What's Next in Stroke Care?

Experts discuss the next stages of stroke treatment, focusing on new technologies, systems of care improvements, and clinical trials.

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TECHNOLOGIES AND TECHNIQUES ON THE HORIZON

The last decade has seen the development and arrival of the first efficacious technologies for retrieving clot from the large arteries of the brain. These technologic improvements have transformed the field and made the procedural component of treating large vessel stroke straightforward and safe in most cases. Seven clinical trials have demonstrated that stroke can be halted and disability can be prevented using thrombectomy as the standard of care for many patients with this devastating disease.[1-7] Much of the current work that needs to be done to disseminate the treatment across the country concerns the systems of care and not technology. However, there are some important technologic developments in the works.

The first exciting developments are likely outside of the treatment arena. We will soon see the emergence of easy-to-use, handheld technologies that will be available in ambulances for emergency medical services (EMS) to screen for and diagnose intracranial large vessel occlusions (LVOs) with adequate sensitivity and specificity to immediately triage patients to the appropriate centers. The technologies under development by various companies and university research ventures include the use of microwaves, ultrasound, blood oxygen sensors, and radiowaves. Some of these devices are currently used for neuromonitoring and are now being tested in the field for large vessel stroke detection. This is important because it may solve the prevalent problem of delays in patient care due to interhospital transfers. Patients with LVOs can bypass stroke centers that do not have intervention capability and be brought directly to comprehensive stroke centers when appropriate.

Modern stroke devices in clinical use (eg, stent retrievers, large-bore aspiration catheters) achieve high rates of recanalization from 58% to 88% in the recent trials.[1-7] However, approximately 15% to 25% of patients still do not achieve adequate recanalization. New devices in current trials may allow for an even greater percentage of good recanalization. The EmboTrap revascularization device (Neuravi, Inc.), which is being evaluated in the ARISE 2 clinical trial, is a stent retriever designed to allow flow to be restored immediately upon deployment.

There is an inner flow channel surrounded by several petal-shaped meshes, which are designed to trap the clot. The distal tip of the device has a filter-type design to catch any loose clot fragments. The Embolus Retriever with Interlinked Cages (ERIC) stent retriever (MicroVention Terumo) was designed to reduce the amount of time needed for thrombus integration. As the name suggests, the ERIC stent retriever is composed of spherical wire cages that come in different sizes and are linearly linked together. The DAISe retrieval and protection device (Mivi Neuroscience) differs from stent retrievers in that it is composed of interwoven, individual soft fibers that can conform to the vessel and act as a backstop for aspiration. The clinical trial for this device has not yet started. These are only a sample of the current devices in development that aim to push recanalization rates toward 100%.

Another important technologic advancement will be in the ability to retrieve more distal clots in the cerebrovasculature. We have seen the increased use of the smaller-diameter stent retrievers in branches of anterior, middle, and posterior cerebral arteries. Finally, patient selection with the help of technologies to differentiate the ischemic penumbra from established stroke continues to be the holy grail of multimodal stroke imaging. If ongoing trials of endovascular therapies for stroke beyond 6 hours demonstrate treatment efficacy, more emphasis will be placed on identifying and selecting patients for treatment using imaging technology. Moving this acute imaging into the angiography suite by using innovative flat panel technology is already underway and will allow for the ultimate, one-stop suite of the future—direct from EMS to the angiography table.

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FUTURE IMPROVEMENTS FOR SYSTEMS OF CARE

There is overwhelming evidence that patients with emergent LVOs benefit from mechanical thrombectomy. This presents a challenge for our systems of care to ensure that every patient has the best chance to receive this therapy. Current stroke systems of care have been predominantly designed around delivering intravenous (IV) tissue plasminogen activator (tPA). Although this structure was adequate before the "emergent LVO" era, it is not sufficient moving forward. Most current stroke systems of care operate with the concept of a "hub-and-spoke" hospital system, with most modalities focused on sending patients to the closest hospital first. However, the closest hospital may not always be the most appropriate treatment center for a particular patient.

Interfacility transfers are slow, and up to one-third of patients become ineligible for thrombectomy after transfer due to logistic delays.[1] This begs the question of whether a patient should be transported to the closest hospital (which may be a primary stroke center [PSC] capable of delivering IV tPA but not mechanical thrombectomy) or instead be transported to the closest appropriate hospital for their condition. A recent experiment modeling a variety of scenarios using data from the ESCAPE trial showed that in most scenarios, transporting patients directly to an endovascular-capable center (ECC) is likely to result in better outcomes.[2] This occurred even with the assumption of a door-to-needle time of 30 minutes at the PSC and the patient departing the PSC within 15 minutes of the IV tPA bolus. These times are rarely achieved in the real world. For example, Sun and colleagues showed a median time of 83 minutes from arrival at the outside hospital to notification of the endovascular center.[3] Additional time after that notification is necessary

to prepare the patient for transport. Indeed, Holodinsky and colleagues commented that, "On the basis of this modeling, it is abundantly clear that the door-to-needle time at the non-ECC must be reduced to an average of 30 minutes for the drip-and-ship model to be viable."[2] Those times are not routinely achieved at most PSCs.

This brings us to perhaps the most important decision in the stroke chain of survival—how do we get the patient to the right hospital the first time? Current EMS protocols primarily focus on recognition of possible stroke in the field with screening tools such as FAST (Field Assessment Stroke Triage). However, routine stroke severity assessment is not part of the protocol in most areas. As such, every stroke is treated the same, whether someone has mild facial droop or a complete hemiparesis with aphasia and gaze deviation. The introduction of field severity scales is a must. These few seconds spent in the field can save hours down the road. A variety of scales exist, including the Los Angeles Motor Scale (LAMS), Rapid Arterial Occlusion Evaluation (RACE), FAST for Emergency Destination (FAST-ED), Cincinnati Prehospital Stroke Severity Scale (CPSSS), and the Stroke Vision, Aphasia, Neglect (VAN) assessment. The optimal scale for stroke assessment is unknown at this time, but the use of any stroke severity scale is better than none at all.

Once stroke severity has been assessed, the critical question becomes, "What is the best hospital to take this patient to?" In this case, stroke and trauma share similarities. Both are time sensitive with potential life-threatening diagnoses. In both, the assessment made in the field is based on mechanism and physical examination findings and a suspicion of a severe injury or stroke. In both situations, the final diagnoses will be made at the hospital after performing a more detailed assessment of the patient, including the use of advanced imaging.

Another important similarity is that there are centers of varying capabilities, and the closest center to the patient may not be the most appropriate. Therefore, it is reasonable to suggest that patients who have a high likelihood of an emergent LVO based on a field assessment should be transported directly to the ECC if it is in close proximity. If an ECC and non-ECC are equidistant, there is no question that the patient should be taken to the ECC. Even with an additional 30-minute transport time, in most scenarios modeled, a patient would be better off being taken directly to an ECC.[2] If the endovascular recanalization rate achieved at the ECC is at 90%, then even with an additional 90-minute transport time, direct transport to the ECC was found to result in better outcomes in the model used by Holodinsky et al.[2] Local politics may interfere, but the precedent certainly exists for trauma—the closest center is often not the most appropriate based on clinical findings in the field. Why should stroke be any different?

In summary, the next challenge for stroke systems of care is effective prehospital triage. EMS personnel must grade stroke severity rather than simply screen for possible stroke. Point-of-entry protocols specific to every region will need to be developed, taking local geography and capabilities into account. For patients with a suspected emergent LVO based on a field stroke severity assessment, direct transport to an ECC will save lives, prevent disability, and improve outcomes.

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UPCOMING AND ONGOING CLINICAL TRIALS

Recent clinical trials have established mechanical thrombectomy as the standard of care treatment for LVO stroke. Nevertheless, only a minority of stroke patients are eligible for thrombectomy, and 50% of patients still experience poor clinical outcomes even after successful thrombectomy.[1] Additional work is necessary to understand ways to increase the number of stroke patients eligible for thrombectomy, as well as the number of patients with improved clinical outcomes after successful reperfusion.

One important focus of investigation is to optimize the speed of recanalization. A strong time-outcome relationship has been demonstrated across multiple clinical trials, with a 10% decrease in good outcomes occurring with every 30 minutes of persistent occlusion.[2] A reduction in time to reperfusion can be achieved at many levels of the stroke systems of care. For instance, the use of stroke severity scales in the field can allow for prehospital triage of patients with suspected LVOs, thus facilitating direct transport to a center capable of performing endovascular thrombectomy. This process would be compared against the standard process of care, which involves transport to a PSC, followed by transfer to the comprehensive center, the so-called drip-and-ship paradigm. Although there will always be concern regarding

delays to administration of IV tPA, a minority of patients with LVOs will reperfuse with IV tPA alone, and the transfer delays associated with a drip-and-ship paradigm can be substantial.

Another area of active investigation involves broadening the eligible population to include patients who are not covered under the current guidelines for mechanical thrombectomy. Several clinical trials are evaluating the use of mechanical thrombectomy in patients presenting beyond 6 hours of onset (POSITIVE, DEFUSE-3, DAWN). If these trials show a benefit for thrombectomy, the pool of patients considered for endovascular treatment will be greatly expanded. In addition, patients with LVOs but low stroke severity, occlusion of the middle cerebral artery M2 segment, and moderate-to-large core infarcts do not fall under current treatment guidelines. Future trials will likely identify the subset of these patients that would benefit from endovascular treatment.

Finally, the clinical efficacy of recanalization might be increased with adjunctive neuroprotection, and the efficacy demonstrated with thrombectomy has reinvigorated the quest for the clinical translation of a neuroprotective agent. Many neuroprotective agents were highly effective in preclinical animal models but later failed when tested in human stroke clinical trials. Selection criteria for thrombectomy ensure a more homogenous population of stroke patients, which could potentially increase the likelihood of realizing a benefit for neuroprotection.

Several neuroprotective strategies are currently being evaluated in the setting of reperfusion therapy. First, the RHAPSODY trial is currently evaluating the use of a highly promising neuroprotective agent (3K3-APC, ZZ Biotech LLC) following IV tPA and/or thrombectomy. In addition, the neuroprotectant NA-1 has been evaluated extensively in small and large animal models as well as in a human trial of aneurysm coiling and has shown remarkable efficacy. This drug will be administered to patients who undergo thrombectomy in the upcoming ESCAPE NA-1 trial. Clinical success with any of these adjunctive neuroprotectants will undoubtedly spur additional efforts to determine the optimal neuroprotective strategy to pair with endovascular thrombectomy.

We have only scratched the surface of the potential for endovascular treatment of stroke. Future clinical trials will likely expand the number of eligible patients for thrombectomy, as well as increase likelihood of improved outcome after recanalization. ■

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