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 at 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 stroke and covert as subclinical brain infarction. 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, even after accounting for diagnoses of AF during follow-up. P-wave terminal force in lead V1 (PTFV1)—a consistently used marker of left atrial abnormality on a 12-lead ECG—has been associated with stroke risk, even in the absence of documented AF. 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. 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). PTFV1, 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 PTFV1, as the main predictor variable and also examined maximum P-wave duration and maximum P-wave area. PTFV1 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 scan were excluded from analyses of worsening white matter grade on the initial scan.

Figure. Illustration of ECG parameters used to calculate P-wave terminal force, defined as the duration of the downward deflection (terminal portion) of the P-wave in lead V1, multiplied by the absolute value of its amplitude.

Statistical Analysis

We excluded values >99.9th percentile for PTFV1, 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 PTFV1 (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 (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.
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. These 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. 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 PTFV1 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 PTFV1 (2160 μV 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 PTFV1 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 PTFV1; 95% CI, −0.01 to 0.10). PTFV1 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 PTFV1

<table>
<thead>
<tr>
<th>Characteristic†</th>
<th>PTFV1=0 μV ms (n=758)</th>
<th>PTFV1=0–207 μV ms (n=799)</th>
<th>PTFV1=207–2494 μV ms (n=789)</th>
<th>PTFV1=2495–3780 μV ms (n=778)</th>
<th>PTFV1=3781–19474 μV ms (n=778)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTFV1, mean (SD), μV ms</td>
<td>0 (0)</td>
<td>1786 (471)</td>
<td>3088 (367)</td>
<td>5436 (1715)</td>
<td>5436 (1715)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>74.5 (5.2)</td>
<td>74.5 (4.9)</td>
<td>73.4 (4.8)</td>
<td>74.8 (5.2)</td>
<td>74.8 (5.2)</td>
</tr>
<tr>
<td>Men</td>
<td>300 (39.6)</td>
<td>318 (39.8)</td>
<td>337 (42.7)</td>
<td>308 (39.6)</td>
<td>308 (39.6)</td>
</tr>
<tr>
<td>Black</td>
<td>96 (12.7)</td>
<td>99 (12.4)</td>
<td>126 (16.0)</td>
<td>155 (19.9)</td>
<td>155 (19.9)</td>
</tr>
<tr>
<td>High school graduate</td>
<td>580 (76.5)</td>
<td>592 (74.1)</td>
<td>599 (75.9)</td>
<td>553 (71.1)</td>
<td>553 (71.1)</td>
</tr>
<tr>
<td>SBP, mean (SD), mm Hg</td>
<td>131.9 (19.6)</td>
<td>134.1 (19.80)</td>
<td>134.6 (20.5)</td>
<td>138.1 (22.3)</td>
<td>138.1 (22.3)</td>
</tr>
<tr>
<td>HDL, mean (SD), mg/dL</td>
<td>54.6 (14.6)</td>
<td>54.2 (14.5)</td>
<td>53.6 (14.5)</td>
<td>54.1 (14.5)</td>
<td>54.1 (14.5)</td>
</tr>
<tr>
<td>LDL, mean (SD), mg/dL</td>
<td>127.0 (33.7)</td>
<td>128.7 (32.7)</td>
<td>128.4 (33.9)</td>
<td>128.3 (35.2)</td>
<td>128.3 (35.2)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>119 (15.7)</td>
<td>126 (15.8)</td>
<td>133 (16.9)</td>
<td>188 (24.2)</td>
<td>188 (24.2)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>21 (2.8)</td>
<td>18 (2.3)</td>
<td>24 (3.0)</td>
<td>42 (5.4)</td>
<td>42 (5.4)</td>
</tr>
<tr>
<td>Diabetes status</td>
<td>Normal</td>
<td>601 (80.2)</td>
<td>597 (75.9)</td>
<td>586 (75.0)</td>
<td>571 (74.1)</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>67 (8.9)</td>
<td>88 (11.2)</td>
<td>85 (10.9)</td>
<td>89 (11.5)</td>
<td>89 (11.5)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>81 (10.8)</td>
<td>102 (13.0)</td>
<td>110 (14.1)</td>
<td>111 (14.4)</td>
<td>111 (14.4)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Never</td>
<td>344 (45.4)</td>
<td>412 (51.6)</td>
<td>360 (45.6)</td>
<td>373 (47.9)</td>
</tr>
<tr>
<td>Former</td>
<td>337 (44.5)</td>
<td>316 (39.5)</td>
<td>352 (44.6)</td>
<td>322 (41.4)</td>
<td>322 (41.4)</td>
</tr>
<tr>
<td>Current</td>
<td>77 (10.2)</td>
<td>71 (8.9)</td>
<td>77 (9.8)</td>
<td>83 (10.7)</td>
<td>83 (10.7)</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; PTFV1, P-wave terminal force in lead V1; and SBP, systolic blood pressure.

*Baseline characteristics are displayed by category of PTFV1; 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.
PTFV$_1$ on the baseline 12-lead ECG was significantly associated with baseline and worsening white matter disease but was not associated with incident infarcts. Nonlacunar infarcts were associated with prevalent MRI-defined infarcts, especially involving the deep white matter, and with leukoaraiosis. These associations held regardless of whether we adjusted for variables in model 2 plus incident atrial fibrillation diagnosed after the ECG and before the MRI under analysis.

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 PTFV$_1$ 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 PTFV$_1$ 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 PTFV$_1$ and vascular brain injury in patients undergoing continuous heart-rhythm monitoring. Second, given the modest strength of association between P-wave measurements and risk of 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 PTFV$_1$ and vascular brain injury.

Discussion

In this large, prospective cohort study, PTFV$_1$—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. PTFV$_1$ 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 PTFV$_1$ on the baseline 12-lead ECG was significantly associated with a higher risk of subsequent ischemic stroke, even after adjusting for incident AF. PTFV$_1$ was more strongly associated with incident stroke than with incident AF, making it less likely that subclinical AF predominantly mediated the link between PTFV$_1$ and stroke. Two other studies, one of which was focused primarily on prediction of AF, have also demonstrated an association between PTFV$_1$ and stroke although these analyses did not adjust for AF when examining this association. Our present results provide further evidence that PTFV$_1$ is associated with brain infarcts in the absence of documented AF, and novel evidence that PTFV$_1$ is associated with leukoaraiosis.
Current ECG machines do not routinely report PTFV1, and its values show a moderate degree of measurement-to-measurement variation, 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, PTFV1 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. Because PTFV1 has long been established as a marker of increased left atrial pressure and hypertrophy, associations between PTFV1 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, possibly because of the cerebral hypoperfusion seen in AF. Our finding of an association between PTFV1 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. 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 PTFV1, echocardiographic measurements of left atrial size and function, and serum biomarkers, such as NT-pro-BNP, 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 Biotheremtry on the subject of cardiac monitoring for paroxysmal AF. The other authors report no conflicts.

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