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Role of PR-Interval In Predicting the Occurrence of Atrial Fibrillation

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Abstract

The identification of individuals at high risk of developing atrial fibrillation (AF) is important to prevent potentially lethal and invalidating complications of this arrhythmia. Recently, several studies have investigated the association between PR-interval and the risk of AF and have tested the value of PR-interval in personalized risk scores for AF. However, the results of these studies are generally conflicting. When looking for an association between a prolonged PR-interval (first-degree atrioventricular [AV] block vs. normal PR-interval) and an increased risk of AF, not all studies were able to find a consistent and statistically significant association. In two recent studies, however, the investigators were able to show an increased risk of AF for individuals with PR-intervals in the short range compared with individuals in the middle range. The existence of a true U-shaped relationship could potentially explain part of the conflicting results from investigators only looking for an increased risk for longer PR-intervals. However, regardless of these speculations, the association seems relatively weak. The significance of PR-interval in risk prediction of AF has been tested in three independent risk scores where model selection primarily was based on improvement in c-statistics. In one risk score, PR-interval improved the predictive value of the risk model, whereas it did not in the other two risk scores. Further studies are warranted before any final conclusion can be drawn, although based on the current evidence, it is reasonable to conclude that the predictive value of PR-interval in AF risk prediction is limited.

Introduction

The PR-interval (PQ-interval) on the electrocardiogram (ECG) is measured from the beginning of the P-wave to the beginning of the following QRS complex. This interval reflects the time required for an electrical impulse to propagate from the myocardial tissue surrounding the sinus node through the atrioventricular (AV) node to the Purkinje fibers. Consequently, PR-interval duration can be affected by several factors influencing atrial or AV node conduction, including myocardial fibrosis, ischemia, the tone of the autonomic nerve system, and inherent properties of the proteins underlying cardiac impulse propagation at these sites.

Atrial fibrillation (AF) is the most common cardiac arrhythmia and it has shown increasing incidence and prevalence in recent years. AF has major public health implications and considerable associated costs due to its high burden of morbidity and mortality.[1,2] Stroke, in particular, is one of the most devastating consequences of AF, and the arrhythmia is estimated to account for one in five of all strokes.[1]

Algorithms for AF risk prediction are important to identify high-risk individuals, especially because AF-related strokes are potentially preventable. The PR-interval is a readily obtainable and non-invasive parameter, and therefore, it is potentially important as a tool for identifying individuals at high risk of developing AF.

Several studies have recently investigated the association between PR interval and the risk of AF and tested whether PR-interval is of value in personalized risk scores for AF.[3–8] However, the results of these studies are conflicting.

The present review was undertaken to summarize the current evidence for use of PR-interval duration in risk prediction of AF.

Literature Search Methods

The PubMed- and Medline databases were searched (October 7th 2013) to identify studies investigating the association between PR interval and the risk of AF and studies investigating the predictive value of PR interval in AF risk models. The following search criteria were used to identify relevant studies: "PR interval AND atrial fibrillation", "PQ interval AND atrial fibrillation", and "prediction AND atrial fibrillation". The references of the eligible literature were assessed to identify additional relevant studies.

Disclosures:
None.

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The Evidence

Association between PR-Interval and the Risk of Atrial Fibrillation

The Framingham Heart Study (FHS) and the Atherosclerosis Risk in Communities (ARIC) Study were the first to investigate the association between PR-interval prolongation and the risk of incident AF.[3,4] In the FHS, the risk of AF was found to be significantly higher in subjects with first-degree AV-block (PR-interval >200ms) compared with subjects without first-degree AV-block (HR 2.06; 95% CI 1.36-3.12; P <0.001). In addition, the linear relationship between PR-interval and the risk of AF was examined. This revealed that each 1-standard deviation (20ms) increment in PR-interval duration was associated with a HR of 1.11 (95% CI; 1.02-1.22; P = 0.02) for AF.[3] In the ARIC study, however, the results were not as unambiguous as those found in the FHS. As in the FHS, PR-interval duration was examined as both a continuous linear and a categorical variable (first-degree AV-block vs. no AV-block). While the former was significantly associated with a risk of incident AF (HR 1.41 per 1-standard deviation [25.4ms] change; 95% CI 1.20-1.65), the latter did not reach statistical significance (HR 1.59; 95% CI 0.77-3.30).[4] Both in the FHS and the ARIC study, the reported associations were adjusted for a number of potential confounders, including age, gender, hypertension, body mass index, diabetes, and smoking status.[3,4]

Following the two cohort studies, a smaller case-control study found that PR-interval was approximately 10ms longer in patients with early-onset lone AF (i.e., AF in the absence of traditional cardiovascular risk factors), remote from episodes of AF, compared with healthy controls.[5]

The association between PR-interval prolongation and risk of AF has also been addressed in more recent studies. The Health ABC study was able to demonstrate a linear increase in the risk of AF with longer PR-intervals (HR 1.13 per 1-standard deviation [29ms] increase; 95% CI 1.04-1.23; P = 0.005).[6] In the same study, there was a trend towards an increased risk of AF for individuals with a PR-interval >200ms compared with individuals with PR-intervals <200ms, however this association did not reach statistical significance at the P<0.05 level (HR 1.26; 95% CI 0.99-1.61; P = 0.059). In contrast to the results from the FHS, and the Health ABC study, a Finnish cohort study comprising more than 10,000 individuals and 30 years of follow-up the investigators did not find, even a trend, towards an increased risk of AF for individuals with first-degree AV-block (PR-interval >200ms) compared with individuals without AV-block (HR 1.03; 95% CI 0.74-1.45; P = 0.85).[7] Altogether; out of four important cohort studies, one study was able to show a statistically significant relationship between first-degree AV-block and the risk of AF, whereas one study showed a trend towards an increased risk and two studies showed no association.[3,4,6,7] More consistent results were, on the other hand, seen when the relationship between PR-interval prolongation, assessed as a linear parameter, and the risk of AF was investigated. With this approach, both the FHS, ARIC and Health ABC studies were able to show a statistically significant association between PR-interval prolongation and the risk of AF,[3,4,6] whereas this was not reported for the Finnish cohort study.[7]

Recently, the Copenhagen ECG Study also provided results on the association between PR-interval and the risk of AF.[8] In this study, almost 300,000 individuals were followed for a median of approximately 6 years, and during this period, more than 11,000 study subjects developed AF. The relatively large statistical power in this study allowed for a more flexible and non-linear approach for investigating the association between PR-interval duration and incident AF. As a result of this, it was found that both women with a short PR-interval (≤121ms; HR 1.32; 95% CI 1.12-1.56; P = 0.001) and women with a long PR-interval (≥196ms; HR 1.18; 95% CI 1.06-1.30; P = 0.001) have an increased risk of AF compared with the reference group (a PR-interval of 148-157ms). For the men, however, only a long PR-interval (≥204ms; HR 1.30; 95% CI 1.17-1.44; P <0.001) was statistically significantly associated with an increased risk of AF whereas the association between shorter PR-intervals and AF did not reach statistical significance (HR 1.09, 95% CI 0.92-1.29; P = 0.33).[8] In an important paper from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)-AF Consortium (which included data from the ARIC, CHS, and FHS cohorts) also published recently, the investigators, in line with the results from the Copenhagen ECG Study, also found evidence for an increased risk of AF for short PR-intervals. In this study, PR-intervals <120ms conferred an increased risk of AF compared with PR-intervals in the range 120-199ms (HR 1.91; 95% CI 1.29-2.82). However, the investigators did not find a statistically significant association for PR-intervals >199ms (HR 1.13; 95% CI 0.97-1.31).[9]

Risk Prediction of Atrial Fibrillation

In a clinical setting, an AF risk score can serve as a tool in determining an individual's risk of developing AF. Recently, such AF risk models have been developed and validated.[9–12] In the FHS-derived risk model for AF, the predictive value of several clinical risk factors for the assessment of long-term AF was investigated. Known risk factors for AF were incorporated into the risk score if they improved model discrimination (estimated by c-statistics) and calibration ($\chi 2$ test) in a setting of internal cross validation.[10] As a result of these computations, PR-interval was incorporated into the risk model in the way that 0 points were given for a PR-interval <160ms, 1 point for 160-199ms, and 2 points for a PR-interval ≥200ms. Later, the FHS-derived risk algorithm was externally validated in two independent cohorts; the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES)- and the Cardiovascular Health Study (CHS)-cohorts with subdivision of the CHS-cohort based on ethnicity (CHS Whites; CHS African Americans).[11] Although the FHS-derived AF risk score was still of value in risk prediction of AF, the score had a considerably lower discriminative value in the external validation cohorts compared with the FHS derivation cohort. Whereas the c-statistic decreased from 0.78 (95% CI 0.76-0.80) to 0.76 (95% CI 0.74-0.79) in the original FHS-cohort when internal cross validation was applied (using bootstrapping with 1,000 replications of individuals sampled with replacement), the c-statistic decreased much further in the external cohorts where values of 0.67 (95% CI 0.64-0.71), 0.68 (95% CI 0.66-0.70), and 0.66 (95% CI 0.61-0.71) were obtained in the AGES-, CHS Whites-, and CHS African Americans-cohorts, respectively.[11] The investigators did not report the extent to which PR-interval improved discrimination and calibration in these cohorts. However, a statistical significant association between a linear increase in PR-interval and the risk of incident AF was found in the AGES-, CHS Whites-, and FHS-cohorts. However, the association did not reach statistical significance in the CHS African American cohort.

Later, another AF risk score was developed based on the ARIC study cohort. Selection of prediction variables was based on Cox regression and the use of backward stepwise elimination where variables were eliminated in case of an association less statistical significant than P<0.10.[12] As a result of this, PR-interval was not included in the final risk model. C-statistics for the final model was 0.76 when internal validation was not applied and 0.77 when interval validation was applied (1,000 bootstrap samples with replacement). In the same study, the investigators tested the FHS-derived risk score and found c-statistic of 0.68, hence a number which is in accordance with previous external validations of the FHS-derived AF risk score.[12]

More recently, the CHARGE-AF Consortium constructed another AF risk score by pooling data from the ARIC-, CHS-, and FHS- cohorts. This score was externally validated in the AGES- and Rotterdam Study (RS)-cohorts. The derivation cohort (the ARIC-, CHS-, and FHS- cohorts) and the validation cohort (the AGES- and the RS- cohorts) were comprised of 18,556 and 7,672 participants, respectively. The CHARGE-AF Consortium investigators developed a simple risk model, based on readily available clinical variables (e.g., age, weight, current smoking), and found that this "simple model" achieved good performance with regards to model discrimination (c-statistic, 0.765; 95% CI 0.748-0.781). However, when externally validated, discrimination dropped from 0.765 in the pooled derivation cohort to 0.664 (95% CI 0.632-0.697) and 0.705 (95% CI 0.663-0.747) in the AGES- and RS-cohorts, respectively. The addition of electrocardiographic variables (electrocardiogram-derived LVH and PR-interval) into the "augmented model" did not lead to an increase in the predictive ability. As such, after addition of the electrocardiographic variables to the model in the pooled derivation cohort, c-statistic only changed from 0.765 (95% CI 0.748-0.781) in the "simple model" to 0.767 (95% CI 0.750-0.783) in the "augmented model". Similar results were found in the validation cohorts; in the AGES- cohort the c-statistic changed from 0.664 (95% CI 0.632-0.697) to 0.665 (95% CI 0.633-0.697) when the electrocardiographic parameters were added while the c-statistic in the RS- cohort changed from 0.705 (95% CI 0.663-0.747) to 0.716 (95% CI 0.680-0.761).[9]

Comments

In this comprehensive review, we provide current evidence for the association between PR-interval and the risk of AF as well as the evidence regarding the predictive value of PR-interval in personalized risk prediction of AF.

The findings regarding the association between PR-interval prolongation and the risk of AF were conflicting. Only one out of four cohort studies that investigated the association between either first-degree AV block or the association between a linear increase in PR-interval as a risk factor for AF was able to demonstrate a consistent and statistically significant association.[3,4,6,7] One study showed a trend toward an association,[6] whereas two studies could not show a consistent association between PR-interval and the risk of AF.[4,7] In the Copenhagen ECG study, the investigators were, as a consequence of the relatively large statistical power, able to provide evidence for a non-linear relationship between PR-interval duration and the risk of AF and found that both short and long PR-intervals increase the risk of AF, at least in women.[8] This finding of an increased risk of AF also for shorter PR-intervals was found not only in the Copenhagen ECG study but also by the CHARGE-AF Consortium, which is a collaboration between a number of important cohort studies.[9] The existence of a true U-shaped relationship can potentially explain why some investigators could not detect a signal if they investigated the association between an upper PR-interval cut-off (e.g., first-degree AV-block vs. no AV-block) and the risk of AF. Additionally, differences in population sizes, the age and gender compositions of the study cohorts, the covariates included in the various statistical models, and the time of follow-up also likely explain some of the conflicting results. However, despite these considerations, the presence of a possible true association seems to be relatively weak.

Keeping the conflicting results in mind, it is worth noticing the many different etiologies that potentially underlies the association between PR-interval duration and AF. Whereas the association between longer PR-intervals and the risk of AF might partly be explained by "advanced physiological age" (i.e., accumulation of fibrosis and calcification) of the myocardium and in particular the conduction system, the relationship between shorter PR-intervals and the risk of AF is less intuitively explained. Several decades ago, Lown, Ganong, and Levine described, for the first time, a syndrome of short PR-intervals, normal QRS complexes, and a high prevalence of AF.[13] This syndrome was later reported to be explained by a congenital hypoplastic AV node, with a decreased bulk of specialized tissue to slow down impulse transmission from atria to ventricles.[14] Whether a mechanism similar to the one thought to underlie this syndrome is accountable for the association between shorter PR-intervals and the risk of AF is obviously speculation. However, the original report by Lown, Ganong, and Levine interestingly states that this syndrome is primarily observed in women. A finding which is in line with the observations from the Copenhagen ECG study where the investigators found an increased risk of AF for shorter PR-intervals in women but not in men.[8] However, the most convincing evidence for a true association between shorter PR-intervals and the risk of AF comes from recent and convincing genome-wide association studies on the PR-interval.[15,16] In these studies, it was found that both genetic loci that shorten PR-interval and loci that prolong PR-interval were associated with an increased risk of AF. This strongly indicates that at least a small part of the association between shorter and longer PR-intervals is explained by genetics and that the association between shorter (and longer) PR-intervals and the risk of AF is not explained by ECG artifacts or some random errors.

There have been at least three attempts in developing a personalized risk score for longitudinal AF based on simple clinical parameters. In the first attempt, derived from the FHS, the investigators reported that individual risk prediction was improved when PR-interval was introduced into the predictive model, whereas in two other risk scores, derived from the ARIC study and the CHARGE-AF Consortium, PR-interval did not improve risk prediction.[9,10,12] For the three risk scores, selections of model parameters were based on either performance in c-statistics (FHS and CHARGE-AF models) or the level of significance in Cox regression model (ARIC model). Although the FHS risk score was later externally validated, it was developed based on internal validation, as was the case for the ARIC-derived risk score, whereas the CHARGE-AF score was developed based on external validation.[11,12,9] For both the FHS-derived risk score and the CHARGE-AF-derived risk score, the c-statistics dropped significantly when the models were externally validated. This emphasizes the well-known problem of over-optimism in the development of models for risk prediction and underscores

the importance of external validation in independent cohorts. The ARIC-derived AF risk score has, to the best of our knowledge, not been externally validated. Moreover, variable selection in this AF risk score was based on the significance level in the Cox model: a parameter which is not always directly related to the importance of a variable for risk prediction on an individual level.

With respect to both the FHS- and the CHARGE-AF-derived risk scores, the value of PR-interval duration in personalized risk prediction of AF was evaluated with the use of c-statistics. However, this approach can be limited when evaluating predictive models for which the task is to assess future risks in a largely healthy population.[17] In particular, the c-statistic is known to underestimate clinically important effects of known risk factors for cardiovascular diseases such as lipids, hypertension, and smoking status; factors that might well affect treatment decision according to current clinical guidelines.[17] Therefore, it would be of interest to know if PR-interval duration is of value in reclassifying individuals into clinically relevant AF risk groups that will affect clinical decisions before any final conclusions can be drawn on the predictive value of PR-interval. To the best of our knowledge, this has not been investigated for the PR-interval. It is also worth noticing that the commonly applied statistical software packages used for estimating c-statistics do not take competing risk into account. This can in particular be a problem when estimating the risk of AF in an elderly population with a high risk of death, where an individual who has not (yet) developed AF can die without occurrence of AF despite having many risk factors for the arrhythmia. Moreover, PR-interval, like other risk factors for AF, ultimately needs to be proven of value in reducing morbidity and mortality before they finally can be said to be of value as a screening tool for incident AF.

Finally, it would be interesting to see if the PR-interval could be of predictive value in combination with other electrocardiographic markers of AF, such as p-wave duration[18] and the heart rate-corrected QT interval.[19,20]

Conclusions:

Current evidence for the relationship between PR-interval duration and the risk of AF is far from unambiguous. Although the association seems relatively weak it is reasonable to believe that an association exists between both short and long PR-intervals and increased AF risk, a fact that is supported by convincing genetic evidence. The value of PR-interval in personalized risk prediction of AF needs further investigation before any final conclusions can be drawn. However, based on current evidence, the value is most likely limited.

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