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

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Abstract

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 an etiology for many strokes currently classified as cryptogenic.

Methods—Among 6,741 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 electrocardiogram (ECG)—specifically, P-wave area, duration, and terminal force in lead V₁ (PTFV₁)—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%) suffered a stroke and 541 participants (8.0%) were diagnosed with AF. In Cox proportional hazards models adjusting for potential baseline confounders, PTFV₁ was more strongly associated with incident stroke (hazard ratio [HR] per 1-SD increase, 1.21; 95% confidence interval [CI], 1.02–1.44) than with incident AF (HR per 1-SD, 1.11; 95% CI, 1.03–1.21). The association between PTFV₁ and stroke

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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.

Keywords

Arrhythmia; atrium; electrocardiography; embolism; stroke

Atrial ECG signs have been associated with stroke in the absence of atrial fibrillation (AF),^{1–3} 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,⁴ 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.⁵ Institutional review boards at all participating sites approved this study, and all participants provided written, informed consent.

Participants

MESA enrolled 6,814 men and women 45 to 84 years of age 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 one 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 electrocardiograph machines (GE, Milwaukee, WI) calibrated at 10 mm/mV with a speed of 25 mm/s. 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). P-wave terminal force in lead V₁ (PTFV₁) is the most widely accepted marker of left atrial abnormality; P-wave area and duration may also be useful.⁶ Based on this and prior work,⁴ 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 (μ V) (Figure 1).⁷ 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.⁴ 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, chronic obstructive pulmonary disease, chronic kidney disease, body mass index, and smoking status (Supplemental Methods).

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 (Supplemental Methods).

Results

The 6,741 eligible participants were followed for a median 8.5 years (interquartile range, 7.7–8.6 years). Ischemic stroke occurred in 121 participants (1.8%), and 541 participants (8.0%) were diagnosed with AF. Participants with stroke were older, had more vascular risk factors, and manifested significantly higher PTFV₁ (Table 1; Supplemental Table I).

In Cox proportional hazards analysis, PTFV₁ was more strongly associated with incident stroke (hazard ratio [HR] per 1-SD increase, 1.21; 95% confidence interval [CI], 1.02–1.44; Table 2) than with incident AF (HR per 1-SD, 1.11; 95% CI, 1.03–1.21). The association between PTFV₁ and stroke was similar when we adjusted for incident AF (HR per 1-SD, 1.21; 95% CI, 1.02–1.44) or removed the AF covariate from our model (HR per 1-SD, 1.22; 95% CI, 1.03–1.45). The association held true in numerous sensitivity analyses accounting for AF in other ways, such as excluding those with any incident AF or modeling any incident AF as having been present from baseline (Supplemental Results).

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 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.⁴ 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.⁶ 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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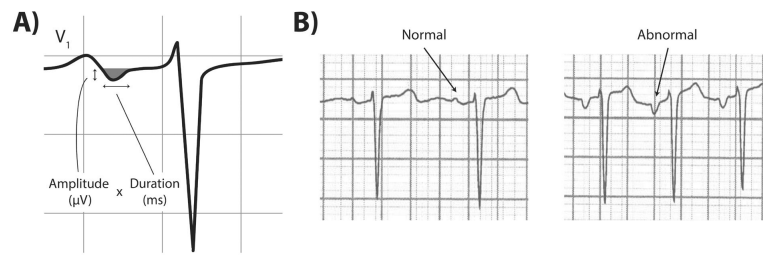


Figure 1.

A. Illustration of components of P-wave terminal force (PTFV₁), defined as the duration (ms) of the downward deflection (shaded grey area) of the P-wave in lead V₁ multiplied by the absolute value of its amplitude (µV).⁷

B. Representative examples of ECGs with normal and abnormal P-wave terminal force in lead V₁ (PTFV₁). Note the deep downward deflection of the terminal portion of the P-wave in the ECG on the right, compared with the absence of a deep downward deflection in the normal ECG on the left.

Table 1

Baseline Characteristics of Participants, Stratified by the Occurrence of Incident Ischemic Stroke

Characteristic*	Stroke (N = 121)	No Stroke (N = 6,620)	P value
Age, mean (SD), y	68.2 (9.8)	62.0 (10.2)	<.001
Female	58 (47.9)	3,509 (53.0)	.27
Race/ethnicity:			.13
White	51 (42.1)	2,525 (38.1)	
Black	35 (28.9)	1,844 (27.9)	
Hispanic	29 (24.0)	1,455 (22.0)	
Asian	6 (5.0)	796 (12.0)	
Diabetes status:			<.001
Normal	69 (57.5)	4,868 (73.8)	
Impaired fasting glucose	18 (15.0)	911 (13.8)	
Untreated diabetes	5 (4.2)	172 (2.6)	
Treated diabetes	28 (23.3)	646 (9.8)	
Hypertension	88 (72.7)	2,931 (44.3)	<.001
Chronic obstructive pulmonary disease	10 (8.3)	740 (11.2)	.31
Chronic kidney disease	29 (24.0)	1,105 (16.7)	.03
Current smoker	18 (14.9)	864 (13.1)	.56
Left ventricular hypertrophy	17 (14.1)	408 (6.2)	<.001
Total cholesterol, mean (SD), mg/dl	198.0 (33.9)	194.1 (35.8)	.24
High-density lipoprotein, mean (SD), mg/dl	47.8 (12.3)	51.0 (14.8)	.02
Low-density lipoprotein, mean (SD), mg/dl	121.6 (30.2)	117.2 (31.5)	.13
Body mass index:			.23
<25 kg/m ²	25 (20.7)	1,906 (28.8)	
25–25.99 kg/m ²	51 (42.1)	2,591 (39.1)	
30–39.99 kg/m ²	41 (33.9)	1,881 (28.4)	
>40 kg/m ²	4 (3.3)	242 (3.7)	
P-wave terminal force in lead V ₁ (PTFV ₁):			
Mean (SD), μ V*ms	2,860 (1,996)	2,171 (1,786)	<.001
95 th percentile	14 (11.6)	324 (4.9)	.001

Abbreviations: SD, standard deviation.

* Data are presented as Number (%) of participants unless otherwise specified.

Table 2

Associations Between P-Wave Morphology and Incident Ischemic Stroke

Characteristic	HR per 1-SD Increase (95% CI)
P-wave terminal force in lead V ₁ (PTFV ₁), $\mu\text{V}\cdot\text{ms}$	1.21 (1.02–1.44)
P-wave mean area, $\mu\text{V}\cdot\text{ms}$	1.16 (0.98–1.39)
P-wave maximum area, $\mu\text{V}\cdot\text{ms}$	1.16 (0.99–1.37)
P-wave mean duration, ms	1.11 (0.92–1.34)
P-wave maximum duration, ms	1.12 (0.93–1.35)

Abbreviations: CI, confidence interval; HR, hazard ratio; SD, standard deviation.