From Bench to Brain (and back)

Improving Mechanical Thrombectomy

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Disclosures

- Research Grants (last 36 months):
  - NINDS, NIA, NCI
  - Philips Healthcare
  - BRACCO
  - Fraunhofer Institute
  - Stryker Neurovascular
  - Codman Neurovascular
  - Medtronic Neurovascular
  - InNeuroCo Inc
  - Blockade Medical
  - CereVasc LLC
  - Cook Medical
  - Medtronic
  - Microvention
  - NPS LLC
  - Neuravi
  - Rapid Medical
  - Wyss Institute
  - The Stroke Project

- Consulting (fee-per-hour, last 12 months):
  - Stryker Neurovascular
  - Harris Beach, Expert Witness
  - Codman Neurovascular
  - In Neuro Co

- Investment (Stocks)
  - Hologic (Spouse)
  - Boston Scientific Inc (Spouse)
  - InNeuroCo Inc

- Travel Support
  - Neuravi

Model development supported by the NIH NIBIB, device testing supported by Codman Neurovascular, Medtronic Neurovascular, Neuravi, and Stryker Neurovascular.

Support for imaging equipment generously provided by Philips Healthcare.
Clot Integration Factor

Unsheathing

Unsheath-Push
Clot Integration Factor
Considerations

Safety
1. Distal Emboli
2. Vascular Trauma
3. Brain/BBB (energy)

Efficacy
1. Ability to restore flow
2. Speed

Patient
1. Pt selection
2. Co-morbidities
...
Distal Emboli: Reperfusion versus Recanalization

Normal → Occlusive clot → Fragmentation*

Thrombectomy <8hrs

Partial Recovery or Deterioration

Occlusion
13%

Occlusion
9%

* Bonafe: ESMINT 2012
In Vitro Assessment of Safety and Efficacy

Circulation Loop Imaging/Medical Device Bench-top Treatment Optimization

Clot Model Circulation Loop Vascular Model Imaging/Medical Device

I. Pre-occlusion
II. Post-occlusion
III. Device with clot
IV. Post-treatment
<table>
<thead>
<tr>
<th></th>
<th>8-200µm</th>
<th>200-1000µm</th>
<th>&gt;1mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Movie</td>
<td>121,450</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>Stroke, 2013 (n=16)</td>
<td>&gt;100,000</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>
Population Based Vascular Replica

MRA Dataset → Computer Core-Shell Model → Fused Deposit Manufacturing

Silicone Replica → Physical Core-Shell Model

J Chueh, AK Wakhloo, and MJ Gounis. AJNR 2009
Mechanical Analysis of Clot Modeling

- 64 y-o M, Acute Ischemic Stroke
  - Entered ED >4.5hrs after symptom onset
  - CBV-MTT Mismatch
- Thrombus retrieved from R MCA with Penumbra Aspiration Device
Mechanical Analysis of Clot

- Clot modeling – Need to know bulk mechanical properties
  - Stress-Strain: DMA compression test
  - Stress relaxation: Propensity for fragmentation

Chueh, Silva, Hendricks, Wakhloo, Gounis. AJNR 2011 32:1237
“Model System”

- **Efficacy**
  - Measures time and amount of flow restoration to thrombosed MCA in model

- **Safety**
  - Blood analog fluid is captured for particle/fragmentation analysis
Vascular Occlusion

Hemodynamic Variables

Flow (mL/s)

Pressure (mmHg)

CCA
MCA

Time (s)
Translation?

Experimental

Clinical

Table 2. Neurological and Functional Outcomes From Open versus Closed Vessels

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percent With Outcome</th>
<th>Overall (N=125)</th>
<th>TIMI 2–3 (N=102)</th>
<th>TIMI 0–1 (N=23)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge NIHSS 0–1 or improved by ≥10</td>
<td>27</td>
<td>32</td>
<td>5</td>
<td>0.0127</td>
<td></td>
</tr>
<tr>
<td>Good clinical outcome at 30 days†</td>
<td>30</td>
<td>35</td>
<td>9</td>
<td>0.0199</td>
<td></td>
</tr>
<tr>
<td>mRS ≤2 at 90 days</td>
<td>25</td>
<td>29</td>
<td>9</td>
<td>0.0596</td>
<td></td>
</tr>
<tr>
<td>Death at 90 days</td>
<td>33</td>
<td>29</td>
<td>48</td>
<td>0.1384</td>
<td></td>
</tr>
</tbody>
</table>


Stroke 2009;40:2761
Translation?

Experimental


Clinical

Nguyen T et al. *Stroke* 2014;45:141-5

Table 3. Independent Predictors of Clinical Outcome With Solitaire Treatment for Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nparm</th>
<th>DF</th>
<th>χ²</th>
<th>P Value &gt; χ²</th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>2</td>
<td>1</td>
<td>94.54</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>1</td>
<td>3.93</td>
<td>0.0476</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2</td>
<td>1</td>
<td>16.8</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Initial NIHSS score</td>
<td>2</td>
<td>2</td>
<td>9.47</td>
<td>0.0088*</td>
</tr>
<tr>
<td>Site</td>
<td>8</td>
<td>5</td>
<td>9.85</td>
<td>0.08</td>
</tr>
<tr>
<td>IV tPA</td>
<td>2</td>
<td>1</td>
<td>128.46</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>TOG</td>
<td>2</td>
<td>1</td>
<td>0.58</td>
<td>0.45</td>
</tr>
<tr>
<td>TIMI success</td>
<td>2</td>
<td>2</td>
<td>2.75</td>
<td>0.25</td>
</tr>
<tr>
<td>BGC</td>
<td>2</td>
<td>1</td>
<td>66.66</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>General anesthesia</td>
<td>2</td>
<td>2</td>
<td>5.56</td>
<td>0.026</td>
</tr>
<tr>
<td>Procedure time</td>
<td>2</td>
<td>2</td>
<td>5.56</td>
<td>0.06</td>
</tr>
</tbody>
</table>

BGC indicates balloon guide catheter; DF, degrees of freedom; IV tPA, Intravenous tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; Nparm, number of parameters; TIMI, thrombolyis in myocardial infarction; and TOG, time of onset to groin puncture.

*Statistically significant.
Proximal Flow Control: Embolic Protection Evidence
Flow Restoration Procedure

• **Group 1:**
  Thrombectomy through an 8Fr balloon guide catheter (BGC) positioned at the cervical ICA

• **Group 2:**
  Thromboaspiration via a 5Fr intracranial guide catheter (Solumbra) in the origin of the MCA

• **Group 3:**
  Thrombectomy through a 6Fr guide catheter (CGC) with the tip placed at the origin of the cervical ICA

• **Group 4:**
  A Direct Aspiration first Pass Technique (ADAPT). Aspiration through a 5MAX
Total Number of Distal Emboli

- **Hard clot model:** Solumbra or BGC most effective in reducing the rate of forming clot fragments compared to the CGC or the ADAPT technique.

- **Soft clot model:** BGC technique reduced 2-fold total embolic particle creation compared to the other techniques.
Conclusion

• Use of the BGC technique during a SR thrombectomy was associated with statistically lower rates of soft distal emboli across a broad range of embolic particle sizes.

• The Solumbra technique was shown to be numerically, although not statistically, superior in several hard clot subgroups.

• When encountering hard clot, use of the Solumbra or ADAPT techniques in addition to the BGC may provide an additional reduction in distal emboli and may be considered for comprehensive distal emboli reduction.

Clinical Translation
ARTS Technique

Comparison of a Balloon Guide Catheter and a Non-Balloon Guide Catheter for Mechanical Thrombectomy

**Purpose:** To evaluate the effectiveness of mechanical thrombectomy with the use of a stent retriever in acute ischemic stroke, performed by using a balloon guide catheter or non-balloon guide catheter.

**Materials and Methods:** In accordance with the institutional review board approval obtained at the two participating institutions, retrospective analysis was performed in 183 consecutive patients treated between 2013 and 2014 for occlusions in the middle cerebral artery or carotid terminus by using a stent retriever with a balloon guide catheter (n = 102) at one center and a non-balloon guide catheter (n = 81) at another center.

**Results:** The primary success rate for patients treated with the balloon guide catheter was 70% (70/102) compared to 53% (44/81) for the non-balloon guide catheter (P = 0.016). The overall 90-day mRS score was 1 or less in 67% (68/102) of patients treated with the balloon guide catheter compared to 40% (32/81) of patients treated with the non-balloon guide catheter (P < 0.001).

**Conclusion:** The use of a balloon guide catheter during mechanical thrombectomy is associated with improved clinical outcomes compared to the use of a non-balloon guide catheter.

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**Analysis of Workflow and Time to Treatment on Thrombectomy Outcome in the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) Randomized, Controlled Trial**

**Background:** The Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial used innovative imaging and aggressive target time metrics to demonstrate the benefit of endovascular treatment in patients with acute ischemic stroke. We analyze the impact of time on clinical outcome and the effect of patient, hospital, and health system characteristics on workflow within the trial.

**Methods and Results:** Relationship between outcome (modified Rankin Scale) and interval times was modeled by using logistic regression. Association between time intervals (stroke onset to arrival in endovascular-capable hospital, to qualifying computed tomography, to groin puncture, and to reperfusion) and patient, hospital, and health system characteristics were modeled by using negative binomial regression. Every 30-minute increase in computed tomography-to-reperfusion time reduced the probability of achieving a functionally independent outcome (90-day modified Rankin Scale 0–2) by 8.3% (P = 0.006). Symptom onset-to-imaging time was not associated with outcome (P > 0.5). Onset-to-endovascular hospital arrival time was 42% (24 minutes) longer among patients receiving intravenous alteplase at the referring hospital (drip and ship) versus direct transfer (mothership). Computed tomography-to-groin puncture time was 15% (8 minutes) shorter among patients presenting during work hours versus off hours, 41% (24 minutes) shorter in drip-ship patients versus mothership, and 43% (22 minutes) longer when general anesthesia was administered. The use of a balloon guide catheter during endovascular procedures shortened puncture-to-reperfusion time by 21% (8 minutes).

**Conclusions:** Imaging-to-reperfusion time is a significant predictor of outcome in the ESCAPE trial. Inefficiencies in triaging, off-hour presentation, intravenous alteplase administration, use of general anesthesia, and endovascular techniques offer major opportunities for improvement in workflow.

**Clinical Trial Registration—URL:** http://www.clinicaltrials.gov. Unique identifier: NCT01778335. (Circulation. 2016;133:2279-2286. DOI: 10.1161/CIRCULATIONAHA.115.019983.)

**Key Words:** cerebrovascular disorders, emergency treatment, endovascular procedures, stroke, thrombolytic therapy.

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**Balloon Guide Catheter Improves Revascularization and Clinical Outcomes With the Solitaire Device: Analysis of the North American Solitaire Acute Stroke Registry**


*Stroke. 2014;45:141-145; originally published online December; doi: 10.1161/STROKEAHA.113.002407*
## Evidence: Proximal Flow Control

<table>
<thead>
<tr>
<th></th>
<th>NASA</th>
<th>ESCAPE</th>
<th>Velasco et al</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Multicenter Registry</td>
<td>RCT</td>
<td>2-center, retrospective case series</td>
</tr>
<tr>
<td><strong>Procedure Time</strong></td>
<td>25% (40 min)</td>
<td>21% (8 min)</td>
<td>50% (21 min)</td>
</tr>
<tr>
<td><strong>Recanalization Rate</strong></td>
<td>21% (TICI 3)</td>
<td>N/A</td>
<td>21.3% (TICI≥2b within 3 passes)</td>
</tr>
<tr>
<td>mRS≤2 @90 days</td>
<td>30%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Ref</strong></td>
<td>Stroke 2013</td>
<td>Circulation 2016</td>
<td>Radiology 2016</td>
</tr>
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</table>
Results from cases studies are not predictive of results in other cases. Results in other cases may vary.

### Table 3: Trials on endovascular treatment of anterior circulation stroke: clinical outcome in relation to baseline NIHSS score and endovascular techniques applied

<table>
<thead>
<tr>
<th>Study designation</th>
<th>Number of patients undergoing endovascular treatment</th>
<th>Baseline NIHSS score, median</th>
<th>Favorable outcome (mRS score 0–2) at 3 months (%)</th>
<th>Endovascular techniques applied</th>
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<tbody>
<tr>
<td>PROACT II [18]</td>
<td>121</td>
<td>17</td>
<td>40</td>
<td>ia prourokinase</td>
</tr>
<tr>
<td>MELT [9]</td>
<td>57</td>
<td>14</td>
<td>49</td>
<td>ia prourokinase</td>
</tr>
<tr>
<td>Mattal et al. [26]</td>
<td>55</td>
<td>17*</td>
<td>53</td>
<td>ia prourokinase</td>
</tr>
<tr>
<td>Galimani et al. [31]</td>
<td>623</td>
<td>15</td>
<td>49</td>
<td>ia prourokinase, aspiration,</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>stent retriever (Solitaire)</td>
</tr>
<tr>
<td>Multi MERCI trial [7]</td>
<td>164</td>
<td>19</td>
<td>36</td>
<td>Distal Thrombectomy (Merci)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Penumbra)</td>
</tr>
<tr>
<td>SWIFT [10]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Merci</td>
<td>58</td>
<td>18</td>
<td>28</td>
<td>Merci</td>
</tr>
<tr>
<td>- Solitaire</td>
<td>55</td>
<td>17</td>
<td>37</td>
<td>Solitaire (protection not</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mandatory)</td>
</tr>
<tr>
<td>TREVO 2 [5]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Merci</td>
<td>90</td>
<td>18</td>
<td>22</td>
<td>Merci</td>
</tr>
<tr>
<td>- TREVO</td>
<td>88</td>
<td>19</td>
<td>40</td>
<td>Stent retriever (Trevo, protection</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>not mandatory)</td>
</tr>
<tr>
<td>MR CLEAN [1]</td>
<td>233</td>
<td>17</td>
<td>33</td>
<td>ia alteplase or prourokinase,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>thrombus retraction, aspiration,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>wire disruption, stent retriever</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(protection not mandatory)</td>
</tr>
<tr>
<td>IMS III [15]</td>
<td>434</td>
<td>17</td>
<td>41</td>
<td>Merci, Penumbra, Solitaire</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(protection not mandatory), ia tPA</td>
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<tr>
<td>MR RESCUE [16]</td>
<td>64</td>
<td>16 (penumbral), 19 (non-penumbral)</td>
<td>19</td>
<td>Merci, Penumbra, ia tPA</td>
</tr>
<tr>
<td>SYNTHESEIS [17]</td>
<td>181</td>
<td>13</td>
<td>42</td>
<td>ia tPA, wire disruption, Merci,</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Penumbra, Trevo, Solitaire</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(protection not mandatory)</td>
</tr>
<tr>
<td>Dávalos et al. [2]</td>
<td>141</td>
<td>18</td>
<td>55</td>
<td>Solitaire (protection in 74% of</td>
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<td></td>
<td></td>
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<td>interventions)</td>
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<td>STAR trial [3]</td>
<td>202</td>
<td>17</td>
<td>58</td>
<td>Solitaire (protection mandatory)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(protection recommended)</td>
</tr>
<tr>
<td>EXTEND-I trial [12]</td>
<td>35</td>
<td>17</td>
<td>71</td>
<td>Solitaire (protection mandatory)</td>
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<tr>
<td>REVASCAT [13]</td>
<td>103</td>
<td>17</td>
<td>44</td>
<td>Solitaire (protection not</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mandatory)</td>
</tr>
<tr>
<td>SWIFT prime [14]</td>
<td>98</td>
<td>17</td>
<td>60</td>
<td>Solitaire (protection mandatory)</td>
</tr>
</tbody>
</table>

Protected stent retriever thrombectomy prevents iatrogenic emboli in new vascular territories.
Vascular Safety
A Brain Artery is NOT Just an Artery

- Well developed internal elastic lamina
- Higher percentage of smooth muscle cells and a paucity of elastic fibers in the media
- Absent external elastic lamina
- Less adventitia
- Float freely in the cerebrospinal fluid within the subarachnoid space unsupported by muscle, bone or deep fascia and experience significant vessel straightening during endovascular access

Standard Approach

- Endpoints:
  - Acute vascular safety of a systemic artery
  - Angiographic recanalization

Nogueira, et al. JNIS 2011
Angiographic Assessment

Pretreatment

First Pass
Grade 3

Fourth Pass
Grade 0

Stent-trievers

Merci V2-Firm

Gounis, et al. Stroke 2013
Histology Assessment

Stent-triever

Merci V2

Control microcatheter
Stent-Thrombectomy
(Rabbit CCA)


1 Pass  2 Pass  3 Pass
Stent-Thrombectomy

• Each pass causes more injury.

Future for Endovascular Therapy

• Rapid diagnosis - Systems of Care
• Couple with Neuroprotection

• FASTER
  1. First-pASs
  2. TICI = 3
  3. Easy to use
  4. Reliable results (~95%)
- Ajay Wakhloo, MD, PhD
- Ajit Puri, MD
- **Juyu Chueh, PhD**
- Miklos Marosföi, MD
- Martijn van der Bom, PhD
- Kajo van der Marel, PhD
- Anna Kühn, MD, PhD
- Frédéric Clarençon, MD, PhD
- Ivan Lylyk, MD
- Mary Howk, MS, CRC
- Thomas Flood, MD, PhD
- Erin Langan, BS
- Olivia Brooks
- Olena Fartushna, MD
- Chris Brooks, PA
- Mary Perras, NP
- Shaokuan Zheng, PhD