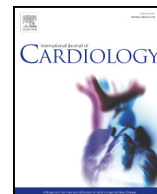




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Asymptomatic versus symptomatic episodes in patients with paroxysmal atrial fibrillation via long-term monitoring with implantable loop recorders☆

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ABSTRACT

Background: The presentation of atrial fibrillation (AF) varies remarkably, from totally asymptomatic to symptomatic patients, while the same individual may present symptomatic and asymptomatic episodes. We aimed to identify electrocardiographic differences between symptomatic and asymptomatic episodes and to find parameters related to the appearance of symptoms.

Methods: Thirty consecutive patients (age 66.9 ± 10 years) with paroxysmal AF received an implantable loop recorder. Three types of episodes were defined: asymptomatic (ASx), symptomatic (Sx), and mixed asymptomatic-symptomatic (AS-Sx). The heart rate (HR) and heart rate variability (HRV) were recorded during the first 2 min of each ASx or Sx episode, and during the first 2 min of both the symptomatic and asymptomatic periods in AS-Sx. **Results:** Eighty-two episodes from twenty-five patients were evaluated. Mean HR was 142.48 ± 25.84 bpm for Sx and 95.71 ± 19.29 bpm for ASx ($p < 0.001$). Mean HRV was 92.62 ± 42.29 ms for Sx and 150.06 ± 49.68 ms for ASx ($p < 0.001$). In AS-Sx, mean HR was 102.91 ± 24.54 bpm for the asymptomatic and 141.88 ± 23.43 bpm for the symptomatic period ($p < 0.001$). Mean HRV was 173.55 ± 61.30 ms for the asymptomatic and 87.33 ± 30.65 ms for the symptomatic period ($p = 0.003$). There were no significant correlations between patients' characteristics and the clinical presentation of the arrhythmia.

Conclusions: The ASx were characterized by a lower HR and higher HRV compared to Sx. In AS-Sx, the asymptomatic period was characterized by a lower HR and higher HRV compared to the symptomatic. These findings suggest a possible contribution of variations in the autonomic nervous system activity to the perception of the arrhythmia.

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1. Introduction

Although atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and significant progress has been made in the understanding of its pathophysiology and treatment, there are still many unresolved issues related to this rhythm disturbance. One such issue is why, even in the same patient, the arrhythmia sometimes presents with symptoms, whereas it is often totally asymptomatic. Though the reason for this peculiar presentation is still unknown, it may have serious diagnostic and therapeutic implications, since silent AF is at least as dangerous as the symptomatic arrhythmia [1,2]. In some patients,

AF is diagnosed incidentally [3], while in symptomatic patients 30% of episodes are asymptomatic and this percentage increases to 50% after initiation of a specific treatment [4–7]. In patients with paroxysmal or persistent AF it is important to know the total burden of AF, to which symptomatic and asymptomatic episodes contribute equally, as it seems that the burden of AF is of prognostic significance and may be used as a basis for therapeutic decisions [8]. Nowadays, we are able to precisely estimate the AF burden with the use of implantable loop recorders (ILRs), which have the ability to record and store AF episodes with high sensitivity (96.1%) and good specificity (85.4%) [9]. In the present study, we used ILR recordings to identify electrocardiographic differences between symptomatic and asymptomatic AF episodes and to explore possible demographic, clinical or echocardiographic parameters related to the clinical manifestation of this arrhythmia.

2. Methods

Thirty consecutive patients older than 18 years (mean age 66.9 ± 10 years; 14 men) who had a first ECG documented episode of paroxysmal AF were included. After sinus

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rhythm restoration, an ILR (Reveal XT 9529; Medtronic, Minneapolis, Minnesota, USA) was inserted subcutaneously under local anesthesia. Patients' medical history was recorded, and a physical examination, a 12-lead standard ECG recording, and an echocardiographic study were performed at the time of enrollment. The patients underwent a stress ECG with the Bruce treadmill protocol and/or nuclear single photon emission computed tomography (SPECT) stress testing using thallium nuclear agents, in order to determine the possibility of coronary artery disease (CAD). If there was strong evidence of CAD a coronary angiogram was performed. Stroke risk was assessed by the CHA₂DS₂-VASc score [10]. The EHRA score [10] was used for the classification of the AF-related symptoms. Follow-up visits were scheduled to be performed after one month, three months, and every three months thereafter for a period of three years.

All patients gave written informed consent, the study was organized according to ethical considerations, as described in the Declaration of Helsinki for human medical studies, and the protocol was approved by the institutional medical ethics committee. Types of AF were defined according to the 2016 ESC guidelines [10]. We excluded patients with persistent or permanent AF, patients with an episode of AF attributed to reversible or transient causes such as acute myocarditis or pericarditis, acute coronary syndromes, acute pulmonary embolism, metabolic disorders (hyperthyroidism, pheochromocytoma), drug abuse (e.g. cocaine), and caffeine and alcohol intake (holiday heart syndrome). Pregnant women and patients who declined to give written consent were also excluded.

2.1. Implantable loop recorder (ILR)

After the implantation, all the patients were trained and were instructed to activate the device after the onset of symptoms indicative of the arrhythmia (palpitations, dizziness, fast heartbeat, syncope or presyncope). The Reveal XT detects the occurrence of AF episodes using an automatic algorithm based on the pattern of R-wave interval variability within 2-minute periods. The memory of the device can store up to 22.5 min of ECG recordings from patient-activated episodes and up to 27 min of ECG recordings from automatically detected arrhythmias. For each automatically detected AF episode the Reveal XT stores an ECG of the first 2 min of the episode, while for each patient-activated episode it stores the ECG 6.5 min before the patient's activation and 1 min after. The device's memory was reset after a patient's visit. All the recorded episodes were reviewed by two physicians of our department, who had full access to the data and take responsibility for their interpretation, while the statistical analyses were carried out by our department's statistician.

2.2. Paroxysmal atrial fibrillation (PAF) episodes

We recorded the total number of AF episodes during the follow-up period for each patient. The AF episodes were classified as: asymptomatic (ASx) AF episodes (the patient was unaware of the arrhythmia throughout the episode); symptomatic (Sx) AF episodes (the patient suffered from symptoms indicative of the arrhythmia during the AF episode); and AF episodes that were initially asymptomatic but became symptomatic later on (AS-Sx). In ASx, Sx and AS-Sx episodes we calculated the heart rate (HR1) and the heart rate variability (HRV1) during the first 2 min of each episode. In addition, in AS-Sx episodes, we analyzed HR and HRV 2 min before the activation of the device by the patient (HR2, HRV2). We analyzed HRV by manually applying time-domain methods to the available ECG data of each AF episode. The HR and HRV for each PAF were calculated manually from the device memory by two physicians of our department. We considered the mean value of the two measurements as the HR and HRV of each episode. We excluded from our analysis episodes with a duration <10 min, as in short-duration episodes a few patients were unable to activate the patient's external device at the time they felt symptoms indicative of the arrhythmia. In addition, we investigated the distribution of AF episodes during the day, as well as the seasonal variation of the Sx, ASx, and AS-Sx AF episodes.

2.3. Definitions of the analyzed parameters in AF episodes

The HR1 (bpm) was defined as the mean HR during the first 2 min of episodes [ASx, Sx, AS-Sx (asymptomatic period)], while the HR2 (bpm) was the mean HR during 2 min before the activation of the device from the patient [only in AS-Sx episodes (symptomatic period)]. The HRV1 (ms) was defined as the standard deviation of all RR intervals during the first 2 min of episodes [ASx, Sx, AS-Sx (asymptomatic period)], while the HRV2 (ms) was the standard deviation of all RR intervals during 2 min before the activation of the device from the patient [only in AS-Sx episodes (symptomatic period)]. Mean RR (ms) was the mean of all RR intervals during the AF episodes. HRp (bpm) was the mean HR of the patient during the follow-up period. The delta hr (%) was defined as $[(HR1 - HRp) / HR1] \times 100$.

2.4. Echocardiographic measurements

All the patients underwent two-dimensional transthoracic echocardiography at the time of their enrollment. The echocardiographic study was performed after the restoration of sinus rhythm so that left ventricular function could be evaluated effectively. The parameters recorded for the purpose of this study were left atrial (LA) diameter, left ventricular end-diastolic diameter (LVEDD) and left ventricular ejection fraction (LVEF). The echostudies were performed by two cardiologists in our department who are specialized in echocardiography.

2.5. Statistics

Summary descriptive statistics are presented as frequency (%) or mean \pm standard deviation, as appropriate. Comparisons of continuous variables between purely asymptomatic and symptomatic episodes were carried out using the independent samples *t*-test. In AS-Sx episodes, the comparison between the asymptomatic and symptomatic period was performed using the paired samples *t*-test. Chi-square tests were used to compare categorical variables. All statistical tests were carried out at the two-sided 5% level of significance using IBM-SPSS 21 software.

3. Results

The clinical and demographic characteristics of the study population are listed in Table 1. The most common comorbidity was arterial hypertension (83.3%) followed by dyslipidemia (70%). The mean CHA₂DS₂-VASc score was 2.83 ± 1.66 . The mean duration of the follow-up period after the implantation of the device was 18.7 months. The mean duration of the AF episodes included in this study was 738 (range 10–5115) minutes. No thromboembolic episode or death occurred during the follow-up period. A total number of 82 AF episodes (lasting > 10 min) from 25 patients were included in our analysis. The total number of patients who suffered only from symptomatic AF episodes was 6. In 11 patients, only asymptomatic episodes were recorded, while there were 8 patients who had both types of AF episode. In 5 patients, no AF episode was recorded during the follow-up period. The most common symptom indicative of the arrhythmia in our population was palpitations (9 patients) followed by dizziness (2 patients).

3.1. Asymptomatic versus symptomatic AF episodes

A total of 43 ASx episodes, 27 Sx episodes, and 12 AS-Sx AF episodes were included in our analysis. The mean HR1, HRV1 and delta hr during the first 2 min of ASx and Sx AF episodes are shown in Fig. 1; there were significant differences in HR1, HRV1, and delta hr between Sx and ASx episodes. The Sx episodes were characterized by higher mean HR and delta hr, and lower mean HRV than the ASx episodes. The analysis of AF episodes in each individual patient who suffered from both types of AF episodes (symptomatic and asymptomatic) was in line with the above results. There was no statistically significant association between specific patients' clinical characteristics (age, body mass index, smoking, hypertension, dyslipidemia, heart failure, diabetes mellitus, history of transient ischemic attack or stroke) and the occurrence of symptomatic or asymptomatic AF episodes. However, significant seasonal variation in the distribution of the AF episodes was observed (Fig. 2a). Most AF episodes that occurred during the winter season (December, January, February) were asymptomatic (65.5%), while during the summer season (June, July, August) the majority of AF episodes were symptomatic (30.8%) or AS-Sx (46.2%). Furthermore, a large majority of AF episodes recorded between midnight and 6 am began as asymptomatic (78.6%), while 53.6% of episodes were totally asymptomatic (Fig. 2b). In contrast, 47.8% of AF episodes that began between 6 pm and midnight were totally symptomatic.

3.2. Asymptomatic versus symptomatic periods in AS-Sx AF episodes

Twelve AS-Sx AF episodes that were initially asymptomatic and subsequently became symptomatic were included in our analysis. The most common symptom was palpitations. The average time between the onset of AF and the activation of the device by the patient was 244 min. The mean duration of the AS-Sx episodes was 13 ± 9 h. HR and HRV measurements did not differ significantly between the two observers. The mean HR1 (asymptomatic period) was 102.91 ± 24.54 bpm and the mean HR2 (symptomatic period) was 141.88 ± 23.43 bpm ($p < 0.001$). The mean HRV1 (asymptomatic period) was 173.55 ± 61.30 ms, while the mean HRV2 (symptomatic period) was 87.33 ± 30.65 ms ($p = 0.003$). In these episodes the change from asymptomatic to symptomatic AF was associated with a significant

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