The Future of Endovascular Therapy

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Abstract

Purpose of the Review
This article summarizes a broad range of the most recent advances and future directions in stroke diagnostics, endovascular robotics, and neuromodulation.

Recent Findings
In the past 5 years, the field of interventional neurology has seen major technological advances for the diagnosis and treatment of cerebrovascular diseases. Several new technologies became available to aid in complex prehospital stroke triage, stroke diagnosis, and interpretation of radiologic findings. Robotics and neuromodulation promise to expand access to established treatments and broaden neuroendovascular indications.

Summary
Mobile applications offer a solution to simplify prehospital diagnostic and transfer decisions. Several prehospital devices are also under development to improve the accuracy of detection of large vessel occlusion (LVO). Artificial intelligence is now routinely used in early diagnosis of LVO and for detecting salvageability of the affected brain parenchyma. Technological advances have also paved the way to incorporate endovascular robotics and neuromodulation into practice. This may expand the deliverability of established treatments and facilitate the development of cutting-edge treatments for other complex neurologic diseases.

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Glossary

AI = artificial intelligence; ASPECTS = Alberta Stroke Program Early CT Score; CSC = comprehensive stroke center; EMS = emergency medical services; FDA = Food and Drug Administration; HIPAA = Health Insurance Portability and Accountability Act; LVO = large vessel occlusion; MSU = mobile stroke unit; MT = mechanical thrombectomy; OCT = optical coherence tomography; PACS = picture archiving and communication system; PCI = percutaneous coronary intervention; PSC = primary stroke center; TCD = transcranial Doppler; tPA = tissue plasminogen activator; VCI = velocity curvature index; VIPS = volumetric impedance phase shift spectroscopy.

Mechanical thrombectomy (MT) emerged as the most impactful and time-dependent breakthrough treatment for ischemic stroke patients with large vessel occlusion (LVO), which triggered massive efforts to reorganize the stroke systems of care and prompted rapid growth in diagnostic and therapeutic technologies. Endovascular management of hemorrhagic strokes and intracranial aneurysms continues to evolve steadily, and new endovascular approaches are also being developed in an attempt to expedite stroke recovery.

We summarize the most recent technological advances and future directions in diagnostics (Smartphone apps, helmets), endovascular robotics, and neuromodulation.

Diagnostics

Prehospital Triage

MT is the most effective treatment for patients with ischemic stroke due to LVO and the probability of good clinical outcome is directly related to timely intervention. Several prehospital stroke severity scales have been developed and validated to help emergency medical services (EMS) personnel determine which patients have a high likelihood of a LVO and may benefit from direct transfer to a comprehensive stroke center (CSC). However, many barriers exist in the efficient transfer and triage of patients with stroke. Transfer of an MT candidate to a primary stroke center (PSC) may unintentionally preclude up to one-third of patients from endovascular thrombectomy and may result in worse clinical outcomes.1,2 This is especially evident at PSCs, which have long door-in-door-out times. On the other hand, overtriage of patients to the highest level of care may result in overburdening of CSCs and may theoretically delay thrombolytic administration.

Although the DIRECT-MT (Endovascular Thrombectomy With or Without Intravenous Alteplase in Acute Stroke) and DEVT (Direct Endovascular Thrombectomy vs Combined IVT and Endovascular Thrombectomy for Patients With Acute Large Vessel Occlusion in the Anterior Circulation) trials had limitations, they demonstrated that direct MT had noninferior clinical outcomes when compared with combination of MT and IV tissue plasminogen activator (tPA) in CSCs.3,4 Multiple other randomized controlled trials, including SWIFT-DIRECT (Solitaire With the Intention for Thrombectomy Plus Intravenous t-PA vs DIRECT Solitaire Stent-retriever Thrombectomy in Acute Anterior Circulation Stroke; Europe & Canada), DIRECTSAFE (Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval vs Standard Bridging Thrombolysis With Endovascular Clot Retrieval; Australia), MR CLEAN No-IV (Intravenous Treatment Followed by Intra-arterial Treatment vs Direct Intra-arterial Treatment for Acute Ischemic Stroke Caused by a Proximal Intracranial Occlusion), are evaluating the effect of IV tPA in patients undergoing MT and may ultimately influence prehospital triage protocols. Preliminary results from the RACECAT trial (Direct Transfer to an Endovascular Center Compared to Transfer to the Closest Stroke Center in Acute Stroke Patients With Suspected Large Vessel Occlusion) conducted in Catalonia, Spain, failed to show superiority of a mothership transfer protocol compared with a drip-and-ship protocol in patients with suspected LVO. Results from the TRIAGE randomized controlled trial (Treatment Strategy in Acute Ischemic Large Vessel Stroke: Prioritize Thrombolysis or Endovascular Treatment) will help determine the most effective triage process for patients with suspected LVOs.

Mobile Applications

Linear communications by telephone and reliance of EMS on radio technology have often led to slow triage times and impaired communications between teams. Mobile stroke units (MSUs) have allowed administration of IV tPA before arrival to the hospital. However, MSU technology is yet to be widely accepted, has significant limitations such as the requirement to be stationary for image acquisition, and is expensive to establish and maintain. Mobile applications may provide a scalable and more affordable solution to prehospital management of patients with stroke as they allow for effective mass communication among EMS and multiple treatment teams. Ideally, an app for prehospital stroke triage would be customizable, user-friendly, and cost-effective; deliver prehospital stroke diagnostic solutions; allow 2-way Health Insurance Portability and Accountability Act (HIPAA)–compliant communication (including the ability to send videos and images); have real-time GPS tracking; and have real-time nearby PSC and CSC information (i.e., hospital performance metrics, local weather and traffic conditions).

Current Prehospital Mobile Apps

Join, Twiage, and Stop Stroke Pulsara mobile apps are a few solutions to aid in prehospital diagnosis, decision-making, and reducing door to treatment times. These applications use combinations of stroke scales for EMS, HIPAA-compliant
2-way communication, group messaging, GPS tracking, and streaming of video, clinical, and radiologic data, and aim to improve hospital hand-off. Some applications allow for integration with hospital picture archiving and communications systems (PACS) and electronic medical records. These applications can improve interhospital transfers via direct interhospital messaging for referrals. All of the applications provide similar services with unique capabilities; however, no one application provides the best solution for every region. Whereas EMS applications may increase EMS workload, in one survey, most EMS providers recommended continued use, possibly because involved personnel can follow the case to its conclusion and see results such as pictures of retrieved thrombus from endovascular intervention. Use of EMS applications has been shown to reduce door-to-needle time by up to 40 minutes.

Future improvements in mobile technology, such as 5G services, will likely include smart ambulances, which may allow for location-based changes in traffic signals to allow for faster delivery of care, rapid transmission of MSU-based radiographic data, better integration of mobile apps with electronic medical records, and updated real-time hospital performance metrics.

Prehospital Devices
Although a prehospital stroke severity scale improves clinical outcomes and treatment times, mobile applications and decisions to bypass PSC by EMS are limited by the accuracy of such a scale. Prehospital stroke scales have a positive predictive value of approximately 35%–50% and result in improper delivery of patients with LVOs to PSC in about 20% of cases. Hence, patients with stroke need a brain ECG: a prehospital diagnostic test that is simple to use, cheap, fast, accurate, and compact. Several technologies based on asymmetry between cerebral hemispheres have been developed that may improve prehospital diagnostic accuracy of LVOs.

The most exciting advancement in prehospital LVO detection is the volumetric impedance phase shift spectroscopy (VIPS) device (Cerebrotech) (Figure 1). VIPS is a visor-helmet that transmits low-frequency energy radio waves from 2 transmitters on each side of the head and has a receiver in the forehead portion of the visor. It compares bioimpedance of both cerebral hemispheres and determines asymmetry resulting from changes in electrical signatures from alterations in the distribution of fluid and electrolytes in intracelluar, extracellular, and intravascular spaces of the brain. The VIPS for the noninvasive detection of hemispheric bioimpedance asymmetry in severe brain pathology study (VITAL) examined 248 patients and found the VIPS device to have 93% sensitivity and 87% specificity for detecting large anterior circulation strokes compared with others.

Similar to VIPS, the Lucid Robotic System (Lucid M1 transcranial Doppler [TCD] ultrasound system; Neural Analytics) is a robotically assisted ultrasound device that uses a TCD-derived biomarker to detect asymmetry between cerebral hemispheres. The cerebral blood flow velocity waveform and velocity curvature index (VCI) has been shown to correlate with the presence and site of arterial occlusion.

VCI measurements allow for an accuracy of 88% in detecting LVOs, with a sensitivity of 91% and specificity of 85%. Future directions may allow for rapid scanning and mapping of multiple vessels combined with artificial intelligence (AI) to provide practical models of cerebral hemodynamics. Combination of this technology with other TCD or bioimpedance modalities could improve early LVO detection accuracy.

Other devices for early detection of LVOs include the SONAS (BURL Concepts) device, BrainPulse, and EEG-based devices. These devices use a battery-powered TCD that utilizes microbubbles as acoustic traces, machine learning based on blood surge asymmetry, and EEG asymmetry, respectively.

Although preliminary, these promising technologies represent improved opportunities for early LVO detection allowing for more accurate triage of patients with stroke.

AI and LVO Detection
MT candidates in the late time window after stroke onset (6–24 hours) frequently undergo noninvasive angiography and perfusion imaging. Perfusion imaging takes about 60–90 seconds for acquisition and requires postprocessing of imaging (<5 minutes), which may be significantly delayed by inexperienced radiology technicians. Machine learning algorithms have been designed to simplify the process of obtaining and interpreting neuroimaging and have been integrated into mobile apps. Many of these neuroimaging technologies allow images and AI outputs to be automatically pushed to PACs, a mobile app, and email notifications, with some offering an integrated mass communication platform (Figure 2).

Upcoming AI-based software such as MethinksLVO aims to reliably detect LVO on noncontrast CT scans, which may...
significantly reduce door-to-groin times and reduce the need for noninvasive vessel imaging. Currently available AI-based software includes Brainomix e-Stroke Suite (Brainomix/Olea Medical), which provides a numerical Alberta Stroke Program Early CT Score (ASPECTS) and determines the volume of hypodensity from noncontrast CT scans and the presence of LVOs by assessment of asymmetry in collateral blood vessel density. Similarly, FastStroke and CT perfusion 4D Neuro (GE Healthcare) provide arterial and venous displays for collateral circulation assessment and visualization of perfusion maps. Although AI-based perfusion imaging allows for adjudication of results, the accuracy of most AI-based perfusion algorithms has not been validated and may result in over-imaging and exclusion of patients who may benefit from MT, particularly those who present within 6 hours of symptom onset.

The largest advantage of AI-based neuroimaging software has become mass communication of automated LVO detection. Viz.ai LVO and CT perfusion has automatic activation of treatment systems without any action required by a provider when an LVO is detected. This US Food and Drug Administration (FDA)–approved app has resulted in faster detection in more than 95% of cases and saved a mean of 52 minutes in interhospital transfers. Similarly, iSchemaView RAPID (Rapid Processing of Perfusion and Diffusion), the only validated perfusion (MRI) imaging algorithm, can perform automated ASPECTS scoring, infers LVO from asymmetry in collateral blood vessel density, and has mass communication abilities. Lastly, AI-based neuroimaging software logs stroke-related data, which allows for analysis of practice trends through administrative platforms.

There is limited comparison among machine learning algorithms for neuroimaging. However, all AI algorithms may miss LVOs and are not a substitute for human decision-making. Failures may occur in patients with previous neurologic injury, inadequate contrast bolus, or significant patient motion. Similar to currently available self-driving cars, machine learning in medicine requires close human supervision.

**Endovascular Robotics**

Over the past 2 decades, there has been dramatic growth in the use of robotic systems for selected procedures in urologic,
gyneecologic, orthopedic, cardiothoracic, gastrointestinal, and
general surgery.20 In the neurosciences, stereotactic neuro-
surgical applications such as pedicel screw targeting, stereo-
EEG, and tumor resection now routinely benefit from the
combination of image guidance and high precision robotic
guide placement. While minimally invasive neurosurgical
procedures are becoming mainstream, the use of robotic in-
struments for performance of neuroendovascular procedures
is in its infancy.

Pioneered for percutaneous coronary intervention (PCI), ro-
botic systems for endovascular procedures consist of a master
control interface for the operator and a robot that manipulates
the catheters and wires.21 The robot is mounted to a conven-
tional angiography table in an existing angiography suite. After
arterial access is obtained, catheters and wires are introduced
through the sheath and connected to the robot. This electro-
mechanical manipulator permits axial advancement/retraction
and rotation through a series of stepper motors and roller
bearings.21 The networked control interface may be placed
within the angiography suite behind shielding, in the control
room, or an arbitrary distance away. These remote-control
systems utilize joysticks and touchscreens rather than con-
ventional catheter manipulation. This arrangement permits
both high precision of movement (<0.2 mm axially, <2° rota-
tionally) as well as arbitrary separation of operator and
patient.22

Several endovascular robotic systems have been developed.
These include prototypes such as the VIR-2 (Beijing Navy
General Hospital),23 as well as FDA-cleared devices including
the Magellen (Hansen Medical)24 and the Corpath 200 and
GRX (Corindus/Siemens) (Figure 3). To date, FDA-approved
indications for these systems have been in the cardiac space.
A series of large registries including PRECISE and CORA PCI
demonstrated that complex PCIs can be performed safely, with
high technical success, with more precise stent placement, and
dramatically reduced operator radiation dose as compared to
conventional PCI.25-27 Taking advantage of remote operation
capability for proof of concept, telerobotic PCI over a 20-mile
distance was recently demonstrated in 5 patients with complete
technical success and no complications.28

Robotics and Neurointervention

Although no systems are available with a neuroendovascular
indication and only one has been submitted for approval to
the FDA, multiple case reports have demonstrated successful
diagnostic cerebral angiographic procedures with the existing
units indicated for cardiac procedures.22-24 These early small
case series suggest that robotic cerebral angiography can be
performed safely, with no excess complications, and with
elimination of operator radiation exposure.23,29 Although
initial procedure times were prolonged, after a short learning
curve, procedure time, fluoroscopy time, and contrast use
became equivalent to conventional angiography.23,24,30 Be-
yond neurodiagnostic procedures, there have been recent
reports of stent-assisted cerebral aneurysm coiling and carotid
artery stenting utilizing an endovascular robot system.3,31

Despite these technical successes, the potential benefits of
endovascular robotics remain to be proven in the neuro-
vascular space. Posited benefits include shorter procedure
time, decreased endothelial damage, decreased contrast dos-
age, and reduced radiation exposure.24

Benefits of Robotics to Operator

The separation of the operator and the robot from across the
room to a great distance away enables multiple benefits.
Shielding or remote location of the control unit has been
shown to dramatically reduce or eliminate the operator radia-
tion dose that may contribute to attributable cancer risk and
posterior subcapsular lens opacities in endovascular opera-
tors.30 Reduced need to wear heavy radiation protection
garments and the ability to sit at an ergonomic console may
also reduce orthopedic injuries including cervical and lumbar
disk disease.30 Beyond benefits to the operator, the ability to
remotely operate these systems could have substantial effect
on cerebrovascular systems of care.

Geographic and workforce constraints, as well as the recent
coronavirus disease 2019 (COVID-19) pandemic, have
combined with technological advances to drive the growth of
tele-neurologic consultation, particularly in cerebrovascular
disease. However, although patients may be examined by
video, imaging reviewed, and thrombolysis initiated remotely,
MT requires transport to a neuroendovascular specialist at a
thrombectomy-capable center. In situations where transport
is time-prohibitive, endovascular robotics has the potential to
allow remote MT for stroke without prolonged transport,
reducing door-to-groin time and potentially improving out-
comes. The presence of robots at multiple spoke hospitals
associated with a master control unit at a hub may also allow
expanded neurointerventional coverage by a single on-call
physician in situations where travel to all potential spoke
hospitals in a timely fashion is not feasible. In addition to time-
sensitive interventions, remote neuroangiography would

Figure 3 Demonstration of a Robotic Neuroendovascular
Device
spread expertise virtually across a region and potentially reduce transfers for routine diagnostic angiography. One can further envision using telerobotic systems in telementoring of junior operators and teleproctoring for new devices.

Barriers to deployment of neuroendovascular robotic systems in-house include a high upfront cost and operator acceptance. The lack of haptic or tactile feedback and the use of joysticks and touchscreens rather than conventional catheter manipulation in current-generation devices may limit operator acceptance. For remote use, the need to have a modern biplane angiography suite and a highly trained local team of radiologic technologists and nurses restricts feasible deployment to a narrow case use.

Endovascular Neuromodulation and Imaging
Recent advances in endovascular device fabrication have the potential to add neurophysiologic monitoring and treatment to the endovascular toolbox. Endovascular approaches for neurophysiologic recording have been investigated since the 1970s, when the use of venous cavernous sinus electrodes in humans was reported. The modification of a guidewire for use as an intraarterial electrode for the detection of seizures in the middle cerebral artery of patients undergoing endovascular arteriovenous malformation embolization was subsequently described. This includes multielectrode designs that have been placed deep into the cerebral venous system of animal models to demonstrate the potential for multichannel recording with high resolution. After the introduction of the stent-retriever for stroke treatment by MT, the stent-retriever skeleton was used as a basis for a novel multichannel electrode. Other variations on stent-retriever–based electrodes are possible. Beyond electrographic sensing, intravascular stents have been created that are fitted with physiologic sensing capability including monitoring of intracranial pressure and assessment of in-stent stenosis.

Endovascular Electrodes
The Synchron Stentrode consists of an array of five to ten 750-μm platinum electrodes affixed to a Medtronic Solitaire revascularization device: a self-expanding laser-cut nitinol stent permanently mounted on a guidewire. The electrodes are welded to insulated leads wrapped around the guidewire. The electrode characteristics of the stent-retriever–based electrodes have been well-characterized from the materials used to electrode impedance using a bovine model. Endovascular electrodes, as with other intracranial, epidural, subdural, and depth electrodes, have significantly higher signal to noise ratio than scalp electrodes due to the lack of interposed insulating cranium. In comparison to invasive electrode systems, endovascular stent-based electrodes have equivalent performance in terms of signal strength, spatial resolution, and bandwidth as epidural arrays but are marginally inferior to subdural grids due to the interposed dura layers between the electrode and the brain parenchyma. A limitation of endovascular electrodes is limited anatomical reach. Although each individual scalp electrode for routine EEG has a receptive field less than 2 cm, an array of 16 or more electrodes covers the brain. The receptive field of a single stent-based electrode is similar in size to that of a scalp electrode. However, this electrode system has more constrained targeting due to confinement within existing large vascular channels. Furthermore, the system has a smaller net receptive field due to restricted number of individual electrodes on a stent and number of stent-based electrode systems that can be placed within the vasculature. Like subdural grid electrodes and epidural arrays, this makes endovascular electrodes more applicable to targeted applications rather than generalized recording.

Venous Electrodes
Venous endovascular conduits provide access to midline and deep structures that are difficult to record or stimulate from using cortical electrodes and may otherwise require invasive monitoring. The Stentrode has been shown in ovine models to permit monitoring of EEG via superior sagittal sinus access. The endovascular stent-based electrode has also been placed into cortical veins as small as 1.7 mm overlying the sensory and motor strips. Electrodes placed in dural venous sinuses can record from regions currently requiring penetrating depth electrodes or implanted electrode arrays in deep structures closer to midline such as the cingulate gyrus, hippocampus, and insular cortex. Vascular conduits directly over sulcal folds provide unique access with close apposition to the underlying sulcus for endovascular electrodes. As vascular channels may prevent penetrating depth electrode placement and interfere with grid array recordings, the use of endovascular electrodes could provide complementary data in regions not directly covered by traditional invasive electrodes.

Application of Endovascular Electrodes
Potential applications of endovascular electrodes beyond seizure detection and localization include therapeutic tissue ablation, deep brain stimulation, and input for prosthetic limb control. Seizure reduction with monitoring and feedback with focal stimulation using implanted stimulators, grids, and depth electrodes is an evolving field. Focal stimulation using endovascular electrodes has been demonstrated in animals. In addition, the use of focal cortical ablation for seizure control using temporary endovascular electrodes has been demonstrated in an animal model. The utility of deep brain stimulation using penetrating depth electrodes is well-established for movement disorders and numerous other clinical targets including dementia and behavioral disorders are under study. Based on human venous anatomy, adjacent functional regions, and required energy delivery thresholds, computational modeling indicates that the subthalamic nucleus, internal capsule, nucleus accumbens, hippocampus, and subgenua white matter are all feasible targets for endovascular deep brain stimulation. Finally, the use of invasive recordings for control of prosthetic limbs, the brain–computer interface, is an active area of study for the developers of the Stentrode. The first therapeutic use of a stent-electrode array in humans...
was recently described where a motor neuroprosthesis was implanted in the superior sagittal sinus of 2 patients with amyotrophic lateral sclerosis and enabled digital device control in conjunction with eye movements to allow them to perform remote communication, online shopping, and banking tasks.

Long-term seizure monitoring, deep brain stimulation, and brain–computer interface applications require permanently implantable systems. Chronic implantation of endovascular electrodes for as long as 238 days has been shown to be feasible and safe in humans. CT imaging in chronic implants demonstrates integration of endovascular electrodes into the vessel wall with improvement in electrode impedance due to integration. No venous sinus thrombosis or other complications have been reported. Development of fully implantable endovascular neuromodulation systems including wireless charging and data transfer are ongoing.

**Optical Coherence Tomography**

Another exciting technology in neurointerventional surgery is the use of optical coherence tomography (OCT). OCT uses low-coherence light to develop high-resolution cross-sectional imaging from optical scattering tissue. It is currently used clinically to detect abnormalities of the retina and intravascular OCT.
was approved by the FDA for coronary imaging in 2009. Data from cardiac literature shows that intravascular OCT can visualize plaque morphology, thrombus formation, and interaction of the vessel wall with stents better than other techniques, including coronary angiography. Intravascular OCT in neurointervention is promising and would potentially allow high-resolution imaging of plaques, luminal stenosis, visualization of perforators for planning and treatment with intravascular devices, and may help make antplatelet decisions in patients with intravascular devices. In vivo canine studies have shown that OCT can more reliably detect flow diverter wall apposition and early thrombus formation. Other uses may include detection of aneurysm coil herniation into the parent vessel and high-resolution imaging of aneurysm wall structure. However, current intravascular OCT technology limits intracranial imaging due to possible device fracture with high-frequency rotation of the imaging lens, stiffness of intravascular OCT devices, which makes navigating around tortuous segments such as the internal carotid artery siphon challenging, and limited tissue depth penetration. As intravascular OCT technology evolves, it will likely play a significant role in neurointerventional procedural planning, patient selection, assessment of intravascular devices and intra-procedural complications, as well as antplatelet regimens. The Table summarizes the advantages and disadvantages of new technologies in interventional neurology.

Over the past few years, there has been rapid development of diagnostic and treatment techniques in cerebrovascular diseases. This reflected positively on the mortality rates of stroke in the developed world. With the creativity of physicians in the field, this benefit will continue to spread to other parts of the world and new treatment windows will likely open up for stroke and other challenging neurologic diseases.

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Appendix
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