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Editorial on the Article «Natriuretic Peptide Concentrations and Echocardiography Findings in Patients With Micro-atrial Fibrillation»

In relation with the published article «Natriuretic Peptide Concentrations and Echocardiography Findings in Patients with Micro-atrial Fibrillation», we have issued a comment. The authors of the article addressed a widely discussed topic of «Short episodes of fast arrhythmias initially detected in records on implantable devices». Further, these episodes are studied already by Holter monitoring of different durations with assessment of their clinical significance. This is the subject of the cited article and our comment.

Keywords Atrial high rate episodes; atrial fibrillation; subclinical atrial fibrillation

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In recent years, an increasing number of reports have documented the occurrence of clinically silent episodes of rapid atrial rhythm in patients with implanted devices, including pacemakers, implanted cardioverter-defibrillators, and resynchronization devices [1]. The atrial electrode permitted the evaluation of a patient's long-term history of arrhythmias, thus enabling the identification of atrial arrhythmic episodes irrespective of the presence or absence of symptoms. [2]. Such episodes are frequently designated as atrial high-rate episodes (AHREs), or alternatively, as subclinical atrial fibrillation (AF) [3].

In accordance with the extant definition, clinically overt classical AF is a supraventricular tachyarrhythmia characterized by disorganized electrical activity of the atria, occurring at a frequency of 350–700 contractions per minute with the absence of a P wave on ECG, which precludes the possibility of coordinated contraction. Additionally, and with an irregular ventricular rhythm. In accordance with the Russian clinical guidelines, it is recommended that AHRE be distinguished from classical AF. Upon detection of atrial electrograms during analysis of electrode recordings, it is recommended that a more detailed examination be conducted to ascertain the presence of true AF [3]. It is also acknowledged that a significant proportion of AF episodes are entirely asymptomatic. Such episodes may not be identified even during a clinical event (e.g., a stroke or systemic thromboembolism) and may be discovered fortuitously during an examination of the patient for any reason. The terms «subclinical AF» and «AHRE» are used synonymously in the literature. However, it is necessary to distinguish between them precisely, as many authors define AHRE as episodes of hidden arrhythmias in individuals without clinically diagnosed AF [4]. Atrial tachyarrhythmias are episodes of rapid atrial rhythms identified through the analysis of long-term recordings obtained from the atrial electrode. These episodes are characterized by a frequency of more than 170–190 contractions per minute and a minimum duration of 10–20 consecutive contractions [5]. Moreover, it has been demonstrated that some AHREs derived from the electrode may be false positives or artifacts, for instance, resulting from electrical noise. Consequently, a visual assessment of each such episode is necessary [6].

Patients with implanted devices represent a distinctive population, exhibiting a range of comorbidities that render them vulnerable to the development of atrial arrhythmias. The majority of AHREs are asymptomatic and are identified during routine stimulator testing. The prevalence of episodes of rapid rhythms in patients without a history of AF is approximately 25% per year and 35% per two years of follow-up. Additionally, AHREs differ from AF in that no ff waves are observed [2]. Nevertheless, numerous authors refer to AHREs as a form of silent or subclinical AF or microfibrillation.

Furthermore, the potential progression of arrhythmia episodes into classical fibrillation pauses is also addressed in the existing literature [7] .

The emergence of this relatively novel phenomenon gives rise to a number of questions.

1. It is pertinent to inquire whether AHREs can potentially result in clinically overt AF.

In 2022, J. F. Imberti et al. demonstrated that episodes of atrial arrhythmias with frequent ventricular contractions,

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detected by cardiac implantable electronic devices, may be associated with an increased risk of further progression to prolonged episodes of clinically overt AF.

The identification of this subgroup of patients is of paramount importance for the prompt administration of oral anticoagulant therapy and potentially for the prevention of stroke and systemic thromboembolism. The aforementioned study delineates the clinical characteristics of 104 patients retrospectively included in the study (mean age 79.7 (74.0–84.2) years, 33.7% female) who experienced AHREs lasting from 5 minutes to 23 hours and 59 minutes, with no AF seen on 12-lead ECG and no clinical manifestations. During the mean follow-up period of 24.3 (10.6–40.3) months, 31 (29.8%) of the 104 patients experienced AF. The baseline CHA2DS2 – VASc score and the longest AHRE in the study, which lasted from 12 hours to 23 hours and 59 minutes, were found to be independently associated with the composite endpoint and an incident of clinical AF [7].

2. The risk of stroke in paroxysmal AF is elevated even in the presence of sinus rhythm [8], suggesting that, in addition to hemodynamic mechanisms, there are likely additional factors contributing to thrombosis.

It is conceivable that extensive atrial fibrosis may be involved in the development of thrombosis. Moreover, it establishes an environment conducive to micro-reentry tachycardia, such as AF, by isolating cardiomyocytes [9, 10]. These findings suggest that AF, supraventricular tachycardia, supraventricular extrasystoles, and AHREs may be indicative of atrial cardiomyopathy and, thus, may be independently associated with an elevated risk of stroke.

In a recent study, Kulach et al. investigated the potential association between AHREs and cryptogenic ischemic stroke (CS). It is important to note that the study did not include patients with implanted devices. The objective of this study was to assess the efficacy of 72 hour Holter monitoring, 7 day Holter monitoring, and patient-activated manual ECG recorders in patients with CS. The study population consisted of 72 patients (mean age 60 ± 9 years, 44 male) with CS and without arrhythmias within 24 hours during Holter monitoring. All patients underwent 7 day Holter monitoring. The incidence of AF, supraventricular tachycardia (SVT ≥ 5 QRS complexes), and other arrhythmias was evaluated over a 72-hour period through Holter monitoring, utilizing a seven day recording and patient-activated manual ECG recorders. The 72-hour ECG recording revealed the presence of silent AF in four cases (5.6%) and SVT in 18 cases (25%). Day 7 Holter monitoring confirmed AF in seven patients (10%) and SVT in 27 patients (37.5%). The patient-activated manual ECG recorders were used with an acceptable level of compliance. The mean number of recordings was 49 ± 30, indicating that episodes of frequent atrial rhythm can be detected by 24-hour Holter monitoring, with 7-day monitoring demonstrating superior efficacy compared to 72-hour monitoring. Supraventricular arrhythmias were identified in one-third of patients, and clinically silent AF was observed in 10% of patients with CS who had no arrhythmia in 24-hour Holter monitoring [11].

3. Another question is whether there is an association between cardioembolic stroke and the presence of AHREs?

The relatively large-scale ASSERT study has demonstrated that subclinical AF (AHRE) is frequently first detected in patients having a pacemaker. Such patients are at an elevated risk of ischemic stroke or systemic embolism. The duration of AHREs is variable, and there is a paucity of data regarding the incidence and prognosis of different durations of AHREs.

The ASSERT study included 2,580 patients with pacemakers or implantable cardioverter-defibrillators (ICDs) aged > 65 years with hypertension and without a history of clinically overt AF. The influence of AHRE duration on the subsequent risk of ischemic stroke or embolism was assessed using a Cox model with time-dependent covariates. Patients with a maximum AHRE duration of less than six minutes were excluded from the analysis (n = 125). Over a 2.5-year follow-up period, among the 2,455 patients, a single AHRE was observed to last between six minutes and six hours in 462 patients (18.8%), between six minutes and 24 hours in 169 patients (6.9%), and for a duration exceeding 24 hours in 462 patients (18.8%). A duration of AHRE longer than 24 hours was found to be significantly associated with an increased risk of stroke or systemic embolism (adjusted hazard ratio [HR] 3.24, 95% confidence interval (CI) 1.51–6.95, p = 0.003). The risk of ischemic stroke or systemic embolism in patients with AHREs lasting between six minutes and 24 hours was not found to differ significantly from that of patients without AHREs. It was thus concluded that a period of latent AF exceeding 24 hours was associated with an elevated risk of ischemic stroke or systemic embolism [12].

The presented data primarily concern the variety of AHRE variants (latent AF), which approach clinically significant arrhythmia when prolonged. In consideration of these findings, it is reasonable to pose the following question.

4. The question is whether this variant of arrhythmia should be treated, and if so, how.

The authors of the cited study correctly identify that the clinical significance of AHREs remains unclear, and that the evidence is limited [12]. The objective of this review is to present and discuss the current evidence regarding the

clinical impact of latent AF and AHREs on major potential clinical outcomes, primarily thromboembolic events. The authors conducted an analysis of data from 12 studies, the majority of which were conducted between 2020 and 2021. The total number of patients included in the analysis was 8,720, and the duration of AHREs and/or subclinical AF ranged from 30 seconds to several hours. The review encompassed data from a number of studies, including ASSERT and REM-HF. The authors conclude that long-term continuous ECG monitoring using implantable cardiac monitors and loop ECG recorders, which have been demonstrated to be effective, is essential for the detection of AHREs and subclinical AF. Furthermore, the authors suggest that the probability of thromboembolic events may be elevated with an increase in the frequency and duration of AHREs and/or episodes of subclinical AF. It has been proposed that the risk of stroke and/or systemic embolism is significantly increased in individuals with a high CHA2DS2 VASc score. Nevertheless, the current body of evidence is insufficient to determine the clinical significance of subclinical episodes of AF/AHREs [13].

In 2023, the findings of the NOAH-AFNET 6 and ARTESiA studies on the efficacy and safety of edoxaban and apixaban for stroke prevention in patients with AHREs, as identified through the analysis of electrode recordings from implanted devices, were published. The incidence of stroke in these patients was found to be significantly lower than that observed in patients with clinically overt AF. The use of oral anticoagulants (OACs) was observed to reduce the incidence of stroke. However, this was accompanied by an unacceptably high number of major bleeding events [1, 14–16].

It would be reasonable to question whether the cited studies have definitively resolved the question of whether OAC administration is an appropriate method of preventing stroke and embolism in patients with AHREs and silent AF. It is unlikely that this is the case, given that the patient population with implanted intracardiac devices differs from that of patients with atrial fibrillation AF. For instance, the incidence of stroke has been shown to be higher in patients with an implanted pacemaker and AHREs compared to those without AHREs. However, it remains lower than in patients with clinically overt AF [1].

The authors of the discussed article, aware that AHREs (micro-AF) can precede or coexist with clinically overt AF, sought to identify alterations in NT-proBNP levels and left atrial (LA) parameters obtained via transthoracic echocardiography (TTE) in patients with AHREs (micro-AF). It is noteworthy that the study included 45 patients who presented with irregular heartbeats and a further 45 patients who constituted the control group. The interval between the onset of the P wave on the ECG and the onset of the late diastolic wave was considered to be the time of atrial electromechanical delay. This was also determined by the time distance to the late wave of the lateral and medial parts of the fibrous annuli of the mitral and tricuspid valve walls on tissue Doppler imaging. During periods of sinus rhythm, the duration of the P wave was quantified on a standard ECG.

NT-proBNP and serum troponin T concentrations were found to be elevated in the micro-AF group ($p < 0.001$ in both cases), with a 1 pg/mL increase in serum NT-proBNP levels associated with an 1.8% increased risk of micro-AF. In ROC analysis, the threshold for diagnosing micro-AF was determined to be 63.4 pg/mL, with sensitivity of 91.1% and specificity of 73.3%. Atrial electromechanical delay was found to be significantly longer in the micro-AF group. Electromechanical delay in the left plane of the mitral valve fibrous annulus at a threshold value of 11.5 s predicted the presence of AHREs with a sensitivity of 95.6% and a specificity of 75.6%. The maximum and minimum duration of the P wave and its variance were higher in the micro-AF group.

Ultimately, the authors have demonstrated predictors of AHREs (micro-AF), which exhibit notable similarities with clinical conditions associated with overt AF. This suggests that the mechanisms underlying the development of AHREs and overt AF may be similar, emphasizing the necessity for a more rigorous approach to the diagnosis of AF when AHREs are identified using any type of ECG monitoring [3].

No conflict of interest is reported.

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