Short P-Wave Duration Is Associated with Incident Atrial Fibrillation
A Registry-Based Cohort Study

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Summary

Atrial fibrillation (AF) is common and increases the risk for stroke and heart failure (HF). The early identification of patients at risk may prevent the development of AF and improve prognosis. This study, therefore, aimed to test the effect of the association between P-wave and PR-interval on the ECG and incident AF.

The PIVUS (Prospective Investigation of the Vasculature in Uppsala Seniors) study (1016 individuals all aged 70 years; 50% women) was used to identify whether the ECG variables P-wave duration (Pdur) and PR-duration in lead V1 were related to new-onset AF. Exclusion criteria were prevalent AF, QRS-duration > 130 milliseconds (msec), atrial tachyarrhythmias and implanted pacemaker/defibrillator. Cox proportional-hazards models were used for analyses. Adjustments were made for gender, RR-interval, beta-blocking agents, systolic blood pressure, body mass index, and smoking.

Of 877 subjects at risk, 189 individuals developed AF during a 15-year follow-up. There was a U-shaped relationship between the Pdur and incident AF (P = 0.017) following multiple adjustment. Values below 60 msec were significantly associated with incident AF, with a hazard ratio of 1.55 (95% confidence interval 1.15-2.09) for a Pdur ≤ 42 msec. There was no significant relationship between incident AF and the PR-interval.

A short Pdur derived from the ECG in V1 may be a useful marker for new-onset AF, enabling the early identification of at-risk patients.

Key words: Short P-wave as predictor, P-wave in atrial fibrillation, P-wave indices, New-onset atrial fibrillation

Atrial fibrillation (AF) is the most common arrhythmia, with a prevalence rising steeply to > 10% at age > 75 years.1,2) AF is related to a variety of pathophysiological processes, among which cardiovascular risk factors play an important role. The presence of triggers in the pulmonary veins promotes the initiation of AF, resulting in electrical remodelling and eventually structural remodeling of the atria.3) When a substrate has developed, AF tends to be self-perpetuating, and once established, there is an increased risk for stroke, heart failure (HF), and mortality.1,2,4)

The impact of clinical risk factors, including multiple comorbidities, on the lifetime risk of AF suggests that modification and treatment of risk factors for AF may reduce its incidence and stop its progression.5,6) A reliable long-term predictor of AF may be crucial for improving the outcomes.

Several studies have found an association between Pdur and incident AF7) as well as AF in various clinical settings.8,9) A large Danish population study found a strong correlation between incident AF and both short and long Pdur,10) but failed to demonstrate an association with certain important risk factors, such as hypertension, smoking, and obesity.

The PR-interval, mainly reflecting the electrical conduction from the sinus node to the atrial tissue and across the AV node, has been associated with incident AF, HF, and increased mortality.11,12) Several risk scores for new-onset AF have been published, but only a few have included the PR-interval and the Pdur as parameters.13-16) Although a long P-wave duration was associated with incident AF in one study, it had limited predictive value beyond the traditional risk factors and biomarkers.17)

Other P-wave indices, such as P-wave dispersion, reflecting delayed and inhomogeneous intra- and interatrial conduction and P-wave terminal force in lead V1, a marker of atrial enlargement or fibrosis, have also been associated with incident AF and AF in different clinical settings.17,18)

Given the limited data on the role of an altered atrial conduction for new-onset AF in the elderly (> 70 years of age) in the long term, the association between the P-wave

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and PR-interval duration and incident AF was studied in the population-based Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) registry with 15 years of follow-up.

Methods

Study population and design: Data were used from the PIVUS study, which invited all individuals aged 70 years from Uppsala, Sweden, to participate. Of 2025 invited subjects, 1016 agreed to participate, 50% of whom were women. A medical history with medications was registered and a cardiovascular examination, including blood pressure, ECG, echocardiography, and blood sampling for traditional risk factors, such as glucose, low-density lipoprotein (LDL)-, and high-density lipoprotein (HDL)-cholesterol in the fasting state, was performed at baseline.

The six-lead ECG (V1 through V6) was recorded digitally in the supine position for 5 minutes. EClysis (AstraZeneca R&D, Molndal, Sweden) semiautomatic software, designed to calculate mean amplitudes and intervals for every lead with proven high accuracy and reliability, was used to analyze the baseline ECGs. EClysis used unfiltered signals from the continuous ECG recording, sampling 10-second periods twice per minute. The sampled beats were then evaluated by an experienced car-

Figure 1. Electrocardiographic example of P-wave measurement in lead V1 by EClysis software. A: Markers (Pstart, Pend) suggested by EClysis software. B: Markers corrected manually (Pend moved).
diologist, who rejected all aberrant or distorted signals and was able to adjust the indicated markers (P-onset, P-offset, and QRS-onset) if needed. In the case of biphasic P-waves, the second negative deflection was included in the P-wave (Figures 1, 2). Subsequently, the mean Pdur and PR-duration of all selected and adjusted beats were calculated separately in every lead by the EClYsis software. At two follow-up visits after 5 and 10 years, the ECG was recorded for the detection of AF only.

Blood pressure was measured in the right arm in the supine position after 15 minutes of rest. Fasting blood glucose, LDL-, and HDL-cholesterol were measured by standardized methods. Diabetes was defined as a fasting blood glucose level ≥ 7.0 mmol/L or a previous diagnosis of diabetes.

The target population in this study consisted of subjects included in the PIVUS study after excluding those with rhythms other than sinus on baseline ECG, second- or third-degree atrioventricular block, delta waves, history of AF, and a permanent pacemaker/defibrillator, leaving 877 individuals for further analyses (Figure 3).

Data on AF (ICD 8-10 codes 427.X, I48.X), HF (ICD-8 codes 427.00, 427.10, 428.99, ICD-9, 428, and ICD-10 codes 150 and I11.0), and myocardial infarction (MI) (ICD codes 4109, 4110, 410.X, and I21.X) were obtained from the Swedish Cause of Death Register and the Swedish Hospital Discharge Register, both with high quality and accuracy. Moreover, new AF on the ECG recorded at the reexaminations at age 75 and 80 years was defined as new-onset AF. Finally, the diagnoses of AF, HF, and MI were validated by an experienced clinician (LL) who reviewed the hospital records.

All participants gave their written informed consent. The PIVUS study was approved by the ethics committee of Uppsala University.

**Statistical methods:** Cox proportional-hazards analyses were used to relate Pdur and PR-intervals to incident AF. The ECG variables were modeled as restricted cubic spline function with three knots (10th, 50th, and 90th percentiles) because of the possibility of nonlinear relationships.

In the first set of models, adjustment was performed for sex only (age was the same in all subjects). In a second set of models, the adjustment was performed for traditional risk factors for AF (systolic blood pressure, smoking, and body mass index (BMI)) along with a HF diagnosis prior to AF diagnosis (n = 78), the RR-interval, and use of beta-blocking agents. Diabetes, LDL-, and HDL-cholesterol were not included as traditional risk factors, as they were not significantly related to incident AF in the present sample.

C-statistics based on logistic regression was used to evaluate any improvement in discrimination of AF of adding P-wave indices to the abovementioned risk factors for AF:

A P value < 0.05 was regarded as significant. STATA 16 (Stata Inc., College Station, TX, USA) was used for the calculations.

**Results**

A total of 877 individuals were included in the analysis after exclusion of subjects with prevalent AF or other exclusion criteria at baseline. During 15 years of follow-up (10,748 person-years), 189 (21.5%) individuals (incidence = 17.6/1000 person-years) experienced a new-onset AF. The basic characteristics of the cohort are shown in the Table.

A spline function for Pdur (in lead V1) showed a significant relationship with incident AF (P = 0.017) when adjusted for sex only (age was the same in all subjects) (Figure 4). This relationship was unaffected by adjustments for systolic blood pressure, smoking, and BMI along with HF diagnosis prior to AF diagnosis, the RR-interval, and use of beta-blocking agents (P = 0.017 for Pdur following multiple adjustments). Further addition of
Figure 3. Flowchart of the study design. AF indicates atrial fibrillation.

Table. Clinical Baseline Characteristics of 877 Individuals Included in This Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females, n (%)</td>
<td>454 (52)</td>
</tr>
<tr>
<td>Beta-blocking agents, n (%)</td>
<td>182 (21)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>150 (22)</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>81 (10)</td>
</tr>
<tr>
<td>BMI</td>
<td>27.0 (4.2)</td>
</tr>
<tr>
<td>RR-interval in V1 (msec)</td>
<td>982 (137)</td>
</tr>
<tr>
<td>PR-interval duration in V1 (msec)</td>
<td>157 (28)</td>
</tr>
<tr>
<td>P-duration in V1 (msec)</td>
<td>71 (21)</td>
</tr>
<tr>
<td>Presence of PR-interval in V1 &gt; 200 msec, n (%)</td>
<td>60 (6.8)</td>
</tr>
<tr>
<td>Presence of P-duration in V1 &gt; 110 msec, n (%)</td>
<td>18 (2.0)</td>
</tr>
<tr>
<td>Presence of P-duration in V1 &lt; 70 msec, n (%)</td>
<td>404 (46)</td>
</tr>
</tbody>
</table>

Figures are means ± one SD unless otherwise stated. BMI indicates body mass index; msec, milliseconds; and SD, standard deviation.

the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers to the model did not change the results. The Pdur was still significantly related to incident AF (\( P = 0.030 \)).

As shown in Figure 4, mainly short Pdur values were associated with incident AF. As the lower boundary for the 95% confidence interval (CI) crosses the hazard ratio = 1 at 60 msec, values below 60 msec were significantly associated with incident AF. At 42 msec (10th percentile of the distribution), the risk estimate was 1.55 (95% CI 1.15-2.09). A long Pdur might also confer a risk, but this tendency was not significant.

When Pdur in V1 was divided into quartiles, the lowest quartile Q1 showed the highest incidence of AF (27% in Q1 compared to 18-21% in Q2-Q4). When the Q1 for Pdur in V1 (range 19-57 msec) was compared to the Q2 in a logistic regression model also, including all confounders, a significant increase in the risk of future AF was seen (OR 1.60, 95% CI 1.07-2.40, \( P = 0.022 \)). Q3 and Q4 were not significantly different from Q2.

The addition of a short Pdur (≤ 60 msec) did not improve the discrimination of AF when added on top of traditional risk factors [area under the curve 0.607 (95% CI 0.563-0.651), versus 0.594 (95% CI 0.549-0.638) without a short Pdur, \( P = 0.30 \)].

A similar relationship between incident AF and Pdur was observed when the analysis was restricted to the first 5 years of follow-up (Figure 5). As only 48 cases of AF
occurred during the first 5 years, compared to 189 during the 15 years of follow-up, the power was poor and the relationship with Pdur did not reach statistical significance ($P = 0.18$).

The PR-interval in V1 was not significantly related to incident AF (Figure 6). Neither was the isolated “PR minus Pdur” interval associated with incident AF.

**Discussion**

The findings of a significant association between incident AF and a short Pdur and a lack of a significant association with a prolonged Pdur ($\geq 110$ msec) and the PR-interval in this cohort of elderly subjects deserves further comments.

The finding of a robust relationship between a short Pdur and incident AF, consistent with others, may have several potential explanations. First, the autonomic nerv-
ous system may affect the Pdur, which seems to be shortened by beta-adrenergic stimulation, such as isoproterenol, and prolonged by beta-blockers. In this study, however, the adjustments made for both RR-interval, reflecting the autonomic tone, and treatment with beta-blockers would probably have eliminated these confounders. A second explanation may be a heritability for a short Pdur encompassing an increased susceptibility to AF. A third hypothetical mechanism may be increased levels of relaxin, a new biomarker of HF, with the ability to enhance atrial conduction velocity through ion channels. Relaxin is a naturally occurring peptide hormone, exerting anti-inflammatory, anti-fibrotic, anti-hypertrophic, and antiapoptotic effects on the myocardium. It was previously reported to promote nitric oxide formation and to inhibit fibroblast activation, collagen accumulation, and various inflammatory pathways in the myocardium. The primary relaxin receptors RXFP1 are present in many tissues, including the heart. Increased levels of relaxin accompanied by a possible consecutive downregulation of RXFP1 receptors were found in HF and AF. Given that inflammation and fibrosis are pivotal mechanisms for AF, the enhanced secretion of relaxin may reflect a pro-fibrotic process in the atria prior to the onset of AF. Thus, relaxin-induced enhanced atrial conduction velocity, being the main contributor to the duration of the P-waves, may cause their shortening. Relaxin has already been described as a novel biomarker for the early detection of MI, but it might as well prove useful for the prediction of incident AF.

The strong U-shaped relationship between Pdur and incident AF found in this study is consistent with the findings in a large Danish population study. In that study, the short Pdur seemed to have a short-term effect, whereas effects of the prolonged Pdur were constant over time. The authors hypothesized that an enhanced atrial conduction time, reflected by short Pdur, resulted in an electrical atrial remodeling and subsequently AF. Their demonstration of a weaker association between Pdur and the risk of cardiovascular death may indicate that the short Pdur is an atrial-specific index rather than a marker of a general cardiac dysfunction. Their study was, however, limited by the lack of data on blood pressure, obesity, and smoking status. Whether the short Pdur plays a causative role in AF or merely reflects an early pathological process in the atria, is unclear.

The normal values of the P-wave duration (Pdur) have not been standardized, but upper cut-offs of 110-120 msec have been proposed. It is well known that the Pdur reflects the time of the electrical conduction in the atria. A P-wave prolongation reflects an increased atrial conduction time and may be due to atrial enlargement or fibrosis, both of which have been shown to increase the risk for AF recurrence. The lack of relationship between a prolonged Pdur and incident AF in this study may be related to the limited number (2%) of subjects with prolonged Pdur in the study cohort.

As only precordial ECG leads were available at inclusion and the terminal portion of the P-waves was not analyzed separately, it precluded the calculation of the P-wave dispersion and P-terminal force in V1, which may be a limitation. Measuring the Pdur in V1 alone may be an underestimation of the atrial activation time, which is another limitation.

The finding that a prolonged PR-interval was not significantly related to incident AF in this study is in contrast to findings in other studies, and may well be explained by the limited numbers (6.8%) of individuals with prolonged PR-intervals at baseline. A prolonged PR-interval (≥ 200 msec) is uncommon (0.5-2%) in the healthy popu-

Figure 6. Relationship between PR-interval duration in lead V1 and incident atrial fibrillation. The solid line represents the hazard ratio for incident atrial fibrillation. The dashed line represents the 95% confidence interval and the red line represents hazard ratio = 1. PQ-duration indicates PR-interval duration.
The major strengths of this study are the use of a digital ECG analysis performed by using a validated software and the complete set of data on epidemiological risk factors used in our statistical calculations. Other strengths of the study are the long follow-up period, the validation of medical records for AF diagnosis, and the repeated ECG recordings after 5 and 10 years, enabling the detection of the majority of AF cases. The incidence of AF in the present study (17.6/1000 person-years) is comparable with that observed in a large epidemiological German study (12.5-25.8/1000 person-years), which used both in-hospital records and outpatient diagnoses. Paroxysmal AF, particularly if asymptomatic, may well have been underdiagnosed in our cohort, which is a limitation.

The lack of data on the Pdur at 5 and 10 years of follow-up and the fact that not all subjects included in the PIVUS came for these reexaminations precluded an update of confounders (BMI, blood pressure, etc.) in the analyses due to risk of major loss of power. We, therefore, evaluated whether the U-shaped relationship between Pdur and incident AF was also present after only 5 years of follow-up. Although the shape of the relationship after 5 years of follow-up was similar to the one evaluated after 15 years, this relationship was not significant because of a limited number of events after 5 years (Figure 5).

In conclusion, the relationship between a short Pdur and incident AF is confirmative of a prior report. Pdur is a simple and easily available parameter, suitable for repetitive measurements in everyday clinical practice and may prove useful for the prediction of incident AF beyond the traditional risk factors.

Disclosure
Conflicts of interest: None.

References