Ischemic Stroke Phenotype in Patients With Nonsustained Atrial Fibrillation

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Background and Purpose—The widespread use of ambulatory cardiac monitoring has not only increased the detection of high-risk arrhythmias like persistent and paroxysmal atrial fibrillation (AF), but also made it possible to identify other aberrations such as short-lasting (<30 seconds) irregular runs of supraventricular tachycardia. Ischemic stroke phenotype might be helpful in understanding whether these nonsustained episodes play a similar role in stroke pathophysiology like their persistent and paroxysmal counterparts.

Methods—In a consecutive series of patients with ischemic stroke, we retrospectively determined clinical and imaging features associated with nonsustained AF (n=126), defined as <30-second-lasting supraventricular tachyarrhythmias with irregular RR interval on 24-hour Holter monitoring, and compared them to patients with persistent/paroxysmal AF (n=239) and no AF (n=246).

Results—Patients with persistent/paroxysmal AF significantly differed from patients with nonsustained AF by a higher prevalence of female sex (odds ratio [95% confidence interval], 1.8 [1.1–2.9]), coronary artery disease (1.9 [1.1–3.0]), and embolic imaging features (2.7 [1.1–6.5]), and lower frequency of smoking (0.4 [0.2–0.8]) and hyperlipidemia (0.5 [0.3–0.8]). In contrast, patients with no AF were younger (0.5 [0.4–0.6] per decade) and more likely to be male (1.7 [1.0–2.8]) in comparison with nonsustained AF population. The prevalence of nonsustained AF was similar among cryptogenic and noncryptogenic stroke patients (32% versus 29%). Voxel-wise comparison of lesion probability maps revealed no significant difference between cryptogenic stroke patients with and without nonsustained AF.

Conclusions—Clinical features of patients with nonsustained AF exhibited an intermediary phenotype in between patients with persistent/paroxysmal AF and no AF. Furthermore, imaging features did not entirely resemble patterns observed in patients with longer durations of AF. **(*Stroke*. 2015;46:634-640. DOI: 10.1161/STROKEAHA.114.006396.)**

Key Words: atrial fibrillation ■ electrocardiography, ambulatory ■ magnetic resonance imaging

See related article, p 605.

Paroxysmal atrial fibrillation (AF) is considered to carry a similar risk of ischemic stroke compared with persistent AF,[1,2] and the management algorithm in terms of choosing the appropriate antithrombotic regimen is not different for both these types of AF.[3] The widespread use of ambulatory cardiac monitoring,[4–6] together with advances in implantable devices[7–9] and arrhythmia recognition algorithms, has not only increased the detection rate of high-risk atrial tachyarrhythmias like persistent and paroxysmal AF but also made it possible to identify other aberrations such as short-lasting (<30 seconds) irregular runs of nonsustained supraventricular tachycardia in patients with ischemic stroke.[10] Despite their resemblance to AF, these rhythms cannot be formally classified as paroxysmal AF because of their nonsustained nature.[11] More importantly, although shown to be predictive of future conversion to chronic AF,[12,13] it is currently unknown whether nonsustained AF episodes play a similar role in stroke pathophysiology like their persistent and paroxysmal counterparts. Previous studies have revealed a close relationship between total AF burden and embolic complications; data obtained from recordings in patients with implanted pacemakers show an increase in the incidence of embolic events when the duration of AF is >5 minutes, and this risk further escalates when the episodes last >24 hours.[13–16] This information, however, does not answer the question of whether more brief episodes are enough to trigger the formation of intracardiac thrombi and thereby result in further embolic complications.

The ideal approach to understand the pathophysiologic role of nonsustained AF in stroke would be to perform prospective population-based studies in which the risk of ischemic stroke is compared between cohorts with and without such an arrhythmia. Until this information becomes available

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in the literature, some clues obtained by looking into the stroke phenotype might be helpful in providing preliminary answers to the question. If indeed nonsustained AF exhibits a similar behavior like persistent or paroxysmal AF in terms of stroke risk, then it would be reasonable to hypothesize that phenotypic features like stroke risk factors, stroke pathogenesis, and lesion patterns would not differ significantly among patients with nonsustained and longer durations of AF. In this study, we therefore determined clinical and imaging features of patients with ischemic stroke harboring nonsustained AF on 24-hour Holter monitoring and compared them to those patients with persistent/paroxysmal AF and no AF to obtain some insight into the pathophysiologic role of nonsustained AF in ischemic stroke.

Methods

This was a retrospective analysis of patients with ischemic stroke consecutively admitted to a tertiary care center over a period of 3 years. The analyses were restricted to patients who had undergone 24-hour Holter ECG monitoring for determination of stroke pathogenesis. In addition, patients with stroke with either a history of persistent or paroxysmal AF or newly documented AF on ECG strips or during inpatient heart rhythm monitoring were also included into the study. To be included into the imaging analyses, patients had to have undergone an MRI study within 72 hours after symptom onset. The flowchart of patients included to and excluded from the study is shown in Figure I in the online-only Data Supplement. The study was approved by the local institutional review board.

A 24-hour Holter monitoring was performed with a 3-electrode recorder with standard and identical settings in all patients (Lifecard CF, Spacelabs Healthcare, Washington, USA). The presence of supraventricular runs with >3 beats and lasting <30 seconds, where RR interval was irregular and no evident p-waves detectable, was considered as nonsustained AF. Longer, self-terminating runs of fibrillation were considered as paroxysmal AF. The evaluation of Holter recordings primarily relied on the original clinical reports and the readjudication of ECG strips present on the enclosed report summaries. MRI, performed by a 1.5-T scanner (Magnetom TIM, Siemens, Erlangen, Germany), included axial T2-weighted (W) turbo spin echo (TR/TE; 3900/100 ms), FLAIR (TR/TE/TI; 8900/100/2000 ms) imaging, and diffusion-weighted imaging (DWI) (single-shot echo planar, TR/TE; 5100/137 ms; with a maximum of 1,000 s/mm^2) together with isotropic diffusion images and apparent diffusion coefficient maps calculated online immediately after completion of the scan.

Comparison of Clinical Stroke Features

The purpose of this analysis was to compare clinical stroke features among 3 groups of patients: (1) patients with chronic or persistent/paroxysmal AF determined either by history, conventional ECG, inpatient cardiac monitoring, or 24-hour Holter ECG; (2) patients without evidence of AF lasting ≥30 seconds but with nonsustained AF on 24-hour Holter ECG; and (3) patients without any duration of AF by ECG, cardiac monitoring, and 24-hour Holter ECG. For this purpose, age, sex, stroke risk factors (hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, prior history of transient ischemic attack and stroke, current smoking), admission National Institute of Health Stroke Scale score, and stroke pathogenesis were determined in all patients. All patients underwent a thorough evaluation regarding the intracranial and extracranial vasculature (either by magnetic resonance angiography, computed tomography angiography, or carotid/vertebral/transcranial Doppler studies) as part of the standard of care in our institution. The Causative Classification of Stroke system was used for etiologic subtyping[17]; as per the purposes of the study, which basically aims to determine whether nonsustained AF is equivalent to paroxysmal or persistent AF, the presence or absence of AF episodes <30 seconds was not included into the classification algorithm. In addition, where available, we collected information regarding left ventricular ejection fraction, left atrial diameter, and admission brain natriuretic peptide levels from patient charts. If the null hypothesis tested in the study (nonsustained AF~persistent/paroxysmal AF) is correct, one would expect no significant differences in clinical and laboratory features between nonsustained AF and persistent/paroxysmal AF groups, while both these groups would differ greatly from the group of patients with no AF. Concordantly, the prevalence of nonsustained AF would be higher among the otherwise cryptogenic patients, in comparison with patients with apparent causes of stroke.

Comparison of Imaging Stroke Features

These analyses were restricted to patients with MRI obtained within 72 hours of symptom onset. The purpose of this analysis was to compare imaging stroke features across 3 groups of patients: (1) patients with persistent/paroxysmal AF determined either by history, conventional ECG, inpatient cardiac monitoring, or 24-hour Holter ECG; (2) patients with cryptogenic stroke and nonsustained AF on 24-hour Holter ECG; and (3) patients with cryptogenic stroke and no evidence of any duration of AF on 24-hour Holter ECG. Patients with persistent/paroxysmal AF and a concomitant stroke pathogenesis (like large artery atherosclerosis, small artery occlusion) or cardiac pathology (like prosthetic valve disease, rheumatic valve disease) were left out of these analyses as these additional pathologies might potentially interfere with lesion patterns on MRI. The initial set of comparisons among these 3 groups focused on the prevalence of imaging and angiographic features suggestive of cerebral embolism. These features included the number of acute ischemic lesions, presence of isolated acute cortical lesions, and simultaneous acute ischemic lesions in multiple arterial territories on admission DWI, angiographic evidence of cutoff or recanalization on magnetic resonance angiography or computed tomographic angiography studies, and chronic territorial infarcts (excluding deep infarcts suggestive of small vessel disease) on T2W or FLAIR images, and were determined by consensus agreement between an experienced neuroradiologist and stroke neurologist. In the second stage, admission DWI of all patients were coregistered to MNI152 T1 template using the FSL-FLIRT (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software [FSL, www.fmrib.ox.ac.uk/fsl] Linear Image Registration Tool).[18,19] After coregistration, acute ischemic lesions on DWI were outlined using a semiautomated segmentation algorithm (MRIcro software; University of Nottingham, UK, www.mricro.com) to create region of interest masks. In addition to calculation of admission DWI lesion volumes, these region of interests in each group were used to calculate group-wise lesion distribution probability maps by the add and divide commands in FSL. The randomize command was then used to perform voxel-wise comparisons of lesion distributions among these 3 groups of patients.[19] All image analyses were performed while blinded to clinical information of patients. Similar to the analyses mentioned above focusing on clinical stroke features, the null hypothesis of the study would be rejected if imaging features differed significantly between patients with nonsustained AF and persistent/paroxysmal AF.

Numeric variables are expressed as median (interquartile range) and categorical variables as n (%). Kruskal–Wallis and Mann–Whitney *U* tests were used to assess the difference between numeric variables, and χ^2 test to assess differences with respect to categorical variables among study groups. A multinomial regression model was performed to assess clinical characteristics independently associated with the 3 study groups (no AF, nonsustained AF, and persistent/paroxysmal AF) which constituted the dependent variable in this multivariate model; baseline demographic and clinical characteristics (age, sex, history of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, prior stroke and transient ischemic attack, current smoking) were included in the model as independent variables. Nonsustained AF group comprised the reference category in the model. A $P<0.05$ was considered statistically significant. SPSS version 16.0 was used for statistical analyses.

Results

The study population consisted of 611 patients; 239 (39%) of these patients had evidence of persistent or paroxysmal AF (≥30 seconds) detected either by ECG, inpatient routine cardiac monitoring, or 24-hour Holter ECG. On the other hand, 126 (21%) patients had no arrhythmia on ECG or cardiac monitoring, while episodes of AF lasting <30 seconds were present on 24-hour Holter monitoring. The remaining 246 (40%) patients had no documented episode of AF, regardless of duration, on ECG, cardiac monitoring, and 24-hour Holter monitoring. Holter monitoring was performed after a median (interquartile range) delay of 12 (7–18) days after the onset of stroke symptoms.

Table 1 summarizes the clinical and laboratory features of the study cohort. Overall, patients with nonsustained AF exhibited an intermediary phenotype between patients with persistent/paroxysmal AF and without AF. The mean patient age, prevalence of female sex, hypertension, coronary artery disease, and prior history of stroke demonstrated a sequential stepwise increase from no-AF group to nonsustained AF group and finally to persistent/paroxysmal AF group (P=0.023 for history of stroke and P<0.001 for the remaining). A similar but inverse relationship was present with respect to hyperlipidemia (P=0.002) and current smoking (P<0.001). In multivariate analysis, younger (odds ratio [OR] 0.5 per decade, 95% confidence interval [CI], 0.4–0.6; P<0.001) and male (OR, 1.7; 95% CI, 1.0–2.8; P=0.038) patients were more likely to exhibit no-AF phenotype in comparison to nonsustained AF. On the other hand, female patients (OR, 1.8; 95% CI, 1.1–2.9; P=0.013) and those with coronary artery disease (OR, 1.9; 95% CI, 1.1–3.0; P=0.013) were more likely to have persistent/paroxysmal AF. In addition, current smoking (OR, 0.4; 95% CI, 0.2–0.8; P=0.013) and hyperlipidemia (OR, 0.5; 95% CI, 0.3–0.8; P=0.007) were factors significantly and negatively associated with persistent/paroxysmal AF in comparison to nonsustained AF (Figure 1). Patients with persistent/paroxysmal AF had more severe strokes when compared with patients with nonsustained AF or no AF (P<0.001). The median (interquartile range) left ventricular ejection fraction and left atrial diameter were 60% (50–64) and 43 mm (38–49), 61% (55–65) and 37 mm (35–40), and 64% (60–67) and 35 mm (32–38) in patients with persistent/paroxysmal AF, nonsustained AF, and no AF, respectively (P<0.001). Among patients with an admission plasma brain natriuretic peptide level available, there was again a sequential distribution, with highest levels observed in persistent/paroxysmal AF patients and lowest levels in patients without any AF (P<0.001). The distribution of stroke subtypes differed significantly between

Table 1. Comparison of Clinical Stroke Features and Laboratory Findings Among Patients With Persistent/Paroxysmal AF, Nonsustained AF and No AF

	Group I: Persistent/ Paroxysmal AF (n=239)	Group II: Nonsustained AF (n=126)	Group III: No AF (n=246)	*P* Overall (Group I vs II vs III)	*P* Post Hoc1 (Group I vs II)	*P* Post Hoc2 (Group II vs III)
Age (median, IQR); years	75 (66–80)	71 (64–77)	60 (47–68)	<0.001	0.009	<0.001
Female sex	62%	46%	35%	<0.001	0.005	0.031
Hypertension	87%	80%	66%	<0.001	0.106	0.005
Diabetes mellitus	30%	30%	31%	0.983	0.929	0.948
Coronary artery disease	44%	33%	27%	<0.001	0.029	0.286
Hyperlipidemia	34%	47%	50%	0.002	0.020	0.613
Prior history of TIA	13%	16%	15%	0.576	0.380	0.915
Prior history of stroke	30%	27%	20%	0.023	0.530	0.100
Current smoking	8%	21%	37%	<0.001	<0.001	0.002
Admission NIHSS (median, IQR)	8 (2–16)	4 (1–9)	3 (1–7)	<0.001	<0.001	0.220
CCS stroke subtype						
Large artery atherosclerosis	8%	30%	27%			
Cardioaortic embolism	69%	6%	7%			
Small artery occlusion	1%	11%	9%	<0.001	<0.001	0.314
Other causes	2%	10%	17%			
Undetermined—cryptogenic	0%	32%	35%			
Undetermined—unclassified/ incomplete evaluation	10%	10%	6%			
Left ventricular ejection fraction (median, IQR)*; %	60% (50%–64%)	61% (55%–65%)	64% (60%–67%)	0.001	0.016	0.024
Left atrium diameter (median, IQR)*; mm	43 (38–49)	37 (35–40)	35 (32–38)	<0.001	<0.001	<0.001
Plasma brain natriuretic peptide (median, IQR)†; pg/mL	445 (239–911)	125 (85–275)	54 (26–146)	<0.001	<0.001	<0.001

Analyses limited to 532* and 241† patients. AF indicates atrial fibrillation; CCS, Causative Classification of Stroke; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; and TIA, transient ischemic attack.

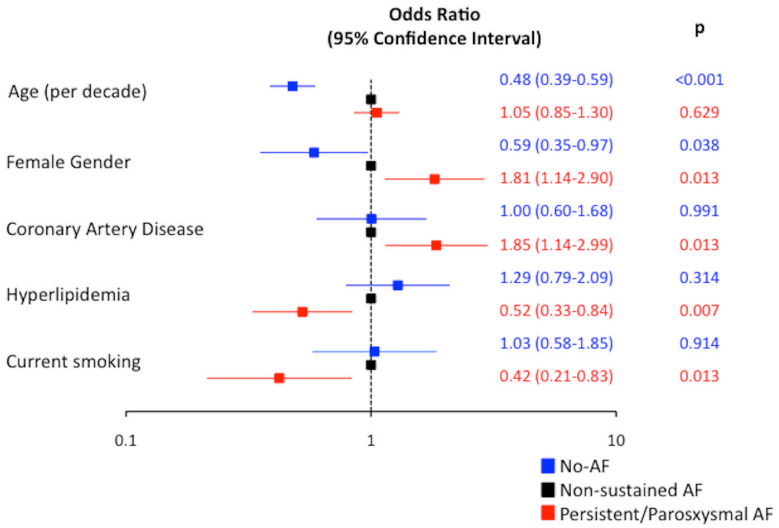

Figure 1. Results of the multivariate model with nonsustained atrial fibrillation (AF) group as the reference category, and persistent/paroxysmal AF and no-AF groups constituting the other dependent variables. Bars show the odds ratio and 95% confidence intervals.

persistent/paroxysmal AF patients and patients in the other 2 categories (Table 1). When the prevalence of nonsustained AF was evaluated among noncardioembolic stroke subtypes, no statistically significant difference was observed (P=0.445; Table 2). Specifically, nonsustained AF was not more common among cryptogenic stroke patients, compared with patients with other identified causes of stroke.

Table 3 summarizes the imaging features of patients with persistent/paroxysmal AF and patients with cryptogenic stroke with and without nonsustained AF. The 3 groups were not significantly different with respect to the number of acute ischemic lesions, presence of simultaneous acute lesions in multiple arterial territories, and isolated cortical lesions. On the other hand, patients with persistent/paroxysmal AF had larger acute ischemic lesions on DWI, had more chronic embolic infarcts, and were more likely to have angiographic features suggestive of embolism. In addition, when the presence or absence of any embolic imaging features was evaluated as a composite imaging signature, it was observed that these features were significantly more common among patients with persistent/paroxysmal AF (Table 3). The multivariate model, which took into account clinical features significantly related to type of AF (age, sex, coronary artery disease, hyperlipidemia, current smoking; per prior analyses), showed a significantly higher prevalence of any embolic feature among persistent/paroxysmal AF patients in comparison to nonsustained AF group (OR [95% CI], 2.7 [1.1–6.5]; P=0.035). The lesion distribution probability maps of acute ischemic lesions on DWI are shown in Figure 2. No significant difference was present in lesion distributions among cryptogenic stroke patients with and without nonsustained AF. On the other hand, the distribution pattern was significantly different between patients with persistent/paroxysmal AF and cryptogenic stroke patients without nonsustained AF (Figure 3A), with a propensity for left striatal and insular lesions in the former group. There was also a higher likelihood of left insular lesions when persistent/paroxysmal AF patients were compared with cryptogenic stroke patients with nonsustained AF; however, the significance level was between 0.05 and 0.10 in all of the relevant voxels (Figure 3B).

Table 2. Prevalence of Nonsustained AF Among Noncardioembolic Stroke Subtypes

Large artery atherosclerosis (n=123)	31%
Small artery occlusion (n=37)	38%
Other causes (n=59)	22%
Cryptogenic causes (n=125)	32%
Unclassified causes (n=37)	24%

P=0.445. AF indicates atrial fibrillation.

Discussion

Our findings show that patients with nonsustained AF show an intermediary phenotype with respect to clinical, laboratory, and echocardiographic features in between patients with persistent/paroxysmal AF and no AF. We were not able to demonstrate a selective variability in the prevalence of <30 seconds-long AF episodes among various stroke subtypes. Furthermore, lesion patterns in cryptogenic stroke patients with nonsustained AF resembled to those patients without any AF, while patients with persistent/paroxysmal AF segregated significantly from both of these groups in terms of lesion volume, lesion distribution, and imaging features suggestive of embolism.

Studies performed by various long-term ECG monitoring tools like inpatient cardiac telemetry, Holter ECG, and external or implantable loop recorders have shown that a new diagnosis of AF can be established in up to 28% of patients presenting with ischemic stroke.[4–9,20,21] Nonetheless, most of these studies, which show significant variation in terms of type, timing, and duration of monitoring; ECG analysis algorithm; and patient cohort characteristics, generally focus on the detection of AF episodes lasting ≥30 seconds, which is well known to alter the therapeutic management plan once if identified. On the other hand, knowledge is limited regarding the role of brief episodes of AF in the ischemic stroke setting. Outpatient cardiac monitoring studies performed in cryptogenic and noncryptogenic stroke cohorts have revealed that these shorter runs of AF are encountered much more commonly than the conventional, ≥30-second-lasting AF episodes.[10,22–24] The yield of 24-hour Holter ECG was 2% in terms of detecting ≥30-second-lasting

Table 3. Comparison of Imaging Features Among Patients With Persistent/Paroxysmal AF and Cryptogenic Stroke

	Group I: Patients With Persistent/ Paroxysmal AF (n=102)	Group II: Patients With Cryptogenic Stroke and With Nonsustained AF (n=38)	Group III: Patients With Cryptogenic Stroke and Without Nonsustained AF (n=80)	*P* Overall (Group I vs II vs III)	*P* Post Hoc1 (Group I vs II)	*P* Post Hoc2 (Group II vs III)
Number of acute ischemic lesions (median, IQR)	3 (1–6)	3 (1–8)	3 (1–6)	0.879	0.934	0.786
Simultaneous acute lesions in multiple arterial territories	21%	18%	18%	0.865	0.776	0.903
Isolated acute cortical lesions	20%	29%	20%	0.455	0.237	0.280
Angiographic evidence of cutoff or recanalization	42%	29%	20%	0.003	0.120	0.280
Chronic embolic infarcts	47%	32%	28%	0.019	0.100	0.648
Any embolic feature	85%	68%	61%	0.001	0.030	0.449
DWI lesion volume (median, IQR)	21.2 (5.2–66.9) mL	7.0 (2.5–35.3) mL	7.6 (1.2–30.5) mL	0.008	0.035	0.674

AF indicates atrial fibrillation; DWI, diffusion-weighted imaging; and IQR, interquartile range.

paroxysmal AF episodes in our cohort, while 31% of patients undergoing Holter monitoring had <30-second-lasting episodes (data not shown). In terms of clinical characteristics, prior studies that involved patients with nonsustained AF generally have not evaluated them as separate cohorts, but rather combined them with group of patients that had longer durations of AF; their findings highlight that patients with any duration of AF are more likely to be older[10,24] and have a history of diabetes mellitus[10] compared with patients devoid of AF. Our study, which not only includes the largest cohort of patients with brief durations of AF reported in the literature, but also analyzes them separately from patients with longer durations of AF, suggests that combining patients with short and long durations of AF might not be entirely a correct approach. Demographic, clinical, and laboratory features that are well known to be related to the interplay between ischemic stroke and AF are more commonly observed in patients with nonsustained AF with respect to patients with normal findings on Holter monitoring, but are still not as common as those observed in longer durations of AF.[25–27] All these findings fit well into the recent observations that short supraventricular runs designate initial stages of left atrial remodeling and therefore are a predictor of future AF.[12,13]

Leaving aside the prognostic value in predicting conversion into persistent AF, the more critical question is whether nonsustained AF plays a similar role in stroke pathophysiology like its persistent or paroxysmal equivalents. One way to answer this question might be to assess the presence of nonsustained AF in various stroke subtypes and look for a higher prevalence of this arrhythmia in cryptogenic strokes. In concordance with this hypothesis, the yield of long-term rhythm monitoring for conventionally defined AF episodes lasting ≥30 seconds is higher in patients with cryptogenic stroke, suggesting that ≥30-second AF episodes are causally linked to the ischemic event and underlie the otherwise cryptogenic pathophysiology in a proportion of these patients.[21] However, this is not the case for nonsustained AF; neither our findings, nor previous reports in the literature,[24] were able to identify a higher rate of nonsustained AF episodes in cryptogenic stroke patients. An alternative clue regarding the pathogenic role of nonsustained AF might come from analyses involving imaging features of patients with stroke; the identification of embolic stroke features and characteristic lesion patterns in these patients might provide the missing link between nonsustained AF and ischemic stroke pathophysiology. Some of

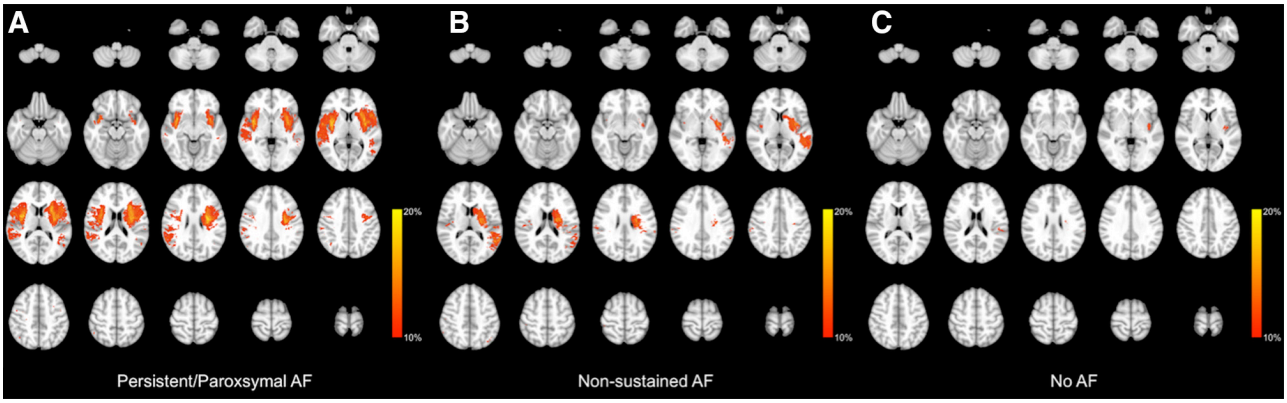

Figure 2. The lesion distribution probability maps of acute ischemic lesions on diffusion-weighted imaging in patients with persistent/paroxysmal atrial fibrillation (AF; **A**), cryptogenic stroke with nonsustained AF (**B**), and cryptogenic stroke without nonsustained AF (**C**). Highlighted regions signify voxels with acute ischemic lesions present in >10% of patients.

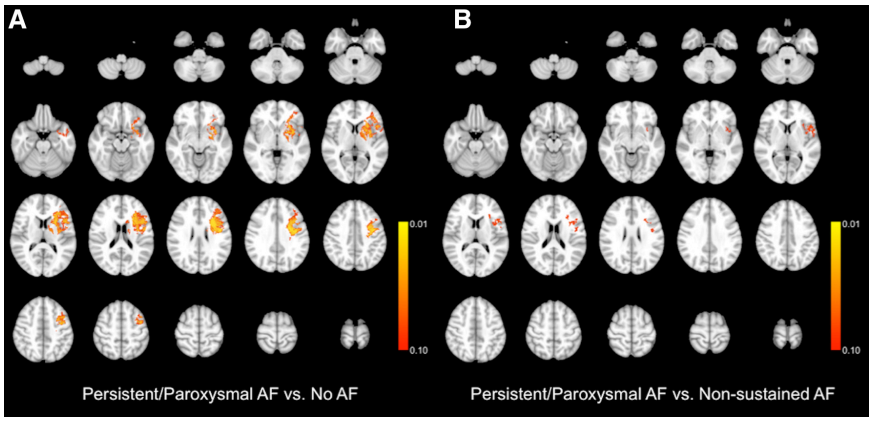

Figure 3. Voxel-wise comparison of lesion distribution probability maps among patients with persistent/paroxysmal atrial fibrillation (AF) vs cryptogenic stroke without nonsustained AF (**A**), and patients with persistent/paroxysmal AF vs cryptogenic stroke with nonsustained AF (**B**). Highlighted regions signify voxels that are more commonly involved in patients with persistent/paroxysmal AF with a $P<0.10$.

the previous studies, not independently analyzing patients with <30- and ≥30-second-long AF, have suggested that a new diagnosis on AF on prolonged monitoring was related to anterior circulation infarcts,[5] and acute cortical and chronic infarcts on computerized tomography or MRI,[23] while others were not able to identify any difference in terms of lesion topogprahy.[10,24] Our analyses which separately evaluated patients with nonsustained and persistent/paroxysmal AF have shown that lesion patterns in nonsustained AF did not resemble those patterns in patients with longer durations of AF. Presence of imaging and angiographic features suggestive of embolism and distribution of acute ischemic lesions were not significantly different between patients with and without nonsustained AF. Therefore, neither the analyses focusing on the distribution of nonsustained AF among various stroke subtypes nor the stroke-related imaging features were supportive of an exact similarity between nonsustained AF and persistent/paroxysmal AF in ischemic stroke. These findings can be considered as concordant with previous reports suggesting that left atrial stunning, the inciting event of atrial appendicular thrombus formation, is relatively uncommon before 15 to 20 minutes after the onset of AF episode.[28]

Several limitations of our study merit consideration. An inherent selection bias is unavoidable because of the retrospective nature of the study; although it is a standard of care to perform Holter monitoring to all stroke patients with no apparent AF on ECG or inpatient rhythm monitoring (regardless of the presence or absence of alternative stroke pathogeneses), there were still patients that were not able to undergo Holter monitoring because of various reasons like early mortality, physician discretion, and early discharge with loss to follow-up. There were however no significant differences in terms of age and baseline cardiovascular risk factors among patients with and without Holter monitoring. Excluded patients primarily resembled those patients with no evidence of AF on Holter monitoring, except for a higher number of patients with cryptogenic stroke in the latter group. This variability might hinder the applicability of our analyses regarding the relationship between stroke pathogenesis and nonsustained AF to the general stroke population. Another source of selection bias arose from the restriction of imaging analyses to patients who had undergone MRI within 72 hours of symptom onset. Nonetheless, none of the demographic and clinical variables, including admission stroke severity—which is closely related to lesion volume and location—differed substantially between patients with and without MRI. The presence or absence of nonsustained AF was defined per 24-hour Holter monitoring; it is highly probable that runs of AF lasting either <30 or ≥30 seconds would be detected in a certain amount of these patients if they were monitored for longer durations or by other tools. Still, 24-hour Holter monitoring is the most widely available ambulatory monitoring tool, and we therefore think that our approach reflects the everyday clinical practice. We only evaluated left atrial diameter and left ventricular ejection fraction as echocardiographic parameters in our study; however, many other measures of left atrium function determined either by transthoracic or transesophageal echocardiography are gaining importance in predicting AF and the associated stroke risk,[29,30] and therefore should also be studied in this context. Finally, our analyses comparing lesion distribution probability maps have shown a borderline difference between persistent/paroxysmal AF and nonsustained AF patients, and no difference between nonsustained AF and no-AF patients; although the size of patient groups was considerably sufficient for voxel-wise analyses, future studies performed with larger number of patients might identify additional disparities in lesion patterns that could have been missed in our study.

In conclusion, our findings suggest that clinical and imaging characteristics observed in patients with nonsustained AF do not entirely resemble patterns observed in patients with longer durations of AF. Because of the retrospective nature of the study and absence of a control group, these findings should be considered as hypothesis generating at best, and not be used to refute the causative role of nonsustained AF in stroke. For now, these findings, together with the already published literature, can be interpreted such that patients with ischemic stroke and nonsustained AF should be followed up closely for conversion to persistent AF, but may not necessarily need to be treated as patients with persistent/paroxysmal AF in terms of stroke prophylaxis. Considering the possible rise in recognition of these arrhythmias in the near future by advances in heart rhythm monitoring technologies and their ease of accessibility, we definitely need further studies to clarify the causative role of nonsustained AF during ischemic stroke and how they should be handled regarding secondary stroke prevention.

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Disclosures

None.

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