Left Atrial Abnormality by Electrocardiogram and the Risk of Subsequent Cryptogenic or Cardioembolic Stroke: The Northern Manhattan Study

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Background

Atrial fibrillation (AF) is a common cause of stroke.

Evidence suggests that undiagnosed AF is a frequent cause of unexplained ischemic stroke.


Because AF may come and go, and need not be present at time of stroke, AF may be just one of many manifestations of an underlying “atrial cardiopathy” that is the underlying substrate for stroke risk.


Thus other markers of atrial cardiopathy, even in the absence of AF, may serve as risk factors, especially in patients with unexplained stroke:

Serum levels of Brain Natriuretic Peptide (NT-proBNP)
Left atrial size
Other atrial arrhythmias

P wave Terminal Force in EKG lead V1 reflects left atrial electrical and structural properties

Hypothesis

Increased P wave terminal force in lead V1 (PTV1) is associated with an increased risk of stroke, and particularly cardioembolic and cryptogenic stroke subtypes
Northern Manhattan Study: Prospective Cohort

- N= 3298
  - Stroke free at time of enrollment
- Baseline Assessment
  - Race-ethnicity self-defined
  - Fasting bloods
  - Medical history
  - Neuro Exam
  - ECG
- Subgroups
  - Ultrasound
  - TT echocardiogram
  - TE echocardiogram
  - Inflammatory markers

Annual Telephone and Hospital Surveillance
- Stroke
- MI
- Death
Study Design

Case-Cohort design
• Random subsample of 30% from original cohort (subcohort)
• Ischemic stroke during follow-up (cases)

Outcomes
• Primary: ischemic stroke
• Secondary: stroke subtypes determined by two neurologists using TOAST and adjudication by a third when needed

Main predictor, PTV1, was measured manually using digital calipers from baseline ECGs, pre-stroke
• Readers blinded to outcome
Methods: Statistical Analysis

• Inter and intra-rater reliability assessed for PTV1

• Weighted Cox proportional hazard regression models
  • Calculated Hazard Ratio (HR) and 95% confidence interval (95% CI) for the associations between PTV1 and risk of ischemic stroke
  • Adjusted for:
    • Demographics: age, sex, race-ethnicity, education
    • Risk factors: AF, congestive heart failure, hypertension, diabetes, cholesterol levels, smoking
Analytic Cohort

3298 NOMAS stroke free participants

2887 (87.5%) had baseline EKG

Random Sub-cohort (n=866)

789 AIS-free + 77 AIS + 195 AIS

Cases (272)

734 AIS-free + 64 AIS + 177 AIS

Poor quality EKG
Results: Reliability of the measures of PTV1

- 30 EKGs independently assessed by two investigators and intra-correlation coefficient for PTFV1 assessed
  - Excellent intra-rater reliability (ICC=0.87; 95% CI, 0.79-0.92)
  - Moderate inter-rater reliability (ICC=0.69; 95% CI, 0.45-0.80)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (N=241)</th>
<th>Sub cohort (N=798)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AIS</td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>70±8.5</td>
<td>70±9.1</td>
</tr>
<tr>
<td>Male, %</td>
<td>41.5</td>
<td>51.56</td>
</tr>
<tr>
<td>Race-Ethnicity, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>17.4</td>
<td>21.9</td>
</tr>
<tr>
<td>Black</td>
<td>27.4</td>
<td>12.5</td>
</tr>
<tr>
<td>Hispanic</td>
<td>53.1</td>
<td>65.6</td>
</tr>
<tr>
<td>Other</td>
<td>2.1</td>
<td>0</td>
</tr>
<tr>
<td>Education (≥HS), %</td>
<td>46.1</td>
<td>42.19</td>
</tr>
<tr>
<td>Current Smokers, %</td>
<td>17.4</td>
<td>15.6</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>37.3</td>
<td>32.8</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>83.0</td>
<td>78.1</td>
</tr>
<tr>
<td>Low-density lipoprotein, mean (SD), mg/dl</td>
<td>128±38</td>
<td>130±40</td>
</tr>
<tr>
<td>High-density lipoprotein, mean (SD), mg/dl</td>
<td>45±13</td>
<td>45±16</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>7.1</td>
<td>7.8</td>
</tr>
<tr>
<td>PTV1, mV*ms</td>
<td>4,452±3,368</td>
<td>4,053±2,826</td>
</tr>
</tbody>
</table>
### Associations between PTV1 and risk of Ischemic Stroke

Hazard ratios (95% CI) per standard deviation increase PTV1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadj</th>
<th>Adj for demographics(^1)</th>
<th>Fully adjusted(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ischemic stroke (N=241)</td>
<td>1.24 (1.07-1.42)</td>
<td>1.21 (1.04-1.39)</td>
<td>1.20 (1.03-1.39)</td>
</tr>
</tbody>
</table>

**Ischemic stroke subtypes**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Unadj</th>
<th>Adj for demographics(^1)</th>
<th>Fully adjusted(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptogenic or cardioembolic</td>
<td>1.31 (1.10-1.55)</td>
<td>1.28 (1.07-1.53)</td>
<td>1.31 (1.08-1.58)</td>
</tr>
<tr>
<td>Cryptogenic (n=50, 21%)</td>
<td>1.29 (0.99-1.68)</td>
<td>1.25 (0.95-1.65)</td>
<td>1.29 (0.96-1.72)</td>
</tr>
<tr>
<td>Cardioembolic (n=80, 33%)</td>
<td>1.32 (1.07-1.62)</td>
<td>1.30 (1.05-1.62)</td>
<td>1.23 (0.97-1.56)</td>
</tr>
<tr>
<td>Non-cardioembolic (n=109, 44%)</td>
<td>1.14 (0.94-1.40)</td>
<td>1.12 (0.92-1.37)</td>
<td>1.14 (0.92-1.40)</td>
</tr>
</tbody>
</table>

\(^1\)Adjusted for age, sex, race-ethnicity, and high school education.

\(^2\)Adjusted for above plus baseline smoking status, diabetes, hypertension, lipid levels, history of atrial fibrillation, and heart failure.
Results: Sensitivity Analyses

• Among patients without AF at baseline
  • Results unchanged
  • For cryptogenic/cardioembolic infarcts: adj HR 1.34, 95% CI 1.11-1.63

• Inclusion of LA size
  • LA size was available for only 60% of the cohort
  • For cryptogenic/cardioembolic infarcts: adj HR 1.20, 95% CI 0.93-1.56
  • Effect size essentially unchanged
Limitations

• Small number of cryptogenic and cardioembolic strokes
• Monitoring for AF not exhaustive
• Manual measurements
  • nearly identical hazard ratios as seen with computer-measured PTV1 in MESA

Kamel H Stroke 2014;45:2786-2788.
Conclusions

• Higher PTV1 is associated with increased stroke risk

• PTV1 is associated with increased risk of cardioembolic and cryptogenic stroke > non-cardioembolic stroke

• PTV1 may indicate an atrial cardiopathy independent of atrial fibrillation

• Further research is needed to determine whether measurement of PTV1 can be used to determine whether patients should be treated with anticoagulant agents for primary or secondary prevention of stroke
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