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Excessive atrial ectopic activity as an independent risk factor for ischemic stroke

Rita Marinheiro *[,1], Leonor Parreira [1], Pedro Amador [1], Catarina Sá [1], Tatiana Duarte [1], Rui Caria [1]

Centro Hospitalar de Setubal, Cardiology Department, Setubal, Portugal

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ABSTRACT

Background: Excessive atrial ectopic activity (EAEA) has been related with an increased risk of atrial fibrillation (AF) and stroke but different cutoff values have been used. We aimed to determine the association between EAEA and stroke, AF and overall death.

Methods: Consecutive 24-hour Holter monitoring performed between 2005 and 2010 in a single center was evaluated. Patients with a previous diagnosis of stroke or AF were excluded. The number of premature atrial contractions (PACs) during 24 h was analyzed in 2480 subjects and according to that 3 sub-groups were defined: >97 PACs/h (above the top 5th percentile of the population) (EAEA+); intermediate value of PACs/h (below the top 5th percentile but above 30 PACs/h) (EAEA+/−) and <30 PACs/h (EAEA−).

Results: After adjusting for risk factors, laboratory findings and medication, EAEA+ was associated with ischemic stroke (hazard ratio [HR] 2.83; 95% confidence interval [CI], 1.65–4.84, $p < 0.001$). Both EAEA+ and EAEA+/− were independently associated with AF (HR 2.05; 95% CI 1.31–3.23, $p = 0.010$ for EAEA+ and HR 1.90; 95% CI 1.10–2.78, $p = 0.020$ for EAEA+/−) and overall death (HR 2.17; 95% CI 1.48–3.28, $p = 0.031$ for EAEA+; HR 2.01; 95% CI 1.06–2.52, $p = 0.029$ for EAEA+/−).

Conclusion: In this population, having >30 PACs/h was independently associated with a higher risk of AF and overall death but only subjects with >97 PACs/h had a higher risk of ischemic stroke. In the majority of subjects with stroke and EAEA+, AF has not been detected before stroke event.

1. Introduction

The role of atrial ectopic activity in the initiation of atrial fibrillation (AF) is well established. In 1998, Haissaguerre et al. demonstrated that the pulmonary veins are an important source of ectopic beats, initiating frequent paroxysms of atrial fibrillation [1]. Premature atrial contractions (PACs) may be a marker for foci that are or will be capable of firing rapidly to initiate AF [2] through a reentry-maintaining substrate. Rapid and repetitive stimulation of the atrial muscle is known to alter its electrophysiological properties by shortening atrial refractoriness, leading to the development and maintenance of AF. Alternatively, PACs may be a marker of developing atrial electrophysiological changes that promote AF, such as interstitial fibrosis and abnormal intracellular calcium handling [3]. Recent studies suggested that excessive atrial ectopic activity (EAEA) not only increases risk of AF but it is also associated with an increased risk of stroke, adverse cardiovascular events and death [4–8]. The lack of precise definition for "excessive" atrial ectopy leads investigators to use arbitrary cut-off values according to top percentiles for frequency of PACs [6–8]. However, considering the number of PACs as a continuous variable, the risk of adverse events is related to the number of PACs. The aim of this study was to use a higher *cutoff* value in order to identify high risk patients that would benefit from therapeutic intervention.

2. Methods

2.1. Patients

Between January 2005 and December 2010, 3589 consecutive patients were referred to our non-invasive cardiology laboratory for elective 24-hour (h) Holter monitoring. Patients were excluded if they had previously documented AF (n = 396), AF diagnosed during the exam (n = 206), history of stroke or transient ischemic attack (n = 409) or if they were under medication with anticoagulants (n = 98). The final analysis thus involved 2480 subjects.

2.2. Study design

Demographic data, cardiovascular risk factors, indications for 24 h Holter monitoring, transthoracic echocardiograms and medications were recorded. Hypertension was defined as resting systolic or diastolic blood pressure ≥140/90 mm Hg on two occasions or prescription of anti-hypertensive drugs. Diabetes mellitus was defined as a serum fasting glucose ≥7.0 mmol/L or prescription of anti-diabetic medication. Smoking status was recorded as

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CV, cardiovascular; EAEA, excessive atrial ectopic activity; ECG, electrocardiogram; h, hour; HR, hazard ratio; LDL, low-density lipoprotein; PACs, premature atrial contractions.

* Corresponding author.
E-mail addresses: ritamarinheiro@gmail.com (R. Marinheiro), leonor.parreira@gmail.com (L. Parreira).

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current smoker or non-smoker. The CHA_2DS_2VASc (congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female) score was calculated [9]. All transthoracic echocardiograms were retrospectively collected and reviewed by study personnel. Holter recording was performed with the use of 3-channel tape recorders (*GE SEER LIGHT®*). Recordings had to exceed 20 h and be of good quality to be analyzed and all of them were reviewed and edited manually. Subjects were asked about PACs-related symptoms, namely palpitations during the exam. Premature atrial complexes were quantified using the number of PACs/h (PACs/h). Patients with PACs/h at the top 5th percentile in the present cohort were considered to have EAEA (n = 124) (EAEA+). Subjects with less than the commonly accepted *cutoff* value for frequent PACs (30 PACs/h) were assumed to have no EAEA (EAEA−). Patients with >30 PACs/h but <97 PACs/h were considered as an intermediate group with frequent but not excessive PACs/h (EAEA+/−). According to gender and age, propensity score matching method was used to obtain pairs of matched subjects: 124 for EAEA– group and 114 for EAEA+/− group, in order to exclude bias in recruitment. The selection of patients for analysis is shown in the study flow diagram (Fig. 1).

Events of stroke, AF and overall death were retrieved from the national patient registry and from medical records or discharge letters and were validated by reviewing patients' files. Patients who failed to have recent clinical records were contacted by phone. Ischemic stroke was defined as a neurological deficit of sudden onset that persisted for >24 h, corresponded to a vascular territory in the absence of primary hemorrhage and that could not be explained by other causes (trauma, infection, vasculitis). It was confirmed by computerized axial tomography or magnetic resonance imaging of the brain. New occurrence of AF was defined as AF documented by a standard 12 lead electrocardiogram (ECG) or a new 24-h Holter monitoring.

2.3. Ethics

All participants provided written informed consent. The Ethical Committee of Centro Hospitalar de Setubal approved the study. The study is in compliance with the Helsinki Declaration.

2.4. Statistics analysis

SPSS version 23 software (SPSS Inc., Chicago, Illinois) was used for statistical analysis. Data is expressed as means ± standard deviation for continuous variables and as frequencies and percentages for categorical variables. Baseline characteristics and outcomes were compared using the chi-square test for categorical variables and the ANOVA test for continuous variables. Univariate and multivariate Cox-proportional-hazards regression analysis was used to calculate the hazard ratios (HR) and 95% confidence intervals (CI) of ischemic stroke, new-onset AF and overall death between patients in the studied groups. Kaplan–Meier survival function and the log-rank test were used to compare the survival distributions. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Study population

Clinical characteristics are shown in Table 1. Median follow-up was 7.1 years and it was similar between the groups. No patients were lost to follow-up.

3.2. Follow-up

Events per 1.000 person-years observed in up to 11 years of follow-up in the three studied groups are shown in Table 2. Supplementary Fig. 1 represents the percentage of events that occurred during the follow-up in the three groups.

3.2.1. Stroke

Stroke occurred in 54 of all patients. Subjects who experienced a stroke were older (74 ± 6 years versus 70 ± 9 years; $p < 0.001$), had more hypertension (76% versus 89%, $p = 0.02$) and had a higher CHA_2DS_2VASc score ($CHA_2DS_2VASc \geq 3$ in 78% versus 61%; $p = 0.03$). Other baseline variables and risk factors were not significantly different between the groups (Supplementary Table 2).

Subjects with EAEA+ had 34.9 strokes/1.000 person-years; those with EAEA+/− had 15.1 strokes/1.000 person-years and those with EAEA− 11.5 strokes/1.000 person-years ($p < 0.001$ for EAEA+). In univariate analysis, EAEA+ was associated with ischemic stroke (HR 2.71; 95% CI 1.60–4.61, $p = 0.002$ for EAEA+ group). This remained significant after adjustment for conventional risk factors (sex, age, body mass index, current smoking, hypertension, diabetes mellitus) (HR 2.87; 95% CI 1.68–4.91, $p < 0.001$). Further adjustment for blood glucose, creatinine, low-density lipoprotein (LDL) cholesterol, coronary or peripheral arterial disease and heart failure did not affect the results (HR 2.83; 95% CI 1.65–4.84, $p < 0.001$). If use of medication is considered, including aspirin, the results will remain almost unchanged. Of note, EAEA+/− were not included in the model, regardless of adjustments. Fig. 2A shows Kaplan-Meier curve for stroke-free survival in patients with and without EAEA.

In patients with stroke, AF was detected in 18 (60%) of patients with EAEA+ and in 8 (62%) of patients with EAEA+/− comparing to 4

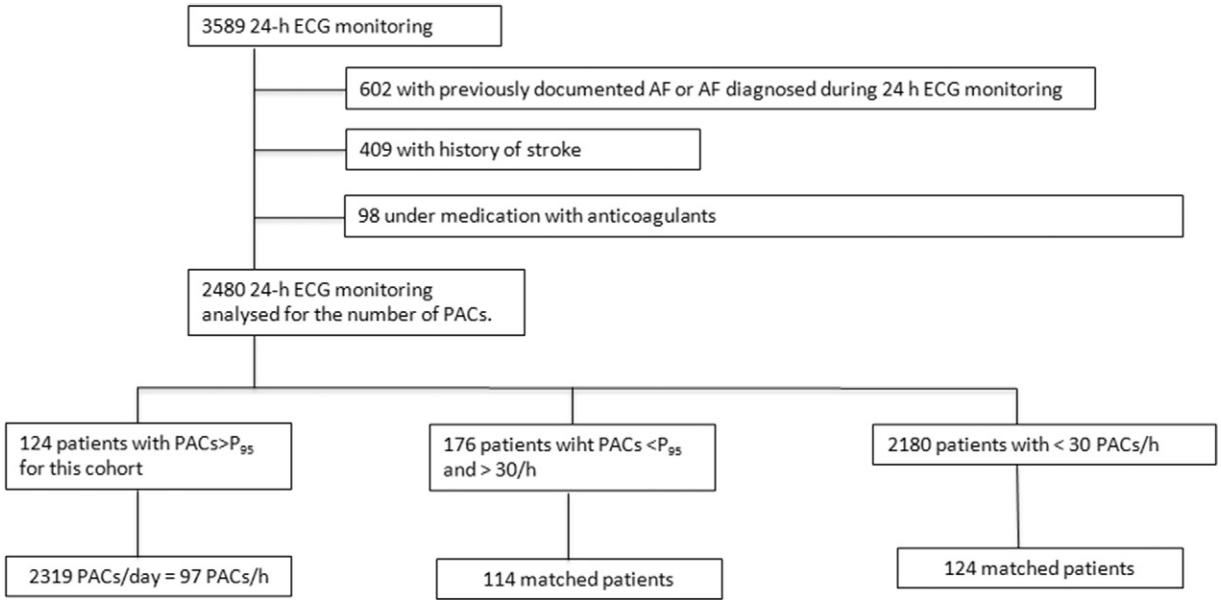

Fig. 1. Flow diagram of the study selection process. Flow diagram of patients included in analysis: 124 patients with EAEA, 114 age- and gender-matched subjects with intermediate EAEA and 124 age- and gender-matched subjects with no EAEA. EAEA: excessive atrial ectopic activity. ECG: electrocardiogram. h: hour. PACs: premature atrial contractions.