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Relationship between QRS duration and incident atrial fibrillation

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ABSTRACT

Background: QRS duration (QRSd), a measure of ventricular conduction, has been associated with adverse cardiovascular outcomes, but its relationship with incident atrial fibrillation (AF) is poorly understood.
Methods and results: This study included 15,314 participants from the *Atherosclerosis Risk in Communities* (ARIC) study who were free of AF at baseline. QRSd was automatically measured from resting 12-lead electrocardiograms (ECGs) at baseline. Incident AF cases were systematically ascertained using ECGs, hospital discharge diagnoses and death certificates. Multivariable adjusted Cox regression analyses were performed to investigate the relationship between QRSd and incident AF. Mean age of our population was 54 ± 6 years (55% females). During a median follow-up of 21.2 years, 2041 confirmed incident AF cases occurred. In multivariable adjusted Cox models, a 1-SD increase in QRSd was associated with a hazard ratio (HR) (95% CI) for AF of 1.05 (1.01; 1.10), p = 0.01. This relationship was significant among women (HR per 1-SD increase in QRSd (95% CI) 1.13 (1.06; 1.20), p < 0.001), but not among men (1.00 (0.95; 1.06), p = 0.97) (p for interaction 0.005). Compared to individuals with a QRSd <100 ms, the HRs for incident AF in individuals with a QRSd of 100–119 and ≥120 ms were 1.13 (1.02; 1.26) and 1.35 (1.08; 1.68), respectively (p for trend 0.002). Again, this relationship was significant among women (p for trend <0.001) but not among men (p for trend 0.23).
Conclusion: In this large population-based study, QRSd was an independent predictor of incident AF among women, but not in men. Further studies are needed to better understand the underlying mechanisms.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the population [1–4] and the number of individuals with AF is expected to increase substantially over the next years [1,5]. AF is strongly associated with an increased risk of death, stroke and heart failure (HF) [6,7]. While several risk factors for AF development are already known [4,8], they currently explain only about 50% of its population attributable risk [9].

QRS duration (QRSd) represents the time of ventricular depolarization and depends on age, heart rate and sex, with a longer QRSd in men compared to women [10]. A prolonged QRSd on the resting electrocardiogram (ECG) is associated with cardiac structural and functional abnormalities [11,12] and was shown to be an independent predictor of congestive HF [11,13] and death [14]. Little evidence is available on the association between QRSd and incident AF. In a cross-sectional study of 25,000 patients with left ventricular dysfunction, the authors found a higher prevalence of AF in patients with prolonged QRSd [15]. Similar results were found in patients with septic shock or ischemic stroke [16,17].

However, limitations of these previous studies include their small sample size, the study design and/or the inclusion of selected patient groups, such that the generalizability to general population samples remains unclear and the directionality of the association unknown. To overcome these limitations, we investigated the relationship between

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; ECG, electrocardiogram; HF, heart failure; HR, hazard ratio; LVH, left ventricular hypertrophy; $PTFV_1$, P wave terminal force in lead V1; QRSd, QRS duration; SD, standard deviation.

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QRSd and incident AF in a large prospective sample representative of the general population.

2. Methods

2.1. Study population

The *Atherosclerosis Risk in Communities* (ARIC) study is a prospective, community-based cohort study. Overall, 15,792 individuals aged 45 to 64 years were enrolled between 1987 and 1989 at four centers in the United States (Washington County, MD; Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN). Participants returned for 4 follow-up examinations (1990–1992, 1993–1995, 1996–1998 and 2011–2013). Additionally, there were annual phone calls to ascertain study end points. Detailed study procedures have been published previously [18]. The study was approved by the institutional review boards at all participating universities and all participants provided written informed consent at each study visit.

For this analysis we excluded participants with AF, non-sinus rhythm or pacemaker rhythm on the baseline ECG (n = 37), those with missing baseline covariates (n = 240), participants with missing information on AF during follow-up (n = 99), and individuals with race other than black or white, and the small number of black participants from Washington County and Minneapolis (n = 102), leaving 15,314 participants for this analysis.

2.2. Electrocardiogram

A resting 12-lead ECG was obtained in every participant at baseline and at all follow-up examinations using MAC PC ECG machines (Marquette Electronics, Milwaukee, WI). All ECGs were inspected for technical errors and adequate quality at the Epidemiology Coordinating and Research Center at the University of Alberta (Edmonton, Alberta, Canada) during the initial phases of the study and at the Epidemiological Cardiology Research Center at the Wake Forest School of Medicine (Winston-Salem, North Carolina, USA) during later phases. QRSd was measured automatically as the average value in all leads. The Cornell voltage was calculated as the sum of R in aVL and S in V_3 and left ventricular hypertrophy (LVH) was defined as a sum of ≥20 mm in women and ≥28 mm in men. The PR interval and P wave terminal force in lead V_1 ($PTFV_1$) were measured automatically.

2.3. Ascertainment of atrial fibrillation

Incident AF cases were systematically ascertained using study visit ECGs, review of hospital discharge diagnoses or death certificates through December 31st 2010. ECG recordings that were automatically defined as AF were visually checked by a trained cardiologist to confirm the diagnosis. Information on hospitalization during follow-up was obtained from annual follow-up calls and surveillance of local hospitals, with hospital discharge diagnosis codes collected by trained abstractors. AF during follow-up was defined by *International Classification of Diseases, 9th Revision* codes 427.31 or 427.32. AF cases detected in the same hospitalization as open cardiac surgery were not included since these cases were considered transient.

2.4. Ascertainment of other covariates

Information on age, sex, race, body mass index (BMI), blood pressure, heart rate, smoking status (current versus former and never smoker), medication, and history of diabetes mellitus, coronary heart disease and HF was obtained during the baseline examination. Age, sex, race and smoking status were self-assessed. BMI was calculated as body weight in kg divided by height in m^2. Diabetes mellitus was defined as a fasting glucose of >125 mg/dl, a non-fasting glucose of >200 mg/dl, a self-reported physician diagnosis, or intake of antidiabetic drugs. Blood pressure was measured three times in a sitting position after 5 min of rest using sphygmomanometers. The average of the last two blood pressure measurements was used as the final reading. Prevalent coronary heart disease was defined as having a history of a myocardial infarction, coronary artery bypass surgery, coronary angioplasty or electrocardiographic evidence of myocardial infarction. Prevalent HF was defined as taking HF medication or fulfilling the Gothenburg criteria, which is a points system that assigns HF grades depending on medical history, physical findings and drug treatment.

2.5. Statistical analysis

Baseline characteristics were stratified according to the predefined QRSd categories <100 ms, 100–119 ms and ≥120 ms. We also assessed differences in baseline characteristics according to sex. Continuous variables were presented as mean ± standard deviation (SD) and compared using analysis of variance or student's *t*-tests. Categorical variables were presented as numbers (percentages) and compared using chi-square tests.

Person-years of follow-up were calculated as the time between the recording of the baseline ECG until AF onset, loss to follow-up, death or end of follow-up (December 31, 2010), whichever occurred first. The cumulative incidence of AF across QRSd categories was examined through Kaplan-Meier estimates. Differences across strata were compared using log-rank tests. We then constructed multivariable Cox regression models to compute hazard ratios (HR) with 95% confidence intervals (CI), and to adjust for potential confounders. QRSd was used both as a categorical and a continuous variable. p-Value for trend was calculated using the category-specific median. In a first step, multivariable models were adjusted for age, sex, race and study site. A second model additionally adjusted for BMI, systolic blood pressure, smoking status, heart rate, antihypertensive treatment, diabetes mellitus, coronary heart disease and a history of HF. We also examined the dose-response relationship between QRSd and AF using a restricted cubic spline model with knots at the 5th, 50th and 95th percentile. Subgroup analyses were performed to investigate whether the relationship between QRSd and incident AF differs between men and women, different race groups and age categories. Multiplicative interaction terms were included in the non-stratified multivariable Cox models to formally assess differences across subgroups.

We performed several additional analyses. First, to assess the influence of LVH on the association between QRSd and incident AF, we added electrocardiographic LVH to the multivariable model. Second, due to the known relationships of PR-interval and $PTFV_1$ with AF [19] we built separate Cox models additionally adjusting for these variables. Third, as a sensitivity analysis we excluded individuals with complete bundle branch block (i.e. QRSd ≥120 ms) and repeated the main multivariable analyses among those with QRSd <120 ms.

Categorical variables were entered in all models using binary indicator variables. Statistical significance was pre-specified as a p-value < 0.05 and all analyses were performed using SAS version 9.4 (Cary, NC).

3. Results

The mean age of our study population at baseline was 54 ± 6 years, 8452 (55%) were females and 4051 (26%) were black. QRSd was <100 ms in 11,898 (78%), 100–119 ms in 2990 (19%) and ≥120 ms in 426 (3%). Baseline characteristics stratified by QRSd categories are presented in Table 1. Individuals with longer QRSd were more likely to be older, male or active smokers and they had a higher prevalence of hypertension, coronary heart disease, HF and diabetes mellitus. Mean QRSd was significantly higher in men compared to women (97 ms vs. 88 ms, p < 0.001). Baseline characteristics stratified by sex are shown in Table S1.

Over a median follow-up of 21.2 years (interquartile range 16.6; 22.1 years), a total of 2041 incident AF cases were detected, 1109 in

Table 1
Baseline characteristics stratified according to QRS duration categories.

Characteristics	QRS duration (ms)			p-Value[a]
	<100 (n = 11,898)	100–119 (n = 2990)	≥120 (n = 426)	
Age, mean ± SD (years)	54 ± 5.8	54 ± 5.7	57 ± 5.5	<0.001
Male (%)	4352 (37)	2221 (74)	289 (68)	<0.001
Black (%)	3240 (27)	700 (23)	111 (26)	<0.001
Current smoker (%)	6717 (56)	1946 (65)	278 (65)	<0.001
Body mass index, mean ± SD (kg/m^2)	28 ± 5.4	28 ± 5.1	28 ± 5.1	<0.001
Systolic blood pressure, mean ± SD (mm Hg)	121 ± 19	123 ± 19	124 ± 20	<0.001
Heart rate, mean ± SD, (bpm)	67 ± 10	64 ± 10	65 ± 11	<0.001
Antihypertensive medications (%)	3419 (29)	1058 (35)	185 (43)	<0.001
Diabetes mellitus (%)	1363 (11)	378 (13)	64 (15)	0.02
Coronary heart disease (%)	393 (3.3)	269 (9.0)	72 (17)	<0.001
Heart failure (%)	494 (4.2)	174 (5.8)	39 (9.2)	<0.001

SD = standard deviation.
[a] Statistical significance for categorical data was tested using the chi-square procedure and continuous data was tested using the analysis of variance procedure.