Impact of Hemodynamics on Stroke Risk in Symptomatic Vertebrobasilar Disease: Results of the VERiTAS Study

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for the VERiTAS Study Group

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Background

Posterior circulation stroke
  • ~30% of all ischemic stroke
  • Eloquent territory:
    20-50% suffer major disability/mortality
Frequency of stroke mechanisms in the New England Medical Center Posterior Circulation Registry

**Embolism**
- Cardiac/aortic 24%
- Intraarterial 14%
- Cardiac & intraarterial 2%

**Large artery disease**
- 32%

**Penetrating artery disease**
- 14%

**Migraine**
- 3%

**Dissection/other**
- 10%

*Stenosis or occlusion where hypoperfusion determined to be primary etiology, rather than distal embolism*

(Caplan et al, Ann Neurol, 2004)
Symptomatic VBD: high recurrent stroke risk (especially intracranial disease) 10-15% per year

Current treatment risks (PTA/stent): up to 26% procedural risk for posterior circulation

Interventions will need to focus on highest risk patient

DOES FLOW MATTER?
Evaluation of posterior circulation hemodynamics

Standard perfusion imaging modalities are limited:
- regional imaging resolution inadequate for compact brainstem territory
- skull base artifacts

An alternative strategy is direct measurement of large vessel flow
- Measure flow in vessel of interest
- Measure flow in vessels within the distal territory
NOVA technique for QMRA
- Axial 3-D TOF MRA with 3-D surface rendering of cerebral vasculature
NOVA technique for QMRA

- Double oblique cine phase contrast MR to measure volumetric flow rate (ml/min)
QMRA flow measurement:
flows considered reduced if >20% lower than baseline flows in normal volunteers

- BA flow normal (>120cc/min)
  - yes
  - PCA flows normal (>40cc/min)
    - Criteria absent
    - NORMAL FLOW
  - no
    - Measure PCA flow*
      - PCA flows normal (>40cc/min)
      - Low flow - one PCA (<40cc/min)
        - Criteria absent
        - BORDERLINE FLOW
          - Consider additional criteria¶
      - Low flow – both PCAs (<40cc/min)
        - Criteria present
        - LOW FLOW

* Flow only considered if non-fetal PCA; if both PCAs fetal, only flow in BA considered (low flow if <40cc/min);
¶ Additional criteria: ominous BA waveform oscillating around zero; ominous symptom complex; flow in non-occluded BA <40cc/min.
Stroke Free Survival

- Retrospective study of 50 pts with VBD (≥50% stenosis) stratified as “normal flow” or “low flow” based on QMRA flows.

- Normal flow: 100% at 2 years (n=31)
- Low flow with intervention: 82% at 2 years (n=12)
- Low flow: 71% at 2 years (n=16)

*p=Amin-Hanjani et al, Stroke, 2005*
Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke

VERiTAS study*

Start Date: July 2008
NIH funded: supported by NINDS grant RO1 NS059745

Design: Prospective blinded observational study

Subjects: Patients with recently symptomatic intracranial or extracranial vertebrobasilar disease: ≥ 50% up to occlusion

Hypothesis: Patients with flow compromise based on QMRA will have a higher risk of recurrent stroke than those with normal flow

Inclusion:

- Stroke or TIA in vertebrobasilar territory*
- Angiographic (CTA or conventional angiography) demonstration of ≥50% stenosis or occlusion of extracranial or intracranial vertebral or basilar artery
- Symptoms within 60 days of enrollment
- Age 18 and above

*Within the territory of the qualifying vertebrobasilar disease
Study Protocol

Exclusion:

• Major disabling stroke
• Conditions with high cardioembolic risk (e.g. afib)
• Blood dyscrasias (e.g. sickle cell)
• Nonatherosclerotic disease (e.g. dissection, vasculitis)
• Unable to undergo MRI or angiography
• Renal dysfunction precluding CTA/ conventional angiography
• Unilateral vertebral stenosis or occlusion*

* protocol change (09/2010)
Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke

Study protocol
- QMRA/MR perfusion imaging
- Blinded to study investigators/patients

Clinical Follow-up
- Minimum 12 months, up to 24 months
Endpoints

- **Primary endpoint (centrally adjudicated):** Ischemic stroke in the vertebrobasilar territory within 12 months

  *Definition:* new neurological symptoms or signs with new infarct on CT or MR in a region of brain supplied by the vertebrobasilar system, or (in absence of brain imaging) new neurological symptoms or signs lasting 24 hours, localizing to an area of the brain supplied by the vertebrobasilar arterial system
Final Cohort (n=72*):

- **Age**: 65.7 yrs (range 40-90)
- **Gender**: 32 (44%) female; 40 (56%) male
- **Race**: 18 (25%) Black
  49 (68%) Caucasian
  5 (7%) Other
- **Ethnicity**: 64 (89%) non-Hispanic
  8 (11%) Hispanic
- **Distal Flow Status**: 18 (25%) Low
  54 (75%) Normal

*Cohort following exclusion of unilateral vertebral occlusion (n=8), VB junction fenestration (n=1), and resolved basilar occlusion (n=1)*
### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Low flow</th>
<th>Normal flow</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>68</td>
<td>65</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Gender - Female</strong></td>
<td>8 (44%)</td>
<td>24 (44%)</td>
<td>1.00</td>
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<td><strong>Race - Black</strong></td>
<td>4 (22%)</td>
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<td></td>
<td>12 (67%)</td>
<td>40 (74%)</td>
<td>0.54</td>
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<tr>
<td><strong>Prior Posterior Circulation Event (%)</strong></td>
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<td>11 (61%)</td>
<td>31 (57%)</td>
<td>0.78</td>
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<td>27 (50%)</td>
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<tr>
<td><strong>Time to enrollment (≤21 days – median)</strong></td>
<td>11 (61%)</td>
<td>27 (50%)</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Vascular Risk Factors</strong></td>
<td></td>
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<tr>
<td><strong>Hypertension</strong></td>
<td>17 (94%)</td>
<td>51 (93%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus</strong></td>
<td>6 (33%)</td>
<td>17 (31%)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong></td>
<td>13 (72%)</td>
<td>45 (83%)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Coronary artery disease</strong></td>
<td>5 (28%)</td>
<td>11 (20%)</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Chronic renal insufficiency/failure</strong></td>
<td>0 (0%)</td>
<td>2 (4%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Smoking - Current</strong></td>
<td>4 (22%)</td>
<td>20 (37%)</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Alcohol - None</strong></td>
<td>11 (61%)</td>
<td>33 (61%)</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>BMI: ≥30</strong></td>
<td>8 (44%)</td>
<td>18 (33%)</td>
<td>0.40</td>
</tr>
</tbody>
</table>
Baseline disease

Disease Severity (Worst Disease)

Occlusion
Severe (70-99%)
Moderate (50-69%)

$p=0.08$
Baseline disease

Disease Location

- Intracranial
- Extracranial
- Both

$p=0.39$
Standard medical management by treating physicians (guidelines provided in protocol, but no central risk factor management)

Follow-up laboratory data collected when available

‘On target’ for medical management defined as:
- On antithrombotic therapy
- BP ≤ 140/90 (≤130/80 for diabetics)
- On statin or other anti-hyperlipidemic therapy
- HbA1c ≤ 7%
- LDL ≤ 100 mg/dL
## Medical Management

<table>
<thead>
<tr>
<th>‘On target’*</th>
<th>6m</th>
<th>12m</th>
<th>18m</th>
<th>24m</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antithrombotics</strong></td>
<td></td>
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</tr>
<tr>
<td>Low flow</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>0.92</td>
</tr>
<tr>
<td>Normal Flow</td>
<td>100%</td>
<td>98%</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low flow</td>
<td>50%</td>
<td>31%</td>
<td>55%</td>
<td>33%</td>
<td>0.82</td>
</tr>
<tr>
<td>Normal Flow</td>
<td>35%</td>
<td>40%</td>
<td>49%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td><strong>Statin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low flow</td>
<td>88%</td>
<td>94%</td>
<td>91%</td>
<td>89%</td>
<td>0.88</td>
</tr>
<tr>
<td>Normal Flow</td>
<td>92%</td>
<td>89%</td>
<td>92%</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td><strong>HbA1c</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Low flow</td>
<td>50%</td>
<td>50%</td>
<td>60%</td>
<td>100%</td>
<td>0.71</td>
</tr>
<tr>
<td>Normal Flow</td>
<td>80%</td>
<td>67%</td>
<td>43%</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td><strong>LDL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low flow</td>
<td>75%</td>
<td>83%</td>
<td>100%</td>
<td>100%</td>
<td>0.99</td>
</tr>
<tr>
<td>Normal Flow</td>
<td>74%</td>
<td>65%</td>
<td>50%</td>
<td>87%</td>
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</table>

*Based on available data at each time point*
Final Cohort (n=72):

- Median follow-up 23 months
- 10 primary events – ischemic stroke in the vertebrobasilar territory
Stroke Free Survival

Product-Limit Survival Estimates

- 96% at 12m
- 87% at 24m
- 78% at 12m
- 70% at 24m

$p=0.039$
Multivariate analysis

- Backward stepwise elimination strategy
  - Age, Sex, Race
  - DM, HL, HTN, CAD, CRI
  - Smoking, BMI, Alcohol
  - Qualifying event, time lag to enrollment, prior stroke/TIA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (≤65)</td>
<td>0.006</td>
<td>21.8</td>
<td>2.4 196.3</td>
</tr>
<tr>
<td>Flow status (low)</td>
<td><strong>0.002</strong></td>
<td>9.4</td>
<td>2.4 37.6</td>
</tr>
<tr>
<td>CAD</td>
<td>0.02</td>
<td>4.8</td>
<td>1.2 18.7</td>
</tr>
<tr>
<td>DM</td>
<td>0.04</td>
<td>4.4</td>
<td>1.1 17.8</td>
</tr>
</tbody>
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Disease location/severity

- Location (basilar vs nonbasilar) and severity (<70% vs ≥ 70%) not predictive on univariate analysis
- Multivariate model

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<tr>
<td>Flow status (low)</td>
<td>0.04</td>
<td>3.8</td>
<td>1.06 102.7</td>
</tr>
<tr>
<td>Basilar involved</td>
<td>0.32</td>
<td>0.49</td>
<td>0.12 1.99</td>
</tr>
<tr>
<td>≥70% stenosis</td>
<td>0.92</td>
<td>1.07</td>
<td>0.27 4.22</td>
</tr>
</tbody>
</table>
For patients with symptomatic vertebrobasilar atherosclerotic disease:

- Distal flow status is a robust independent predictor of subsequent stroke
- Non-invasive flow measurements with QMRA are an easily applicable method for risk stratification

Implications for investigation of future interventional or aggressive medical therapies.
VERiTAS Study Group

**Clinical Coordinating Center**
- University of Illinois at Chicago
  - PI: Sepideh Amin-Hanjani, MD
  - Project Manager: Linda Rose-Finnell, MPA CCRA

**Data Management Center**
- Center for Stroke Research, University of Illinois at Chicago
  - Director: DeJuran Richardson, PhD, Dilip Pandey, MD PhD
  - Biostatisticians: Xinjian Du, MD, Hui Xie, PhD
  - Database Administrator: Xinjian Du, MD

**Committees and Panels**

**Operations Committee**
- Sepideh Amin-Hanjani, MD, FACS (Chair)
- Fady T. Charbel, MD, FACS
- Dilip K. Pandey, MD, PhD
- DeJuran Richardson, PhD
- Keith R. Thulborn, MD, PhD

**Advisory Committee**
- Colin P. Derdeyn, MD (Chair)
- Louis R. Caplan, MD
- Philip B. Gorelick, MD, MPH, FACP

**Adjudication Committee**
- Scott E. Kasner, MD (Chair)
- Brett Kissela, MD
- Tanya N. Turan, MD

**Angiography Committee**
- Victor Aletich, MD

NIH/NINDS Program Officer: Tom P. Jacobs, MD/ Scott Janis PhD

**Participating sites** (in descending order of number of enrollees)

**University of Illinois at Chicago**
- Site PI: Sepideh Amin-Hanjani, MD
- Project Manager: Linda Rose-Finnell, MPA CCRA
- Site MR Team: Keith Thulborn, MD, PhD, Michael P. Flannery, Hagai Ganin
- Study Physician(s): Sean Ruland, DO, Rebecca Gryszewicz, DO, Aslam Khaja, MD, Laura Pedelty, MD, Fernando Testai, MD, Archie Ong, MD, Noam Epstein, MD, Humina Muqtadar, MD
- Coordinator(s): Karriem Watson, MD, Nada Minarevich, RN, Maureen Hillmann, RN

**Columbia University, New York:**
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- Site MR Team: Joy Hirsch, PhD, Stephen Dashnaw
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- Site MR Team: Katie Vo, MD, Glenn Foster
- Study Physician(s): Andria Ford, MD, Abdullah Nassief, MD
- Coordinator(s): Abbie Bradley, RN, BSN, Jannie Serna-Northway, RN, BSN, Kristi Kraus, RN, Lina Shiwani, BS, Nancy Hantler, BS, CCRC

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- Site MR Team: Jeffrey Alger, PhD, Sergio Godinez
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- Coordinator: Jignesh Gadhia, BS, Hannah Smith, BS, Gilda Avila, BS, Johanna Avelar, BA

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- Site PI: Frank L. Silver, MD
- Site MR Team: David Mikulis, MD, Jorn Fierstra, Eugen Hlasny
- Study Physician(s): Leanne K. Casaubon, MD, Mervyn Vergouwen, MD, J.C. Martin del Campo, MD, Cheryl S. Jaigobin, MD
- Coordinator(s): Cherissa Astorga, RN, Libby Kalman, RN

**Satellite Site**
- Mercy Hospital and Medical Center, Chicago:
  - Site PI: Jeffrey Kramer, MD
  - Study Physician(s): Susan Vaughan, MD
  - Coordinator(s): Laura Owens, RN