Validation of PR interval length as a criterion for development of atrial fibrillation in non-Hispanic whites, African Americans and Hispanics ☆

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Abstract

Background: PR interval prolongation on electrocardiogram (ECG) increases the risk of atrial fibrillation (AF). Non-Hispanic Whites are at higher risk of AF compared to African Americans and Hispanics. However, it remains unknown if prolongation of the PR interval for the development of AF varies by race/ethnicity. Therefore, we determined whether race affects the PR interval length's ability to predict AF and if the commonly used criterion of 200 ms in AF prediction models can continue to be used for non-White cohorts.

Methods: This is a retrospective epidemiological study of consecutive inpatient and outpatients. An ECG database was initially interrogated. Patients were included if their initial ECG demonstrated sinus rhythm and had two or more electrocardiograms and declared a race and/or ethnicity as non-Hispanic White, African American or Hispanic. Development of AF was stratified by race/ethnicity along varying PR intervals. Cox models controlled for age, gender, race/ethnicity, systolic blood pressure, BMI, QRS, QTc, heart rate, murmur, treatment for hypertension, heart failure and use of AV nodal blocking agents to assess PR interval's predictive ability for development of AF.

Results: 50,870 patients met inclusion criteria of which 5,199 developed AF over 3.72 mean years of follow-up. When the PR interval was separated by quantile, prolongation of the PR interval to predict AF first became significant in Hispanic and African Americans at the 92.5th quantile of 196–201 ms (HR: 1.42, 95% CI: 1.09–1.86, p=0.01; HR: 1.32, 95% CI: 1.07–1.64, p=0.01, respectively) then in non-Hispanic Whites at the 95th quantile at 203–212 ms (HR: 1.24, 95% CI: 1.24–1.53, p=0.04). For those with a PR interval above 200 ms, African Americans had a lower risk than non-Hispanic Whites to develop AF (HR: 0.80, 95% CI: 0.64–0.95, p=0.012), however, no significant difference was demonstrated in Hispanics.

Conclusions: This is the first study to validate a PR interval value of 200 ms as a criterion in African Americans and Hispanics for the development of AF. However, a value of 200 ms may be less sensitive as a predictive measure for the development of AF in African Americans compared to non-Hispanic Whites.

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Keywords: PR interval; Atrial fibrillation; Effect modification; White; African American; Hispanic; Racial disparities

Introduction

The PR interval on electrocardiogram (ECG) reflects the time required for electrical activity to spread from the

sinoatrial node through the atrial myocardium to the atrioventricular node and then to the Purkinje fibers. Prolongation of the PR interval, particularly beyond 200 ms – the criterion for first degree heart block – has been shown to significantly increase the risk of atrial fibrillation (AF) [1–4] and atrial flutter [5], in addition to coronary heart disease, heart failure (HF), pacemaker implantation, and overall mortality.

The incidence and impact of AF varies by race/ethnicity. Non-Hispanic Whites have a significantly increased risk of AF, compared to African Americans [6,7], Asians, or

Hispanics [8]. However non-Hispanic Whites have lower traditional risk factors for AF. This is known as the "racial paradox [9]." Recent studies have suggested that genetic factors – which may play an important role in the pathophysiology of AF and PR interval – could explain this discrepancy [10]. However, a limited number of studies have investigated the effect that race/ethnicity plays on PR interval's ability to predict AF. [11] Magnani et al have demonstrated that effect modification does not exist between PR interval and risk of developing AF [12]. However, it is not known if race plays a role for the risk of developing AF, particularly in varying PR intervals. Recent studies have suggested other possible factors to explain the ambiguity in the "racial paradox [3]".

Given that AF is the most common chronic arrhythmia in adults, with an increasing prevalence and with serious implications for morbidity/mortality [13,14], there is a need to better understand predisposing risk factors including those related to race/ethnicity and if a PR interval of 200 ms (a criterion used in common prediction models for the development of AF, such as the Framingham Heart Study Risk Score for Atrial Fibrillation [22] and CHARGE-AF [15]) can be applied to varying races/ethnicities. Moreover, to the authors' knowledge, there is no study investigating the impact of PR interval on AF in Hispanics – the second largest segment of the US population [16]. Thus, we sought primarily to determine how race/ethnicity (non-Hispanic White, African American and Hispanic) affects the prolongation of the PR interval's predictive ability to determine atrial fibrillation and to secondarily validate the commonly used criterion of 200 ms as an independent risk factor for the development of atrial fibrillation in those racial/ethnic cohorts.

Methods

Study design

This is a retrospective epidemiological study of consecutive inpatient and outpatients (n=239,741) with cumulative ECGs (n=1,239,593) obtained at Montefiore Medical Center between January 1st, 2000 and September 8th, 2013. Patients were excluded if they had only one ECG, if they had AF on their initial ECG or had incomplete data. Patients whom were included were then evaluated for development of AF (Fig. 1). All clinical variables were extracted from non-ECG database electronic medical records via medical record number. Race/ethnicity were reported as by medical record. We have chosen to use the term race/ethnicity as Hispanics are generally considered to be a multi-racial group, composed largely of White, but also African American and other races [16].

ECG analysis

Montefiore Medical Center uses a computerized ECG system (GE Healthcare, Wauwatosa, Wisconsin) to collect, store and analyze ECGs. This system has been validated by the FDA and is used across the world and meets all applicable standards for resting computerized ECG analysis [17]. This computerized system includes the 12SL® program, which can be used to analyze varying ECGs and

was used in this study. A board certified cardiologist confirmed all automated ECG readings included in our study. The 12SL algorithm to detect AF has been validated in multiple studies [18,19] with validations of up to 90.8% sensitivity and 98.9% specificity [20].

Generally, the 12SL® algorithm for atrial fibrillation looks for an irregular rhythm or fibrillatory waves in the presence of a slow heart rate without the presence of particular concurrent abnormal rhythms [21]. Specifically, this algorithm requires one of the following test statements then to be true:

1. An irregularly irregular rhythm (range of RR intervals more than 15% of average RR interval and RR intervals not organized) and no regular atrial rhythm detected, or
2. Atrial rate >400

Data analysis

The PR interval was further evaluated to determine if a non-linear ability to predict AF existed, and if it varied by race/ethnicity. A receiver operating characteristic (ROC) curve was generated by plotting the PR interval against the development of AF as an outcome, stratified by race/ethnicity. Inflection points were visually inspected to determine at what PR interval the sensitivity in respect to the ability to predict AF first changed. These points, which varied by race/ethnicity, were then chosen as potential PR interval areas for further investigation.

In order to validate the visual inspection of the ROC curves, PR interval length was separated into deciles, with the 90th decile further split into 2.5 unit quantiles. A Cox model controlling for the above-mentioned variables was run by respective PR interval decile group, which was also stratified by race/ethnicity. The hazard ratio and p-value were then plotted against PR interval decile group. The decile group in which the p-value became significant and the hazard ratio was above 1.0 was chosen as the PR interval boundary, by race/ethnicity, to predict AF.

Follow-up started from the first normal sinus ECG. All patients were excluded if their first ECG demonstrated AF. For those whom did not develop AF, survival days were counted from initial normal sinus ECG until the last normal sinus ECG. For those whom developed AF, days were counted from initial normal sinus ECG to the first ECG that demonstrated AF.

Statistical analysis

Unpaired 2-sided t tests were used for the comparisons of continuous variables, and χ^2 tests were used to compare dichotomous variables between patients. Analysis of variance (ANOVA) was performed between continuous variables by race/ethnicity. Statistical significance was defined by $p < 0.05$. Cox model analysis was performed to determine whether mean PR interval length was predictive of AF. The Cox model controlled for age, gender, race/ethnicity, systolic blood pressure, body mass index (BMI), QRS, QTc, heart rate, presence of murmur, treatment of hypertension, HF and