Atrial fibrillation: An early marker of ventricular myocardial dysfunction

Stergios Soulaidopoulos[1], Anastasia Xintarakou[1], Nikolaos Vogiatzakis[1], Ioannis Doundoulakis[1], Petros Arsenos[1], Stefanos Archontakis[2], Christos-Konstantinos Antoniou[3], Maria Drakopoulou[1], Athanasios Kordalis[1], Ioannis Skiadas[2], Dimitris Tsiachris[3], Polychronis Dilaveris[1], Skevos Sideris[2], Panagiotis Xydis[1], Konstantinos Tsioufis[1], Konstantinos A Gatzoulis[1]

[1]1st Department of Cardiology, Hippokration General Hospital, Athens Medical School, National and Kapodistrian University of Athens, Athens, Greece
[2]State Department of Cardiology, Hippokration General Hospital, Athens, Greece
[3]Athens Heart Center, Athens Medical Center, Athens, Greece

Correspondence to:
Konstantinos A Gatzoulis MD, PhD,
Professor of Cardiology,
1st Department of Cardiology,
National and Kapodistrian University of Athens,
School of Medicine
"Hippokration" General Hospital,
114 Vasilissis Sofias Avenue,
11527, Athens, Attica, Greece
phone: +30 69 445 803 69,
fax: 0030 213 208 86 76,
e-mail: kgatzoul@med.uoa.gr

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INTRODUCTION

Whether patients with atrial fibrillation (AF) and structurally normal hearts carry a higher risk of life-threatening ventricular arrhythmias and sudden cardiac death (SCD) remains currently uncertain [1]. It is possible that factors causing atrial interstitial fibrosis underlying atrial myopathy also impact the ventricular myocardium, creating conditions for ventricular ectopia. In that case, AF could rather imply silent, generalized myocardial dysfunction than isolated atrial myopathy in patients with apparently normal hearts.

In this context, we sought to assess the risk of ventricular arrhythmogenesis in patients with AF in the absence of structural heart disease using ventricular late potentials (LPs) detected by signal-averaged electrocardiography (SAECG).

METHODS

We recruited patients aged 18 to 80 years with documented, permanent, or paroxysmal AF and no apparent organic heart disease, referred to the Electrophysiology Department at the Hippokration General Hospital in Athens from September 2018 until June 2022 for AF evaluation. The demographic and clinical patient data were collected. All subjects were submitted to SAECG according to a previously described protocol [2]. SAECG tests from healthy subjects, used as a control group, were also obtained. The test was considered positive for the presence of ventricular LPs if 2 of the following 3 criteria were met: 1) filtered QRS duration was ≥114 msec, 2) duration of low amplitude signal (LAS) was ≥38 msec and 3) root mean square amplitude of the last 40 ms of the QRS signal (RMS40) was ≤20 μV. The protocol of this prospective, single-center study was approved by the institutional ethics review board.

Statistical analysis

Data analysis was performed using SPSS Statistical Package (version 26.0, IBM Corp., Armonk, NY, US). Descriptive statistics were used for the presentation of baseline characteristics. Continuous variables were expressed as mean values with standard deviation. Categorical variables were expressed as frequencies and percentages. Student's t-test was used for the comparison between continuous variables. Potential correlations were evaluated with Pearson correlation or Spearman rank correlation tests, as appropriate. Categorical data were analyzed with the chi-square test or Fisher's exact test, as appropriate. Control for potential confounding factors was performed with multivariable regression analysis. A two-tailed $P<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

In total, 158 patients and 45 healthy adults, matched for age, were studied. Their mean age was 65 (13.2) years while 85 (53.8%) patients were men. The majority of patients had paroxysmal AF (96.2%), and only 6 (3.8%) patients had permanent AF. Twelve (7.6%)

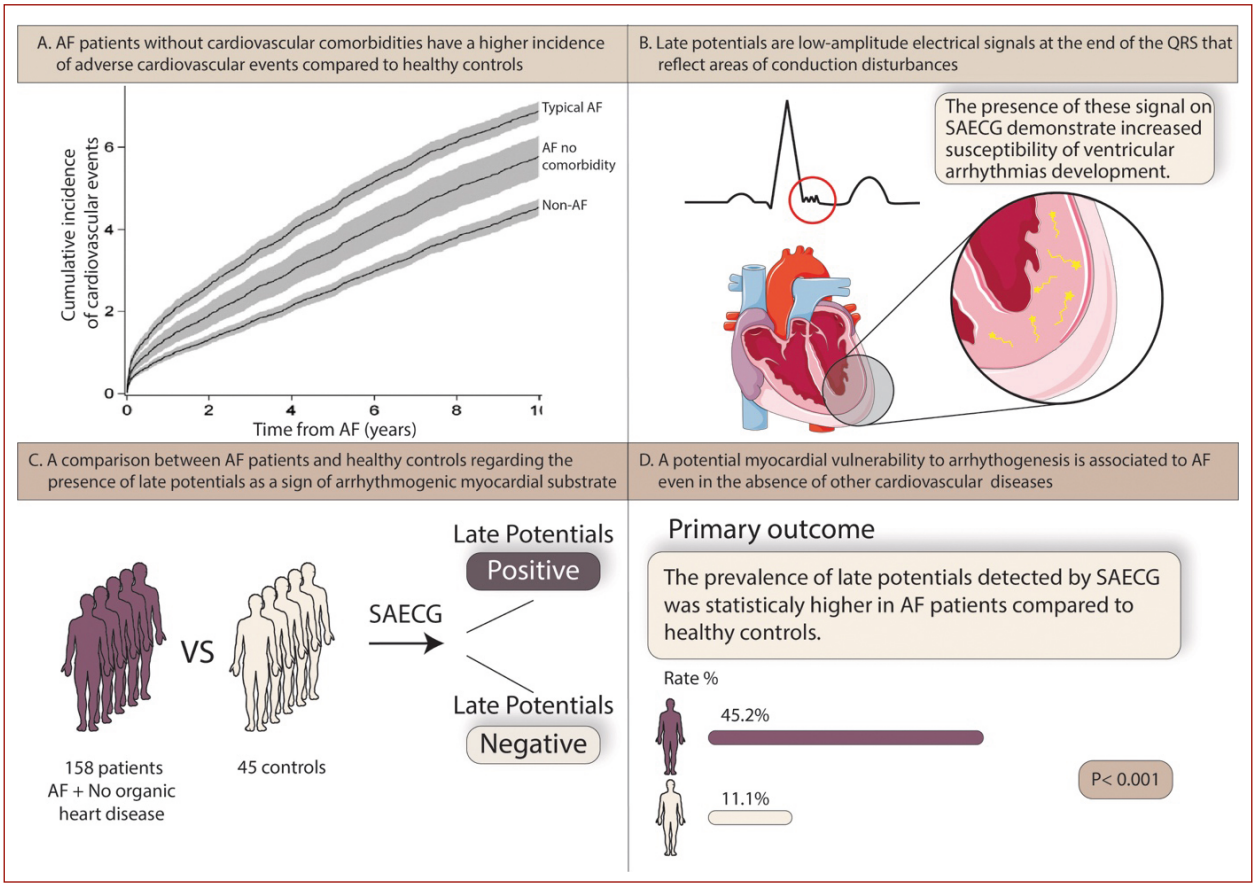

Figure 1. Graphical abstract. The chart presented in quartile (**A**) has been adapted from: Kim et al. Atrial fibrillation without comorbidities: Prevalence, incidence and prognosis (from the Framingham Heart Study). Am Heart J. 2016; 177: 138–144 [3]

Abbreviations: AF, atrial fibrillation, SAECG, signal-average electrocardiogram

patients had undergone one or more catheter ablation procedures for paroxysmal AF, whereas ablation for complex ventricular ectopic activity had been performed in 2 patients. Besides AF, frequent (>1000/24 hours) ventricular contraction or short episodes of non-sustained ventricular tachycardia were detected in 14 (8.8%) patients on 24-hour Holter monitoring. Baseline and demographic data are summarized in the Supplementary material, *Table S1*.

Most patients were on antiarrhythmic medication for sinus rhythm maintenance. Sixty-one (38.5%) patients were in treatment with flecainide, 24 (15.4%) on amiodarone, 18 (11.5%) on propafenone, and only 6 (3.8%) were treated with sotalol.

Concerning SAECG tests, a significantly higher proportion of AF patients met either 2 or 3 criteria for the diagnosis of ventricular LPs compared to the control group (72 [45.2%] vs. 5 [11.1%]; P <0.001). Most patients in flecainide treatment had at least 2 positive criteria for LPs (60.6%) (Figure 1). Nevertheless, no significant correlation between flecainide treatment and a positive SAECG test for LPs was observed (P = 0.379).

The principal findings of our study can be summarized in the following way: 1) Patients with a history of AF and normal heart structure had a higher prevalence of ventricular LPs compared to healthy controls, as detected by SAECG, and 2) treatment with antiarrhythmic drugs may induce the development of LPs but cannot completely explain their high prevalence in this population.

The association of AF with development of life-threatening ventricular arrhythmias is controversial, particularly in the absence of structural heart disease. A recent analysis of a Korean nationwide database including approximately 10 million patients, demonstrated an association of new-onset AF with 4.6-fold increased risk of ventricular tachyarrhythmia over a 10-year follow-up [3]. While evidence in this field is scarce, the precise pathogenetic mechanisms that could explain the link between AF and ventricular arrhythmias in the absence of organic heart disease are yet to be investigated. On the other hand, a link between AF and heart failure has been previously established. More specifically, in patients with heart failure, AF is considered a marker of a more advanced ventricular dysfunction as well as a predictor of worse clinical prognosis. In the presence of impaired left ventricular systolic function, AF and an elevated heart rate have also been identified as independent predictors of concomitant right ventricular dysfunction, which may also constitute another marker of advanced heart failure [4]. A holistic and multidisciplinary

approach, including regular assessment of left ventricular function as well as management of comorbidities, is, therefore, of crucial importance in AF patients [5].

There is a growing recognition that atrial myopathy characterized by atrial fibrosis is strongly related to the development of AF, especially in the absence of other prominent risk factors [6]. Multiple factors have been proposed as potential contributors to atrial remodeling, including intrinsic cardiac aging, oxidative stress, inflammation, and abnormal intracardiac pressures [7]. The same processes may account for pathologic changes in the ventricular myocardium, such as scar tissue formation, which gives rise to ventricular arrhythmogenesis. Another possible explanation is that genetic variations affect both the atria and ventricles and, hence, result in the development of both AF and ventricular arrhythmias. Specific genetic variations underlying the phenotypic expression of channelopathies or cardiomyopathies have been found to play a role in AF pathogenesis [8].

The increased prevalence of LPs in AF patients, compared to healthy controls, could indicate co-existing, clinically silent, dysfunction of the ventricular myocardium. LPs represent low-amplitude electrical signals at the end of the QRS complex that arise from areas of the slowly depolarizing myocardium and are considered to form a substrate for ventricular arrhythmogenesis. Obtained by signal-averaging techniques, LPs represent a recognized, non-invasive marker for the prediction of potential arrhythmic events [9]. Their prognostic value has been more thoroughly investigated in coronary artery disease and arrhythmogenic right ventricular cardiomyopathy, while their role in nonischemic cardiomyopathy is currently limited [10]. At the moment, though, the observed association between AF and the presence of LPs on SAECG does not necessarily establish a cause-effect sequela.

Class I antiarrhythmic drugs commonly used for rhythm control in AF, reversibly bind to and block fast sodium channels, thereby reducing cardiac conduction velocity. Sodium channel blockers have been found to selectively prolong QRS LPs due to preferential effects on the slowly conducting myocardium [11]. That means that they induce a more pronounced conduction delay in cardiac tissue with decreased baseline conduction velocity compared to cardiac tissue with normal baseline conduction. In fact, when studied in patients with symptomatic and repetitive ventricular arrhythmias, propafenone, mexiletine, and flecainide produced significant changes in SAECG parameters, unrelated to their antiarrhythmic efficacy. Moreover, in a study of 25 patients, flecainide induced significant changes to SAECG indices regardless of the underlying disease or a history of ventricular tachycardia [12] Whether such SAECG changes indicate a greater risk of ventricular arrhythmogenesis, reflecting a proarrhythmic activity of the specific drug, especially in patients with normal heart structure, remains an open question.

Limitations

This study is not without limitations. The relatively small sample size and lack of follow-up data do not allow for drawing valid conclusions about the study hypothesis that should be ideally assessed in a long-term randomized controlled clinical study. Due to missing data, we did not search for imaging or ECG factors that could potentially predict the presence of LPs in our cohort. We acknowledge that LP detection demonstrates a low positive predictive value for arrhythmic events. Yet, SAECG remains an inexpensive, reproducible, and non-invasive tool that provides valuable information regarding the risk of malignant arrhythmic events in various clinical settings.

CONCLUSIONS

Patients with AF and no structural heart disease present more often LPs on SAECG compared to healthy controls, which cannot be solely explained by the use of antiarrhythmic drugs.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

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