Mohamed Mohamed Khalifa: https://orcid.org/0000-0002-1456-0098

Abstract

Background: Cerebrovascular stroke is a major cause of morbidity and disability. Many etiologies may contribute to its presence. Some patients have none of the identifiable risk factors yet face the consequences of stroke or transit ischemic attack. This type of stroke is known as embolic stroke of undetermined source (ESUS). It has a high rate of recurrence due to the presence of an unknown uncorrected etiology. Paroxysmal atrial fibrillation remains a hidden bottom of an iceberg, representing a major hidden etiology of ESUS. We aimed to determine the prevalence of paroxysmal atrial fibrillation in patients with ESUS using 72-h Holter monitoring. **Methods:** Patients diagnosed with ESUS underwent 72-h Holter monitoring within the 1st week of the incident stroke. Holter monitors determined whether atrial fibrillation (more than 3 s) is present or not. **Results:** This study included 200 patients with stroke of an undetermined source who underwent 72-h Holter monitoring within 1 week of the incident stroke. The patients' ages ranged between 22 and 77 years (mean age 48.46 ± 12.74 years); 136 were males and body mass index (BMI) ranged from 21 to 35 kg/m^2, with a mean BMI of 24.78 ± 2.99 kg/m^2. Their left atrial anteroposterior diameter in the parasternal long-axis view ranged from 26 mm to 47 mm, with a mean diameter of 36.08 ± 5.23 mm. Thirty-two out of the 200 patients were diagnosed with paroxysmal atrial fibrillation, representing 16%. There was a statistically significant association between the presence of paroxysmal atrial fibrillation and both age ($P = 0.009$) and left atrial diameter ($P = 0.001$). There was an associated finding that needs further investigation regarding the significant association between supraventricular ectopic beats and the presence of atrial fibrillation or stroke. **Conclusion:** Paroxysmal atrial fibrillation is an important hidden etiology of embolic stroke of undetermined etiology that can be detected early using 72-h Holter monitoring within 1 week of the incident stroke.

Keywords: Covert atrial fibrillation, embolic stroke of undetermined source, holter monitoring, paroxysmal atrial fibrillation

Introduction

Cerebrovascular stroke is a leading cause of morbidity and disability. Many strokes have a likely explanation, such as carotid disease, uncontrolled hypertension, diabetes mellitus, hyperlipidemia, smoking, thrombophilia, and atrial fibrillation. Approximately 25% of ischemic strokes are of cardio-embolic origin. Nonvalvular atrial fibrillation accounts for 50% of these cases; other causes include left ventricular thrombus and valvular heart disease.[1] However, 25% of patients have none of the defined risk factors and yet face the consequences of stroke or transient ischemic attack, and this is defined as embolic stroke of undetermined source (ESUS). ESUS is shown to have a higher rate of recurrence than other types of stroke due to the lack of prevention of the undetermined etiology.[2] Paroxysmal atrial fibrillation is one of the most

Address for correspondence: Dr. Emad Effat Fakhry, Cardiology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
E-mail: emad_effat@med.asu.edu.eg

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common causes of ESUS together with patent foremen ovale, However, the actual percentage that it represents is variable depending on the method of detecting atrial fibrillation, duration, and timing during which it is being detected.[3] Covert atrial fibrillation is a terminology used to describe those who had asymptomatic episodes of atrial fibrillation without being noticed. However, these episodes still can cause cardioembolic stroke.[4] Based on these considerations, the detection of atrial fibrillation as an etiology and evaluating its prevalence among patients with ESUS will provide help to focus our resources for the management of ESUS. Once identified, the introduction of oral anticoagulant provides an additional 40% risk reduction of recurrent stroke compared with antiplatelet therapy.[5] Atrial fibrillation is associated with a 5-fold increase in stroke risk and a doubled risk of mortality; adequate anticoagulation therapy can decrease the risk of ischemic stroke in patients with atrial fibrillation by more than 70%, that's why early detection and treatment of atrial fibrillation is crucial.[6] A lot of methods are available for the detection of paroxysmal atrial fibrillation. Initial evaluation is performed with electrocardiogram (ECG), telemetry monitoring during inpatient stay, and ECG Holter monitoring devices.[7] We aimed to determine the prevalence of paroxysmal atrial fibrillation in patients with ESUS using 72-h Holter monitoring.

Methods

The study was approved by the Research Ethics Committee, and all patients signed an informed written consent for participation in the study in accordance with the Declaration of Helsinki.

This study included 200 patients diagnosed with ESUS, patients were chosen according to the classification of TOAST.[8] All patients were in sinus rhythm at presentation with no known history of atrial fibrillation.

ESUS was diagnosed according to the following criteria: nonlacunar stroke detected by computed tomography (CT) or magnetic resonance imaging (MRI), absence of major risk factor of cardioembolic source, absence of extracranial or intracranial atherosclerosis causing 50% luminal stenosis in arteries supplying the area of ischemia, and no other specific cause of stroke identified (e.g., arteritis, dissection, migraine/vasospasm, and drug misuse).[9]

All the following patients were excluded from the study population: patients with known etiology of stroke (known history of atrial fibrillation, left ventricle thrombus, small-vessel disease as an etiology of stroke evidenced by imaging study, or significant atherosclerosis of the carotid vessels); in addition, patients with hemorrhagic stroke by imaging studies, patients with implantable cardiac pacemaker, and patients with chronic valvular lesions were excluded from the study.

All patients were subjected to (1) careful history taking with special emphasis on age, gender, hypertension (defined as arterial blood pressure of more than 140/90 mmHg and/or receiving oral antihypertensive agents); diabetes mellitus (defined as elevated fasting blood sugar ≥126 mg/dL, 2-h plasma glucose level of 200 mg/dL or higher during a 75-g oral glucose tolerance test, random plasma glucose of 200 mg/dL or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, or a hemoglobin A1c level of 6.5% or higher[10]); peripheral arterial diseases; any known hematological or immunological disease; known previous cardiac history and drug history; (2) physical examination for localization and identifying the underlying etiology of stoke; (3) 12-lead surface ECG was recorded on presentation, and those who were newly diagnosed with atrial fibrillation were excluded from the study; (4) transthoracic and transesophageal echocardiography: a comprehensive transthoracic echocardiographic examination was done according to the American Society of Echocardiography Guidelines for all patients in left lateral position.[11,12] We measured the left ventricular dimensions and left atrial anteroposterior dimension in the parasternal long-axis view using M mode[13] we estimated the ejection fraction (EF),[14] and we excluded any underlying structural heart disease or recent left ventricular thrombus. All patients underwent transesophageal echocardiographic examination in the left lateral position using GE Vivid S6 ultrasound machine using probe 6TC for: exclusion of structural heart disease including atrial septal defect or patent foremen oval and evaluation of left atrium and left atrial appendage and exclusion of any mass or thrombi. All patients abstained from food and beverages (other than clear fluids) for 6 h and restrained from any oral intake for 3 h. All patients underwent conscious moderate sedation using midazolam; (5) 72-h Holter monitoring: the patients were typically connected within 1 week of the stroke onset during the hospital stay using 3–5 ECG electrodes that yielded three ECG vectors. After completing the 72-h recording period, the data stored within the flashcard memory were digitized and downloaded to a local workstation where the ECG tracings were checked to ensure their quality and give a final review and official interpretation by a well-trained specialized physician using a Norav Medical - NH301 - Analysis software for interpretation. Assuming that the recording quality was adequate, Holter monitors determined whether atrial fibrillation is present or not according to the following definition: the presence of any atrial fibrillation episodes for more than 3 s. Information about the shortest and longest duration of atrial fibrillation was recorded; and (6) CT brain and MRI stroke protocol were applied to all patients during admission to exclude hemorrhagic stroke, small-vessel disease, and lacunar infarctions. Analysis of data was done using the Statistical Package for Social Sciences (IBM SPSS version 16); quantitative variables were described as mean, standard deviation (SD), and range. Qualitative variables were described as number and percentages. Unpaired *t*-test was used to compare quantitative variables, in parametric data (SD <50% mean). Comparison between groups regarding qualitative variables was done by using Chi-square test. Fisher's exact test was used instead when one expected cell is <5.

One-way ANOVA test was used in comparing more than two groups regarding quantitative variables. Spearman's correlation coefficient test was used to rank variables versus each other positively or inversely. Receiver operator characteristic curve was used to find out the best cutoff value and the validity of certain variables. $P > 0.05$ was nonsignificant (NS), $P < 0.05$ was significant (S), and $P < 0.001$ was highly significant (HS).

Results

This study included 200 patients with ESUS who underwent 72-h Holter monitoring during the 1st week of their admission: 136 were males (68%), with a mean age of 48.46 ± 12.74 years and a mean body mass index (BMI) of 24.78 ± 2.99 kg/m^2; and 40 patients were diabetics (20%) and 52 were hypertensives (26%).

Regarding the echocardiographic examination, with a mean EF of 62.5% ± 6.6%, left ventricular end-diastolic diameter varied from 40 mm to 55 mm with a mean diameter of 46.78 ± 4 mm, left ventricular end-systolic diameter (LVSDD) varied from 22 mm to 40 mm with a mean diameter of 30.6 ± 4,97 mm, left atrial diameter ranged from 26 to 47 mm, with a mean diameter of 36.08 ± 5.23 mm.

Seventy-two-hours Holter monitoring was applied to the whole study population, which revealed the presence of atrial fibrillation episodes among 32 patients (16%). Atrial fibrillation episodes' duration range was between 10 s and 900 s with a median value of 240 s and interquartile range (IQR) of 68.5–720.

Other arrhythmias were recorded during the period of monitoring; about twenty patients had supraventricular ectopic beats, and their burden ranged from 2% to 12.5% with a median of 5% and an IQR of 2%–11%.

Patients who were first diagnosed with paroxysmal atrial fibrillation detected by the Holter were found to be older with a mean age of 59 ± 9.47 years and a range of 46–74 years (P = 0.009). They were equally distributed between both genders: 16 males and 16 females. Their BMI ranged from 23 to 27 kg/m^2 with a mean of 25.63 ± 1.51 kg/m^2 [Table 1]. Larger left atrial diameter ranged from 39 to 47 mm with a mean of 41.88 ± 2.90 mm (P = 0.001) [Table 2]. Their Holter recorded more frequent supraventricular ectopic beats with a median burden of 5% and a range of 2%–11% (P = 0.005) [Table 3].

The frequency of atrial fibrillation episodes of the 32 patients on days 1, 2, and 3 was determined where the sum of episodes of day 1 was 24 episodes, that of day 2 was 19 episodes, and that of day 3 was 23 episodes, with no statistically significant difference between the different days of Holter monitoring (P = 0.72).

Table 1: Relation between baseline characteristics and the presence of atrial fibrillation

	AF episodes		*P*
	Not present (*n*=168), *n* (%)	Present (*n*=32), *n* (%)	
Age (years)			
Mean±SD	46.45±12.36	59.00±9.47	0.009
Range	22-77	46-74	
Gender			
Female	48 (28.6)	16 (50.0)	0.234
Male	120 (71.4)	16 (50.0)	
DM			
Not present	132 (78.6)	28 (87.5)	0.563
Present	36 (21.4)	4 (12.5)	
HTN			
Not present	132 (78.6)	16 (50.0)	0.091
Present	36 (21.4)	16 (50.0)	
BMI (kg/m^2)			
Mean±SD	24.62±3.18	25.63±1.51	0.389
Range	21-35	23-27	

Patients with AF were found to be older (P=0.009). AF: Atrial fibrillation, BMI: Body mass index, DM: Diabetes mellitus, HTN: Hypertension, SD: Standard deviation

Table 2: The relation between left atrial diameter and the presence of atrial fibrillation

Left atrial A-P diameter (mm)	AF episodes		*P*
	Not present (*n*=168)	Present (*n*=32)	
Mean±SD (mm)	34.98±4.84	41.88±2.90	0.001
Range (mm)	26-44	39-47	

Patients with AF were found to have larger left atrial diameter (P=0.001). AF: Atrial fibrillation, SD: Standard deviation

Table 3: Association between supraventricular ectopic beats and the presence of atrial fibrillation

Supraventricular ectopic beats	AF episodes		*P*
	Negative (*n*=168), *n* (%)	Positive (*n*=32), *n* (%)	
Negative	160 (95)	20 (62.5%)	0.005
Positive	8 (5)	12 (37.5%)	
Median (IQR)	7.25 (2-12.5)	5 (2-11s)	
Range	2-12.5	2-11	

Holter monitoring recorded more frequent supraventricular ectopic beats in patients with atrial fibrillation (P=0.005). AF: Atrial fibrillation, IQR: Interquartile range

Discussion

The prevalence of paroxysmal atrial fibrillation among patients presenting with ischemic cerebrovascular stroke varied widely among different studies. These differences may be due to the difference in the selected population and different methods of detection of atrial fibrillation. For example, a study that includes high-risk individuals of old age will observe a higher prevalence of atrial fibrillation, a study that defines atrial fibrillation with shorter duration of 2 or 3 s presents more positive data, moreover the longer the duration of the Holter monitoring, the higher the prevalence of detecting paroxysmal

atrial fibrillation.[15] In this study, we performed early 72-h Holter monitoring to 200 patients with ESUS within 1 week from the onset of stroke; our main findings were: 32 out of the 200 patients were found to have first diagnosed atrial fibrillation with a prevalence of 16%. A strong association was detected between the age of the population and the detection of the paroxysmal atrial fibrillation with $P = 0.009$, The left atrial diameter is a strong predictor of paroxysmal atrial fibrillation with a $P < 0.001$; supraventricular ectopic beats were strongly associated with the presence of atrial fibrillation with a burden that ranges from 2% to 11% and a median of 5%.

There are many studies that determine the prevalence of paroxysmal atrial fibrillation among individuals with ESUS by different monitoring methods, different monitoring periods (48 h and 72 h and 7 days or more), and different timings after stroke. In a systemic review and meta-analysis, Kishore *et al*. have reported that 11% of patients with ESUS had newly diagnosed atrial fibrillation by different detection modalities.[16] This is close to our present study that concluded a prevalence of 16%.

In another comparable study, Higgins *et al*. compared the "Standard Practice" (SP) of 12-lead ECG, echocardiography, and 24-h Holter monitoring to 7 days of noninvasive cardiac monitoring "Additional Monitoring" (AM) for the detection of atrial fibrillation in fifty patients with ESUS after 7 days from the onset of the stroke. Their results reported that sustained (as they defined as more than 20 s rhythm strip) paroxysms of atrial fibrillation were detected in 18% of patients undergoing SP-AM versus 2% undergoing SP only with $P < 0.01$. Paroxysms of any duration (stated as more than six consecutive complexes but <20 s) were detected in 44% of patients undergoing SP-AM versus 4% undergoing SP with $P < 0.001$.[17] They concluded that additional extending monitoring should be considered for all eligible patients soon after the onset of acute stroke. Despite the impressive previous results, the extended monitoring is still questionable. The definitive duration of extended monitoring that comes with the best cost-effective result still needs further studies and more enormous cohorts are needed. Every modality has its own advantage and disadvantage, but what really matters is about the cost and patient compliance. For 7-day extended noninvasive cardiac monitoring, the dislocation of the electrodes is the main problem. The same problem was encountered by Stahrenberg *et al*. who were able to receive >5 days of ECG signals in only 69% of the patients.[18]

Ritter *et al*. preferred the invasive extended cardiac monitoring rather than extended noninvasive cardiac monitoring.[19] Sixty patients (median age 63; IQR, 48.5–72 years) with ESUS were included. Internal cardiac monitoring (ICM) was implanted 13 days after the event. Seven-day Holter performed after the ICM was implanted. Paroxysmal atrial fibrillation was detected by the ICM in ten patients (17%; 95% confidence interval [CI], 7%–26%). Only one patient had atrial fibrillation detected during 7-day Holter monitoring as well ($P = 0.0077$). Episodes of atrial fibrillation lasting 2 min or more were detected 64 days after implantation. There were no recurrent strokes during the period of observation. The low unexpected number of atrial fibrillation detected in the Ritter study was extremely different from most of the other studies. This can be explained by the time of the initiation of the 7-day ECG monitoring. Extensive 72-h stroke unit monitoring has recently shown to be very sensitive for detecting atrial fibrillation.[20]

This leads us back to the controversy about the best modality and the best duration and timing of cardiac monitoring. From the previously reported data and other studies, the best time of the initiation of cardiac monitoring is within the 1st week of the insulting event, however, we still need more studies to prove it.

Grond *et al*. performed a prospective cohort study to reach an assumption about the best feasible and cost-effective monitoring modality that can be applied. They performed 72-h Holter monitoring on a large scale of population that reached up to 1135 patients. During their study, survivors of stroke without known atrial fibrillation were enrolled in a prospective study of 72-h Holter ECG monitoring. In addition to the standard workup, all patients underwent 72-h Holter ECG monitoring directly after admission. They compared the detection rates of 72- and 24-h monitoring.[21] Atrial fibrillation was detected in 49 out of the 1135 patients by 72-h ECG monitoring. First diagnosed atrial fibrillation was detected in 2.6% of patients within the first 24 h of ECG monitoring, and other twenty more patients by 72 h of ECG monitoring. The number needed to screen by 72-h ECG was 55 patients for each additional atrial fibrillation diagnosis.[22] Consequently, further studies are needed to evaluate the best early noninvasive cardiac monitoring and to compare 48 h with 72-h noninvasive cardiac monitoring for the best cost-effective results. The different results from our study despite similar detection period may be due to the different definition of atrial fibrillation, as an episode of >30 s duration of an absolute arrhythmia without detectable P waves and without a pattern more consistent with an alternative diagnosis.[22]

In concordance to a review by Sanna *et al*., our study found that age is an important risk factor for atrial fibrillation development. Our study reported that those who were newly detected by the Holter were found to be older with a mean age of 59 ± 9.47 years and a range of 46–74 years.[15]

In concordance with a study performed by Hamatani *et al*. which proved that the left atrial diameter can be used as an independent risk factor for the prediction of stroke.[23] The left atrial diameter was an important risk factor for atrial fibrillation found in our study, in patients who developed atrial fibrillation left atrial diameter ranges from 39 to 47 mm with a mean of 41.88 ± 2.90 mm ($P < 0.05$) and the left atrial diameter of the study cohort ranges from 26 to 47 mm, with a mean diameter of 36.08 ± 5.23 mm.

Our study reported a strong association between atrial fibrillation and the supraventricular ectopic activity. Binici *et al*., in a

retrospective cohort study of 678 individuals, found that the risk of primary end point (death or stroke) was significantly higher in patients with excessive supraventricular ectopic activity compared with those without, after adjustment for conventional risk factors (hazard ratio 1.64; 95% CI, 1.03–2.60; $P = 0.036$).[24] This matches with the pathophysiology of the enhanced automaticity for triggering atrial fibrillation.

Conclusion

The prevalence of paroxysmal atrial fibrillation among the population of ESUS is 16%. Early extended 72-h Holter monitoring within 1 week of onset of stroke is useful for the detection of paroxysmal atrial fibrillation so that we can start anticoagulation to avoid recurrence of stroke.

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Conflicts of interest

There are no conflicts of interest.

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