The Evolution of Technology

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The historical development of technologies for catheter-based reperfusion of the acutely ischemic human brain is brief but eventful (Table). The first clinical patients were treated with local microcatheter delivery of intra-arterial fibrinolytics in the mid-1990s. The first mechanical recanalization technique, primary intra-arterial balloon angioplasty, was described a few years later. Over the subsequent decade and a half, successive waves of innovative mechanical thrombectomy devices were introduced. The rapid proliferation of technology reflects the inherent dynamic of biomechanical device development, characterized by rapid engineering innovation focused on a well-circumscribed target, in contrast to the slower, more deliberate arc of drug development, which requires extensive testing of each new molecular entity for unexpected off-target effects on diverse organs.

The heterogeneity of target vascular lesions in cerebrovascular disease mandates a diversity of mechanical treatment options for deployment by interventionalists. In many patients, the intracranial occlusion is an embolus that has arisen from the heart or a proximal aortocervical arterial source and landed in a relatively normal recipient artery. Such target thrombi respond well to retrieval and aspiration strategies. In other patients, the occlusive lesion is comprised of an in situ intracranial atherosclerotic plaque with supervening thrombosis. These target lesions will not respond well to retrieval devices, which catch on the plaque, or to aspiration devices, which are effective only for the thrombus component. However, they do respond well to angioplasty and stenting, which accomplish controlled cracking and dissection of the underlying atherosclerotic lesions. There is a notable race, ethnic variation in the composition of intracranial occlusions. Among whites, emboli from the heart or extracranial arterial sources are common; among Asians and blacks, in situ intracranial atherosclerosis with supervening thrombosis is more frequent. As a result, the most effective and commonly used mechanical treatment strategies vary regionally across the globe.

The endovascular recanalization techniques that gained wide employment may be classified into the categories of microcatheters to deliver fibrinolytic drug directly on clot, angioplasty/stent devices, suction thrombectomy devices, and thrombus retrieval devices. In local intra-arterial fibrinolysis, fibrinolytic agents are infused distal to, proximal to, and directly within thrombotic occlusions using a microcatheter delivery system. In comparison with standard intravenous administration, the intra-arterial route offers several theoretical advantages, including higher concentrations of fibrinolytic agent at the clot site; reduced systemic exposure to thrombolytics; an opportunity to carry out gentle mechanical disruption of the clot with the delivery catheter and wire; and precise imaging of case-specific vascular anatomy, pathology, and collateral patterns. Because of the ease of delivery of a simple microcatheter versus bulkier and less flexible thrombectomy devices, intra-arterial lysis is distinctively beneficial for smaller, more distal thrombi beyond the reach of mechanical approaches, including emboli fragments generated by mechanical treatment of proximal, large occlusions.

Angioplasty and stenting are highly effective acute recanalization strategies when target occlusions are in situ atherosclerotic plaques with supervening thrombosis. These devices crack open the atherosclerotic plaque but are less effective for spongy thrombi that spring back after balloon expansion. Across several early series, the recanalization rate of acute intracranial angioplasty, largely without stenting, was 84%. Suction thrombectomy devices use vacuum aspiration to remove occlusive clot in acute ischemic stroke. Progress in developing aspiration devices required a technical solution to the problem of clogging of aspiration tips, a common occurrence when applying suction through a bore small enough to fit within intracranial arteries. The Penumbra System successfully overcame this obstacle by adding an in-bore separator wire with a bulbous tip that the operator continually advances and retracts, disrupting attached clot and pulling in thrombus ahead of the catheter.

Clot retrieval devices were first developed to capture errant coils and other foreign bodies that had embolized within the cerebral circulation during endovascular procedures. A natural next step was to apply these devices to capture and remove naturally arising thromboemboli. These devices ensnare a thrombus and then withdraw it out of the body via the guide catheter. For cerebral revascularization, the first approved family of retrieval devices was the Merci Retriever helical nitinol coils that entrap the clot, like a corkscrew removing a cork from a wine bottle. Additional first-generation devices approved in Europe used bristle brush (Phenox Retriever) and mesh basket (Catch Device) designs.
The most recent generation of devices is a novel form of clot retriever, the stent retrievers. When these retractable stents are deployed within the target clot in the occluded vessel, they immediately establish an open channel and flow restoration. Simultaneously, the multiple crossing stent struts entraps the thrombus. The stent is then withdrawn back into the delivery catheter in its unfolded state, and the enmeshed thrombus is concurrently extracted from the vessel. Stent retrievers are currently the focus of intense industry development programs, with 28 different devices having received CE Mark in Europe.

Until the advent of stent retrievers, recanalization strategies for acute cerebral thrombosis were only of modest technical efficacy at actually opening arteries, although more successful than intravenous tissue-type plasminogen activator. Intravenous tissue-type plasminogen activator achieves partial recanalization in 40% of cases and complete recanalization in 5%. In registration trials of endovascular intervention, partial reperfusion rates were 65% for intra-arterial fibrinolysis, 65% for the Merci Retrievers, and ≤82% for the Penumbra aspiration devices, but complete recanalization rates were only 20% for intra-arterial fibrinolysis, 23% for the Merci Retrievers in registration trials, and 23% for the Penumbra System. Accordingly, first-generation endovascular therapies achieved somewhat higher rates of recanalization than intravenous tissue-type plasminogen activator, but complete success frequency was still far below the 80% to 95% rates achieved in acute myocardial reperfusion and the 100% that is ideal. Moreover, first-generation endovascular interventions were all associated with high rates of symptomatic hemorrhagic transformation, affecting ≥1 of every 10 treated patients.

A paradigm shift has occurred over the past 2 years with the development and clinical trial validation of stent retrievers. In preclinical models, the stent retrievers show substantially higher rates of recanalization with less local vessel injury and distal clot fragmentation than earlier devices. In early open series, the stent retrievers demonstrated high rates of recanalization. For example, the first 8 series testing the Solitaire stent retriever, collectively encompassing 196 patients, reported an aggregate partial recanalization rate of 93% and complete recanalization rate of 66%.

The technical efficacy of stent retrievers relative was then definitively tested in 2 head-to-head randomized trials versus the first-generation Merci coil retriever. The first to be presented was the Solitaire With the Intention For Thrombectomy (SWIFT) trial, a multicenter, prospective, randomized, blinded end point assessment trial. SWIFT was designed to enroll 200 patients undergoing neurothrombectomy, randomizing them to treatment with the Solitaire stent retriever or the Merci coil retriever as the first deployed device. However, the trial was stopped early by the Data Safety and Monitoring Board as a result of overwhelming demonstration of superiority of the Solitaire device at an interim analysis. Recanalization was achieved substantially more often with the stent retriever. On the core laboratory readings, stringent successful recanalization was achieved by the initial device in 63% of randomized Solitaire patients versus 30% of randomized Merci patients (odds ratio [OR], 5.0 [95% confidence interval (CI), 2.2–13.7]; P=0.0001). This angiographic success translated into better clinical outcomes. Good neurological outcome at 3 months was achieved by 58% of randomized Solitaire patients versus 33% of Merci patients (OR, 2.8 [CI, 1.3–6.2]; P=0.017). The rates of symptomatic intracranial hemorrhage were markedly low in Solitaire patients, 1.7%, versus 10.9% in Merci patients (P=0.057). Moreover, cumulative 3-month mortality was reduced in the Solitaire arm, 17.2% versus 38.2% (OR, 0.34 [CI, 0.14–0.81]; P=0.02). SWIFT was the first randomized trial of any recanalization therapy for acute cerebral ischemic to find a beneficial effect of increased achievement of reperfusion on mortality.

Generally, comparable results were found in the Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke (TREVO 2) trial which randomized 178 patients to initial treatment with the Trevo stent retriever or the Merci coil retriever. Again a marked technical superiority of the stent retriever was seen, with partial or better recanalization rates (thrombolysis in cerebral infarction 2a–3) achieved with the first device type deployed in 86% of Trevo patients versus 60% of Merci patients (OR, 4.2 [CI, 1.9–9.7]; P<0.0001). Better functional outcome resulted, with independence (modified Rankin scale, 0–2) at 3 months in 40% of Trevo patients versus 22% of Merci patients (OR, 2.4 [CI, 1.2–5.0]; P=0.013). However, unlike in SWIFT, hemorrhage rates were not reduced in the Trevo group and mortality point estimates were higher, Trevo versus Merci, 34.1% versus 24.1% (P=0.19).

The results of SWIFT and TREVO suggest that we are now entering a new era in reperfusion therapy for acute cerebral ischemia (Figure). With the advent of stent retriever technology, stroke physicians for the first time can offer...
patients a highly effective recanalization intervention, achieving partial reperfusion in 80% to 90% and complete reperfusion in >50%. This type of punctuated evolution in technology is extremely challenging for clinical trialists seeking to demonstrate that endovascular intervention is better than supportive medical care for patients with acute stroke. Trials that, over the past several years, have been testing first-generation interventions against supportive care, such as the National Institutes of Health Interventional Management of Stroke 3 (IMS 3) and Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trials, now will be interpreted as not interrogating the current, best approaches. Nonetheless, this transformative advance is most welcome, a boon to current and future patients.

**Disclosures**

The University of California (UC) Regents receive funding for Dr Saver’s services as a scientific consultant regarding trial design and conduct to Covidien,BrainsGate, CoAxia, and Grifols. Dr Saver is an investigator in the NIH FAST-MAG, MR RESCUE, ICES, CUFFS, CLEAR-ER, and IMS 3 multicenter clinical trials for which the UC Regents received payments based on clinical trial performance; has served as an unpaid site investigator in a multicenter trials run by Covidien and Lundbeck for which the UC Regents received payments based on the clinical trial contracts for the number of subjects enrolled; and is an employee of the UC, which holds a patent on retriever devices for stroke.

**Table. Historical Development of Endovascular Technologies for Acute Recanalization**

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<tr>
<th>Technology</th>
<th>First Human Studies</th>
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<tbody>
<tr>
<td>Intra-arterial microcatheter lysis</td>
<td>1996</td>
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<td>Balloon angioplasty</td>
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<td>Aspiration thrombectomy</td>
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<td>Ultrasound sonothrombolysis</td>
<td>1999</td>
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<td>Laser clot destruction</td>
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<td>Archimedes screw</td>
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<td>Coil retrievers</td>
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<td>Basket/brush retrievers</td>
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<td>Stent retrievers</td>
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**References**


**Key Words:** acute ischemic stroke ■ neurothrombectomy ■ recanalization ■ reperfusion
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