Original Article

Predictive Value of Supraventricular Short Runs for New-Onset Atrial Fibrillation in Patients with Ischemic Stroke

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Abstract

Background: The clinical importance of supraventricular run (SVR) is uncertain in the management of patients with previous cerebrovascular events. We aim to evaluate the role of SVRs in the development of future atrial fibrillation (AF) in patients diagnosed with ischemic stroke. **Methods:** We retrospectively evaluated patients who underwent 24-h Holter monitoring for the evaluation of possible AF after ischemic cerebrovascular events. The presence and duration of SVR were noted. Subsequent diagnosis of AF was searched in patients with sinus rhythm. **Results:** A total of 694 patients were included in the analysis. SVR was detected in 104 (14.9%) patients in the study group. Seventy-one (10.2%) patients were diagnosed with AF in the follow-up. SVRs were more prevalent among patients with AF ($P < 0.001$). The median atrial run duration was 5.96 (2.02–17.84) s in the AF absent group vs. 8.76 (3.78–17.62) s in the AF present group ($P < 0.001$). The best predictive cut-off duration of an atrial run was 8 s (sensitivity = 61.5% and specificity = 74.4%, Area Under Curve (AUC) = 0.708). Cox regression analysis showed that age (odds ratio [OR]: 1.03, 95% confidence interval [CI]: 1.00–1.060, $P = 0.020$), presence of short supraventricular run (OR: 2.53, 95% CI 1.40–4.57, $P = 0.002$), and left atrial diameter (OR: 1.13 95% CI: 1.07–1.19, $P < 0.001$) were the independent predictors of AF development in the follow-up. **Conclusion:** Age, left atrial diameter, and the presence of SVRs are associated with an increased risk of future AF after ischemic stroke. SVR duration may be an important parameter in risk stratification.

Keywords: Atrial fibrillation, atrial premature complexes, cardioembolic stroke, cryptogenic stroke

Introduction

The underlying etiology remains undetermined in more than 20% of the patients with ischemic stroke despite comprehensive diagnostic work-up.[1] Irrespective of underlying etiology, identifying subjects with a cardioembolic source is an essential task because patients with ischemic stroke of undetermined origin are more prone to recurrences and have poorer survival rates compared to those with other subtypes.[2] Atrial fibrillation (AF) is the most common chronic arrhythmia and is strongly associated with ischemic stroke. Furthermore, subclinical AF episodes were shown to cause an increased risk of stroke.[3]

Documentation of AF can be challenging, especially in patients with paroxysmal AF.[4] Several diagnostic tools such as continuous Holter monitoring,[5] implantable loop recorders,[6] and recently smartphones/watches[7] are helpful in this regard. Prolongation of electrocardiography (ECG) monitoring or invasive tools[8] may enhance our patient care in patients with no previous AF.[9] Despite all the limitations, 24-h Holter monitoring is the most commonly used initial test for the diagnosis of AF, even in post-stroke patients.[10] Although premature atrial contractions (APCs) and supraventricular runs (SVRs) are frequently detected in this patient population, the data on the clinical significance thereof remain insufficient.

In this study, we investigated the significance of short atrial runs that do not qualify as AF detected by 24-h ECG monitoring in terms of future AF incidence in patients with ischemic stroke.

Methods

Study group

We retrospectively evaluated 726 patients with ischemic stroke who were scheduled for 24-h ECG Holter monitoring to rule out the presence of AF at our neurology department between 01/06/2018 and 30/01/2022. Paroxysmal AF was detected in 32 patients (4.4%) in the initial evaluation. A total of 694 patients were included in the final analysis. The patients with ischemic stroke underwent thorough routine etiological workup in our stroke center. Patients were categorized into five subgroups according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-vessel occlusion, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology.[11] Demographic and clinical

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characteristics and laboratory studies of the patients including detailed medical history, electrocardiography (ECG), and transthoracic echocardiography (TTE) parameters were recorded from our hospital's information management system. CHA_2DS_2-VASc score (congestive heart failure, hypertension, age 65–74 years, diabetes mellitus, stroke/transient ischemic attack/systemic thromboembolism [2 points], vascular disease, age ≥75 [2 points], sex category [female]) was calculated according to the recent AF guidelines.[12] However, because all patients were suffering from stroke, only patients with a previous history of stroke were considered as a component of the CHA_2DS_2-VASc score. Informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee (No: 218/21.03.2022).

Holter monitoring

We routinely performed 24-h Holter monitoring in all ischemic stroke patients without a history of AF at the time of admission, independent of their TOAST class. Holter ECG monitoring (GE medical systems information technologies, Inc., software version 8.0.3, Milwaukee, USA) was performed using a 3-channel recording and then transferred to computer software, and the results were initially analyzed by the Holter program and then manually screened. Narrow QRS complex tachycardia lasting ≥3 beats and ≤30 s was defined as an SVR. The maximum duration of the SVRs was also measured in each patient if the patient had more than one episode.

Follow-up

Our hospital's and governmental electronic health recording system was searched to figure out the presence of AF episodes at follow-up. AF (a 12-lead ECG or a single ECG tracing ≥30 s with irregular RR interval without any discernible *P* waves) was diagnosed if only confirmed by a cardiologist, and the date of diagnosis was noted. Anticoagulation status was also checked in the follow-up. Then, the patient group was divided into two subgroups i) AF present group at follow-up and ii) AF absent group at follow-up.

Patients with acute coronary syndrome, malignancy, acute decompensated heart failure, acute infectious disease, previous diagnosis of paroxysmal AF at the time of Holter monitoring, and suboptimal ECG recordings due to marked noise were excluded from the study.

Statistical analysis

SPSS for Windows version 25.0 (SPSS Inc., Chicago, IL, USA) was used for the analysis. The Kolmogorov–Smirnov test was used to test the normality of distribution for continuous variables. The continuous variables are presented as mean ± standard deviation and median (minimum and maximum) values. The comparisons of categorical variables were performed using the Chi-square test. The possible factors identified in univariate analysis were further entered into a Cox regression analysis to determine the independent predictors of AF development in the entire population. The receiver operating characteristic (ROC) analysis was used to determine a cut-off value for SVR duration. The Cox regression and log-rank tests were used accordingly by dividing the entire group into three predictor subgroups i) SVR absent s, ii) SVR <8 s, iii) SVR ≥8 s and log-rank test to compare survival between groups. A *P* value <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 694 patients were included in the analysis. AF was detected in 71 (10.23%) patients at a median follow-up duration of 24 (5–41) months. Baseline characteristics are depicted in Table 1. Four hundred six patients (51.8%) were male and the median age was 63 (18–93) years for the entire population. Baseline characteristic features differed between AF absent and AF present groups in terms of age (61 [18–97)] vs. 73 [32–92]; respectively, $P < 0.001$], presence of hypertension (53.7% vs. 59%; respectively, $P = 0.001$), coronary artery disease (19.8% vs. 38.9%, respectively; $P < 0.001$), heart failure (8.6% vs. 16.7%, respectively; $P = 0.016$), history of cerebrovascular disease (35.4% vs. 46.7%, respectively; $P = 0.038$), smoking status (30.3% vs. 12.2%, respectively; $P < 0.001$), and CHA_2DS_2-VASc score (3 [0–9] vs. 4 [0–8]; respectively, $P < 0.001$). The presence of diabetes mellitus ($P = 0.260$) and body mass index (BMI) ($P = 0.277$) values were similar between the groups. According to the TOAST classification, 148 patients (21.3%) had large-artery atherosclerosis, 114 patients (16.4%) had a cardioembolic stroke, 154 patients (22.2%) had small vessel occlusion, 96 patients (13.8%) had a stroke of other determined etiology, and 182 patients (26.2%) had a stroke of undetermined etiology. The majority of the patients (46.4%) who were diagnosed with new-onset AF had a cardioembolic stroke, wherein 11 patients (15.4%) were classified as cryptogenic in the first evaluation.

Laboratory and transthoracic echocardiography analysis

Hemoglobin ($P < 0.001$) and triglyceride ($P < 0.001$) levels were significantly different, whereas other laboratory findings were similar between the groups.

In transthoracic echocardiographic analysis, EF values were significantly lower ($P < 0.001$) and LA diameter was larger in the AF group ($P < 0.001$). The presence of severe valvular disease was rare (three patients with severe mitral regurgitation, and two patients with severe tricuspid regurgitation) in the entire population. The median systolic pulmonary artery pressure was 29 (18–65) mmHg [Table 2].

Baseline 24-h Holter monitor findings and development of AF

The median follow-up duration was 25 (5–41) months in patients without SVR, 18 (6–41) months in patients with an SVR duration <8 s, and 23 (7–41) months in patients with an SVR duration ≥8 s. AF was detected in nine (12.6%) patients

Table 1: Baseline demographic and clinical features of the population

	All patients (694)	Atrial fibrillation (−) (*n*: 623)	Atrial fibrillation (+) (*n*: 71)	P
Male gender, *n* (%)	406 (51.8)	377 (59.3)	45 (50.0)	0.095
Hypertension, *n* (%)	421 (53.7)	375 (59.0)	70 (77.8)	0.001
Diabetes mellitus, *n* (%)	208 (26.5)	189 (29.7)	32 (35.6)	0.260
Coronary artery disease, *n* (%)	149 (19.0)	126 (19.8)	35 (38.9)	<0.001
Heart failure, *n* (%)	62 (7.9)	55 (8.6)	15 (16.7)	0.016
Previous CVE, *n* (%)	250 (31.9)	225 (35.4)	42 (46.7)	0.038
Smoking, *n* (%)	201 (25.6)	193 (30.3)	11 (12.2)	<0.001
Age (years)	63 (18-93)	61 (18-97)	73 (32-92)	<0.001
BMI (kg/m^2)	27.17 (19.05-40.76)	27.22 (18.49-40.76)	26.22 (19.88-35.16)	0.277
CHA2DS2-VASc score	3 (0-9)	3 (0-9)	4 (0-8)	<0.001
TOAST Classification, *n* (%)				<0.001
• Large-artery atherosclerosis	148 (21.2)	133 (21.3)	15 (21.1)	
• Cardioembolism	114 (16.4)	81 (13.0)	33 (46.4)	
• Small-vessel occlusion	154 (22.3)	148 (23.7)	6 (8.4)	
• Stroke of other determined etiology	96 (13.8)	90 (14.4)	6 (8.4)	
• Stroke of undetermined etiology	182 (26.2)	171 (27.4)	11 (15.4)	

CVE, Cerebrovascular event; BMI, Body Mass Index; CHA_2DS_2-VASc, Congestive Heart Failure, Hypertension, Age (65–74), Diabetes Mellitus, Stroke/Systemic embolism, Vascular disease, Age ≥75, Sex category; TOAST, Trial of Org 10172 in Acute Stroke Treatment

Table 2: Transthoracic echocardiography, laboratory, and 24-h Holter monitoring findings

	All patients (*n*: 694)	Atrial fibrillation (−) (*n*: 623)	Atrial fibrillation (+) (*n*: 71)	*P*
TTE				
• EF, %	60 (20-71)	61 (20-71)	60 (25-67)	<0.001
• LA diameter, mm	37 (26-70)	37 (26-70)	40 (32-60)	<0.001
• Severe MR, *n* (%)	3 (0.4)	3 (0.5)	0 (0)	0.048
• Severe TR, *n* (%)	2 (0.3)	0 (0)	2 (2.8)	0.331
• sPAP, mmHg	29 (18-65)	28 (18-65)	30 (23-60)	0.024
Laboratory findings				
• Hb, g/dL	13.6 (7-21)	14 (8-21)	13 (7-17)	0.002
• Plt, (1000/m^3)	249 (17-754)	249 (17-754)	242 (112-607)	0.569
• WBC, (1000/m^3)	7.49 (3.12-30.97)	7.52 (3.12-30.97)	7.30 (3.22-13.42)	0.360
• Glucose, mg/dL	114 (55-625)	115 (55-625)	109 (73-391)	0.922
• Creatinine, mg/dL	0.82 (0.33-9.67)	0.81 (0.38-9.67)	0.85 (0.33-2.89)	0.220
• LDL, mg/dL	121 (28-274)	120 (28-274)	113 (45-265)	0.161
• HDL, mg/dL	43 (18-89)	43 (18-89)	45 (29-74)	0.111
• Triglycerides, mg/dL	142 (40-934)	144 (40-934)	116 (46-383)	<0.001
Holter recording				
• SVR, *n* (%)	104 (14.9)	78 (12.3)	26 (28.9)	<0.001
• SVR duration, s	6.54 (2.0-17.8)	5.96 (2.0-17.8)	8.76 (3.7-17.6)	0.002
• APC, *n* (%)	121 (17.4)	100 (16.2)	21 (29.6)	0.005

TTE, transthoracic echocardiography; EF, ejection fraction; LA, left atrium; MR, mitral regurgitation; TR, tricuspid regurgitation; sPAP, systolic pulmonary artery pressure; Hb, Hemoglobin; PLT, platelet; WBC, white blood cell; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SVR, supraventricular run

within a month after initial negative Holter monitoring. There were 104 (14.9%) patients with SVRs and 121 patients (17.4%) with APCs in the study group. Seventy-one (10.2%) patients were diagnosed with atrial fibrillation in the follow-up. AF was not detected in 78 patients with SVRs at baseline, whereas 26 patients (28.9%) were diagnosed with AF in the follow-up, which was significantly different between the groups ($P < 0.001$). The median atrial run duration was 5.96 s (2.02–17.84) in the AF absent group vs. 8.76 s (3.78–17.62) in the AF present group, which constituted a statistically significant difference between the groups ($P < 0.001$). The ROC analysis revealed that the best predictive cut-off duration of the atrial run was 8 s (sensitivity = 61.5% and specificity = 74.4%, Area Under Curve (AUC) = 0.708) [Figure 1].

In the Cox regression analysis, age (odds ratio [OR]: 1.03, 95% confidence interval [CI]: 1.00–1.06, $P = 0.014$), presence of short atrial run (OR: 2.26, 95% CI 1.36–3.74, $P = 0.001$), and left atrial diameter (OR: 1.10 95% CI: 1.05–1.15, $P < 0.001$)

were the independent predictors of AF development in the follow-up [Table 3]. On the other hand; even though the rate of APC was significantly higher in patients who developed AF in the follow-up ($P = 0.005$), there were no differences among the groups in the Cox regression analysis (OR: 1.05, 95% CI: 0.61–1.78, $P = 0.885$). The likelihood of AF development was significantly higher in patients with SVR lasting ≥8 s compared to patients with SVR lasting <8 s (Cox regression with log rank test, P:0.0003) or patients without SVR ($P < 0.001$) [Figure 2]. AF-free survival was 92.4% in patients without SVR and 84.1% in patients with an SVR duration <8 s. Meanwhile, AF-free survival was 57.1% in patients with an SVR duration ≥8 s.

Discussion

Our study findings can be summarized as follows: i) SVR and/or APC is frequently detected during Holter monitoring in the diagnostic evaluation of patients with ischemic stroke, ii) advanced age, larger left atrial diameter, and the presence of SVR are significantly associated with AF development in stroke patients with sinus rhythm, iii) SVR duration (≥8 s) may be utilized in risk stratification for the development of AF in patients without a previous diagnosis, iv) the presence of APCs was not associated with an increased risk of AF according to the multivariate analysis, v) new-onset AF was more prevalent in patients with cardioembolic stroke.

Identifying AF in patients with ischemic stroke is mandatory due to its therapeutic implications. Thus, all efforts should be made to establish the diagnosis of AF in this regard to improve outcomes and prevent future stroke recurrences. The optimal duration of monitoring and the combination of the diagnostic methods are yet to be determined.[13] It is well known that prolonged (≥7 days) ECG monitoring increases the rate of atrial fibrillation detection after ischemic cerebrovascular events.[9] However, the availability of long-term monitoring tools, especially implantable loop recorders is substantially limited because these tests are time-consuming and prohibitively expensive. A sequential combination of cardiac monitoring improves outcomes in patients with ischemic stroke and transient ischemic events, irrespective of the underlying anatomical defect.[14] Yet 24 to 48-h Holter monitoring is still the first-line monitoring strategy after stroke to rule out AF, during which APCs and SVRs are frequently detected even in the absence of paroxysmal AF.[15] Unlike AF, there is no consensus about the management when SVRs and APCs are detected, and the clinical approaches of neurologists and cardiologists differ due to the resultant uncertainty and ambiguity.[16] SVRs were shown to increase the risk of stroke and decrease overall survival, irrespective of the AF status. Kochhäuser *et al*.[17] demonstrated that supraventricular premature beats and short atrial runs detected with the aid of internal loop recorders were associated with future AF events in a number of patients. Up-to-date guidelines[12,18] recommend an AF diagnosis if the arrhythmia is sustained for >30 s; however, to our knowledge, there are no data on the clinical importance of SVR duration in predicting the development of AF. Our study showed that SVR episodes lasting ≥8 s during 24-h Holter monitoring

Table 3: Cox regression analysis for the detection of future atrial fibrillation episodes

Parameters	Multivariate		
	OR	95% CI	*P*
Age	1.03	1.00–1.06	0.014*
Coronary artery disease	1.37	0.73–2.59	0.321
CHA2DS2-VASc score	1.03	0.86–1.24	0.697
HF	1.28	0.37–4.38	0.691
LVEF	0.97	0.92–1.03	0.365
Left atrial diameter	1.10	1.05–1.15	<0.001*
Presence of SVR	2.26	1.36–3.74	0.001*
Presence of APC	1.05	0.61–1.78	0.855

APC, atrial premature beats; CHA_2DS_2-VASc, Congestive Heart Failure, Hypertension, Age (65-74), Diabetes Mellitus, Stroke/Systemic embolism, Vascular disease, Age ≥75, Sex category; HF, Heart Failure; LVEF, Left Ventricular Ejection Fraction; SVR, Supraventricular run

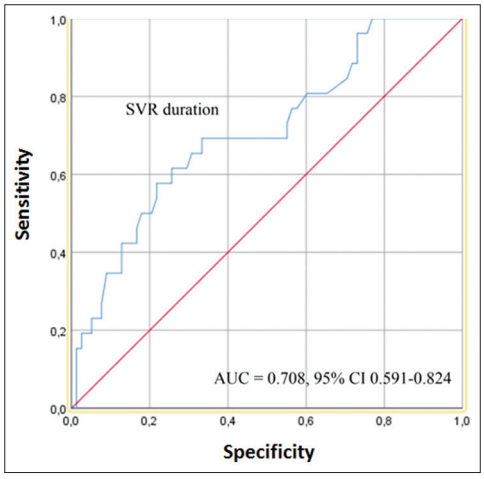

Figure 1: Receiver operating characteristic (ROC) curve of the supraventricular run (SVR) duration. The best predictive duration was 8 s with sensitivity = 61.5% and specificity = 74.4%

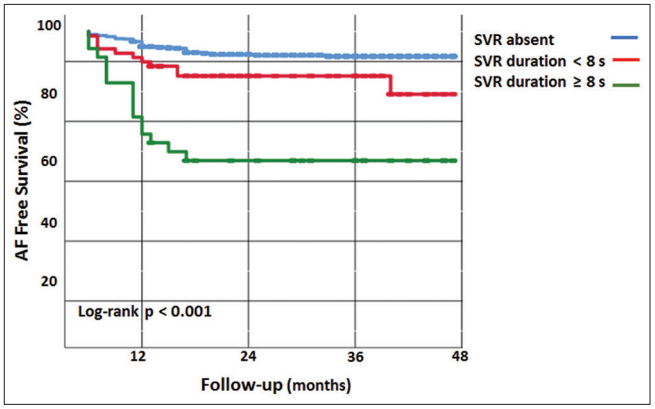

Figure 2: AF-free survival in the study group according to short atrial run status

may have an important predictive role in AF detection. On the contrary, SVR lasting <8 s and no SVR have similar outcomes in terms of AF development. It is well known that AF may be preceded by APCs from certain anatomical origins but not all APCs account for the initiation of AF.[19] Previously, >1,660 APCs during 24-h monitoring were shown to predict future AF with 98% specificity in patients with cryptogenic stroke.[17] However, we found that even though APCs were more prevalent in patients who developed AF, the predictive value of APCs for new-onset AF is limited.

Age and left atrial diameter were the strong predictors of new-onset AF as expected but the diagnostic utility of these parameters is scarce. Although advanced age and larger LA size are associated with a higher incidence of AF, the lack of certain cut-off values for risk assessment is the most important limitation to decision-making in clinical practice. CHADSVASc score is the proposed clinical score to determine the patients who have a high risk of recurrent ischemic events when AF is detected. However, the predictive value of the CHADSVASc score for new-onset AF is also unsatisfactory in AF-naive patients as in our study. This may be attributable to the dynamic nature of clinical risk scores. The development and persistence of AF is a complex process. Thus the reliability of a single clinical risk score for the prediction of AF is poor. Physicians should take into account the conditions associated with AF such as obesity, sleep apnea, and chronic lung disease, to better stratify the risk of developing AF in the follow-up of these patients.

Limitations

Our study had some limitations. First of all, it was a retrospective study. Second, because we only evaluated the role of baseline Holter recordings, the presence of AF may be underdiagnosed due to our design. Moreover; it was a single-center experience but our study population was relatively large. We performed three-dimensional (3D) echocardiography infrequently in stroke patients and only when indicated. All patients underwent standard transthoracic echocardiographic evaluation alone, and hence additional data from imaging techniques with detailed anatomical, volumetric, and functional parameters regarding the left atrium are lacking. The potential impact of concomitantly prescribed drugs such as antiarrhythmic and rate control drugs on the development of AF is also an important confounder, which is another limitation.

Conclusion

SVRs are frequently detected by Holter monitoring in the diagnostic evaluation of stroke. Besides age, left atrial diameter and the presence of SVRs are associated with an increased risk of future AF. SVR duration may be an important parameter in risk stratification. Intensified cardiac evaluation with the aid of extended-duration rhythm monitoring tools should be implemented when SVRs are detected after a stroke.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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