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, 2,041 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 <100ms, the HRs for incident AF in individuals with a QRSd of 100–119 and ≥120ms were 1.13 (1.02; 1.26)

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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.

Keywords

Atrial Fibrillation; QRS duration; sex differences; electrocardiogram; population-based

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

Methods

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 to 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.

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 20mm in women and 28mm in men. The PR interval and P wave terminal force in lead V_1 (PTFV$_1$) were measured automatically.

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.

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 were 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 >125mg/dl, a non-fasting glucose of >200mg/dl, a self-reported physician diagnosis, or intake of antidiabetic drugs. Blood pressure was measured three times in a sitting position after 5 minutes 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.

Statistical analysis

Baseline characteristics were stratified according to the predefined QRSd categories <100ms, 100–119ms and 120ms. 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 120ms) and repeated the main multivariable analyses among those with QRSd <120ms.

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).

Results

The mean age of our study population at baseline was 54 ± 6 years, 8,452 (55%) were females and 4,051 (26%) were black. QRSd was <100ms in 11,898 (78%), 100–119ms in 2,990 (19%) and 120ms 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 (97ms vs. 88ms, 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 2,041 incident AF cases were detected, 1,109 in men and 932 in women. AF incidence rates (95%

CI) were 6.5 (6.2; 6.8), 9.2 (8.5; 10.1) and 13.1 (10.6; 16.2) per 1000 person-years of follow-up in individuals with a QRSd of <100ms, 100–119ms and 120ms, respectively (Table 2), and these differences were significant in Kaplan Meier analyses (p<0.001) (Figure 1). In multivariable Cox regression analysis, the adjusted HR per 1-SD increase (12ms) in QRSd was 1.05 (1.01, 1.10), p=0.01 (Table 2). Compared to individuals with a QRSd <100ms, the multivariable adjusted HR (95% CI) for individuals with a QRSd of 100–119ms and 120ms were 1.13 (1.02; 1.26) and 1.35 (1.08; 1.68), respectively (p for trend 0.002).

Subgroup analyses revealed consistent results across strata of age and race, but not sex (p for interaction 0.005, Table S2). Sex-specific incidence rates are shown in Table 3. Among women, a 1-SD increase (11ms) in QRSd was associated with a HR (95% CI) for incident AF of 1.13 (95% CI 1.06; 1.20), p<0.001. The corresponding HR (95% CI) among men was 1.00 (0.95; 1.06), p=0.97. Compared to women with a QRSd <100ms, multivariable adjusted HRs (95% CI) for incident AF were 1.27 (1.04; 1.54) and 1.86 (1.29; 2.68) among those with a QRSd of 100–119 and 120ms, respectively (p for trend <0.001). The same HR estimates (95% CI) among men were 1.06 (0.94; 1.21) and 1.14 (0.87; 1.51), respectively (p for trend 0.23). In restricted cubic spline models there was no evidence of non-linearity for the relationship with incident AF across the entire spectrum of QRSd in either sex (Figure S1).

Additional adjustment for PR interval or $PTFV_1$ did not change our results (Table S3). Although adjustment for LVH attenuated the relationship between QRSd and incident AF in the overall cohort (HR (95% CI) 1.04 (0.99; 1.08), p=0.11), the results remained statistically significant among women (HR (95% CI) 1.11 (1.04; 1.19), p<0.001), as shown in Table S3. Finally, when individuals with a QRSd 120ms were excluded, the HRs (95% CI) for incident AF per 1-SD increase in QRSd were 1.02 (0.98; 1.08), p=0.34 in the overall cohort, 1.07 (1.00; 1.14), p=0.04 among women and 0.98 (0.93; 1.04), p=0.58 among men (Table S4).

Discussion

In this large well-characterized population based cohort, we found an independent relationship between QRSd and incident AF. Our results were robust and remained significant after comprehensive adjustment for important comorbidities and potential confounders. Our study provides important new information as previous studies in this area were mostly limited by the exclusive inclusion of diseased populations and a cross-sectional study design [15–17]. In addition, our results provide evidence that these relationships may be exclusively present among women but not among men. Further studies are needed to better understand the underlying mechanisms of these potential sex-specific differences.

QRSd is a marker of structural modifications and ventricular remodeling [11, 12]. Based on related risk factors, pathways and mechanisms prior studies have suggested that structural changes in the myocardium coexist in the atria and the ventricles, including cardiomyocyte hypertrophy and fibrosis [12, 20]. Thus, QRSd may be an indirect marker of left atrial disease, which is known to be strongly associated with AF development [21]. For example, prolonged QRSd was found to be associated with left atrial size, again supporting the

concept of simultaneous processes in the atria and ventricles [12]. These modifications impair cardiac function and modify electrophysiological properties, which then may result in a prolonged QRSd and provide an ideal substrate for AF development [21]. Another study also showed that LVH was a strong predictor of atrial fibrosis in AF patients [22]. Interestingly, our findings were attenuated after adjusting for electrocardiographic LVH.

Comorbidities, mainly hypertension and HF may have an important influence on the relationship between QRSd and incident AF based on their impact on ventricular structure and function, and their significant associations with AF. Even though we comprehensively adjusted for hypertension, HF and the other potential confounders, residual confounding is possible. Additionally, there is some evidence that genetic polymorphisms are involved in the relationship between QRSd and incident AF. For example, variations in the gene SCN5A, which is associated with lone AF [23], have shown to accelerate the process of ventricular fibrosis [24] that may in turn be responsible for a prolonged QRSd.

These potential mechanisms do not directly explain the sex-specific differences in the relationship between QRSd and incident AF. Mechanisms, which could be involved include differences in cardiac structure, electrical conduction as well as in hormone and inflammation levels [10, 25–27]. Inflammatory biomarkers, which are known to be strong predictors of AF [28] are higher in women compared to men [29]. Although the role of inflammation in AF pathophysiology is not fully understood, chronic inflammation might induce cardiac remodeling and fibrosis [30]. Sex hormones are known to have an influence on electrical conduction [25]. Cheng et al. found a greater age-associated increase of LV wall thickness in women compared to men [31]. One plausible reason for this disproportional increase in LV wall thickness might be the menopause induced decrease of the endogenous estrogen level [25, 32]. Additionally, a recent study showed a linear association between the number of pregnancies and incident AF, underscoring the importance of sex hormones in AF development [33]. Finally, it is worthwhile to mention that women in our study were between 45 to 64 years old at study entry, such that menopause associated hormonal changes and adaptations of the cardiovascular system might constitute a vulnerable phase in women.

In addition to the multiple strengths of our study, some limitations should be taken into account when interpreting our results. First, detection of AF cases is mainly based on hospitalization discharge codes and death certificates. Misclassification, mainly due to asymptomatic AF, is possible. Sex-specific differences in the perception of AF-related symptoms could potentially affect our results. However, the influence of this misclassification is expected to be small. Second, baseline echocardiograms were not available in this population. Third, as in every observational study, residual confounding may be present, even though we comprehensively adjusted for all known confounders.

Conclusion

In this large population based study, QRSd was an independent predictor of new-onset AF. This relationship remained significant after comprehensive multivariable adjustment and was observed in women, but not men. Our findings suggest that altered ventricular conduction,

potentially related to diffuse modifications in the myocardial tissue, is associated with the development of AF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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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Highlights

- QRSd was an independent predictor of new-onset AF in this population based cohort.

- This relationship was observed in women, but not in men.

- Modified ventricular conduction might be involved in AF development.

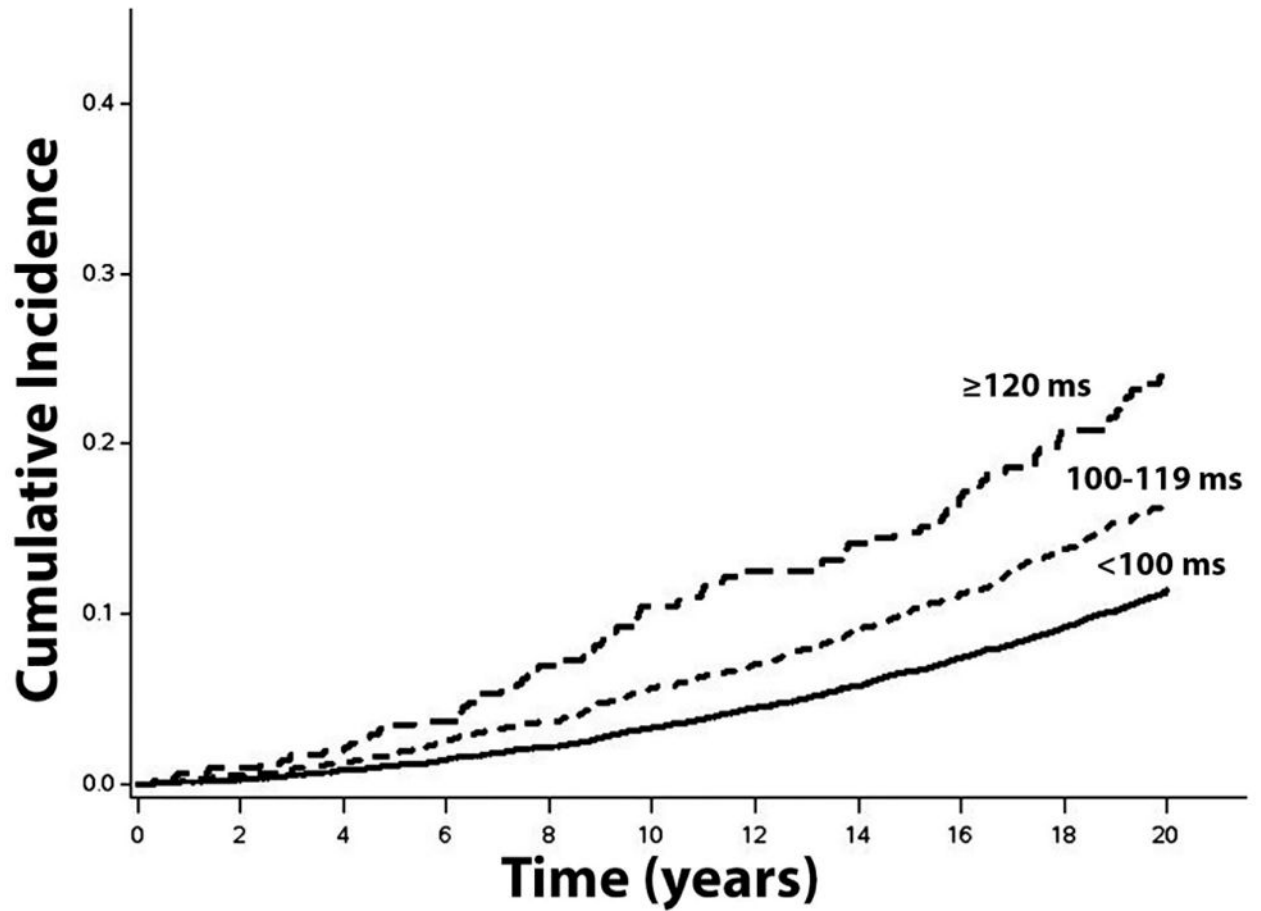- Further studies are needed to investigate the underlying mechanisms.

Figure 1. Cumulative Incidence of Atrial Fibrillation stratified by QRS Duration Category
Cumulative incidence curves are statistically different (log-rank: p<0.001).

Table 1

Baseline characteristics stratified according to QRS duration categories

Characteristics	QRS Duration (ms)			P-value[*]
	<100 (n=11,898)	100–119 (n=2,990)	120 (n=426)	
Age, mean ± SD (years)	54 ± 5.8	54 ± 5.7	57 ± 5.5	<0.001
Male (%)	4,352 (37)	2,221 (74)	289 (68)	<0.001
Black (%)	3,240 (27)	700 (23)	111 (26)	<0.001
Current smoker (%)	6,717 (56)	1,946 (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 (%)	3,419 (29)	1,058 (35)	185 (43)	<0.001
Diabetes mellitus (%)	1,363 (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

[*]
Statistical significance for categorical data was tested using the chi-square procedure and continuous data was tested using the analysis of variance procedure.

SD=standard deviation.

Table 2

Relationship of QRS duration with incident atrial fibrillation

	Events/No. at risk	Person-years	Incidence rate Per 1000 person-years (95%CI)	Model 1[*] HR (95%CI)	P-value	Model 2[†] HR (95%CI)	P-value
QRS, <100 ms	1,457/11,898	224,657	6.5 (6.2, 6.8)	Ref	-	Ref	-
QRS, 100–119 ms	497/2,990	53,764	9.2 (8.5, 10.1)	1.26 (1.13, 1.40)	<0.001	1.13 (1.02, 1.26)	0.03
QRS, 120 ms	87/426	6,628	13.1 (10.6, 16.2)	1.60 (1.28, 1.99)	<0.001	1.35 (1.08, 1.68)	0.008
				P for trend <0.001		P for trend 0.002	
QRS per 1-SD increase[‡]	2,041/15,314	285,050	7.2 (6.9, 7.5)	1.11 (1.07, 1.15)	<0.001	1.05 (1.01, 1.10)	0.01

[*]
Adjusted for age, sex, race, and study site.

[†]
Adjusted for Model 1 covariates plus body mass index, systolic blood pressure, smoking, diabetes, heart rate, coronary heart disease, and heart failure.

CI=confidence interval; HR=hazard ratio; Ref= Reference.

[‡]
1 standard deviation = 12ms.

Table 3

Sex-specific relationship between QRS duration and incident atrial fibrillation

	Events/No. at risk	Person-years	Incidence rate Per 1000 person-years (95% CI)	Model 1 * HR (95%CI)	P-value	Model 2 † HR (95% CI)	P-value
Men							
QRS <100 ms	670	78,435	8.5 (7.9, 9.2)	Ref	-	Ref	-
QRS 100–119 ms	382	39,430	9.7 (8.8, 10.7)	1.16 (1.02, 1.31)	0.03	1.06 (0.94, 1.21)	0.34
QRS 120 ms	57	4,342	13.1 (10.1, 17.0)	1.41 (1.07, 1.84)	0.01	1.14 (0.87, 1.51)	0.34
				P for trend 0.002		P for trend 0.23	
Women							
QRS <100 ms	787	146,222	5.4 (5.0, 5.8)	Ref	-	Ref	-
QRS 100–119 ms	115	14,334	8.0 (6.7, 9.6)	1.52 (1.25, 1.84)	<0.001	1.27 (1.04, 1.54)	0.02
QRS 120 ms	30	2,287	13.1 (9.2, 18.8)	2.04 (1.41, 2.94)	<0.001	1.86 (1.29, 2.68)	0.001
				P for trend <0.001		P for trend <0.001	

*
Adjusted for age, race, and study site.

†
Adjusted for Model 1 covariates plus body mass index, systolic blood pressure, current smoking, diabetes, heart rate, antihypertensive medications, coronary heart disease, and heart failure.

CI=confidence interval; HR=hazard ratio;