Stent-Retriever Thrombectomy: From Bench to Brain, and Back

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Disclosures

• Research Grants (last 12 months):
  – NINDS, NIBIB, NIA, NCI
  – Philips Healthcare
  – Fraunhofer Institute
  – Stryker Neurovascular
  – Codman Neurovascular
  – eV3 Neurovascular / Covidien
  – InNeuroCo Inc
  – Blockade Medical
  – CereVasc LLC
  – Cook Medical
  – Neuronal Protection Systems
  – Spineology Inc
  – Silk Road
  – Wyss Institute
  – Microvention
  – Gentuity

• Consulting (fee-per-hour, last 12 months):
  – Stryker Neurovascular

• Investment (Stocks)
  – Boston Scientific Inc
  – InNeuroCo Inc
Acute Ischemic Stroke: Pre-Clinical Investigations for Devices – Does it Translate to Humans?
Two Approved Treatments: Both Target Vessel Revascularization

- Pre-Clinical Modeling has had an Impact:
  - With and without treatment with IV-tPA
Stent-Retriever Thrombectomy

MR CLEAN, NEJM Jan 2015

SWIFT PRIME, NEJM June 2015

ESCAPE, NEJM March 2015

EXTEND IA, NEJM March 2015

Comments

Wakhloo and Gounis present an efficient, effective, thoughtful, and well-designed approach to the study of a novel application of a device. In this brief report, the authors assessed the feasibility of using a closed-cell, retrievable stent as a foreign body retriever or as an embolectomy/thrombectomy device. They performed a carefully designed analysis using in vitro and in vivo models to assess efficacy in straight and tortuous anatomy. On the basis of their analyses, the authors conclude that this device may be successfully used to retrieve foreign bodies (i.e. errant coils) or an embolus/thrombus from the intracranial circulation.

Although the authors assess the technology for a non-Food and Drug Administration approved use, they do so in a controlled setting outside the clinical realm. This carefully planned and well-executed analysis of a new device may serve as a blueprint for assessing other innovative, off-label applications for existing technologies. Naturally, concerns about its efficacy in the clinical setting are certainly not eliminated: the authors (and I) clearly point out that the aforementioned application should not serve as the first-line technique, especially in light of the fact that Food and Drug Administration-approved devices already exist for each of these “off-label indications.” Additionally, concerns about cost-effectiveness in using this device are not adequately addressed, although it might be argued that this single device may be cost-effective if it alone were to be used for attempted retrieval and/or stenting in place of multiple devices. Nonetheless, in this ever-growing and rapidly expanding field, understanding the limitations of the devices as well as some potential benefits in off-label indications in a controlled, laboratory setting is important. The authors have presented an interesting and innovative application for a closed-cell retrievable stent.

Charles J. Prestigiacomo
Newark, New Jersey

The authors report the use of the Enterprise retrievable closed-cell stent for foreign body and clot removal. Certainly they have demonstrated in a swine model that use of this device is feasible as a last resort. Retrieval of thrombus or coils or other devices is often problematic, and this method may be a useful adjunct as a salvage maneuver. Hopefully, other devices that are more cost effective and easier to use will solve this problem as well.

Robert H. Rosenwasser
Philadelphia, Pennsylvania
Devices for Recanalization

US FDA Cleared

- Merci
- Penumbra
- Solitaire
- MindFrame Capture
- Penumbra Separator 3D

Penumbra

- Reperfusion Catheter/Separator Size
  - 026
  - 032
  - 041
  - 054

Revive

MindFrame Capture

Penumbra Separator 3D

Phenox (AJNR 2011)

Restore
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

Normal $\rightarrow$ Occlusive clot $\rightarrow$ 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

Vascular Model

Circulation Loop

Imaging/Medical Device

Clot Model

I. Pre-occlusion

II. Post-occlusion

III. Device with clot

IV. Post-treatment

*Arrow indicate flow direction
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
Efficacy Metrics

1. Chueh, Wakhloo, Gounis. AJNR 2012
Distal Emboli: A Modifiable Risk
Translation?

Experimental

Clinical

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

<table>
<thead>
<tr>
<th>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>
</tr>
<tr>
<td>Good clinical outcome at 30 days†</td>
<td>30</td>
<td>35</td>
<td>9</td>
<td>0.0199</td>
</tr>
<tr>
<td>mRS ≤2 at 90 days</td>
<td>25</td>
<td>29</td>
<td>9</td>
<td>0.0596</td>
</tr>
<tr>
<td>Death at 90 days</td>
<td>33</td>
<td>29</td>
<td>48</td>
<td>0.1384</td>
</tr>
</tbody>
</table>


Stroke 2009;40:2761
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
• Using CGC during mechanical thrombectomy significantly increased the risk of hard emboli formation.

• There was no statistical difference in the creation or large particle emboli in the soft clot group between all four different access techniques.
Emboli with size between 200-1000 µm

- Average number of emboli (regardless of clot type):
  - ADAPT < Solumbra < CGC < BGC
  - Significant difference was seen between the BGC and the ADAPT techniques in the soft clot group

![Graphs showing particle number comparison between hard and soft clots for different techniques (BGC, Solumbra, CGC, ADAPT)].
Emboli with size between 50-200 µm

- **Figure A and B**
  --- Size range: 100-200µm

- **Figure C and D**
  --- Size range: 50-100µm
The majority of the emboli (>90%) generated during the thrombectomy procedure had a size <50µm (mean size: 12.3µm).

There was a significant increase in the number of particles generated during thrombectomy using the soft clot model.
• PCoM A and ACA present, temporary ICA occlusion provided by the BGC during mechanical thrombectomy didn’t significantly change the restored MCA flow
• Temporary occlusion with the BGC and direct aspiration through the 5MAX resulted in flow reversal in the MCA (Figure B).
Total Number of Distal Emboli

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

- **Soft clot model**: Thrombectomy with the BGC technique reduced total embolic particle creation by at least 2-fold 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.

Balloon guide catheter improves revascularization and clinical outcomes with the Solitaire device: analysis of the North American Solitaire Acute Stroke Registry


Stroke. 2014 Jan;45:141-5
<table>
<thead>
<tr>
<th><strong>Emboli in new territory</strong></th>
<th><strong>8 (5)</strong></th>
<th><strong>10 (5.2)</strong></th>
<th><strong>0.9</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recanalization TICI3</strong></td>
<td><strong>80 (53.7)</strong></td>
<td><strong>61 (32.5)</strong></td>
<td><strong>&lt;0.0001</strong></td>
</tr>
<tr>
<td><strong>Recanalization TICI2b-3</strong></td>
<td><strong>113 (76)</strong></td>
<td><strong>133 (71)</strong></td>
<td><strong>0.3</strong></td>
</tr>
<tr>
<td><strong>Procedural factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Procedure time (SD)</strong></td>
<td><strong>120 (28.5)</strong></td>
<td><strong>161 (35.6)</strong></td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td><strong>Time onset to groin or first angio (SD)</strong></td>
<td><strong>348 (230.7)</strong></td>
<td><strong>375 (252.7)</strong></td>
<td><strong>0.3</strong></td>
</tr>
<tr>
<td><strong>General anesthesia</strong></td>
<td><strong>97 (84.4)</strong></td>
<td><strong>99 (60)</strong></td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td><strong>Number of passes (mean, SD)</strong></td>
<td><strong>1.8 (1.2)</strong></td>
<td><strong>1.9 (1)</strong></td>
<td><strong>0.3</strong></td>
</tr>
<tr>
<td><strong>(Median, IQR)</strong></td>
<td><strong>1 (1-2)</strong></td>
<td><strong>2 (1-3)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>IA tPA</strong></td>
<td><strong>40 (26.9)</strong></td>
<td><strong>60 (31.8)</strong></td>
<td><strong>0.3</strong></td>
</tr>
<tr>
<td><strong>Simultaneous Penumbra &amp; Solitaire</strong></td>
<td><strong>18 (12.1)</strong></td>
<td><strong>34 (18.1)</strong></td>
<td><strong>0.1</strong></td>
</tr>
<tr>
<td><strong>Rescue therapy</strong></td>
<td><strong>29 (20)</strong></td>
<td><strong>54 (28.6)</strong></td>
<td><strong>0.05</strong></td>
</tr>
<tr>
<td><strong>Clinical Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Discharge NIHSS</strong></td>
<td><strong>12 (14.5)</strong></td>
<td><strong>17.5 (16)</strong></td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td><strong>6 (1-18)</strong></td>
<td><strong>11 (4-42)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Median (IQR)</strong></td>
<td><strong>65 (51.6)</strong></td>
<td><strong>52 (35.8)</strong></td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td><strong>Good clinical outcome (3 months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• 183 consecutive patients with MCA/ICA T occlusion in Germany.

• stent retriever with a balloon guide catheter (n = 102) at one center vs non–balloon guide catheter (n = 81) at the other center.

Aglaé Velasco et al Radiology 2016
Results

• Recanalization with BGC in 89.2% of thrombectomies (91 of 102) versus 67.9% (55 of 81) NBGC (P = .0004).

• 1-pass thrombectomy rate with BGC was higher (63.7% [65 of 102] vs 35.8% NBGC [29 of 81] respectively; P = .001).

Aglaé Velasco et al Radiology 2016
• Procedure duration was significantly shorter with BGC than NBGC group (median, 20.5 minutes vs 41.0 minutes, respectively; P < .0001)

• Median number of passes in the BGC group was one (range 1–6) versus two passes (range, 1–7) in the NBGC group (P = .0002).
Clot-Device Interaction
Optimizing Clot Retrieval in Acute Stroke
The Push and Fluff Technique for Closed-Cell Stentriever

Diogo C. Haussen, MD; Leticia C. Rebello, MD; Raul G. Nogueira, MD

Stroke. 2015;46:2838-2842.
• Max. TREVO diameter-1.9 mm, with SUT.
• PFT-max. diameter of 3.3 mm (75% larger) with 25% device foreshortening versus SUT.
• Mean cell size area was 2.4 mm$^2$ for the SUT compared with 3.7 mm$^2$ in the PFT (51% larger)
Results

- PFT - higher rate of first pass reperfusion (54% versus 36%; P=0.03) and a lower number of passes (1.3±0.8 versus 1.8±1.0; P<0.01).

- mTICI-3 reperfusion was achieved more frequently in the PFT group (58% versus 40%; P=0.03).

- PFT was independently associated with a lower number of Trevo passes (P=0.01) and higher rates of first-pass reperfusion (P=0.01) and complete (mTICI-3) reperfusion.
Hypothesis

• Altering technique change clot-device interaction (cheese-grating)

• With NiTi devices, there is temporal increase in clot-device interaction
Clot Integration Factor

High-resolution reconstruction of cone-beam CT image

Extraction of visible marker wires

Segmentation of the contrast-enriched clot

Determination of the inner volume of the stent-retriever

Clot Integration Factor = \frac{\text{Volume of \text{Clot-Device Intersection}}}{\text{Volume of Clot}}

Kajo van der Marel, et al. JNIS 2016
Clot Integration Factor

Kajo van der Marel, et al. JNIS 2016
Pushing increases CIF in Hard Clot
CIF Increases with Time in all Clot

![Bar chart showing the Clot Integration Factor (CIF) for hard inelastic and soft elastic clots across different deployment techniques. The chart indicates that CIF increases with time for both types of clots, with significant differences marked by asterisks.](chart_image)
No Change in Clot Fragmentation

Kajo van der Marel, et al. JNIS 2016
Summary

CIF: pushing vs. unsheathing

- Hard clot: higher CIF with pushing technique

CIF: Time

- Hard clot & pushing technique significantly increased CIF over time between the post-deployment (early) and the final (late) time points.
Summary

- Regardless of delivery technique, CIF increased over time for both hard inelastic clot and soft elastic clot models
• Device development has evolved rapidly (Avg life for a medical device is ~18 months).

• We need better models to address:
  – Combined therapies
  – Subtle differences between technologies
  – What technology to use for what underlying disease

• Unlikely that one model will address all questions. Select a model appropriate to the question asked.

• Multicenter preclinical trials – the way of the future
• UMass Collaborations
  – Marc Fisher, MD
  – Neil Aronin, MD
  – Alexei Bogdanov, PhD
  – Greg Hendricks, PhD
  – Guanping Gao, PhD
  – Miguel Esteves, PhD
  – Linda Ding, PhD
  – Srinivasan Vedantham, PhD
  – John Weaver, MD
• Collaborations
  – Alex Norbash, MD – BU
  – Thanh Nguyen, MD - BU
  – Italo Linfante, MD - Baptist
  – Guilherme Dabus, MD - Baptist
  – Don Ingber, PhD – Harvard
  – Nati Korin, PhD - Technion
  – Johannes Boltze, MD, PhD – Fraunhofer Institute
  – Raul Nogueira, MD - Emory

NECStR
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  – Ajit Puri, MD
  – Juyu Chueh, PhD
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  – Anna Kühn, MD, PhD
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  – 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