Antiphospholipid-Associated Hypercoagulability & Subclinical White Matter Lesions in PFO-Related Stroke

MingMing Ning
Department of Neurology
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts
Presenter Disclosure Information

FINANCIAL DISCLOSURE:
None

UNLABELED/UNAPPROVED USES DISCLOSURE:
None

THESE STUDIES ARE SUPPORTED BY:

NIH/NINDS -- NS051588
NIH/NINDS -- NS052498
Many Thanks To

CardioNeurology Clinic
Igor Palacios
Zareh Demirjian
Ignacio Inglessis
Scott Silverman
DW Dec
Robert Schainfeld
Dabit Arzamendi

Neuroprotection Research Lab
Deepti Navaratna
Xiaoying Wang
Shu -Zhen Janet Guo
Ken Arai

Collaborator/supporters
Anne B Young
Mary Lopez
David Sarracino
Carlos Kase
Pei Chen Ning
Su -Yu Hsu
David McMullin

Clinical Proteomics Research Center
Meng Ran
Kathleen Feeney
Andrea Marckmann
Molly Thayer
Jing Cao
Sherry Chou
Dayse Sena
Diana Walleigh
Mikaela Elia

NIH/NINDS - “CPR” on the Brain
Clinical Proteomic Research on the Brain
ClinicalTrials.gov ID NCT00682331

Our patients and their families
Our clinical and research nursing staff

www.massgeneral.org/neurology/pfo
Antiphospholipid-Associated Hypercoagulability & Subclinical White Matter Lesions in PFO-Related Stroke

**Ferdinando S Buonanno, Ran Meng, Molly Thayer, Kathleen Feeney, Jing Cao, Eng H Lo, MingMing Ning**

I. Brain->Heart Interaction
   - How do the heart and brain injure each other?
   - Neurogenic cardiac injury vs cardiogenic neurovascular injury

II. PFO & Stroke
   - How does PFO physiology participate in underlying mechanisms of clotting and PFO-related strokes?

III. APLAb & Subclinical Infarcts
   - Why study antiphospholipid antibody and subclinical infarcts?
   - Methods
   - Results

IV. Summary
   - Summary & future directions
Brain’s Influence on the Heart

- Cannon (1942) - “voodoo death” – “stress and sudden death after being cursed”
- Engel (1971) - “Death from fright” – grief, happiness, surprise, etc
- Arrhythmia and “cerebral T” improves upon brain death (Stroke 1977)
- Samuels - “neurovisceral damage” (Circulation 2007)
- Wittstein – Neurohumoral features of cardiac stress myopathy - catecholamines, neuronal metabolites and peptides (distinctions differ from cardiogenic MI). (NEJM 2005)

### Table 1. Clinical Characteristics of 16 Patients with Stress Cardiomyopathy on Admission.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Sex</th>
<th>Race or Ethnic-Origin</th>
<th>Coronary Risk Factors</th>
<th>Emotional Stressor</th>
<th>Time after Symptom Onset</th>
<th>Heart Rate (bpm)</th>
<th>MAP (mm Hg)</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>F</td>
<td>B</td>
<td>HTN, smoking</td>
<td>Mother’s death</td>
<td>12</td>
<td>71</td>
<td>96</td>
<td>Chest pain</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>F</td>
<td>AA</td>
<td>HTN, Chol</td>
<td>Car accident</td>
<td>1</td>
<td>84</td>
<td>52</td>
<td>Heart failure, hypotension</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>F</td>
<td>W</td>
<td>HTN, Chol, smoking</td>
<td>Surprise reaction</td>
<td>4</td>
<td>85</td>
<td>88</td>
<td>Chest pain</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>F</td>
<td>W</td>
<td>HTN</td>
<td>Surprise party</td>
<td>2</td>
<td>109</td>
<td>53</td>
<td>Chest pain, hypotension (IABP)</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>F</td>
<td>W</td>
<td>HTN, FH</td>
<td>Father’s death</td>
<td>5</td>
<td>65</td>
<td>94</td>
<td>Chest pain</td>
</tr>
<tr>
<td>6</td>
<td>77</td>
<td>F</td>
<td>W</td>
<td>HTN, FH</td>
<td>Husband’s death</td>
<td>6</td>
<td>106</td>
<td>98</td>
<td>Chest pain</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>F</td>
<td>W</td>
<td>Smoking</td>
<td>Friend’s death</td>
<td>2</td>
<td>97</td>
<td>50</td>
<td>Chest pain, hypotension (IABP)</td>
</tr>
<tr>
<td>8</td>
<td>52</td>
<td>F</td>
<td>W</td>
<td>HTN</td>
<td>Father’s death</td>
<td>5</td>
<td>84</td>
<td>93</td>
<td>Chest pain</td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>F</td>
<td>W</td>
<td>Chol, FH</td>
<td>Mother’s death</td>
<td>1</td>
<td>74</td>
<td>90</td>
<td>Chest pain</td>
</tr>
<tr>
<td>10</td>
<td>61</td>
<td>F</td>
<td>W</td>
<td>Chol</td>
<td>Fear of procedure</td>
<td>1</td>
<td>108</td>
<td>45</td>
<td>Chest pain, shock (IABP)</td>
</tr>
<tr>
<td>11</td>
<td>66</td>
<td>F</td>
<td>W</td>
<td>Smoking</td>
<td>Fierce argument</td>
<td>2</td>
<td>66</td>
<td>109</td>
<td>Chest pain</td>
</tr>
<tr>
<td>12</td>
<td>87</td>
<td>F</td>
<td>W</td>
<td>HTN, Chol, DM</td>
<td>Friend’s death</td>
<td>1</td>
<td>99</td>
<td>75</td>
<td>Chest pain</td>
</tr>
<tr>
<td>13</td>
<td>69</td>
<td>M</td>
<td>W</td>
<td>HTN</td>
<td>Court appearance</td>
<td>2</td>
<td>81</td>
<td>73</td>
<td>Chest pain</td>
</tr>
<tr>
<td>14</td>
<td>50</td>
<td>F</td>
<td>W</td>
<td>None</td>
<td>Fear of twisting</td>
<td>2</td>
<td>84</td>
<td>100</td>
<td>Heart failure</td>
</tr>
<tr>
<td>15</td>
<td>71</td>
<td>F</td>
<td>W</td>
<td>None</td>
<td>Public speaking</td>
<td>1</td>
<td>67</td>
<td>108</td>
<td>Chest pain</td>
</tr>
<tr>
<td>16</td>
<td>76</td>
<td>W</td>
<td>HTN, DM, smoking</td>
<td>Heart attack</td>
<td>2</td>
<td>109</td>
<td>104</td>
<td>Chest pain</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>65</td>
<td>F</td>
<td>W</td>
<td>HTN, Chol, DM, smoking</td>
<td>Armed robbery</td>
<td>2</td>
<td>95</td>
<td>91</td>
<td>Chest pain</td>
</tr>
<tr>
<td>18</td>
<td>71</td>
<td>F</td>
<td>W</td>
<td>HTN</td>
<td>Son’s death</td>
<td>6</td>
<td>70</td>
<td>64</td>
<td>Chest pain, VF</td>
</tr>
<tr>
<td>19</td>
<td>77</td>
<td>F</td>
<td>A</td>
<td>None</td>
<td>Tragic news</td>
<td>3</td>
<td>64</td>
<td>52</td>
<td>Chest pain, hypotension</td>
</tr>
</tbody>
</table>

### Table 2. Plasma Catecholamine and Neuropeptide Levels.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with Stress Cardiomyopathy (N=13)</th>
<th>Patients with Killip Class III Myocardial Infarction (N=7)</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catecholamine precursors (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>2859 (271-2997)</td>
<td>1566 (1005-2011)</td>
<td>907 (749-937)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>2516 (284-2635)</td>
<td>1282 (1124-1606)</td>
<td>1510 (1127-1747)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>1264 (916-1374)</td>
<td>1044 (733-1188)</td>
<td>348 (180-550)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>2284 (1709-2910)</td>
<td>1573 (1235-2589)</td>
<td>1142 (525-1252)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>111 (106-1464)</td>
<td>77 (63-110)</td>
<td>61 (47-77)</td>
</tr>
<tr>
<td>Metanephrine</td>
<td>178 (140-187)</td>
<td>1625 (1412-1702)</td>
<td>1583 (1497-1648)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>2706 (2532-3111)</td>
<td>2689 (2246-2842)</td>
<td>2161 (2095-2416)</td>
</tr>
<tr>
<td>5-Hydroxyindolacetic acid</td>
<td>2758 (2573-3077)</td>
<td>2598 (2359-2854)</td>
<td>1341 (1184-1682)</td>
</tr>
<tr>
<td>5-Hydroxyindolacetic acid</td>
<td>1513 (1218-1872)</td>
<td>1289 (1134-1468)</td>
<td>1259 (1181-1446)</td>
</tr>
<tr>
<td>5-Hydroxyindolacetic acid</td>
<td>2051 (1835-2273)</td>
<td>2206 (1964-2483)</td>
<td>201 (263-274)</td>
</tr>
<tr>
<td>5-Hydroxyindolacetic acid</td>
<td>3051 (205-383)</td>
<td>2340 (212-264)</td>
<td>308 (212-264)</td>
</tr>
</tbody>
</table>

* MAP denotes mean arterial pressure, B = Black, HTN = Hypertension, AA = African American, Chol = Hypercholesterolemia, W = White, IABP = Intracoronary balloon pump, FH = Family history, DM = Diabetes mellitus, VF = Ventricular fibrillation, and AF = Atrial fibrillation.

Values are from the onset of symptoms to presentation at the emergency department.

Heart’s Influence on the Brain

- Up to 30% of clots come from the heart (emboli from cardiac arrhythmia etc)

- Up to an additional 10-20% come from the venous circulation if there is a cardiac structural abnormality allowing them to travel to the brain.

- In all, up to 50% of ischemic strokes may involve the heart.
PFO as a dynamic structure

- First described in 1877 in a young woman with stroke.

- “Back door to the brain” A remnant of maternal-fetal circulation, PFO allows persistent direct communication between right and left atria, bypassing the lung’s filtration, enabling peripheral clots to go to the brain. One-way valve.

- High baseline prevalence of incidental PFO: 25-30% in all normal adults.

- Associated with nearly 40% of all cryptogenic strokes. Accounting for more than 150,000 strokes/year in the United States.

FIGURE 1. Anatomy of Normal, Patent Foramen Ovale (PFO), PFO with ASA, and Atrial Septal Defect (ASD)

Diagram courtesy of Dr PC Ning
PFO-related stroke is a heterogeneous disease with many clinical risk factors.

**Acquired:**
- Long-distance travel
- Valsalva maneuver
- DVT’s
- Immobilization

**Congenital:**
- Hypercoagulable state
- May-Thurner’s Anatomy
- Cardiac Congenital Structural Abnormality
  - Atrial Septal Aneurysm
  - Chiari’s network
  - Eustachian valve

**Additional Information:**
- May-Thurner’s Anatomy disposed to pelvic clots
- Cardiac Eustachian valve helps shunt blood across
- Chiari’s network promotes clot formation

References:
Where do the clots come from?

- The frequency of clots in venous circulation, and the prevalence of known prothrombotic conditions in PFO stroke patients is 5-17%.

- Some studies found no difference between known hypercoagulable states in PFO vs non-PFO stroke.

- While it is very tempting to hypothesize that paradoxical embolic events may trigger subclinical infarcts in the setting of a prothrombotic state (eg. APLab), the associations are unclear.

### Known Clotting factor mutations in PFO Patients (2-17%)

<table>
<thead>
<tr>
<th>Risk factor and study</th>
<th>Risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pezzini et al.</td>
<td>11% vs 2% (Factor V Leiden)</td>
<td>NS</td>
</tr>
<tr>
<td>Pezzini et al.</td>
<td>OR 10.09 (Prothrombin G20210A)</td>
<td>0.04</td>
</tr>
<tr>
<td>Lichy et al.</td>
<td>OR 3.66 (Prtothrombin G20210A)</td>
<td>0.01</td>
</tr>
<tr>
<td>Florez et al</td>
<td>17.3% (combined)</td>
<td>NS</td>
</tr>
<tr>
<td>Karttunen et al.</td>
<td>OR 13.99</td>
<td>0.022</td>
</tr>
</tbody>
</table>
Why Antiphospholipid Antibody (APLAb) and WMD?

- Antiphospholipid antibody titer positivity is very common, especially in women.
- Unclear significance because this is not full Antiphospholipid Syndrome [Definition of APLS—12 weeks apart at least twice normal]
- However, increased aCL titer in normal older individuals are associated with subtle neuropsychological dysfunction on cognitive testing [Schmidt R et al. Stroke 1995]
- PFO-related stroke has been reported to have higher frequency “non-specific” subclinical white matter lesions on MRI and is associated with vascular dementia. [Purandare et al. BJR 2008]
- So is there an association between APLab and WMD in patients with PFO?
- Can a mild prothrombotic condition cause subclinical white matter lesions?

→ We examined antiphospholipid antibody status, with respect to white matter lesions (WMLs) in PFO-related stroke to better understand this relationship.
Method

- N = 78 consecutive prospectively recruited non-migrainous PFO-related stroke patients.

- Anticardiolipin antibody IgG, IgM and lupus anticoagulant measurement.

- Subclinical (or clinically “silent”) white matter lesions (WMLs) were inspected by investigators blind to clinical information using two validated scales (Fazekas and Scheltens) to insure inter-rater reliability and accuracy.

- MRIs were read by two vascular neurologists blinded to clinical data from FLAIR sequence MRI.
Fazekas scale

“A modification of suggested rating scales … was used to describe the different types of hyperintense signal abnormalities surrounding the ventricles and in the deep white matter.

Periventricular hyperintensity (PVH) was graded as
0 = absence,
1 = “caps” or pencil-thin lining,
2 = smooth “halo,”
3 = irregular PVH extending into the deep white matter.

Separate deep white matter hyperintense signals (DWMH) were rated as
0 = absence,
1 = punctate foci,
2 = beginning confluence of foci,
3 = large confluent areas.”

Results

- Similar age (mean = 53 vs 48) and all risk factors
- More women in APSAb group
- More smokers in APSAb group

<table>
<thead>
<tr>
<th>Table 1 Data of patients (ACA-positive versus ACA-negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Items</td>
</tr>
<tr>
<td>Age (year)</td>
</tr>
<tr>
<td>Gender (M / F)</td>
</tr>
<tr>
<td>DM% (n)</td>
</tr>
<tr>
<td>HGBA1C % (n)</td>
</tr>
<tr>
<td>High-fasting Glu % (n)</td>
</tr>
<tr>
<td>Smoking % (n)</td>
</tr>
<tr>
<td>Hypertension % (n)</td>
</tr>
<tr>
<td>Hyperlipidemia % (n)</td>
</tr>
<tr>
<td>Arterial stenosis% (n)</td>
</tr>
<tr>
<td>Alcohol use% (n)</td>
</tr>
<tr>
<td>New postpartum% (n)</td>
</tr>
<tr>
<td>SLE% (n)</td>
</tr>
<tr>
<td>Recurrent miscarriage</td>
</tr>
<tr>
<td>DVT</td>
</tr>
<tr>
<td>WML (scores)</td>
</tr>
<tr>
<td>GWF</td>
</tr>
<tr>
<td>GWS</td>
</tr>
<tr>
<td>DWF</td>
</tr>
<tr>
<td>DWS</td>
</tr>
<tr>
<td>PWF</td>
</tr>
<tr>
<td>PWS</td>
</tr>
</tbody>
</table>

Note: WML represents white matter lesions, GWF and GWS represent the global WML and was evaluated with Fazekas and Scheltens scales respectively, DWF and DWS represent WML distributed in deep white matter and evaluated with the Fazekas and Scheltens scales, PWF and PWS represent WML distributed in periventricular and evaluated with Fazekas and Scheltens scales respectively. DM represents diabetes. SLE represents systemic lupus erythematosus. DVT represents deep venous thrombosis.
Results

- Positive anticardiolipin antibody
  - mean IgG = 27 GPL (range 21.4-38.6; normal range 0-15)
  - mean IgM was 32.7 MPL (range 22.2-36.6; normal range 0-15)
  - none had lupus anticoagulant.

- Overall, global WML burden is statistically significantly increased in PFO stroke patients with positive anticardiolipin antibody compared to those with negative titers.
  - Fazekas scale - 2.333 vs 1.35, p < 0.0001
  - Scheltens scale - 2.5 vs 1.54, p < 0.0001

- Remains statistically significant after adjusting for major confounders associated with WML (diabetes, hypertension, and smoking status, p<0.01)
Comparison of MRI and MRA of age and risk-factor matched patients
APLAb positive patients develop “silent” infarcts over time
Summary

- PFO-related stroke patients with antiphospholipid antibody positivity have greater global WMLs burden than those without APLAb.

- A positive antiphospholipid antibody at one time point (NOT satisfying the definition or severity of antiphospholipid syndrome) is independently associated with global burden of WMLs in PFO-related stroke.

- WMLs found on MRI FLAIR may be “footprints” of subclinical embolic events, which can potentially be used as a non-invasive markers to follow disease progression and triage more aggressive stroke prevention strategy in this cohort.

- Further studies with a larger disease cohort and other hypercoagulable states are needed to validate these preliminary findings.

- Neuropsychiatric testing are ongoing to correlated to clinical symptomology.