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CLINICAL RESEARCH
*Cardiac electrophysiology*

# The circadian variation of premature atrial contractions

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**Aims** The aim of the study was to assess a possible circadian variation of premature atrial contractions (PACs) in a community-based population and to determine if the daily variation could be used to assess a more vulnerable period of PACs in predicting later incidence of atrial fibrillation (AF).

**Methods and results** We studied 638 subjects between the ages of 55 and 75 years from the Copenhagen Holter Study who underwent up to 48 h electrocardiogram recording. Follow-up on cardiovascular endpoints was performed in 2013 with a median follow-up time of 14.4 years. According to previous studies, two subgroups were studied based on a cut-off point of ≥720 PACs/day termed frequent PACs ($n = 66$) and not frequent PACs with <720 PACs/day ($n = 572$). Based on median values, a circadian rhythm could not be demonstrated in the population as a whole and the group without frequent PACs. However, a circadian variation was observed in the group with frequent PACs, who had the fewest PACs/h during the night with a nadir at 6 am and then reaching a peak value in the afternoon at 3 pm. Runs of PACs in all subjects showed a similar circadian variation. Both PACs/h and runs of PACs seemed to follow the daily variation in heart rate. After adjusting for relevant risk factors, the risk of AF was equal in all time intervals throughout the day.

**Conclusion** Premature atrial contractions showed a circadian variation in subjects with frequent PACs. No specific time interval of the day was more predictive of AF than others.

**Keywords** Circadian variation • Premature atrial contractions • Epidemiology • Atrial fibrillation

## Introduction

Circadian variation has been demonstrated in multiple cardiovascular parameters such as blood pressure, heart rate, and haemostasis.[1,2] In relation to pathophysiological events, a circadian variation has been observed in the onset of specific arrhythmias, the time of ischaemic events, and sudden cardiac death, most of these being in the morning hours between 6 am and noon.[3–10] The recognition of such patterns may contribute to identify possible underlying mechanisms behind the circadian variations, which may have potential clinical implications[11] (e.g. chronotherapy).

In the field of chronobiology, premature atrial contractions (PACs) are one of the least studied cardiac parameters. Premature atrial contractions are one of the most frequently encountered arrhythmia when evaluating a standard 12-lead electrocardiogram or an ambulatory electrocardiogram (ECG) recording.[12] In a clinical situation, it is often considered a relative benign finding, but epidemiologic follow-up studies have indicated that the presence of an excessive amount in long-term ECG recordings, or detecting one as a chance finding on a standard ECG, is independently correlated with a long-term increased risk of cardiovascular disease and cardiac arrhythmias especially in the form of atrial fibrillation (AF).[13–15] A circadian variation of PACs has been demonstrated in small healthy cohorts and on individual basis,[16,17] but remains to be studied in a larger community-based cohort with a long follow-up to detect possible association within the rhythmicity of PACs during a 24 h continuous period.

In this study, we examine whether PACs show a circadian variation in a community-based population without manifest heart disease and if there is a vulnerable period of PACs during the course of a day that is more predictive of later incident AF.

## Methods

The study cohort is based on the Copenhagen Holter Study, which commenced in April 1998, with the last subjects included in

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## What's new?

- A circadian rhythm of premature atrial contractions seems to exist in patients with frequent premature atrial contractions (PACs).
- No specific time window of the day is more vulnerable in predicting future incidence of atrial fibrillation when using premature atrial contractions as the predictor.
- Premature atrial contractions are a fairly stable phenomena from day to day, especially in patients with few or frequent PACs.

June 2000. Details of the selection procedures and study protocol have been described previously.[18] In short, the aim of the study was to assess the value of 48 h continuous ECG recording in a middle-aged elderly population in relation to other risk factors. Within a defined area of the city of Copenhagen, all men aged 55 and all men and women aged 60, 65, 70, and 75 ($n = 2969$) received a questionnaire about cardiovascular risk factors, medical history, and use of medication. Of these, 1226 did not respond or declined further contact, and 348 were excluded on the basis of self-reported prior significant heart disease, prior stroke, or other significant life-threatening disease. Remaining individuals with more than 1 risk factor and 60% of randomly selected subjects with 0–1 risk factors were then invited to a physician-based questionnaire, physical examination, laboratory testing, ECG, and 48 h continuous ECG recording. This resulted in 363 subjects with 0–1 risk factor and 412 with 2 or more risk factors. All persons with current or previous AF, cardiac disease, stroke, cancer, or other life-threatening conditions not reported in the questionnaire were excluded ($n = 33$). Incomplete or unacceptable recordings were also excluded ($n = 64$). Thus, the study includes up to 48 h continuous ECG recording in 678 subjects.

The ECG recording was performed with the use of two-channel SpaceLabs tape recorders (9025; SpaceLabs, Inc., Redwood, WA). Recordings were evaluated and interpreted by trained personnel, and the interobserver variability shows $\kappa$ values between 0.91 and 0.94. Median value of technically acceptable recording was 44.1 h, and first and third quartiles (Q1, Q3) were 41.4 to 45.5 h with 98% of the subjects having >24 h of recording. For this study, subjects were excluded if they had <24 h of recording ($n = 8$) or circadian data were not available for analysis ($n = 32$). Thus, data on the daily variation of PACs were available for analysis in 638 subjects (94% of the population).

A cut-off point of ≥30 PACs/h (≥720 PACs/day) was chosen to represent a high frequency of PACs, as it represented the top decile of hourly PACs, and has been demonstrated as a predictive marker for AF in a prior study on the same cohort.[13] This resulted in two groups: frequent PACs ($n = 66$) and not frequent PACs ($n = 572$).

## Follow-up

Follow-up on cardiovascular endpoints and death was performed in 2013. Events of stroke, AF, and death were retrieved from the national central patient registry, discharge letters, and were validated by reviewing patient files. Diagnosis of incident AF was verified with documentation in the form of ECG, telemetry, or both from patient records. All medications were registered at baseline.

## Ethics

All participants provided written informed consent. The regional ethical committee of Copenhagen and Frederiksberg approved the study. The study is in compliance with the Helsinki Declaration.

## Statistics

Means and standard deviations are reported for continuous variables with a normal distribution, and medians and interquartile ranges for not normally distributed data. Pearson's $\chi^2$ test, two-tailed Student's *t*-test, Wilcoxon's rank-sum test (Mann–Whitney *U* test), and Wilcoxon's matched pairs signed rank test were used for the comparison of groups as appropriate. In order to achieve the most representative data, the number of PACs for each subject was averaged on the specific clock hour if they had >24 h of recording.

Graphs of the 24 h variation are based on median values. Average PACs/h in all subjects were categorized into four 6 h time intervals (00–06, 06–12, 12–18, 18–24) to use in Cox proportional hazard models, to assess the risk of incident AF according to an arbitrarily definition of night, morning, afternoon, and evening. As average hourly PAC count were heavily right skewed, we used a log base 2 transformation, which was confirmed to be appropriate by higher log-likelihood in the Cox regression models, and a better linear fit, compared with the untransformed variables. In multivariate analysis, the selection of confounding covariates was based on existing knowledge about their association to AF. The proportional hazard assumption was tested in all Cox regression models based on Schoenfeld residuals. To evaluate the stability of PACs, we calculated $\kappa$-values of different intervals of PACs/h in 2 separate days. Any two-tailed *P*-value <0.05 was considered statistically significant.

All statistical analyses were made with STATA version 13.0.

# Results

The median follow-up time of the population was 14.4 years. Sixty-six patients (10.3%) were classified as having frequent PACs. Baseline characteristics of the population are shown in *Table 1*. The subjects with frequent PACs were more likely to be older, have a higher systolic blood pressure, higher NT-proBNP, and use aspirin. A total of 71 subjects were diagnosed with incident AF in the follow-up (11.1%). Of these, 11 subjects had frequent PACs (15%).

The total number of PACs during the 24 h period was widely dispersed with a median value of 35 PACs (range 1–13 830). There was a significant higher number of total PACs in those who developed incident AF in the follow-up with median 68 (range 3–8713) compared with no AF median 33 (range 1–13 830) $P = 0.0002$.

## The 24 h variation of premature atrial contractions per hour

The circadian variation in median hourly PACs of the whole population is shown in *Figure 1*. The variation, stratified by whether subjects had frequent PACs as previously defined, is depicted in *Figures 2 and 3*. The average heart rate of the corresponding subjects is plotted on the second *Y*-axis.

The distribution of average PACs in all subjects and in subjects with fewer than 30 PACs/h shows a uniform distribution throughout the day, with a median of 1 PAC/h and no apparent pattern or

**Table 1 Cardiovascular risk factors of the study population stratified by frequent PACs at baseline**

| Baseline factors | All subjects | Frequent PACs[a] | | *P*-value |
|---|---|---|---|---|
| | | No | Yes | |
| *N* | 638 | 572 | 66 | – |
| Age, years | 64.5 ± 6.8 | 64.1 ± 6.7 | 68.5 ± 5.7 | <0.001 |
| Female sex, *n* (%) | 272 (42.6) | 250 (43.7) | 22 (33.3) | 0.11 |
| Current smoking, *n* (%) | 2989(46.9) | 269 (47.0) | 30 (45.5) | 0.81 |
| Systolic blood pressure, mmHg | 156.6 ± 24.3 | 155.5 ± 23.8 | 166.9 ± 25.8 | <0.001 |
| Diastolic blood pressure, mmHg | 91.0 ± 11.0 | 90.7 ± 11.0 | 93.4 ± 10.9 | 0.056 |
| Total cholesterol, mmol/L | 6.1 ± 1.1 | 6.1 ± 1.0 | 5.9 ± 1.1 | 0.21 |
| NT-proBNP, pmol/l | 6.9 (3.6, 13.9) | 6.5 (3.4, 12.7) | 13.1 (5.8, 23.6) | <0.001 |
| Log (NT-proBNP) | 2.0 ± 1.1 | 1.9 ± 1.1 | 2.6 ± 1.0 | <0.001 |
| Alcohol, units/week | 13.0 (0.0, 26.0) | 13.0 (1.5, 26.0) | 13.0 (0.0, 24.0) | 0.85 |
| Low level of physical activity, *n* (%) | 163 (25.7) | 144 (25.4) | 19 (28.8) | 0.55 |
| Body mass index, kg/m$^2$ | 26.7 ± 4.4 | 26.6 ± 4.3 | 27.1 ± 4.9 | 0.42 |
| Aspirin use, *n* (%) | 96(15.0) | 77 (13.5) | 19 (28.8) | <0.001 |
| β-Blocker use, *n* (%) | 31 (4.9) | 30 (5.2) | 1 (1.5) | 0.18 |
| Diuretic use, *n* (%) | 114 (17.9% | 98 (17.1) | 16 (24.2) | 0.15 |
| ACE inhibitor use, *n* (%) | 32 (5.0) | 31 (5.4) | 1 (1.5) | 0.17 |

[a]Frequent PACs classified as ≥30 PACs/h (≥720 PACs/day).

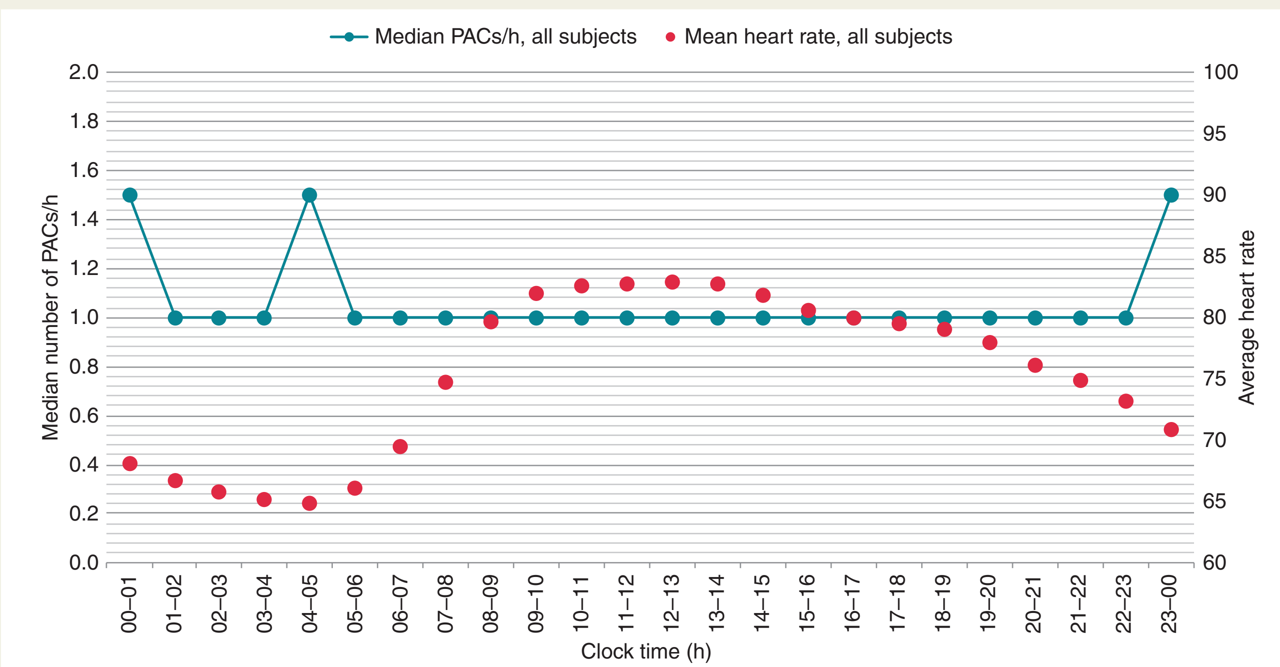


**Figure 1** Median number of PACs/h and mean heart rate in all subjects ($n = 638$).

variation (*Figure 1*). However, the graph for subjects with frequent PACs has an evident nonuniform variation throughout the day. A trend is seen with decreasing PACs during the night with a minimum observed at 6 am and then gradually increasing to a maximum in the afternoon at around 3 pm. The variation in these subjects is fairly consistent with the daily variation of heart rate, which seem to fall and rise in unison with hourly PACs. We also calculated the mean values of the average hourly number of PACs and did a mean cosinor analysis, which resembled the same pattern as the median values, but with higher values and large confidence intervals. As the statistical validity would be questionable, these are not reported (data not shown).

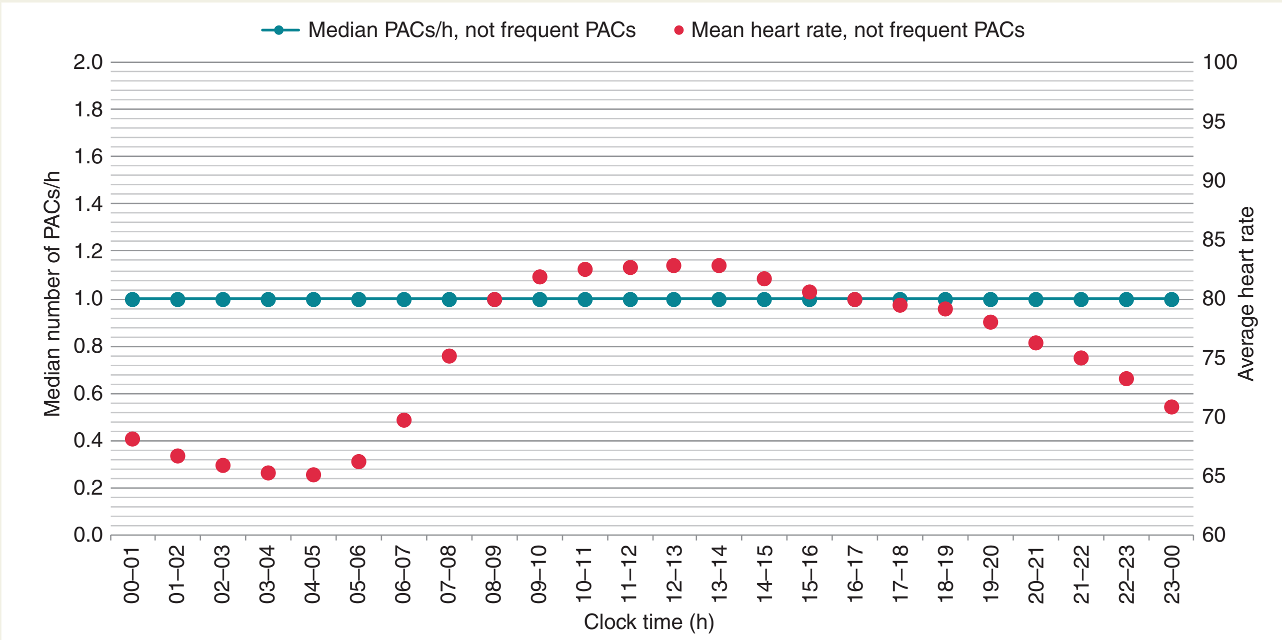


**Figure 2** Median number of PACs/h and mean heart rate in subjects without frequent PACs ($n = 572$).

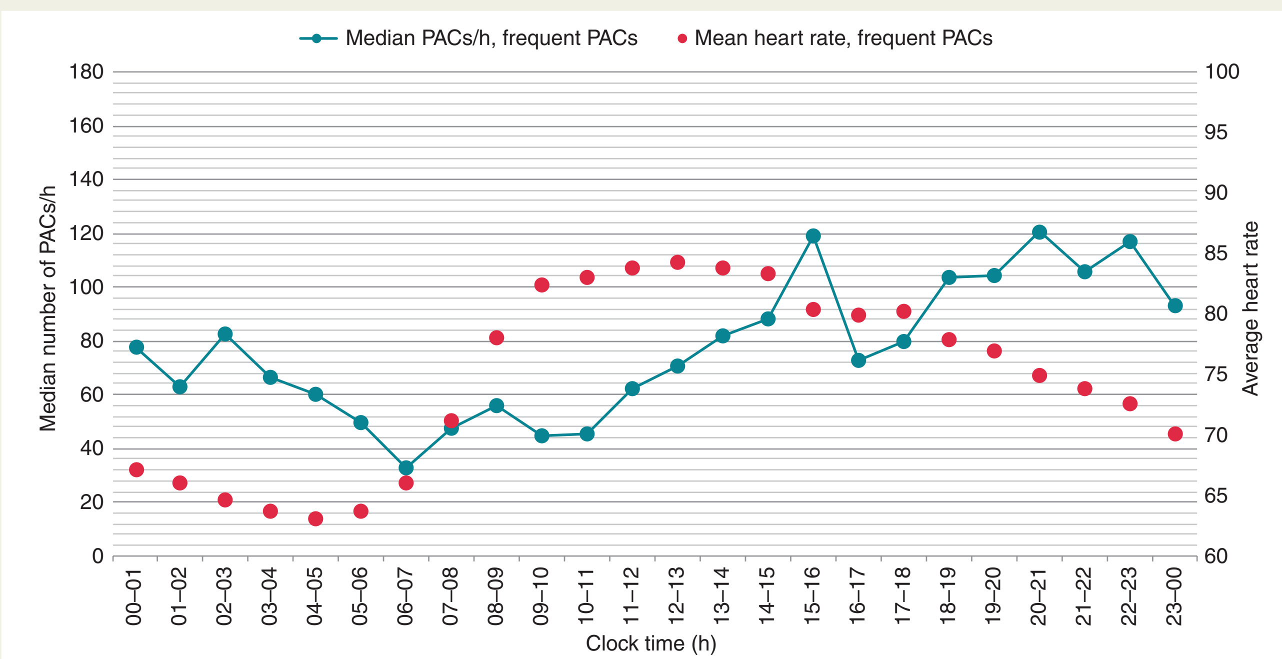


**Figure 3** Median number of PACs/h and mean heart rate in subjects with frequent PACs ($n = 66$).

## The 24 h variation of runs of premature atrial contractions

The circadian variation of the number of runs of ≥3 PACs in all subjects is depicted in *Figure 4*. The pattern observed is a unimodal distribution with a peak at 2 pm and then gradually descending values towards night-time until the number of runs starts ascending again in the morning hours. The peak in the afternoon resembles the one observed in the number of average hourly PACs; however, contrary to hourly PACs, it has a more consistent descend towards evening and night.

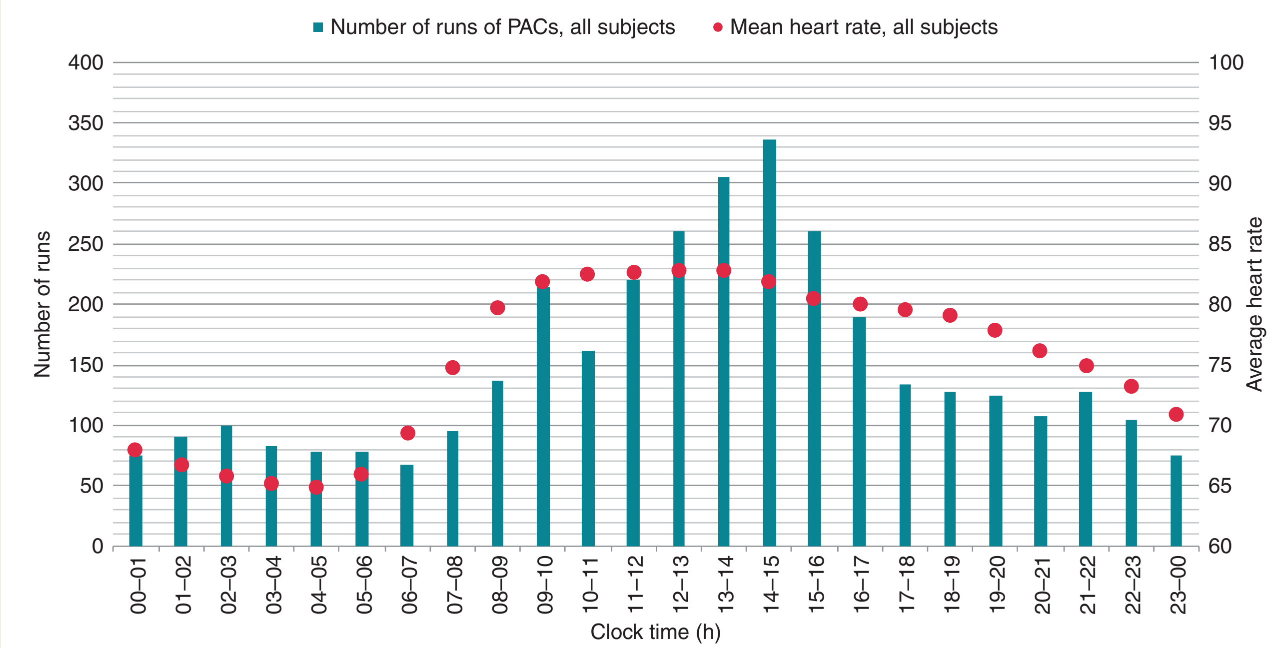


**Figure 4** Episodes of runs of PACs and mean heart rate in all subjects ($n = 638$).

**Table 2** Difference in heart rate according to time spans and frequent PACs

| Clock hour | Mean heart rate (beats/min) | | *P*-value |
|---|---|---|---|
| | Not frequent PACs (95% CI) | Frequent PACs (95%CI) | |
| 00–6 (Night) | 66.3 (65.5–67.1) | 64.7 (61.8–67.6) | 0.21 |
| 06–12 (Morning) | 78.9 (77.9–79.8) | 77.4 (74.0–80.8) | 0.32 |
| 12–18 (Afternoon) | 81.3 (80.3–82.2) | 82.0 (78.6–85.4) | 0.62 |
| 18–24 (Evening) | 75.5 (74.6–76.4) | 74.4 (71.2–77.6) | 0.42 |

## Difference in premature atrial contractions according to heart rate

The circadian variation of average heart rate in the same time intervals shows no significant difference between the two groups studied (*Table 2*). Heart rate alone, it seems, is not the sole reason for the variation of PACs observed in subjects with few and many PACs.

## Risk of atrial fibrillation according to time of day

*Table 3* shows the associated risk of incident AF with each doubling in the amount of PACs/h according to the specified time intervals during a 24 h period. The highest hazard ratio for each doubling is observed at night between 12 pm and 6 am. However, the hazard ratio is almost the same for the different intervals, which is also apparent from the hazard ratio of the total averaged 24 h period.

## Stability of premature atrial contractions from day to day

The stability of intervals of average PACs/h/day from 2 successive days of ECG recording is depicted in *Table 4* using $\kappa$ statistics. The cut-off values are based on relevant centiles from average PAC/h in the total recording period. The results show that the most stable values from day-to-day recordings are either having frequent PACs (>30/h/day) or having very few (<1.5/h/day). The stability of having between 1.5 and 30 PACs/h/day from day to day is less stable but still moderate.

In a sensitivity analysis, we looked at the association of a categorical variable reflecting average PACs/h in the different intervals used in *Table 4* and the risk of incident AF. Increasing PACs/h were significantly associated with increased risk of incident AF when using the group with ≤1.5 PACs/h as the reference group: PACs/h >1.5 and <30 (hazard ratio: 2.41; 95% CI: 1.40–4.14) and PACs/h ≥30 (hazard ratio: 2.88; 95% CI: 1.35–6.14). The analyses were adjusted for age and gender.

**Table 3** Hazard ratio of average PACs/h according to time spans and the association with incident AF[a]

| Clock hour | Unadjusted hazard ratio (95% CI) | *P*-value | Adjusted hazard ratio[b] (95% CI) | *P*-value |
|---|---|---|---|---|
| 00–6 (Night) | 1.24 (1.12–1.37) | <0.001 | 1.18 (1.05–1.32) | 0.005 |
| 06–12 (Morning) | 1.18 (1.06–1.31) | 0.003 | 1.10 (0.97–1.25) | 0.114 |
| 12–18 (Afternoon) | 1.19 (1.09–1.32) | <0.001 | 1.13 (1.02–1.26) | 0.021 |
| 18–24 (Evening) | 1.20 (1.09–1.32) | <0.001 | 1.14 (1.03–1.27) | 0.015 |
| 00–24 | 1.19 (1.10–1.29) | <0.001 | 1.15 (1.05–1.25) | 0.002 |

[a]Log base 2-transformed with hazard ratio interpreted as the increased hazard for each doubling of average PACs/h in the above time spans.
[b]Adjusted for age, gender, systolic blood pressure, PR-interval, and body mass index.

**Table 4** Classification of intervals of PACs/h on two succeeding ECG-recording days

| PACs/h | Centile (%) | Number of subjects | | Agreement on both days | κ-Values |
|---|---|---|---|---|---|
| | | Day 1 | Day 2 | | |
| ≤1.5 | 50 | 331 | 324 | 288 | 0.75 |
| >1.5–<30 | 50–90 | 240 | 245 | 193 | 0.67 |
| ≥30 | 90 | 67 | 69 | 57 | 0.82 |

# Discussion

## Premature atrial contractions as a prognostic marker

In recent years, there has been an increased interest in the prognostic value of PACs. What beforehand was considered as a benign irregularity when observed on a traditional ECG recording or in other long-term ECG-recording modalities has shown to be a risk factor in several cardiovascular outcomes not limited to AF but maybe also predictive of ischaemic stroke and increased cardiovascular mortality.[13–15] To the authors' best knowledge, this is the first study of circadian variation of PACs in a large community-based cohort.

The present study demonstrates that a circadian rhythm seems to exist in this elderly and middle-aged population. However, it is only observable in subjects who have frequent PACs. The difference seems to exist between early morning hours and the time from noon until late evening. Runs of PACs showed a somewhat similar pattern with a maximum around 3 pm but with fewer runs during the evening compared with the rhythm of hourly PACs.

Several mechanisms can be thought to influence the daily variation of PACs. Inappropriate fluctuations in autonomic nervous activity may induce disturbances in atrial bioelectricity and contribute to formation of ectopic activity. Furthermore, levels of catecholamines that influence sympathetic nerve activity may also be able to affect and trigger atrial ectopy.

The risk of AF according to PACs and our specified time intervals suggest that ECG recording at different hours is equally predictive. An interpretation of this finding could be that subjects later developing AF do not have a vulnerable period of frequent PACs that can be used in an assessment of their risk of AF in the future. Our results also show that the burden of PACs on average is significantly higher in the group that develop incident AF compared with the group without incident AF. However, many subjects with a high frequency of PACs will not develop incident AF and when prediction of AF is in sight the frequency of PAC should be combined with other AF risk factors. Furthermore, it is possible that a proportion of those patients without incident AF do have asymptomatic paroxysmal AF. We have recently shown that an excessive number of PACs is associated with ischaemic stroke beyond incident AF.[19]

We also show that having frequent PACs (≥30 PACs/h or ≥720 PACs/day) in 2 successive days seems to be a fairly stable phenomenon. This cut-off point was chosen as it represented the top decile of hourly PACs in our population. In support of this cut-off, a recent study by Gladstone *et al*. shows that in patients aged over 55 years with cryptogenic stroke or transient ischaemic attack without prior AF, the predicted probability of AF detection by all methods in the follow-up increases with the frequency of PACs but reaches its maximum between 500 and 1500 PACs/day.[20] They suggest an algorithm for detecting subclinical AF in patients with ≥500 PACs/day at baseline with a prolonged target monitoring of 4 weeks. Our results show that if subjects have more than 720 PACs/day, it is a relatively stable result. Furthermore, when looking at the circadian variation of subjects with frequent PACs, the median values of each hour of the day are >30 PACs indicating that shorter period of monitoring may be sufficient to establish that a patient has an excessive amount of PACs and hence an increased risk of incident AF. In high-risk patients, this may warrant increased monitoring either by the use of long-term non-invasive ECG recording or an implantable loop recorder capable of AF auto detection. This could help to prevent morbidity in subjects with silent or paroxysmal AF by earlier treatment. However, no studies have of yet established if repeated/continuous measurements in patients with frequent PACs and other risk factors would increase short-term incident AF detection.

## Previous studies of circadian variation in premature atrial contractions

Only a single small study has previously described a circadian rhythm of PACs. Mikulecký *et al*. demonstrated that in 37 healthy male subjects aged between 50 and 76 years, a circadian rhythm was present with peaks around 6–7 am, 9 am, noon, and 4–5 pm with a significant depression around 1–2 am.[16] This is somewhat consistent with our results with a peak in the afternoon and fewer PACs in the night. However, the range of PACs in the subjects from the whole 24 h period was from 0 to 39, not representing our populations' dispersion of PACs.

## Circadian patterns of other arrhythmias in relation to the variation of premature atrial contractions

Patients with paroxysmal supraventricular tachycardia (PSVT) have been reported to have a higher risk of developing AF than the remaining population.[21] Previous studies in the same age group as our study show a similar pattern of circadian variation in PSVT with a peak during daytime and a low incidence during night and early morning.[5–7]

Paroxysmal AF comprises of frequently asymptomatic patients with differences in duration, frequency, and mode of termination. The circadian rhythm of PAF reported by different studies is not consistent. One study reports that the onset of PAF had no significant circadian variation,[7] whereas three more recent publications report a circadian variation with two peaks. The first peak occurred in the morning[9,10] or afternoon[8] and the second peak in the evening.

Although a direct comparison is difficult with other supraventricular arrhythmias, since the mechanisms of initiation and maintenance are not equal to the more sporadic nature of PACs, these studies resemble our findings with more activity during daytime, possibly resembling a sympathetic nervous system component. Interestingly, we could not detect a difference in heart rate throughout the day in the patients with few PACs, compared with the patients with frequent PACs, suggesting other mechanisms at play.

## Limitations

The current study has some limitations. Missing data on 40 subjects or 5.8% of the original cohort can introduce some selection bias. However, it was random which recordings were unavailable for analysis.

The selection of 6 h time intervals in predicting AF was done to increase the statistical credibility; however, it may not represent individual circadian cycles and sleeping habits. Even though the cohort is large, 48 h of monitoring may not be sufficient to determine whether fluctuations in PAC count can help in predicting future incidence of AF. Even though the diagnosis of incident AF was very specific, it only includes cases of incident AF with admission to the hospital. It is very likely that episodes of asymptomatic paroxysmal AF have been missed, which will underestimate the true number of subjects with AF. Additionally, some patients may have been treated without being admitted to the hospital. However, most patients with incident AF in the primary sector will be sent to further cardiologic evaluation at the hospital where the diagnosis would be accounted for.

This population studied is middle-aged elderly consisting mainly of Caucasians, and application to other population and age groups should be done with caution.

Variation of extraneous factors that can influence arrhythmogenic activity during the course of a day such as alcohol, cigarettes, caffeine, and other sympathomimetic substances cannot be accounted for and may have influenced the results. Medication can also influence the variation of PACs. In this study, 31 subjects received β-blockers at baseline, which may have impaired the amount of PACs in these patients because of lowered sympathetic activity. However, there was no significant statistical difference between the two groups indicating that the distribution of subjects with β-blockers is probably incidental. All subjects were asymptomatic at the time of inclusion, and the indications of using β-blockers were hypertension and not palpitations or PAC frequency.

# Conclusion

Our results show that PACs appear to have a circadian rhythm in subjects with frequent PACs. Premature atrial contractions and heart rate seem to fall gradually during the evening and night hours with a nadir in the early morning hours and then a gradual increase during day hours in these subjects. We did not find PAC count on a certain period of the day to be more predictive of incident AF when using PACs as the prognostic marker in this middle-aged, elderly community-based cohort without known heart disease.

**Conflict of interest**: none declared.

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# 'Life-saving' inappropriate ICD shock

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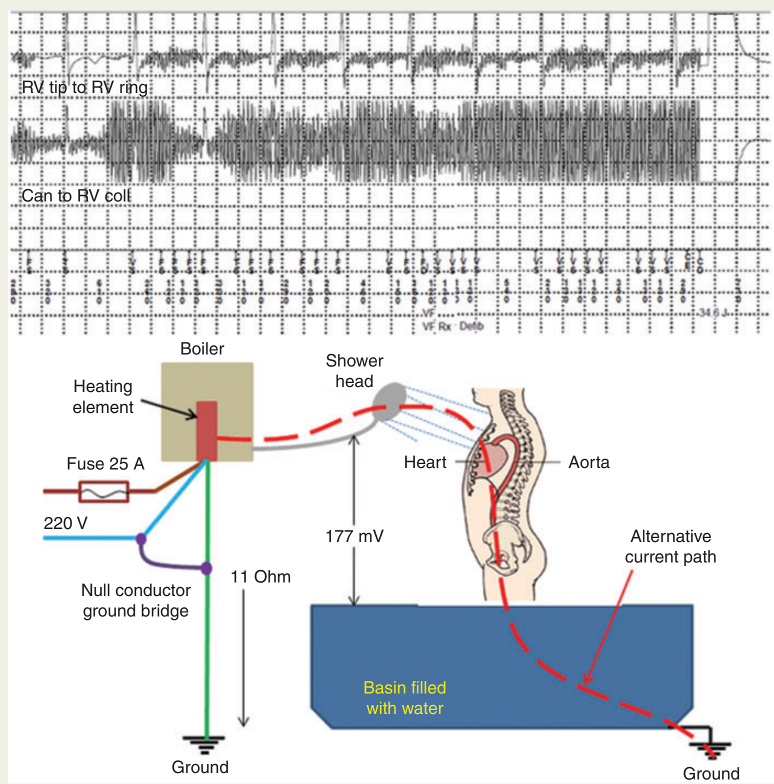
An 81-year-old female patient with ischaemic cardiomyopathy and an ICD implanted for secondary prevention received a shock while showering. The ICD interrogation revealed that a bodily conduction of the mains electric current caused the shock. Similar previously stored episodes were detected by the ICD as unsustained VFs. The intracardiac EGMs exhibit typical waveforms (with AR and FS markers) for oversensing of the 50 Hz electric current. The FD marker designates the VF detection.




The electric power distribution company conducted an analysis of the electric installation, wherein protection is done only by a fuse and the bridged null conductor to the ground. The progressive insulation failure of the water heating element caused the continuous presence of the measured 177 mV (AC 50 Hz) potential between the shower head and the sink hole connected to the lead tubes being an alternative ground path. The alternative current path would be capable to induce the VF in any bathroom user.

The inappropriate shock was a warning to all tenants in the house, potentially 'life-saving'. The renovation of the electric installation including utilization of the residual-current circuit breakers was done.

The full-length version of this report can be viewed at: http://www.escardio.org/Guidelines-&-Education/E-learning/Clinical-cases/Electrophysiology/EP-Case-Reports.