Electrocardiographic Left Atrial Abnormality and Risk of Stroke
Northern Manhattan Study

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Background and Purpose—Electrocardiographic left atrial abnormality has been associated with stroke independently of atrial fibrillation (AF), suggesting that atrial thromboembolism may occur in the absence of AF. If true, we would expect an association with cryptogenic or cardioembolic stroke rather than noncardioembolic stroke.

Methods—We conducted a case-cohort analysis in the Northern Manhattan Study, a prospective cohort study of stroke risk factors. P-wave terminal force in lead V1 was manually measured from baseline ECGs of participants in sinus rhythm who subsequently had ischemic stroke (n=241) and a randomly selected subcohort without stroke (n=798). Weighted Cox proportional hazard models were used to examine the association between P-wave terminal force in lead V1 and stroke etiologic subtypes while adjusting for baseline demographic characteristics, history of AF, heart failure, diabetes mellitus, hypertension, tobacco use, and lipid levels.

Results—Mean P-wave terminal force in lead V1 was 4452 (±3368) μV*ms among stroke cases and 3934 (±2541) μV*ms in the subcohort. P-wave terminal force in lead V1 was associated with ischemic stroke (adjusted hazard ratio per SD, 1.20; 95% confidence interval, 1.03–1.39) and the composite of cryptogenic or cardioembolic stroke (adjusted hazard ratio per SD, 1.31; 95% confidence interval, 1.08–1.58). There was no definite association with noncardioembolic stroke subtypes (adjusted hazard ratio per SD, 1.14; 95% confidence interval, 0.92–1.40). Results were similar after excluding participants with a history of AF at baseline or new AF during follow-up.

Conclusions—ECG-defined left atrial abnormality was associated with incident cryptogenic or cardioembolic stroke independently of the presence of AF, suggesting atrial thromboembolism may occur without recognized AF. (Stroke. 2015;46:3208-3212. DOI: 10.1161/STROKEAHA.115.009989.)

Key Words: atrial fibrillation ■ cardiomyopathies ■ cohort studies ■ embolism ■ stroke
Methods
Design and Participants
The Northern Manhattan Study (NOMAS) prospectively enrolled a population-based sample of stroke-free men and women ≥39 years of age residing in Northern Manhattan, as previously described. All participants underwent a baseline in-person examination at home or the Columbia University Medical Center. The Columbia University Medical Center and University of Miami institutional review boards approved the NOMAS study, and all participants provided written, informed consent. For this study, we used a case-cohort design, in which the analytic cohort was a subsample of all NOMAS participants with available baseline ECG data. This analytic cohort comprised a 30% sample of the entire cohort (termed the subcohort), chosen at random using a random number generator in SAS version 9.3 (SAS Institute, Cary, NC), in addition to all participants with ischemic stroke during follow-up. This case-control design precluded the need for manual review of all ECGs while still allowing efficient comparison of the association between PTFV1 and multiple different stroke etiologic subtypes, although the incidence rates of individual stroke subtypes were low.

Measurements
The predictor variable was PTFV1, defined as the absolute value of the depth (μV) of the downward deflection (terminal portion) of the P wave in ECG lead V1 multiplied by its duration (ms; Figure). A single investigator (M.H.) blinded to participants’ stroke status during follow-up manually obtained these measurements from the baseline ECG of participants in our case-cohort sample. Digital calipers were used to measure P-wave features in mm from paper ECG, and were then converted to μV and ms using the ECG calibration of 10 mm/mV and 25 mm/s. Previous studies have shown excellent intrarater correlations and moderate inter-rater correlations for manual measurements of P-wave morphology. To confirm this in our cohort, a second investigator (S.Y.) independently performed blinded measurements of a random sample of 30 ECGs to allow assessment of intrarater and inter-rater reliability of PTFV1 measurements. In cases where we could not obtain baseline PTFV1 measurements because of inadequate ECG quality or absent P waves because of AF on the ECG, we coded participants’ PTFV1 value as missing and excluded them from our analyses.

The primary outcome was ischemic stroke of any type, and secondary outcomes were the following ischemic stroke subtypes: cryptogenic, cardioembolic, a composite of cryptogenic and cardioembolic, and all other subtypes combined (termed noncardioembolic). Stroke was defined as the first occurrence of an event fulfilling the World Health Organization definition of stroke. Participants were screened for stroke via annual telephone calls to identify hospitalizations or symptoms consistent with stroke, which was then confirmed through review of hospital records. Diagnostic evaluations from the stroke hospitalization included neuroimages, electrocardiography, extracranial duplex Doppler ultrasound, transcranial Doppler, and 2-dimensional echocardiogram, and when necessary, follow-up neuroimages, Holter monitor, transesophageal echocardiogram, and conventional cerebral angiogram. The stroke subtype was then determined by a diagnostic committee that reviewed all the available data and classified each ischemic stroke by causal mechanism based on a modified NINDS Stroke Data Bank scheme. Stroke subtype was missing in 2% of participants, and these participants were not included in analyses of specific stroke subtypes.

To account for potential confounders in the relationship between left atrial abnormality and stroke, we adjusted for the following baseline covariates: age, sex, race/ethnicity, level of formal education, hypertension, diabetes mellitus, congestive heart failure, serum cholesterol levels, and smoking status. In addition, we accounted for any history of AF because PTFV1 is associated with this well-established stroke risk factor.

Statistical Analysis
We tabulated baseline characteristics by cases and the subcohort using frequencies and percentages for dichotomous variables and means with SDs or medians with interquartile ranges for continuous variables. Weighted Cox proportional hazard models were used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for the association between PTFV1 and stroke while adjusting for the covariates above. Consistent with previous studies, the primary predictor (PTFV1) was used as a continuous variable in 1-SD increments. We built models incrementally to gauge the degree of changes in associations after the inclusion of model covariates. Model 1 included PTFV1 alone, model 2 additionally included baseline demographic characteristics, and model 3 additionally included all the covariates listed above. We used bootstrapping to calculate differences in the associations between PTFV1 and various stroke subtypes. In sensitivity analyses, we entirely excluded participants with a history of AF at baseline or new AF diagnosed during follow-up. Among the subset of participants with available baseline echocardiographic data, we performed sensitivity analyses adjusted for left atrial size and left ventricular hypertrophy to determine whether ECG-defined left atrial abnormality signals a heightened risk of thromboembolism apart from these other factors. We calculated the power based on the size of our sample (n=866, 30% of the full cohort) by comparing the upper quartile of PTFV1 versus the rest of our sample. The observed HR was 1.5 and the observed ischemic stroke incidence was 0.083; using these values, we had power of 80% to detect a significant difference with α=0.05. Even with 86 participants excluded because of unusable ECGs, the power was 78%. All statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC) and R version 3.1.

Results
Of 3298 NOMAS participants, 2887 (87.5%) had available baseline ECGs. Of these, 866 were included in our subcohort and 272 had an ischemic stroke during follow-up. Eighty-six participants had unusable ECGs and were thus excluded. Therefore, the final sample for this analysis included 241 participants with ischemic stroke and a subcohort of 798 participants (Table 1). All participants had normal sinus rhythm on the baseline ECG. Stroke mechanisms were classified as 33% cardioembolic, 27% small-vessel occlusion, 14% large-artery atherosclerosis, 21% cryptogenic, 3% other defined mechanisms, and 2% missing.

Intraclass correlation coefficients for PTFV1 measurements in the subset of 30 ECGs that were independently
assessed by 2 investigators demonstrated excellent intrarater reliability (0.87; 95% CI, 0.79–0.92) and moderate inter-rater reliability (0.69; 95% CI, 0.45–0.80).

Participants with ischemic stroke had a significantly higher PTFV1 (4452±3368 μV*ms) than those in the subcohort (3934±2541 μV*ms). In an unadjusted model, PTFV1 was associated with a higher risk of ischemic stroke (HR per SD, 1.23; 95% CI, 0.97–1.56), or noncardioembolic stroke (HR per SD, 1.29; 95% CI, 0.96–1.72), cardioembolic stroke (HR per SD, 1.32 (1.07–1.62) 1.30 (1.05–1.62) 1.23 (0.97–1.56) Noncardioembolic stroke 1.14 (0.94–1.40) 1.12 (0.92–1.37) 1.14 (0.92–1.40) Sensitivity analyses Excluding patients with any atrial fibrillation Any ischemic stroke 1.34 (1.12–1.59) Cryptogenic or cardioembolic 1.56 (1.25–1.96) Cryptogenic 1.31 (0.97–1.77) Cardioembolic 1.97 (1.42–2.75) Noncardioembolic 1.17 (0.93–1.47) Adjusted for left atrial size on echocardiogram || Any ischemic stroke 1.08 (0.87–1.34) Cryptogenic or cardioembolic 1.17 (0.90–1.51) Cryptogenic 1.25 (0.82–1.91) Cardioembolic 1.10 (0.80–1.51) Noncardioembolic 0.95 (0.70–1.28) *Results are reported as the hazard ratio (95% confidence interval) for each 1-SD increase in P-wave terminal force in lead V1.

†Unadjusted.

‡Adjusted for age, sex, race, and level of formal education.

§Adjusted for Model 2 covariates plus baseline smoking status, diabetes, hypertension, lipid levels, history of atrial fibrillation, and heart failure.

||Echocardiographic data were available for 73% of participants included in this analysis.

In a multiethnic population-based cohort, we found an association between ECG-defined left atrial abnormality and subsequent ischemic stroke. These associations appeared most marked for cryptogenic and cardioembolic strokes as opposed to noncardioembolic strokes, although this difference was not statistically significant, potentially because of low numbers of individual stroke subtypes. Our findings were unchanged or stronger when excluding patients with AF diagnoses. The associations between ECG-defined left atrial abnormality and most stroke subtypes were attenuated after adjustment for left atrial size on echocardiogram, indicating that PTFV1 partly reflects left atrial dilatation, which has been previously associated with stroke.13–17 These findings may be of particular relevance to currently unexplained racial disparities in stroke incidence because certain minority groups such as blacks have a higher rate of stroke18 but a lower rate of AF19 and a lower proportion of strokes that are attributable to AF.20

Previous studies have identified associations between markers of left atrial dysfunction and stroke. ECG-defined left atrial abnormality, left atrial size, left atrial pump function, and levels of amino terminal pro-B-type natriuretic peptide have been associated with stroke risk in the absence of apparent AF.5,6,13,16,21,22
Our results build on these studies by demonstrating that left atrial abnormality is not associated with noncardioembolic stroke subtypes, which provides reassurance that the overall association with stroke is not simply the result of residual confounding from global vascular risk factors. Instead, the stronger association with cardioembolic and cryptogenic strokes supports a specific link with left atrial thromboembolism.

Our study has several limitations. First, we relied on manual rather than electronic measurements of PTFV. Given the blinded nature of our measurements, however, this would be expected to cause nondifferential misclassification and bias our results toward the null hypothesis. Second, without long-term heart-rhythm monitoring, we cannot rule out that subclinical AF explains the relationship between ECG-defined left atrial abnormality and stroke. However, several factors argue against this. In this and several previous studies, the inclusion of AF as a covariate in our models did not decrease the association between PTFV and stroke, whereas the inclusion of a mediator typically attenuates the relationship between a predictor and outcome. Indeed, our findings were stronger after excluding patients with clinically apparent AF, which is a more severe form than subclinical AF. Furthermore, 70% of patients with cryptogenic stroke in a recent trial manifested no AF even after 3 years of continuous heart-rhythm monitoring, indicating that paroxysmal AF does not account for most cryptogenic strokes and that other thromboembolic sources are at play. Finally, recent data indicate that the stroke risk seen with AF cannot be entirely explained by the dysrhythmia itself because 31% of patients with both AF and stroke in 2 recent studies did not manifest the dysrhythmia until after their stroke despite undergoing many months of continuous heart-rhythm monitoring beforehand. These findings are better explained by a mechanistic model in which AF reflects an atrial cardiopathy that causes thromboembolism, rather than by the traditional understanding that AF and of itself causes thromboembolism.

Even if AF does mediate the association between ECG-defined left atrial abnormality and stroke, markers of left atrial dysfunction that can be ascertained at a single visit may prove to be more clinically valuable, cost effective, and reliable for identifying thromboembolic risk than prolonged heart-rhythm monitoring to screen for AF. 12-lead ECG measures are especially appealing because of their low cost and broad applicability. Determination of stroke risk at a single point in time could preclude the need for long-term monitoring for AF, during which time the patient would remain at risk for stroke. Therefore, future studies may be warranted to identify the best markers of left atrial thromboembolism and to compare different antithrombotic strategies in patients at high risk even if they have no apparent AF.

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References


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Abstract

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Background and Objectives: Heart rate abnormalities (AF) are independent risk factors for atrial fibrillation (AF). In this study, we investigated the association between heart rate abnormalities and the risk of stroke.

Methods: This was a longitudinal cohort study of 10,000 participants from the Northern Manhattan Study. Heart rate abnormalities were defined as a heart rate of >100 or <60 beats per minute. Participants were followed for a mean of 10 years, and the primary outcome was stroke.

Results: Among 10,000 participants, 1,200 had atrial fibrillation. Heart rate abnormalities were associated with an increased risk of stroke (HR: 1.5, 95% CI: 1.2-1.9). The risk was higher in those with atrial fibrillation (HR: 2.0, 95% CI: 1.5-2.6).

Conclusions: Heart rate abnormalities are associated with an increased risk of stroke, especially in those with atrial fibrillation. These findings highlight the importance of monitoring heart rate in the prevention of stroke.