Association Between Left Atrial Abnormality on ECG and Vascular Brain Injury on MRI in the Cardiovascular Health Study

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Background and Purpose—Emerging evidence suggests that atrial disease is associated with vascular brain injury in the absence of atrial fibrillation.

Methods—The Cardiovascular Health Study prospectively enrolled community-dwelling adults aged ≥65 years. Among participants who underwent MRI, we examined associations of ECG left atrial abnormality with brain infarcts and leukoaraiosis. P-wave terminal force in lead V1 was the primary measure of left atrial abnormality; P-wave area and duration were secondary predictors. We excluded participants with atrial fibrillation before or on their index ECG. Primary outcomes were incident infarcts and worsening leukoaraiosis from initial to follow-up scan =5 years later. Secondary outcomes were prevalent infarcts and degree of leukoaraiosis on initial MRI. Relative risk (RR) and linear regression models were adjusted for vascular risk factors.

Results—Among 3129 participants with ≥1 scan, each SD increase in P-wave terminal force in lead V1 was associated with a 0.05-point (95% confidence interval [CI], 0.0003–0.10) higher baseline white matter grade on a 10-point scale. P-wave terminal force in lead V1 was associated with prevalent infarcts of any type (RR per SD, 1.09; 95% CI, 1.04–1.16) and more so with prevalent nonlacunar infarcts (RR per SD, 1.22; 95% CI, 1.08–1.38). Among 1839 participants with 2 scans, P-wave terminal force in lead V1 was associated with worsening leukoaraiosis (RR per SD, 1.09; 95% CI, 1.01–1.18), but not with incident infarcts (RR per SD, 1.06; 95% CI, 0.93–1.20). Sensitivity analyses adjusting for incident atrial fibrillation found similar results. P-wave area and duration were not associated with outcomes.

Conclusions—ECG left atrial abnormality is associated with vascular brain injury in the absence of documented atrial fibrillation. (Stroke. 2015;46:711-716. DOI: 10.1161/STROKEAHA.114.007762.)

Key words: arrhythmias, cardiac ◼ electrocardiography ◼ embolism ◼ heart atrium ◼ stroke

Atrial fibrillation (AF) has long been recognized as a risk factor for vascular brain injury, in both an overt form as ischemic stroke⁶ and covert as subclinical brain infarction.⁵ Recent evidence suggests that atrial disease may be related to vascular brain injury even in the absence of AF. Previous studies have found associations between premature atrial contractions or paroxysmal supraventricular tachycardia and ischemic stroke,⁶ but not with incident infarcts (RR per SD, 1.06; 95% CI, 0.93–1.20). Sensitivity analyses adjusting for incident atrial fibrillation found similar results. P-wave area and duration were not associated with outcomes.

Because left atrial ECG abnormality indicates derangements in atrial anatomy and physiology, its association with stroke suggests that left atrial disease may produce a substrate for cardiac thrombus formation and embolization even in the absence of AF. To investigate this hypothesis, we examined the association of left atrial ECG abnormality with subclinical vascular brain injury detected by MRI. We examined both covert brain infarcts and the degree of leukoaraiosis because cerebral white matter disease has also been associated with vascular risk factors.¹¹ Because our hypothesis was that left atrial disease and is associated with subclinical cardiac embolism, which
typically results in large or cortical infarcts, we hypothesized that associations would be stronger with nonlacunar rather than aggregate MRI-defined infarcts.

Methods

Design

The Cardiovascular Health Study (CHS) is a prospective, longitudinal cohort study of community-dwelling men and women aged 65 years. In 2 waves, between 1989 and 1993, CHS field centers recruited 5888 participants from a random sample of people on Medicare eligibility lists in 4 counties, one each in California, Maryland, North Carolina, and Pennsylvania. Participants were invited to return for annual in-person study visits from 1998 to 1999 and were followed up after that time via semiannual telephone calls and the use of linked Medicare claims data. Institutional Review Boards at the University of Washington and each field center approved this study, and all participants provided written informed consent.

Participants

The original CHS exclusion criteria were age <65 years, inability to give consent or answer questions without a surrogate, residence in an institutional setting, wheelchair dependence, or active treatment for cancer. For this analysis, we included CHS participants who underwent a brain MRI as part of the study protocol to assess vascular brain injury, including infarcts and leukoaraiosis. We excluded CHS participants who had a clinically recognized stroke before their initial MRI, lacked ≥1 ECG before their initial MRI were diagnosed with AF before or on their index ECG, or lacked data on any of the model covariates described below. An adjudication committee determined stroke status, as detailed previously.

Measurements

The predictor variables were P-wave measurements derived from digital 12-lead ECGs done at baseline and each annual study visit. We obtained P-wave measurements from the latest ECG before the initial MRI. ECGs were obtained on MAC PC ECG machines (Marquette Electronics, Milwaukee, WI) calibrated at 10 mm/mV with a speed of 25 mm/s. P-wave areas, amplitudes, and durations were centrally measured at the Wake Forest Epidemiological Cardiology Research Center using a fully automated program (12-SL, version 2001; GE Marquette). PTFV, is the most frequently used ECG criterion for left atrial abnormality, whereas P-wave area and duration may also be useful. On the basis of this consideration and previous work, we focused on PTFV as the main predictor variable and also examined maximum P-wave duration and maximum P-wave area. PTFV was defined as the duration (ms) of the downward deflection (terminal portion) of the median P wave in lead V1 multiplied by the absolute value of its amplitude (μV; Figure). P-wave areas comprised the sum of the absolute areas of upward and downward P-wave deflections and were multiplied by 19.52 to harmonize the 12-SL program’s calculations with other machines.

The outcomes were infarcts and degree of leukoaraiosis on initial (performed in 1991–1994) and follow-up (performed in 1997–1999) MRI scans, as detailed previously. Infarcts were defined as ≥3 mm areas of abnormal signal intensity in a vascular distribution and lacking mass effect, and leukoaraiosis was graded on a 10-point scale, with a white matter grade of 0 representing the least severe and 9 the most severe. Lacunar infarcts were defined as subcortical infarcts 3 to 20 mm in size, and any other infarcts were considered nonlacunar infarcts. Those with both lacunar and nonlacunar infarcts were classified as having nonlacunar infarcts. The primary outcomes were the presence of any incident infarcts and any worsening of the white matter grade by ≥1 grade among participants who underwent both an initial and follow-up scan. Excluded from all analyses of incident findings were participants who had a clinically recognized stroke before the follow-up scan; furthermore, participants with any infarcts on the initial scan were excluded from analyses of incident infarcts on the follow-up scan, and those with the highest white matter grade on the initial scan were excluded from analyses of worsening white matter grade. Secondary outcomes were prevalent infarcts and white matter grade on the initial scan.

AF was ascertained by hospital discharge diagnoses, diagnoses of AF from outpatient visits or carrier claims from Medicare data, and ECGs done at annual study exams from 1998 to 1999. Additional covariates included age, sex, race, education level, coronary heart disease, congestive heart failure, diabetes mellitus, hypertension (defined by systolic blood pressure or antihypertension drug therapy), dyslipidemia (defined by high- and low-density lipoprotein and triglyceride levels), smoking status, and N-terminal-pro-brain natriuretic peptide (NT-pro-BNP), as detailed previously. These variables were determined from the study visit associated with the 12-lead ECG under analysis. If covariates were not collected in that year or were missing, they were carried forward from previous years when available.

Statistical Analysis

We excluded values >99.9th percentile for PTFV and P-wave area as clinically implausible outliers. After using generalized additive models to confirm the linearity of associations, and consistent with previous work, we evaluated P-wave measurements as linear predictors in SD increments (calculated on the full sample before any exclusions). We displayed the distribution of baseline characteristics by category of PTFV (0 and tertiles of values >0).

We used relative risk regression to examine the associations of P-wave predictors with incident infarcts, prevalent infarcts, and worsening of the white matter grade. We used linear regression to examine associations with the white matter grade on the first scan. The final models controlled for age, sex, race, education level, coronary heart disease, congestive heart failure, diabetes mellitus, hypertension, dyslipidemia, smoking status, and period of time between the index ECG and initial scan. Because left atrial ECG abnormality is associated with AF, which in turn has long been known to be associated with brain infarction, we performed additional analyses that adjusted for incident AF diagnoses in the intervening period after the index ECG and before the MRI under analysis (ie, before the second MRI for analyses of incident findings and before the first MRI for analyses of baseline findings). In additional analyses, we restricted the definition of infarcts to nonlacunar infarcts only. In secondary analyses, we assessed P-wave measurements as binary variables dichotomized at the 95th percentile.

To confirm further that AF did not mediate associations between P-wave predictors and outcomes, we performed sensitivity analyses.
that entirely excluded participants diagnosed with incident AF after the index ECG and before the MRI under analysis. Finally, we performed exploratory analyses adjusting for serum NT-pro-BNP to determine how associations with our electrocardiographic predictors changed after adjusting for this other marker of atrial disease.\textsuperscript{22} Statistical analyses were performed using Stata 12.1 (StataCorp, College Station, TX).

**Results**

Of the 5888 participants in the overall CHS cohort, 3660 underwent an initial MRI scan. When compared with the overall cohort, participants who underwent MRI were significantly younger, had received more education, and had fewer medical comorbidities.\textsuperscript{18} Of these 3660 participants with MRI data, 3129 met the other inclusion criteria for our analyses of prevalent findings on the first scan. Those with higher PTFV, were more likely to be black, lack a high school degree, and have hypertension, coronary heart disease, congestive heart failure, or diabetes mellitus (Table 1). Of these 3129 participants, 1839 underwent a follow-up scan and otherwise met the inclusion criteria for our analyses of incident findings.

In primary analyses limited to participants with 2 scans, 17.1% had new infarcts and 27.4% had worsening of the white matter grade on the repeat scan. Each SD increase in PTFV, (2160 $\mu$V ms) was associated with worsening white matter grade (RR per SD, 1.09; 95% confidence interval [CI], 1.01–1.18). This association did not substantially change after adjusting for incident AF or NT-pro-BNP, or excluding patients with incident AF. Each SD increase in PTFV, was associated with a 0.05-point (95% CI, 0.0003 to 0.10) higher baseline white matter grade. This association did not change appreciably when adjusting for or excluding patients with incident AF although the association was no longer significant after adjusting for NT-pro-BNP (0.04 higher white matter grade for each SD increase in PTFV,; 95% CI, −0.01 to 0.10). PTFV, dichotomized at the 95th percentile was associated with prevalent infarcts of any type (RR, 1.52; 95% CI, 1.26–1.82) and prevalent nonlacunar infarcts (RR, 1.65; 95% CI, 1.06–2.56), but not with the other outcomes.

P-wave area, duration, and the other dichotomized P-wave measurements were not significantly associated with baseline or incident MRI findings (Table 2).

| Table 1. Baseline Characteristics of Cardiovascular Health Study Participants, Stratified by Category of PTFV, |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Characteristic†                | PTFV,=0 $\mu$V ms (n=758) | PTFV,=207–2494 $\mu$V ms (n=799) | PTFV,=2495–3780 $\mu$V ms (n=789) | PTFV,=3781–19474 $\mu$V ms (n=778) |
| PTFV, mean (SD), $\mu$V ms     | 0 (0)           | 1786 (471)      | 3088 (367)      | 5436 (1715)     |
| Age, mean (SD), y              | 74.5 (5.2)      | 74.5 (4.9)      | 74.3 (4.8)      | 74.8 (5.2)      |
| Men                            | 300 (39.6)      | 318 (39.8)      | 337 (42.7)      | 308 (39.6)      |
| Black                          | 96 (12.7)       | 99 (12.4)       | 126 (16.0)      | 155 (19.9)      |
| High school graduate           | 580 (76.5)      | 592 (74.1)      | 599 (75.9)      | 553 (71.1)      |
| SBP, mean (SD), mm Hg          | 131.9 (19.6)    | 134.1 (19.80)   | 134.6 (20.5)    | 138.1 (22.3)    |
| HDL, mean (SD), mg/dL          | 54.6 (14.6)     | 54.2 (14.5)     | 53.6 (14.5)     | 54.1 (14.5)     |
| LDL, mean (SD), mg/dL          | 127.0 (33.7)    | 128.7 (32.7)    | 128.4 (33.9)    | 128.3 (35.2)    |
| Coronary heart disease         | 119 (15.7)      | 126 (15.8)      | 133 (16.9)      | 188 (24.2)      |
| Congestive heart failure       | 21 (2.8)        | 18 (2.3)        | 24 (3.0)        | 42 (5.4)        |
| Diabetes status                |                 |                 |                 |                 |
| Normal                         | 601 (80.2)      | 597 (75.9)      | 586 (75.0)      | 571 (74.1)      |
| Impaired fasting glucose       | 67 (8.9)        | 88 (11.2)       | 85 (10.9)       | 89 (11.5)       |
| Diabetes mellitus              | 81 (10.8)       | 102 (13.0)      | 110 (14.1)      | 111 (14.4)      |
| Smoking status                 |                 |                 |                 |                 |
| Never                          | 344 (45.4)      | 412 (51.6)      | 360 (45.6)      | 373 (47.9)      |
| Former                         | 337 (44.5)      | 316 (39.5)      | 352 (44.6)      | 322 (41.4)      |
| Current                        | 77 (10.2)       | 71 (8.9)        | 77 (9.8)        | 83 (10.7)       |

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; PTFV, P-wave terminal force in lead V1; and SBP, systolic blood pressure.

*Baseline characteristics are displayed by category of PTFV,; 0 and tertiles of values >0. A value of 0 reflects the absence of a downward deflection of the P wave in lead V1.
†Data are presented as number (%) unless otherwise specified.
Discussion

In this large, prospective cohort study, PTFV₁—an established ECG marker of left atrial abnormality—was significantly associated with prevalent MRI-defined infarcts, especially nonlacunar infarcts when compared with infarcts of any type. These associations held regardless of whether we adjusted for NT-pro-BNP and incident diagnoses of AF. PTFV₁ was also associated with baseline and worsening white matter disease grade but was not associated with incident infarcts.

These findings expand on recent data on the relationships between ECG markers of atrial disease and vascular brain injury. Among a prospective cohort of participants enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA), greater PTFV₁ on the baseline 12-lead ECG was significantly associated with a higher risk of subsequent ischemic stroke, even after adjusting for incident AF. PTFV₁ was more strongly associated with incident stroke than with incident AF, making it less likely that subclinical AF predominantly mediated the link between PTFV₁ and stroke. Two other studies, one of which was focused primarily on prediction of AF, have also demonstrated an association between PTFV₁ and stroke although these analyses did not adjust for AF when examining this association. Our present results provide further evidence that PTFV₁ is associated with brain infarcts in the absence of documented AF, and novel evidence that PTFV₁ is associated with leukoaraiosis.

Our results should be considered in light of the limitations of this study. First, participants did not undergo continuous heart-rhythm monitoring to detect subclinical AF, and we cannot exclude the possibility that subclinical AF largely mediates the relationship between PTFV₁ and vascular brain injury. However, if this were the case, the addition of incident AF to our models would be expected to change the strength of association between PTFV₁ and our outcomes, whereas the associations we found were substantially the same regardless of whether we included incident AF diagnoses. Furthermore, even if undetected subclinical AF mediates some of the associations between markers of atrial cardiopathy and vascular brain injury, as a practical matter these measurements are easier and less costly to obtain than prolonged heart-rhythm monitoring. Nevertheless, it will be important to conduct additional studies of the association between PTFV₁ and vascular brain injury in patients undergoing continuous heart-rhythm monitoring. Second, given the modest strength of association between PTFV₁ and our outcomes, as well as the multiple predictors and outcomes tested, these results may simply represent chance findings. This may be less likely because our results are consistent with findings of an association between PTFV₁ and stroke in a separate population-based cohort enrolled in the MESA study. Third, MRIs were performed using earlier-generation machines that are likely to have been less sensitive than current scanners. This would be expected to result in nondifferential misclassification bias that would have attenuated the associations between P-wave measurements and outcomes. In addition, the CHS participants who underwent MRI scans tended to be younger and healthier than the overall cohort, which probably further reduced the associations between ECG markers and vascular brain injury. Furthermore, given a lack of side-by-side imaging review, we were unable to identify new infarcts on follow-up scans reliably among participants with prevalent infarcts on the initial scans and, therefore, had to exclude participants with prevalent infarcts from analyses of incident infarcts. This resulted in a lower risk sample for our analyses of incident infarcts, which would be expected to reduce associations further and may partly explain the lack of association between PTFV₁ and incident infarcts. Additional studies with larger sample sizes may be able to assess the relationship between PTFV₁ and incident infarcts better. Fifth, inclusion of detailed imaging data about the left atrium may allow a more complete assessment of the relationship between left atrial dysfunction and vascular brain injury.
Current ECG machines do not routinely report PTFV₃, and its values show a moderate degree of measurement-to-measurement variation,²⁴ thereby limiting its immediate clinical value as a risk marker for vascular brain injury. However, these technical issues are likely to be surmountable with further clinical development of this marker, and in the meantime, PTFV₃ may serve as an important research tool in the ongoing quest to understand cryptogenic strokes and vascular brain injury better. Many cryptogenic strokes are suspected to arise from occult cardiac embolism.²⁵ Because PTFV₃ has long been established as a marker of increased left atrial pressure and hypertrophy,²⁶,²⁷ associations between PTFV₃ and brain infarcts independent of documented AF suggest that atrial cardiopathy may cause embolism in the absence of AF. Furthermore, AF has been previously associated with periventricular white matter disease independent of other vascular risk factors,²⁸ possibly because of the cerebral hypoperfusion seen in AF.²⁹ Our finding of an association between PTFV₃ and white matter disease suggests that atrial dysfunction might be a marker of cerebral hypoperfusion even in the absence of AF. This possibility would be consistent with the recent finding that left atrial volume and function correlate with white matter disease even in the absence of AF.³⁰ The associations between left atrial abnormality on ECG and vascular brain injury on MRI may also reflect shared vascular risk factors that were not fully adjusted for in our models although the seemingly stronger association we found for nonlacunar rather than lacunar infarcts supports some degree of a causal link between atrial cardiopathy and vascular brain injury. Additional work may be able to identify some combination of ECG markers, such as PTFV₃, echocardiographic measurements of left atrial size and function,³¹,³² and serum biomarkers, such as NT-pro-BNP,³³,³⁴ that predict the risk of vascular brain injury better than simply the presence or absence of apparent AF. Therefore, further confirmation and delineation of atrial cardiopathy as a risk factor for vascular brain injury may help to advance efforts to prevent stroke.

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Disclosures
Dr Elkind reports serving as a consultant for BMS-Pfizer Partnership, Daiichi-Sankyo, Janssen Pharmaceuticals, and Boehringer-Ingelheim on the subject of antithrombotic therapy for AF; and for Biotelemetry on the subject of cardiac monitoring for paroxysmal AF. The other authors report no conflicts.

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