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Diurnal Circadian Variations in Paroxysmal Atrial Fibrillation: the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background—Paroxysmal atrial fibrillation (AF) is challenging to diagnose due to its intermittent nature. Circadian rhythmicity has been reported for cardiovascular events such as myocardial infarction; whether diurnal variation exists for paroxysmal AF is less known. We characterized the temporal pattern of AF initiation in the Atherosclerosis Risk in Communities (ARIC) study, a prospective community-based cohort study.

Methods—We included 74 ARIC study participants with paroxysmal AF detected by the Zio XT Patch at ARIC Visit 6 in 2016–17. We divided each participant's 2-week continuous monitoring data into 3-hour intervals and summed the number of AF episodes in each interval. We performed Poisson regression using generalized estimating equations to estimate the effect of time of day on the number of AF episodes.

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Results—Compared to the reference interval of time 00:00–02:59, the time intervals 12:00–14:59, 15:00–17:59, and 18:00–20:59 had significantly higher frequency of AF initiation. Rate ratios (95% CI) for mean number of episodes in these three intervals were 1.91 (1.11, 2.92), 2.54 (1.42, 4.53), and 1.99 (1.19, 3.25) respectively. Furthermore, we found no significant association between duration of episode and time of day.

Conclusion—There is diurnal variation in the initiation of AF episodes, with a peak in frequency in the late afternoon. Our finding is consistent with sympathetically driven AF. Pulse palpation or obtaining an electrocardiogram in the late afternoon may produce the highest diagnostic yield for AF.

Keywords

Arrhythmia; Atrial Fibrillation; Electrocardiography; Heart Rhythm Disorder

INTRODUCTION

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias with an estimated lifetime risk between 20% and 33%.¹ AF is a serious public health problem because of its increasing incidence and prevalence, and its association with ischemic stroke, heart failure, dementia, and death.^{2,3,4} AF can be asymptomatic or subclinical and is reported to occur in approximately 30% of individuals who experience an ischemic stroke.⁵ Efforts to screen for subclinical AF are complicated by its episodic nature and limit attempts to capture it by intermittent and short-term heart rhythm monitoring.

Technological innovation in ambulatory ECG monitoring in recent years has permitted a longer monitoring period beyond the traditional 24–48 hours of Holter monitoring and better characterization of AF burden.^{6–8} The Zio® XT Patch (iRhythm Technologies; San Francisco, CA) is a leadless, ambulatory ECG monitoring device that can record heart rhythm continuously for 2 weeks. Several studies have used this technology to detect and investigate AF, but these studies were not based on unselected or community-based populations.^{9–11}

Circadian rhythmicity has been reported for cardiovascular events including arrhythmias. For example, Clair et al. reported that the frequency of paroxysmal supraventricular tachycardia (SVT) was lowest between midnight and 4 AM and peaked between 4 PM and 8 PM.¹² Similarly, Lee et al. observed nearly equal peaks in the frequency of SVT in the time periods from 8:00 to 9:00 AM, 12:00 to 1:00 PM, and 5:00 to 6:00 PM, with a trough at night.¹³ Culic et al. found that SVT can be triggered by periods of increased physical activity and meteorological factors.¹⁴ However, little is known regarding the temporal patterns, particularly circadian rhythmicity of AF initiation. A previous study that relied on hospitalization records and emergency telephone calls found some evidence of non-random onset of paroxysmal AF, with clustering in the early morning and late afternoon/evening.¹⁵ Previous work by Yamashita et al. investigated paroxysmal AF in hospitalized patients using Holter monitors and found AF onset to be more likely in the afternoon and around midnight.¹⁶

We aimed to determine whether circadian variation (diurnal and by day of week) exists for initiation of paroxysmal AF episodes, and if so, define the peak and nadir of AF initiation. To this end, we leveraged data from the Atherosclerosis Risk in Communities (ARIC) study, a prospective community-based cohort study in the USA. At ARIC Visit 6 (2016–17), we applied the Zio® XT Patch to more than 2,600 ARIC participants.¹⁷ We observed intermittent AF in 74 participants and sought to characterize the temporal variation of AF episodes in terms of time of day and day of the week. Findings from this investigation may inform the optimal time to screen for subclinical or asymptomatic AF.

METHODS

Study Population and Design

The ARIC Study¹⁸ is a prospective, community-based cohort study, which began in 1987–1989. The 15,792 ARIC study participants at inception were aged 45–64 years and were recruited from four U.S. communities (Forsyth County, NC; Jackson, MS; Washington County, MD; suburbs of Minneapolis-St. Paul, MN). Thus far, seven in-person study visits have been completed. Continuous follow-up through surveillance of each community's hospital discharge lists has occurred, as have regular follow-up telephone calls (annual through 2011, thereafter twice yearly). Participants provided written informed consent at each visit. Relevant to this cross-sectional analysis, 4,003 participants attended the visit 6 clinic exam during 2016–2017 when they were aged 75–94 years. Visit 6 participants at all four sites were invited to wear a Zio® XT Patch and the prescribed wear time was 14 days; exclusion criteria included history of cardiac electronic device implantation or skin allergic reaction to adhesive tape. At the end of the recording period, participants removed the device and mailed the heart rhythm monitor to iRhythm Technologies Inc., where recorded ECG data were processed using a proprietary algorithm and a report was generated.

Of 3,680 visit¹⁷ 6 participants who were eligible to wear the Zio® XT Patch, 2,650 (72.0%) agreed to participate. Of the 2,650 devices, 34 (1.3%) were lost or returned without data resulting in a total of 2,616 Zio® XT Patch devices with analyzable data. Of the devices with analyzable data, AF was detected in 217 with 87 classified as intermittent and 130 classified as continuous.¹⁷ Our final sample consisted of 74 participants with intermittent AF who had an AF burden of at least 0.01% (Supplemental Figure 1). Further information on other relevant aspects of data is provided in the Supplemental Material.

Atrial Fibrillation Diagnosis by the Zio® XT Patch

AF was defined by an irregularly irregular rhythm with absent P-waves lasting ≥ 30 seconds. AF adjudication by iRhythm was based on a 2-step process. First, the ECG data were interrogated using an FDA-cleared, proprietary algorithm to identify potential AF episodes based on detection of the heart rate, irregularity, and morphology. Next, trained and certified cardiovascular technicians re-examined the detected AF episodes to confirm the diagnoses. A standard report was generated and uploaded to a secure website. The standard report included a diagnosis summary and ECGs, which allowed verification of reported AF. Data on wear time and analyzable time were also obtained from the standard report. In our study, a team of physician ECG readers in EPICARE (Wake Forest University) verified the

accuracy of reported AF. Importantly, we were also provided timing data of AF episodes by iRhythm, which enabled us to analyze circadian variation of AF initiation or onset.

Covariates

We assessed the following covariates at visit 6: age, race (self-reported and combined with center to create a 5-level variable), sex, diabetes, hypertension, coronary heart disease (CHD), heart failure (HF), stroke, and medication use. Diabetes was defined by fasting blood glucose ≥ 126 mg/dL, non-fasting glucose ≥ 200 mg/dL, use of diabetes medications or self-report of a physician diagnosis. Hypertension at baseline was defined as a systolic blood pressure of at least 140 mm Hg or a diastolic pressure of at least 90 mm Hg or use of antihypertensive medication. Prevalent CHD¹⁹, HF²⁰ and stroke²¹ were defined using previously described methods. Briefly, possible hospitalized CHD and stroke events were abstracted by trained staff onto standardized forms and classified by physicians using computer-assisted classification algorithms. HF was defined by a prior hospital discharge code of '428' (428.0 – 428.9) in any position.²² Medications for which we adjusted were beta blockers, calcium channel blockers, and digoxin.

Statistical Analysis

We summarized binary and categorical variables as number (%) and continuous variables as mean $\pm$ standard deviation. We performed Poisson regression using Generalized Estimating Equations (GEE) to estimate the effect of different temporal periods (i.e., time of day and day of week) on the count of AF episode initiation or onset. To evaluate the association of time of day with AF episode initiation, we divided each individual's two-week monitoring data into three-hour intervals and counted the number of AF episodes that began within each interval. These counts were used as the dependent variable for a log-linear Poisson GEE regression model with time of day as the independent variable. To evaluate the association of day of week with AF episodes, we divided the monitoring data into days of the week and counted the frequency of episode onset for each day. These counts were used as the dependent variable in another log-linear Poisson GEE regression model with day of the week as the independent variable. Both regressions were performed using three models: Model 1 was unadjusted. Model 2 was adjusted for age, sex, and race. Model 3 additionally adjusted for hypertension, diabetes, stroke, HF, and medication use, and CHD. The GEE approach was used to account for the correlation of time intervals from the same individual. The correlation structure AR1 was specified to account for a stronger expected correlation between time periods that are close together.

Long episodes of AF that span several three-hour time intervals may affect the onset or initiation of AF episodes. To address this concern, we performed a sensitivity analysis by examining the effect of time of day on episode duration. Specifically, to test for potential diurnal variation in episode duration, we ran an inverse-linear Gamma GEE regression model using episode duration as the dependent variable and time of day as the independent variable. As with the previous GEE models, the correlation structure AR1 was specified.

All analyses were performed using R version 3.6.²³ GEE was implemented using the package 'geepack'.²⁴ A two-tailed p-value <0.05 indicated statistical significance.

RESULTS

The analysis cohort consisted of 74 participants (mean $\pm$ SD age, 80.2 ± 4.7 years, 44.6% men, and 14.9% black) (Table 1). The median analyzable time was 13.8 days (25th percentile=12.9 days; 75th percentile=14.0 days; Range=0.1–14.0 days), out of a maximum of 14 days. The median duration of wear time was 14 days.

Frequency of AF Episodes by Time of Day

The median number of AF episodes during the observation period was five (25th percentile=2, 75th percentile=18). Of AF episodes, 89% occurred in a single time-block; the remaining 11% spanned 2 or more time-blocks. There was no significant association between episode duration and time of day.

The AF episodes in our data demonstrate unimodal onset frequency with a peak at 15:00. Figure 1 shows a clear circadian rhythm in the frequency of AF initiation with a nadir in time block 00:00–2:59 rising to a peak in time block 15:00–17:59 and decreasing thereafter. The afternoon/evening time blocks ranging from 12:00–20:59 were associated with a higher frequency of AF initiation (Table 2). Specifically, when compared to the reference time block of 0:00–2:59, we found the rate ratios (95% CI) for mean number of episodes in the intervals 12:00–14:59, 15:00–17:59, and 18:00–20:59 to be 1.91 (1.11, 2.92), 2.54 (1.42, 4.53), and 1.99 (1.19, 3.25) respectively (Figure 1). These effect estimates remained essentially unchanged after further adjustment for covariates in Model 2 and 3.

Frequency of AF Episodes by Day of Week

We failed to find a significant association between day of the week and frequency of AF episodes. Compared with the reference day (Sunday), none of the days were associated with a significantly altered likelihood of AF initiation (Table 3 and Figure 2). Furthermore, in contrast to our analysis by time of day, Figure 2 does not demonstrate a clear pattern of variation in the frequency of AF initiation by day of week.

Impact of Episode Duration

The distribution of episode duration was highly skewed, with a median length of 2.01 minutes (25th percentile=1.9, 75th percentile=8.2) and a mean of 29.5 minutes. Additionally, we found that approximately 89% of episodes in our analysis were confined to only one three-hour time block, 10% spanned two time blocks, and the remaining episodes (<1%) spanned more than two time blocks. Importantly, our GEE regression performed as sensitivity analysis on episode duration with respect to time block found no statistically significant association between episode duration and time of day (**Supplemental Figure 2**).

DISCUSSION

Using 2 weeks of continuous ambulatory ECG monitoring in a community-based sample of 74 elderly black and white individuals aged 75 years, we observed the following key findings. First, there was diurnal variation detected in the initiation of paroxysmal AF episodes with highest frequency in the afternoon and early evening time. Second, analysis by

day of week did not show a clear pattern of variation. Collectively, our findings provide evidence to support circadian rhythmicity in the initiation of AF episodes and suggest that pulse palpation or obtaining an ECG in the late afternoon may produce the highest diagnostic yield for AF.

Although many studies have reported circadian rhythmicity in cardiovascular conditions including supraventricular arrhythmias,^{13,25,26} data on temporal variation of AF episodes are sparse. The few studies that have attempted to characterize the daily circadian rhythm of AF episodes suffer from a major limitation of relying on patient-reported symptoms to determine onset of AF episodes, a notoriously unreliable method since the vast majority of AF episodes are asymptomatic.^{12,15,27} These studies include two that reported a bimodal distribution with the majority of episodes starting between 06:00 and 12:00 or between 18:00 and 00:00.^{15, 28} By contrast, an Italian study reported a single peak with the majority of AF episodes occurring between 21:00 and 02:00.²⁷ In a Japanese study that relied on heart rhythm monitoring—rather than presentation with symptoms—to define the initiation of AF episodes, a bimodal distribution was noted with most episodes occurring between 12:00 and 15:00 or between 20:00 and 00:00.¹⁶ Of note, the heart rhythm monitoring was based on short-term 24-hour Holter recording, which is a critical limitation because the vast majority of AF episodes including their onset would have been missed. Moreover, patients included in the study were highly selected hospitalized patients whose AF episodes could have been triggered by acute medical illness. Another study based on continuous monitoring found a unimodal pattern in AF distribution, with a peak between 8:00 and 11:00 and a trough between 0:00 and 6:00, but this study was similarly based on a highly selected population of patients who were implanted with pacemaker for brady-tachy syndrome.²⁹ Therefore, our findings advance the field by characterizing the onset of spontaneously occurring AF episodes using long-term 2-week continuous heart rhythm recording in community-based free-living individuals. We show evidence for a propensity for AF initiation in the late afternoon but did not find evidence for proclivity of AF initiation for day of the week.

Several mechanisms can explain our observations. The role of the autonomic nervous system (ANS) in initiating AF episodes is well described.^{30–34} During periods of psychological (e.g., severe acute anxiety) or physiological stress (e.g., acute medical illness, post-operative state, severe dehydration, etc.) the sympathetic system is activated and alters atrial electrophysiology and increases susceptibility to atrial arrhythmogenesis. On the other hand, during times of rest or at night (particularly in young and athletic individuals), the vagal or parasympathetic system may play an important etiological role.^{30–32} Our finding of a peak in the initiation frequency of AF episodes in the late afternoon is more consistent with sympathetically driven AF rather than vagal-induced AF. Furthermore, our community-based sample of elderly patients also suggests that the more likely mechanism is sympathetically driven AF, rather than vagal-induced AF.

In 2014, the American Heart Association and American Stroke Association recommended that active screening for AF in the primary care setting among persons older than 65 years using pulse assessment followed by ECG can be useful.³⁵ Furthermore, the European Society of Cardiology recommends opportunistic screening by pulse palpation or an ECG

rhythm strip in persons older than 65 years and recommends considering systematic screening to detect AF in persons older than 75 years or those at high risk of stroke.³⁶ Our research—based on community-dwelling individuals aged 75 years in whom a diagnosis of AF would prompt anticoagulation to prevent stroke—are particularly germane in the current evolving debate on the merits and challenges of opportunistic or systematic screening for AF.³⁷ Specifically, our findings suggest that opportunistic or systematic screening for AF in elderly free-living individuals (either by pulse palpation or ECG) would have the highest yield if conducted in the late afternoon.

One potential challenge in our analysis is that AF episodes that span more than one time block would affect the initiation of AF episodes in subsequent time blocks. Of note, the vast majority of AF episodes (89%) were confined to a single time block; thus, the aforementioned issue should only have minimal impact on our findings. A second potential issue is diurnal variation in episode duration: a single long episode precludes the existence of multiple short episodes, so any diurnal variation in episode duration could bias our results towards time blocks with shorter episodes. Of note, there was no significant association between episode duration and time of day, which indicated a lack of systematic variation in episode duration.

Several limitations of our study should also be noted. First, the limited number of intermittent AF cases resulted in a relatively small sample size for this study. This hindered in-depth subgroup analyses. Second, one might argue that our observed diurnal variation in episodes may be biased due to conditional participation owing to participants surviving to that time-point, opting to wear an ECG monitor, and agreeing to attend a clinic visit. However, this scenario actually reflects reality; this ARIC sample would closely resemble an elderly population that is amenable to a screening program. Finally, our research cannot define the underlying cause of the observed diurnal variation and future studies are required to elucidate the underlying mechanisms.

Conclusion

Based on a community-based sample of elderly individuals, we observed evidence for circadian variation in the onset of AF episodes, with a peak in the late afternoon and a trough after midnight. Pulse palpation or obtaining an electrocardiogram in the late afternoon may produce the highest diagnostic yield for AF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Association Between Time of Day and Prevalence of Paroxysmal Atrial Fibrillation: The ARIC Study, 2016–17 (Rate Ratios and 95% CI)

Abbreviations: AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; CI, Confidence Interval

Figure 2. Association Between Day of Week and Prevalence of Paroxysmal Atrial Fibrillation: The ARIC Study, 2016–17 (Rate Ratios and 95% CI)

Abbreviations: AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; CI, Confidence Interval

Table 1.Clinical Characteristics of Study Participants With AF Detected Through ECG: The ARIC Study, 2016–17 ^{*}

N	74
Age, years	80.2 ± 4.7
Male sex	33 (44.6)
White race	63 (85.1)
Diabetes	11 (14.9)
Coronary heart disease	5 (6.8)
Heart failure	6 (8.1)
Stroke	5 (6.8)
Hypertension	57 (78.2)
Medication [†]	49 (66.2)

Abbreviations: AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; ECG, electrocardiogram.

^{*} Total n=74; data are presented as N (%) or mean ± standard deviation[†] Medications: Beta blockers, calcium channel blockers, digoxin

Table 2.

Association of Atrial Fibrillation Episodes With Time of Day: The ARIC Study, 2016–17

Time Period	Model 1		Model 2		Model 3	
	Rate Ratio (95% CI)	P-value *	Rate Ratio (95% CI)	P-value *	Rate Ratio (95% CI)	P-value *
0:00–2:59	Ref	-	Ref	-	Ref	-
3:00–5:59	1.04 (0.64, 1.70)	0.87	1.04 (0.62, 1.71)	0.87	1.02 (0.60, 1.72)	0.95
6:00–8:59	1.06 (0.62, 1.81)	0.84	1.06 (0.62, 1.81)	0.84	1.08 (0.63, 1.67)	0.87
9:00–11:59	1.73 (0.72, 4.12)	0.23	1.73 (0.72, 4.11)	0.23	1.71 (0.81, 3.58)	0.23
12:00–14:59	1.90 (1.01, 3.57)	0.047	1.90 (1.01, 3.58) *	0.047	1.91 (1.11, 2.92) *	0.049
15:00–17:59	2.55 (1.33, 4.91)	0.005	2.56 (1.33, 4.91) *	0.005	2.54 (1.42, 4.53) *	0.005
18:00–20:59	2.00 (1.07, 3.76)	0.03	2.01 (1.07, 3.76) *	0.03	1.99 (1.19, 3.25) *	0.04
21:00–23:59	1.26 (0.76, 2.08)	0.36	1.26 (0.76, 2.08)	0.36	1.22 (0.83, 1.79)	0.43

* P-value from the Wald Test

Model 1: Unadjusted

Model 2: Adjusted for age, race, and sex

Model 3: Model 2 + hypertension, diabetes, CHD, HF, medication, stroke

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CHD, coronary heart disease; CI, confidence interval; HF, heart failure; Ref, reference

Table 3.

Association of Atrial Fibrillation Episodes With Day of Week: The ARIC Study, 2016–17

Time Period	Model 1		Model 2		Model 3	
	Rate Ratio (95% CI)	P-value *	Rate Ratio (95% CI)	P-value *	Rate Ratio (95% CI)	P-value *
Sunday	Ref	-	Ref	-	Ref	-
Monday	1.60 (0.76, 3.35)	0.22	1.60 (0.76, 3.35)	0.22	1.60 (0.76, 3.35)	0.22
Tuesday	1.26 (0.55, 2.85)	0.59	1.26 (0.55, 2.85)	0.59	1.26 (0.55, 2.85)	0.59
Wednesday	0.52 (0.26, 1.06)	0.07	0.52 (0.26, 1.06)	0.07	0.52 (0.26, 1.06)	0.07
Thursday	1.35 (0.56, 3.24)	0.51	1.35 (0.56, 3.24)	0.50	1.35 (0.56, 3.24)	0.50
Friday	1.06 (0.54, 2.08)	0.87	1.06 (0.54, 2.08)	0.87	1.06 (0.54, 2.08)	0.87
Saturday	1.64 (0.74, 3.67)	0.22	1.64 (0.74, 3.67)	0.22	1.64 (0.74, 3.67)	0.22

* P-value from the Wald Test

Model 1: Unadjusted

Model 2: Adjusted for age, race, and sex

Model 3: Model 2 + hypertension, diabetes, CHD, HF, medication, and stroke

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CHD, coronary heart disease; CI, confidence interval; HF, heart failure; Ref, reference