P-Wave Morphology and the Risk of Incident Ischemic Stroke in the Multi-Ethnic Study of Atherosclerosis

Hooman Kamel, MD; Elsayed Z. Soliman, MD, MS; Susan R. Heckbert, MD, PhD; Richard A. Kronmal, PhD; W.T. Longstreth Jr, MD, MPH; Saman Nazarian, MD, PhD; Peter M. Okin, MD

Background and Purpose—Emerging data suggest that left atrial disease may cause ischemic stroke in the absence of atrial fibrillation or flutter (AF). If true, this condition may provide a cause for many strokes currently classified as cryptogenic.

Methods—Among 6741 participants in the Multi-Ethnic Study of Atherosclerosis who were free of clinically apparent cerebrovascular or cardiovascular disease (including AF) at baseline, we examined the association between markers of left atrial abnormality on a standard 12-lead ECG—specifically P-wave area, duration, and terminal force in lead V1—and the subsequent risk of ischemic stroke while accounting for incident AF.

Results—During a median follow-up of 8.5 years, 121 participants (1.8%) had a stroke and 541 participants (8.0%) were diagnosed with AF. In Cox proportional hazards models adjusting for potential baseline confounders, P-wave terminal force in lead V1 was more strongly associated with incident stroke (hazard ratio per 1 SD increase, 1.21; 95% confidence interval, 1.02–1.44) than with incident AF (hazard ratio per 1 SD, 1.11; 95% confidence interval, 1.03–1.21). The association between P-wave terminal force in lead V1 and stroke was robust in numerous sensitivity analyses accounting for AF, including analyses that excluded those with any incident AF or modeled any incident AF as having been present from baseline.

Conclusions—We found an association between baseline P-wave morphology and incident stroke even after accounting for AF. This association may reflect an atrial cardiopathy that leads to stroke in the absence of AF. 

Key Words: electrocardiography ■ embolism ■ stroke

Atrial ECG signs have been associated with stroke in the absence of atrial fibrillation (AF), suggesting that atrial disease may promote embolization without manifesting with AF. We have shown that P-wave area and terminal force are associated with stroke risk, but did not control for AF, which may mediate the relationship between P-wave morphology and stroke. Therefore, we examined the association between P-wave morphology and stroke while accounting for incident AF.

Methods

Design

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study of risk factors for progression from subclinical to clinical cardiovascular disease. Institutional review boards at all participating sites approved this study, and all participants provided written, informed consent.

Participants

MESA enrolled 6814 men and women aged 45 to 84 years who were free of clinically apparent cerebrovascular or cardiovascular disease, including AF. We excluded 48 participants with missing ECGs, 24 participants receiving warfarin at baseline, and 1 participant whose baseline ECG showed AF.

Measurements

All sites obtained standard digital 12-lead ECGs at the first and last study visits. All ECGs were obtained using GE MAC 1200 ECG machines (GE, Milwaukee, WI) calibrated at 10 mm/mV with a speed of 25 mm/sec. After initial screening for inadequate quality, all ECGs were centrally interpreted at the Wake Forest Epidemiological Cardiology Research Center for abnormalities including AF. The core ECG laboratory automatically measured P-wave areas, amplitudes, and durations using the 12-SL program (version 2001; GE Marquette).

Using standard methodology, we defined P-wave terminal force in lead V1 (PTFV1) as the most widely accepted marker of left atrial abnormality; P-wave area and duration may also be useful.

Based on this and prior work, we prespecified predictor variables as PTFV1, mean and maximum P-wave area, and mean and maximum P-wave duration on the baseline 12-lead ECG. Using standard methodology, we defined PTFV1 as the duration (ms) of the downward deflection (terminal portion) of the P wave in lead V1 multiplied by the absolute value of its amplitude (μV; Figure). P-wave areas were a summation of all P-wave amplitudes at respective sampling points multiplied by the sampling interval. P-wave areas were calculated by summing the absolute values of the areas of the upward and downward deflections of the P wave; in other words,
the areas of downward deflections were assigned positive rather than negative values. To adjust for technical differences in units of measurement and harmonize the 12-SL program’s calculations with other machines, we multiplied P-wave areas by a factor of 19.52.4,8

We accounted for incident AF as a potential mediator and adjusted for the following potential confounders: age, sex, race, hypertension, left ventricular hypertrophy, total cholesterol level, high- and low-density lipoprotein levels, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, body mass index, and smoking status (see the online-only Data Supplement).

Our primary outcome was an adjudicated diagnosis of ischemic stroke, defined as the rapid onset of a neurological deficit that persisted for >24 hours or until death or was accompanied by report of a clinically relevant infarction on brain imaging, in the absence of a nonvascular cause or brain hemorrhage.

Statistical Analyses
We excluded P-wave measurements >99.9th percentile as outliers. Using separate Cox proportional hazards models for each P-wave predictor variable, we standardized these variables around their means and reported their associations with stroke in 1 SD increments. To explore whether AF mediated associations between P-wave morphology and stroke, we compared models with and without a time-varying covariate for incident AF and performed multiple sensitivity analyses accounting for AF in other ways (see the online-only Data Supplement).

Results
The 6741 eligible participants were followed for a median of 8.5 years (interquartile range, 7.7–8.6). Ischemic stroke occurred in 121 participants (1.8%), and 541 participants (8.5%) were diagnosed with AF. Participants with stroke were older, had more vascular risk factors, and manifested a clinically relevant infarction on brain imaging, in the absence of a nonvascular cause or brain hemorrhage (Table 1; Table I in the online-only Data Supplement).

In Cox proportional hazards analysis, PTFV1 was more strongly associated with incident stroke (hazard ratio per 1 SD increase, 1.21; 95% confidence interval, 1.02–1.44; Table 2) than with incident AF (hazard ratio per 1 SD, 1.11; 95% confidence interval, 1.03–1.21). The association between PTFV1 and stroke was similar when we adjusted for incident AF (hazard ratio per 1 SD, 1.21; 95% confidence interval, 1.02–1.44) or removed the AF covariate from our model (hazard ratio per 1 SD, 1.21; 95% confidence interval, 1.03–1.44; Table 2). Our results persisted in participants without any AF during the study period, suggesting that atrial disease may cause stroke even in the absence of AF. Prior studies have suggested that atrial ECG markers besides AF may be associated with stroke [1,2,4,9]; this study represents an important advance because it supports an association between a simple 12-lead ECG and ischemic stroke.

Discussion
In a prospective cohort study, we found a significant association between PTFV1 and subsequent ischemic stroke. This association persisted in participants without any AF during the study period, suggesting that atrial disease may cause stroke even in the absence of AF. Prior studies have suggested that atrial ECG markers besides AF may be associated with stroke [1,2,4,9]; this study represents an important advance because it supports an association between a simple 12-lead ECG and ischemic stroke.
Table 2. Associations Between P-Wave Morphology and Incident Ischemic Stroke

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR Per 1 SD Increase (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-wave terminal force in lead V1, μV*ms</td>
<td>1.21 (1.02–1.44)</td>
</tr>
<tr>
<td>P-wave mean area, μV*ms</td>
<td>1.16 (0.98–1.39)</td>
</tr>
<tr>
<td>P-wave maximum area, μV*ms</td>
<td>1.16 (0.99–1.37)</td>
</tr>
<tr>
<td>P-wave mean duration, ms</td>
<td>1.11 (0.92–1.34)</td>
</tr>
<tr>
<td>P-wave maximum duration, ms</td>
<td>1.12 (0.93–1.35)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and HR, hazard ratio.

ECG measure and stroke and demonstrates that AF does not mediate this association. Instead, elevated PTFV1 may reflect an underlying atrial cardiopathy that predisposes to embolization even in the absence of AF.

This study has several limitations. First, we may have missed subclinical AF that could have mediated the association between PTFV1 and stroke. However, PTFV1 was less strongly associated with AF than with stroke, which would not be expected if AF were an important mediator. Second, we were unable to examine associations with embolic-appearing or cryptogenic stroke specifically. Third, we lacked power to assess interactions between ethnicity and P-wave morphology in relation to stroke risk. Fourth, we lacked imaging of the left atrium. However, P-wave measurements reflect important aspects of atrial disease—such as elevated filling pressures, poor conduction, and fibrosis—that are not necessarily captured by imaging data. Further work will be necessary to fully delineate the ECG, imaging, and biomarker characteristics of atrial cardiopathy as it relates to stroke risk. Eventually, a combination of such markers may better identify the risk of left atrial embolization than simply the presence of AF, which can be difficult to screen for and, as we have shown, may be an imperfect marker of risk.

Sources of Funding
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Disclosures
Dr Kamel reports having served on a medical advisory board and serving as a lecturer for Genentech, Inc on the topic of alteplase for the acute treatment of ischemic stroke. Dr Nazarian reports serving as a scientific advisor to and principal investigator for research funding awarded to Johns Hopkins University by Biosense Webster, Inc on the topic of imaging and ablation for atrial fibrillation. Dr Okin reports serving on a medical advisory board for GE Medical Systems on the topic of new product development.

References
P-Wave Morphology and the Risk of Incident Ischemic Stroke in the Multi-Ethnic Study of Atherosclerosis

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/45/9/2786

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2014/07/22/STROKEAHA.114.006364.DC1

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SUPPLEMENTAL MATERIAL

P-Wave Morphology and the Risk of Incident Ischemic Stroke in the Multi-Ethnic Study of Atherosclerosis

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Supplemental Appendix

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Supplemental Methods

Covariate Definitions

Left ventricular hypertrophy was defined using a standard validated threshold for the Cornell voltage-duration product. Hypertension was defined using Joint National Commission VI guidelines. Diabetes status was based on the American Diabetes Association’s 2003 fasting criteria. A glomerular filtration rate <60 ml/min/1.73 m² was considered chronic kidney disease. Body mass index was categorized into four categories using thresholds of 25, 30, and 40 kg/m².

Ascertainment of Atrial Fibrillation

First, we ascertained AF using the 12-lead ECG done at the final study visit. Second, we recorded all diagnoses of AF identified during the course of endpoint investigation and adjudication. All hospitalizations during study follow-up were investigated, and medical records were reviewed for a predefined list of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes, including codes 427.3x for AF, which was documented in study records even if a study endpoint had not occurred. Similarly, all outpatient events representing possible primary study endpoints were investigated using medical record review and physician questionnaires, and diagnoses of AF associated with these events were recorded. Third, among participants enrolled in Medicare, we searched linked administrative data to identify any inpatient or outpatient claims for AF (ICD-9-CM codes 427.3x). In a sensitivity analysis, we also included self-reports of AF to maximize our sensitivity for this important covariate.

Statistical Analyses

After visually inspecting their distributions, we used means with standard deviations (SD) and t-tests to compare P-wave predictor variables in participants with and without stroke. Among the 4,236 participants with available follow-up ECG data, we compared P-wave measurements at baseline and 5-year follow-up.

All models controlled for AF as a time-varying covariate. Additionally, we included age, sex, race, and any of the above baseline covariates that were significantly associated with incident stroke in univariate analyses at a threshold of P <0.20; sensitivity analyses that forced all baseline covariates into the models did not appreciably change our results. We verified the proportional hazards assumption by checking an interaction term between P-wave predictor variables and time.

In post hoc analyses, we additionally included systolic blood pressure, antihypertensive medication use, and the PR interval on ECG, as these variables are part of the Framingham risk score for AF; prevalent heart failure was not included because MESA participants were free of vascular disease at baseline, and the presence of a heart murmur was not included because this information was not available. Furthermore, to assess whether P-wave measurements have incremental value for stroke prediction in addition to established risk scores, we calculated the
Framingham stroke risk score\textsuperscript{6} and determined changes in the c-statistic and the net reclassification improvement (using standard risk categories of 5\%, 10\%, and 20\%)\textsuperscript{7} after including PTFV\textsubscript{1} in 1-SD increments.

\textit{Sensitivity Analyses}

We performed the Sobel-Goodman mediation test to determine the degree to which AF mediated any associations between P-wave morphology and stroke. This statistical test uses multivariable methods to isolate the pathways between a predictor, a potential mediator, and an outcome; it is considered the gold standard when formally testing the significance of a proposed mediation pathway.\textsuperscript{8} We further assessed the independence of any associations between P-wave morphology and stroke by performing subgroup analyses limited to participants without any AF diagnoses throughout the study period. Since clinically apparent AF often manifests after a prolonged period of subclinical AF,\textsuperscript{9} we performed sensitivity analyses in which AF diagnoses at any time during the entire study period was assumed to have been present from baseline. To ensure that we did not miss cases of AF, we repeated these sensitivity analyses in participants $\geq65$ years of age at baseline and enrolled in Medicare throughout the study period, which ensured AF ascertainment via linked Medicare claims data during the entire duration of follow-up. Lastly, to ensure further that subclinical AF would have had time to manifest, we repeated these Medicare-only subset analyses excluding participants who had a stroke during the 2 years before final follow-up.

To ensure further that associations between our P-wave predictors and stroke were not mediated by non-atrial vascular disease, we performed post hoc sensitivity analyses controlling for carotid intima media thickness and degree of carotid stenosis on ultrasound.

Lastly, we also used our baseline models to examine the associations between P-wave predictor variables and the risk of myocardial infarction (MI) and all-cause mortality. Since we hypothesized that P-wave morphology specifically reflects an atrial cardiomyopathy that causes cardiac embolism, rather than simply reflecting general cardiovascular risk, we expected to find a stronger association with stroke than with MI or death.
Supplemental Results

Among participants with ECG data at 5-year follow-up, PTFV₁ increased by a mean 13.9%, and remained stable or increased in 3,093 participants (67.7%) while regressing in 1,475 participants (32.3%).

The Sobel-Goodman test indicated that AF mediated only 11% of the association between PTFV₁ and stroke. We found the same association between PTFV₁ and stroke in participants free of any AF diagnoses throughout the study (HR per 1-SD, 1.25; 95% CI, 1.02-1.52). In models adjusting for incident AF, our findings were unchanged when we modeled incident AF as having been present from baseline (HR per 1-SD, 1.20; 95% CI, 1.02-1.43), even when including self-reports of AF (HR per 1-SD, 1.21; 95% CI, 1.02-1.43). We found a significant association when limiting this analysis to participants ≥65 years of age at baseline and enrolled in Medicare throughout the study period (HR per 1-SD, 1.31; 95% CI, 1.04-1.66), even for stroke occurring at least 2 years before final follow-up (HR per 1-SD, 1.45; 95% CI, 1.09-1.91).

We found no significant association between baseline PTFV₁ and subsequent MI (HR per 1-SD, 1.06; 95% CI, 0.93-1.20) or death (HR per 1-SD, 1.05; 95% CI, 0.96-1.14). The associations between PTFV₁ and stroke were not materially changed in sensitivity analyses controlling for ultrasound measurements of carotid plaque (HR per 1-SD, 1.20; 95% CI, 1.01-1.43).

The inclusion of additional covariates from the Framingham AF risk score did not change the association between PTFV₁ and stroke (HR per 1-SD, 1.22; 95% CI, 1.03-1.45).

The c-statistic of the Framingham stroke risk score (0.76; 95% CI, 0.72-0.79) did not appreciably change after adding PTFV₁ (0.76; 95% CI, 0.72-0.80), but the addition of PTFV₁ led to a significant net reclassification improvement (0.113, \( P < 0.001 \)).
**Supplemental Table I.** Baseline P-Wave Measurements, Stratified by the Occurrence of Incident Ischemic Stroke

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Stroke (N = 121)</th>
<th>No Stroke (N = 6,620)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-wave terminal force in lead V₁ (PTFV₁):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD), µV*ms</td>
<td>2,860 (1,996)</td>
<td>2,171 (1,786)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥95&lt;sup&gt;th&lt;/sup&gt; percentile, N (%)</td>
<td>14 (11.6)</td>
<td>324 (4.9)</td>
<td>.001</td>
</tr>
<tr>
<td>P-wave mean area:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD), µV*ms</td>
<td>3,702 (1,020)</td>
<td>3,554 (953)</td>
<td>.09</td>
</tr>
<tr>
<td>≥95&lt;sup&gt;th&lt;/sup&gt; percentile, N (%)</td>
<td>11 (9.1)</td>
<td>325 (4.9)</td>
<td>.04</td>
</tr>
<tr>
<td>P-wave maximum area:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD), µV*ms</td>
<td>6,689 (2,507)</td>
<td>6,364 (2,100)</td>
<td>.09</td>
</tr>
<tr>
<td>≥95&lt;sup&gt;th&lt;/sup&gt; percentile, N (%)</td>
<td>8 (6.6)</td>
<td>330 (5.0)</td>
<td>.42</td>
</tr>
<tr>
<td>P-wave mean duration:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD), ms</td>
<td>107.0 (13.0)</td>
<td>103.4 (13.1)</td>
<td>.003</td>
</tr>
<tr>
<td>≥95&lt;sup&gt;th&lt;/sup&gt; percentile, N (%)</td>
<td>13 (10.7)</td>
<td>390 (5.9)</td>
<td>.03</td>
</tr>
<tr>
<td>P-wave maximum duration:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD), ms</td>
<td>109.8 (13.3)</td>
<td>106.0 (12.7)</td>
<td>.001</td>
</tr>
<tr>
<td>≥95&lt;sup&gt;th&lt;/sup&gt; percentile, N (%)</td>
<td>15 (12.4)</td>
<td>411 (6.2)</td>
<td>.006</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation.
Supplemental References


