Atrial Cardiopathy and Cryptogenic Stroke

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Cryptogenic stroke: a useful target

- Best to prevent stroke from occurring at all
- Remaining targets for improving stroke prevention?
  - One-third of ischemic strokes are cryptogenic
  - Uncovering causes may provide novel targets for stroke prevention

Cryptogenic stroke = ESUS?

Personal View

Embolic strokes of undetermined source: the case for a new clinical construct

Robert G Hart, Hans-Christoph Dierer, Shelagh B Coutts, J Donald Easton, Christopher B Granger, Martin J O’Donnell, Ralph L Sacco, Stuart J Connolly, for the Cryptogenic Stroke/ESUS International Working Group

Cryptogenic (of unknown cause) ischaemic strokes are now thought to comprise about 25% of all ischaemic strokes. Advances in imaging techniques and improved understanding of stroke pathophysiology have prompted a reassessment of cryptogenic stroke. There is persuasive evidence that most cryptogenic strokes are thromboembolic. The thrombus is thought to originate from any of several well established potential embolic sources, including minor-risk or covert cardiac sources, veins via paradoxical embolism, and non-occlusive atherosclerotic plaques in the aortic arch, cervical, or cerebral arteries. Accordingly, we propose that embolic strokes of undetermined source are a therapeutically relevant entity, which are defined as a non-lacunar brain infarct without proximal arterial stenosis or cardioembolic sources, with a clear indication for anticoagulation. Because emboli consist mainly of thrombus, anticoagulants are likely to reduce recurrent brain ischaemia more effectively than are antiplatelet drugs. Randomised trials testing direct-acting oral anticoagulants for secondary prevention of embolic strokes of undetermined source are warranted.
Causes of cryptogenic stroke?

• What are potentially undiscovered sources of embolism?
Causes of cryptogenic stroke?

• What are potentially undiscovered sources of embolism?
• Unrecognized large-artery atherosclerosis?

Causes of cryptogenic stroke?

• What are potentially undiscovered sources of embolism?
• Unrecognized cardiac embolism?
Occult atrial fibrillation?

- AF can be paroxysmal and asymptomatic
- Difficult to detect
  - Average burden: 1.8 hours/day
  - Any AF: <10% of days

Ziegler et al, *Stroke*, 2010
Occult atrial fibrillation?

- Delayed detection of AF is common
- Delayed detection may increase risk of recurrence
- Ambulatory heart-rhythm monitoring after stroke is cost-effective to diagnose AF
- Apixaban and dabigatran are cost-effective for prevention of recurrent stroke in AF
- Randomized trial of heart-rhythm monitoring after stroke is feasible

Occult atrial fibrillation?

- Observational studies: heart-rhythm monitoring establishes new diagnosis of AF in 10% of stroke patients
- Corroborated by two recent randomized clinical trials

Occult atrial fibrillation?

Sanna et al, *NEJM*, 2014
Occult atrial fibrillation?

• 70% of cryptogenic stroke patients manifested no AF during 3 years of continuous heart-rhythm monitoring

• Subclinical AF does not explain most cryptogenic strokes

Kamel, *NEJM*, 2014
Other occult atrial disease?

• Could some cryptogenic strokes arise from the left atrium in the absence of AF?
Why is AF associated with stroke?

THE ARREST OF RECURRENT EMBOLISM DUE TO AURICULAR FIBRILLATION WITH MITRAL STENOSIS BY QUINIDINE-ANTICOAGULANT THERAPY*

By Howard Lackay, Lt. Col., M.C., U.S.A.F., and Edmund L. Houseal, M.D., Philadelphia, Pennsylvania

A serious and often fatal complication of auricular fibrillation, especially when associated with mitral stenosis, is the production of intraauricular thrombosis and embolism. When embolism is recurrent, the condition is likely to be fatal unless normal auricular contractions are restored and the source of emboli is thereby eliminated. Although restoration of normal rhythm by quinidine ther-
Why is AF associated with stroke?

- If dysrhythmia itself causes stroke, why is a single episode of 6 minutes of AF associated with stroke months later?

Poor temporal link b/w AF & stroke

• Stroke may occur even before first manifestation of AF
• 31% had no AF until after stroke

Other atrial derangements in AF

- AF is associated with many other atrial derangements besides dysrhythmia
  - Endothelial dysfunction
  - Fibrosis
  - Impaired myocyte function
  - Chamber dilatation
- Dysrhythmia = marker for these derangements?

Other atrial arrhythmias <> stroke

- Other atrial dysrhythmias are associated with stroke even in absence of AF:
  - Frequent PACs <> 2-fold higher risk of stroke

Other atrial arrhythmias <> stroke

**Figure.** Cumulative rates of ischemic stroke are shown according to whether or not patients had a preexisting diagnosis of paroxysmal supraventricular tachycardia (PSVT).

What about self-limited AF?

- Perioperative AF assumed to be self-limited
- Not seen as long-term risk factor for ischemic stroke
- No recommendations for long-term follow-up or management
- But link with long-term stroke is unknown

Epstein et al, *Chest*, 2005
What about self-limited AF?

• 1.7 million patients hospitalized for surgery across CA from 2007-2010
• Excluded those with AF before index hospitalization or stroke before or during index hospitalization
• Predictor variable: new-onset AF during index hospitalization
• Patients followed for up to 4 years for ischemic stroke
What about self-limited AF?
What about self-limited AF?

**Figure 2. Cumulative Rates of Ischemic Stroke After Hospitalization for Cardiac Surgery**

<table>
<thead>
<tr>
<th>Time Since Surgery, d</th>
<th>Perioperative AF</th>
<th>No perioperative AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>365</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>730</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>1095</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>1460</td>
<td>0.05</td>
<td>0.05</td>
</tr>
</tbody>
</table>

No. at risk
- Perioperative AF: 11837, 8424, 5445, 2970, 923
- No perioperative AF: 61706, 51491, 36677, 23475, 11480

Log-rank $P = .02$
What about self-limited AF?

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Cumulative Rate of Stroke 1 Year After Hospitalization, % (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Perioperative Atrial Fibrillation</td>
<td>No Perioperative Atrial Fibrillation</td>
</tr>
<tr>
<td>Noncardiac</td>
<td>1.47 (1.24-1.75)</td>
<td>0.36 (0.35-0.37)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0.99 (0.81-1.20)</td>
<td>0.83 (0.76-0.91)</td>
</tr>
</tbody>
</table>
What about self-limited AF?

• Self-limited perioperative AF signifies a long-term increase in stroke risk
• Clinical implications:
  – Patients should be followed for AF recurrence
  – Anticoagulation?
• Research implications:
  – Is it all about the dysrhythmia?

Gialdini et al, JAMA, 2014
What about even earlier markers?

- Left atrial abnormality on 12-lead ECG is a marker of fibrosis, elevated filling pressures, and dilatation

Hancock et al, *JACC*, 2009
MESA cohort

- 6,741 participants without vascular disease in the Multi-Ethnic Study of Atherosclerosis
- Baseline digital measurements of P-wave area, duration, and terminal force in lead V₁ (PTFV₁)
- Covariates: baseline confounders + incident AF
- Outcome: incident ischemic stroke
MESA cohort

• PTFV₁ associated with incident stroke
  – HR per SD, 1.21; 95% CI, 1.02-1.44
• No change when adjusting for incident AF

CHS cohort

- Association of P-wave morphology with vascular brain injury in the Cardiovascular Health Study
- Predictor: PTFV$_1$
- Covariates: baseline confounders + incident AF
- MRI outcomes:
  - Infarcts
  - White matter grade
CHS cohort

- 3,129 participants with MRI data
- $PTFV_1$ associated with prevalent infarcts
  - RR per SD, 1.09; 95% CI, 1.04-1.16 (any infarcts)
  - RR per SD, 1.22; 95% CI, 1.08-1.38 (non-lacunar)
- No change when adjusting for incident AF

Kamel et al, Stroke, 2015
ARIC cohort

• 14,542 participants without AF in the Atherosclerosis Risk in Communities study
• Predictor: left atrial abnormality (PTFV₁ >4000)
• Covariates: baseline confounders + incident AF
• Outcome: incident ischemic stroke subtypes
ARIC cohort

• 14,542 participants without AF in the Atherosclerosis Risk in Communities study
• Predictor: left atrial abnormality (PTFV₁ >4000)
• Covariates: baseline confounders + incident AF
• Outcome: incident ischemic stroke subtypes
  – Hypothesis: left atrial abnormality is more strongly associated with non-lacunar than lacunar stroke
ARIC cohort

• Associations of left atrial abnormality with stroke:
  – Any ischemic stroke: HR, 1.3 (95% CI, 1.1-1.6)
  – Lacunar stroke: HR, 0.9 (95% CI, 0.6-1.4)
  – Non-lacunar stroke: HR, 1.5 (95% CI, 1.1-2.1)
• No change when adjusting for incident AF

Kamel et al, Ann Neurol, 2015
FIGURE 4: Relationship between P-wave terminal force in electrocardiogram lead V1 (PTFV1) and the risk of incident ischemic stroke. The plot displays the results of a restricted cubic spline model (see text for details). The dotted horizontal lines represent the 95% confidence interval, and the dotted vertical line represents the threshold of 4,000 \( \mu V \times ms \) that was used to define left atrial abnormality.

Kamel et al, Ann Neurol, 2015
NOMAS cohort

- Case-cohort comparison of 241 patients with ischemic stroke versus a random subcohort without stroke (N = 798)
- Predictor: PTFV$_1$ (measured by hand)
- Covariates: baseline confounders + incident AF
- Outcome: incident ischemic stroke subtypes
NOMAS cohort

- Case-cohort comparison of 241 patients with ischemic stroke versus a random subcohort without stroke (N = 798)
- Predictor: PTFV₁ (measured by hand)
- Covariates: baseline confounders + incident AF
- Outcome: incident ischemic stroke subtypes
  - Hypothesis: left atrial abnormality is more strongly associated with cryptogenic or cardioembolic stroke subtypes
NOMAS cohort

- Associations of left atrial abnormality with ischemic stroke:
  - Any stroke: HR per SD, 1.20 (95% CI, 1.03-1.39)
  - Non-cardioembolic stroke: HR per SD, 1.14 (95% CI, 0.92-1.40)
  - Cryptogenic/cardioembolic stroke: HR per SD, 1.31 (95% CI, 1.08-1.58)
- No change when adjusting for incident AF

Limitations

- No direct imaging of left atrial size/morphology
- Potential for residual confounding
- Cannot fully rule out subclinical AF as mediator
Summary

• A commonly used ECG measure of left atrial abnormality (PTFV₁) is associated with vascular brain injury independently of AF.
What does PTFV₁ represent?

<table>
<thead>
<tr>
<th>Index</th>
<th>Per 1 mV*ms of PTFV₁</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum LA volume index (mL/m²)</td>
<td>-1.6 (-2.8 to -0.4)</td>
<td>.010</td>
</tr>
<tr>
<td>Minimum LA volume index (mL/m²)</td>
<td>-1.2 (-1.9 to -0.4)</td>
<td>.003</td>
</tr>
<tr>
<td>Global LAEF (%)</td>
<td>+1.1 (+0.1 to +2.1)</td>
<td>.026</td>
</tr>
<tr>
<td>LA reservoir function (%)</td>
<td>+7.2 (+1.1 to +13.3)</td>
<td>.021</td>
</tr>
</tbody>
</table>

Tiffany Win et al, *Heart Rhythm*, 2015
Evidence from other groups?

- Left atrial size/function and NT-proBNP have been associated with stroke and MRI-defined vascular brain injury independently of AF

Updated hypothesis

• Atrial cardiopathy can cause thromboembolism even in the absence of AF
  – Dysrhythmia that defines AF is a common manifestation of atrial cardiopathy but is not necessary to cause thromboembolism
Atrial Fibrillation and Mechanisms of Stroke
Time for a New Model

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What about other embolic sources?

• Underlying sources of embolism are likely heterogeneous
• Besides atrial cardiopathy, another common cause is likely nonstenosing large-artery atherosclerosis
LETTER TO THE EDITOR

Association Between Nonstenosing Carotid Artery Plaque on MR Angiography and Acute Ischemic Stroke

**TABLE 1** Carotid Artery Characteristics Ipsilateral and Contralateral to This Side of Cerebral Infarction

<table>
<thead>
<tr>
<th></th>
<th>ICA Ipsilateral to Stroke</th>
<th>ICA Contralateral to Stroke</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (N = 109)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of IHIS</td>
<td>22/109</td>
<td>9/109</td>
<td>0.0124</td>
</tr>
<tr>
<td>Median carotid stenosis</td>
<td>0 (0 to 47.5; 0)</td>
<td>0 (0 to 49; 0)</td>
<td>0.6694</td>
</tr>
<tr>
<td>TOAST stroke subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptogenic (n = 50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of IHIS</td>
<td>11/50</td>
<td>0/50</td>
<td>0.0009</td>
</tr>
<tr>
<td>Median carotid stenosis</td>
<td>0 (0 to 47.5; 15.6)</td>
<td>0 (0 to 49; 5.6)</td>
<td>0.4896</td>
</tr>
<tr>
<td>Cardioembolic (n = 37)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of IHIS</td>
<td>7/37</td>
<td>6/37</td>
<td>0.7630</td>
</tr>
<tr>
<td>Median carotid stenosis</td>
<td>0 (0 to 41; 0)</td>
<td>0 (0 to 34.8; 0)</td>
<td>0.4360</td>
</tr>
<tr>
<td>Small vessel occlusion (n = 22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of IHIS</td>
<td>4/22</td>
<td>3/22</td>
<td>0.6547</td>
</tr>
<tr>
<td>Median carotid stenosis</td>
<td>0 (0 to 17.4; 0)</td>
<td>0 (0 to 39.1; 0)</td>
<td>0.1250</td>
</tr>
</tbody>
</table>

Values are n/N or % (range; IQR). *p value by McNemar’s test for correlated proportions or Wilcoxon signed rank sum test, as appropriate. Carotid stenosis calculated using standard North American Symptomatic Carotid Endarterectomy Trial criteria.

ICA = internal carotid artery; IHIS = intraplaque high intensity signal; IQR = interquartile range; TOAST = Trial of Org 10172 in Acute Stroke Treatment.
Therapeutic implications

• Heterogeneous mechanisms require personalized treatment
  – Given parallels to AF, atrial cardiopathy may benefit from anticoagulation
  – Less evidence for benefit of anticoagulation in large-vessel disease
Amino Terminal Pro–B-Type Natriuretic Peptide, Secondary Stroke Prevention, and Choice of Antithrombotic Therapy


Stroke. 2013;44:714-719; originally published online January 22, 2013; doi: 10.1161/STROKEAHA.112.675942

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Next steps

- Left atrial abnormality and racial differences in stroke risk (LANTERN)
- Proposed trial of anticoagulant versus antiplatelet therapy in patients with cryptogenic stroke and atrial cardiopathy (ARCADIA)
- Relationship between atrial cardiopathy and nonstenosing atherosclerotic plaque
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