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Acute Neurointervention for Ischemic Stroke

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KEYWORDS

• Stroke • LVO • Mechanical thrombectomy

KEY POINTS

- Advent and implementation of stent retrievers has revolutionized the management of ischemic strokes caused by large vessel occlusion (LVO).
- Patient selection is complex. Salient variables for case selection include patient age, prestroke disability, National Institutes of Health Stroke Scale score, LVO territory/location, and time of presentation from symptom onset.
- Quality of reperfusion after the first pass of mechanical thrombectomy is associated with better outcomes.

INTRODUCTION

Acute ischemic stroke (AIS) remains one of the major causes of death worldwide and a leading cause of disability. Historically, stroke care has been very challenging, and only recently has major progress been made in improving neurologic outcomes and reducing mortality. A major obstacle to advances in stroke care has been the delayed recognition of stroke symptoms by the lay public as well as clinicians. In addition, the risk of intracranial hemorrhage (ICH) due to revascularization therapies has been the major hurdle to improving stroke outcomes. It is the most feared complication of AIS therapy and when it occurs in this setting it is often catastrophic and essentially untreatable. This risk was very high with early trials of a variety of thrombolytic agents. It was not until 1995 that the first proven treatment of AIS, intravenous tissue plasminogen activator, was confirmed. That treatment was of marginal benefit, and it would take another 20 years before a highly effective treatment of the most severe strokes, large vessel occlusions (LVO), would be validated. This endovascular therapy (EVT), also known as mechanical embolectomy, requires the prompt recognition of stroke symptoms, rapid imaging of the cerebrum and the cerebral vasculature often with advanced imaging of the ischemic penumbra. Once the appropriate patient is selected to minimize the risk of ICH and maximize the potential benefit, then treatment must be initiated quickly to reduce stroke morbidity and mortality.

LARGE VESSEL OCCLUSION, DEFINITION, AND PATHOPHYSIOLOGY

AIS due to LVO is defined as the abrupt neurologic dysfunction caused by a disruption of the arterial blood supply by an occlusion of a cervical or intracranial artery. This occlusion can be in the anterior circulation (ie, internal carotid territory) or posterior circulation (ie, vertebra-basilar territory). LVO accounts for about 30% of all AIS.[1] Cause of LVO can be cardioembolic, thromboembolic (ie, artery to artery), atherosclerotic with in-situ thrombosis, and lastly cryptogenic when no clear cause is identified. The management approach is generally the same in the acute phase regardless of the cause.

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CLINICAL PRESENTATION AND EARLY DETECTION

In LVO stroke, every 1 minute of ischemia destroys about 1.9 million neurons and 14 billion synapses[2]; this makes early recognition and prompt revascularization crucial. Recognition of LVO strokes starts in the prehospital setting with emergency medical services. Various scores have been developed to help recognize LVO stroke and categorize its severity. These scores can facilitate communication with stroke centers before arrival. Although many scores have been developed, none have been shown to be superior to others and they all share a focus on the presence of motor and cortical symptoms. Regardless of the score used, LVO stroke should be suspected when a patient shows cortical signs (**Box 1**). The presence of cortical signs is a good indicator for anterior circulation LVO stroke in the prehospital as well as in-hospital setting.[3] The detection of posterior circulation strokes remains challenging due to their relative rarity (approximately 10% of LVO) but also due to the myriad clinical symptoms as well as the higher likelihood of slow clinical progression and alteration of consciousness, which can often be misdiagnosed as "confusion" or "encephalopathy."

PATIENT SELECTION AND IMAGING IN THE ACUTE PHASE

All patients presenting with strokelike symptoms should undergo a computed tomography (CT) scan of the head without contrast to exclude ICH. The presence of ICH is generally a contraindication to revascularization therapy for AIS. Often LVO can be suspected on clinical grounds if there are signs of cortical ischemia or a high National Institutes of Health Stroke Scale (NIHSS)—the latter is the standard research and clinical scale for defining stroke severity. The scale gives patients points for deficits, and the score can range from 0 for patients who are nearly normal to 42 for those who are comatose and moribund. A score of 7 or more has been found to have a positive predictive value for LVO of 84.2%.[4] The higher the score, the more severe the stroke and the greater the thrombus burden. On imaging with CT head without contrast, a hyperdense vessel sign can be seen, and this can also suggest the presence of an LVO (**Fig. 1**). However, the gold standard for acute phase confirmation of LVO is CT angiography (CTA) of the head and neck, which is used to select the most appropriate candidates for EVT. A recent single-center study revealed increase in LVO detection with performing CTA for all patients presenting with strokelike symptoms with decrease in the door to groin time and a signal toward favorable clinical outcomes.[5] Furthermore, head and neck vessel imaging have been the standard of care for stroke etiology workup. Hence, our practice has been to perform CTA head and neck in addition to CT head in the acute phase for all patients presenting with strokelike symptoms. An alternative approach in case of limited resources is to perform CTA only for patients with high suspicion for LVO such as those with a high NIHSS. The American Heart/Stroke Association (AHA/ASA) guidelines for endovascular treatment of LVO recommends that the NIHSS be 6 or higher. Patients with LVO in the posterior circulation may not show cortical signs/symptoms but rather cranial nerve deficits, motor symptoms, and/or decreased level of alertness.

In addition to the aforementioned criteria, many other clinical criteria must be considered in deciding who is a candidate for revascularization therapy. Baseline blood pressure, glucose levels, the use of anticoagulants, recent stroke symptoms or neurosurgical procedures, baseline cognitive function and level of independence, age, and many others may all affect the risk of ICH with revascularization as well as the potential for clinical benefit. More controversial is the use of advanced imaging techniques such as perfusion imaging to determine eligibility. CT perfusion (CTP) imaging is the most commonly used and is able to determine the presence of a completed infarct (infarct core) as well as regions of critical hypoperfusion, which are still salvageable (ischemic penumbra). Proponents feel that CTP imaging increases the probability of identifying patients who would benefit from treatment, as revascularization of a completed infarct is of no benefit to the patient and only increases the risk of harm. Opponents of CTP argue that the time delay in obtaining and interpreting the studies is unnecessary and only serves the purpose of excluding patients from treatment. They feel a clinical-CT mismatch (ie, a severe clinical deficit with no to minimal signs of early infarct on CT) is comparable to CTP imaging. This issue is currently unresolved but it is hoped that ongoing clinical trials would bring clarity soon.

More recently multiple artificial intelligence software platforms have been developed for the automatic detection of LVO and CTP deficits. Several have received Food and Drug Administration (FDA) approval for clinical use.

Box 1
Cortical Signs and Symptoms

- Gaze deviation
- Homonymous hemianopsia
- Aphasia
- Neglect

These platforms can be installed on the CT scanner and within minutes of image acquisition can send out email and smart phone notifications of the presence of an LVO. Although not perfect, their sensitivity and specificity are high enough (>80% for both) that they are increasingly becoming the standard means of LVO and ischemic penumbra detection especially when specialized neuroradiological interpretation is not emergently available.

THROMBOLYSIS THERAPY

Recombinant Tissue Plasminogen Activator

Intravenous recombinant tissue plasminogen activator (rtPA) remains the standard of care for patients presenting with AIS within 3 to 4.5 hours of symptom onset including patients with LVO. The use of intravenous (IV) tPA is limited to patients who meet specific and extensive criteria aimed at minimizing the risk of ICH. It is dosed 0.9 mg/kg with a maximum dosage of 90 mg; 10% is given as a bolus, and the remainder is infused over 1 hour. rtPA is most effective in patients presenting within 60 minutes of symptom onset and in those with a smaller thrombus burden. The site and size of the thrombus influences recanalization rates after rtPA with more proximal occlusions, for example, internal carotid artery, the least likely to recanalize.[6–8] As with facilitated thrombolysis in patients with ST segment elevation myocardial infarction there has been debate as to whether IV thrombolysis is of utility in the modern era of EVT. Two trials from China and Japan (DIRECT-MT, SKIP) demonstrated noninferiority of EVT with mechanical thrombectomy (MT) alone compared with MT plus intravenous rtPA for functional outcome. However, DIRECT-MT did show that MT alone was associated with significantly lower recanalization. Conversely, combination treatment showed higher rates of symptomatic ICH.[9,10] A meta-analysis of 30 studies showed better clinical outcomes, lower mortality at 90 days, and higher successful recanalization rates, without increasing the risk of hemorrhagic complications with combination therapy.[11] Because EVT is not always feasible or can fail to reach the site of occlusion, in keeping with AHA/ASA guidelines, our practice has been to administer rtPA to all those who qualify in combination with MT, especially if the patient is being transferred from a primary stroke center to a thrombectomy capable center.[12]

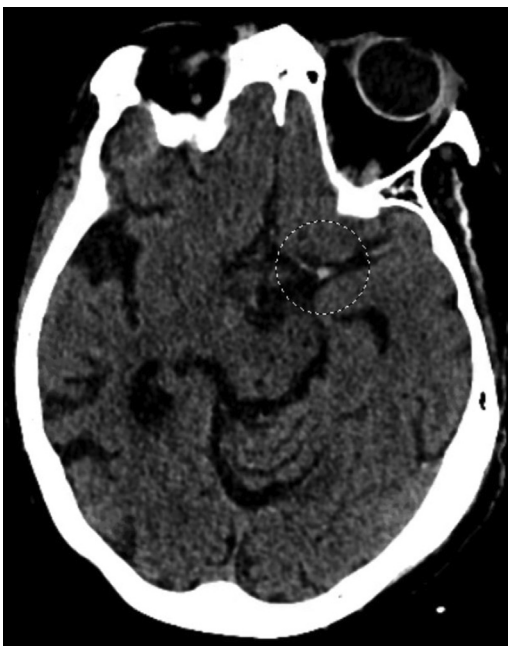

Fig. 1. Circle pointing out a hyperdense left middle cerebral artery suggesting an occlusion.

Tenecteplase

The use of tenecteplase in AIS remains a hot topic for discussion, given that IV rtPA is the only FDA-approved treatment of AIS to date. Tenecteplase, a genetically engineered mutant form of rtPA has been studied as a possible alternative to rtPA because of its longer half-life and higher fibrin specificity; the latter may be associated with lower risks of bleeding. It is also more convenient to administer as an intravenous single bolus as compared with rtPA that requires a bolus followed by an hour-long infusion. A meta-analysis of the major trials (ATTEST and EXTEND-IA TNK) in patients with LVOs showed higher odds of successful recanalization and good functional outcomes with tenecteplase compared with rtPA.[13] Although the optimal dose of tenecteplase for AIS remains unknown, current AHA/ASA guidelines consider tenecteplase (0.25 mg/kg dose with a maximum dose of 25mg) a reasonable alternative for patients undergoing thrombectomy.[12] TNK-S2B trial is currently enrolling to identify the optimal dose of tenecteplase with comparison to rtPA.

MECHANICAL THROMBECTOMY

Initial approaches to the endovascular treatment of AIS consisted of intraarterial thrombolysis with marginal clinical benefits and high complication rates.[14,15] The first FDA-approved device for AIS treatment was the MERCI (Concentric Medical Inc., CA, USA) retriever device of the early 2000s followed by the and Penumbra Inc. aspiration system. Although both devices had variable success in cerebral thrombectomy, these systems failed to show superiority over IV rtPA alone in 3 different trials published in 2013 (IMS-III, MR RESCUE, SYNTHESIS).[14–16] A breakthrough in the management for LVO stroke was the advent of the so-called stent retrievers. These devices consist of self-expanding (nitinol) stents permanently attached to 0.014″ wires. They are deployed within the occlusion/thrombus and removed a few minutes later after the thrombus has been integrated within their interstices. They are often used with a balloon occlusion guide catheter, which is used to occlude antegrade flow and permit the creation of a suction effect while the device is removed, facilitating thrombus removal.

MT has been studied primarily in patients with anterior circulation LVO. The anterior circulation includes the internal carotid (ICA), middle cerebral (MCA), and anterior cerebral arteries (ACA). The posterior circulation includes the vertebral, basilar (BA), and posterior cerebral arteries.

PATIENT SELECTION FOR MECHANICAL THROMBECTOMY IN ANTERIOR CIRCULATION LARGE VESSEL OCCLUSION

Based on the available clinical trials, careful selection of patients for mechanical thrombectomy is crucial for good outcomes. The following aspects must be taken into consideration when selecting patients:

Age Less Than or Equal to 18 Years

The available randomized controlled trials included patients who were 18 years and older. However, good neurologic outcome has been reported in case series and meta-analysis of pediatric age group who received mechanical thrombectomy.[17] In its recent report the Society of Neurointerventional Surgery recommends against withholding mechanical thrombectomy from the pediatric age group.[18] On the other end of the spectrum, the very old (90 years and older) do not have as good of outcomes as younger patients; however, all studies have shown a consistently high relative benefit for this population mostly because lack of recanalization is associated with almost uniformly poor outcomes.

Prestroke Disability

Good baseline functional status prestroke was one of the inclusion criteria for most of the clinical trials in the early and extended time windows; this was defined as a Modified Rankin Scale (mRS) score of 0 or 1 (Table 1), that is, patients with moderate or severe disabilities were excluded. Data from good, randomized trials are lacking for this patient population. Retrospective studies have shown mixed results in terms of good outcomes or return to baseline.[19,20] AHA/ASA guidelines support treatment of patients with independent baseline function, that is, mRS 0 to 1, despite this mechanical thrombectomy should not be withheld blindly for patients with moderate to severe disability, that is, mRS of 2 to 4. Our practice it to assess on a case-by-case basis and to confer with the patient's family.

NIHSS at Presentation

Most of the MT trials enrolled patients with NIHSS greater than or equal to 6, which is generally considered to be disabling. The efficacy of MT in patients with NIHSS less than 6 remains under investigation. Our practice is to offer MT based on the severity of deficits and resultant disability regardless of NIHSS, taking into account unique patient characteristics, for example, an isolated homonymous hemianopsia would result in an NIHSS of 2 but this deficit in a young aircraft pilot would be a career ending deficit but may not affect the life of an octogenarian as severely.

Location of the Large Vessel Occlusion in the Anterior Circulation

In the anterior circulation, most of the clinical trials included patients with ICA and proximal MCA trunk (M1) occlusion (Fig. 2). Patients with more distal MCA trunk or MCA branch occlusions (first-order branches in the Sylvian fissure are referred to as M2 segments) or occlusions of other vessels such as the ACA were either excluded or underrepresented. Hence the data available for safety and efficacy are applicable to distal ICA or proximal MCA LVO. The current AHA/ASA guidelines recommend limiting treatment to those vessels only. Pooled data from multiple series of MT patients with M2 occlusions have revealed generally good functional outcomes with reperfusion (mRS 0–1; OR 2.2, 95% confidence interval [CI] 1.0–4.7).[21]

Table 1
Modified Rankin Scale (mRS)

0	No symptoms
1	No significant disability despite symptoms. Able to carry out all usual activities and duties
2	Slight disability, unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability, requiring some help but able to walk without assistance
4	Moderately severe disability; unable to walk and attend to bodily needs without assistance
5	Severe disability, bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

The major concern is that more distal occlusions tend to involve smaller vessels (<2 mm), which are associated with lower NIHSS scores and which are also more angulated, all of which may be associated with higher risks of ICH and lower net benefit. Our practice for LVO involving the distal M1, M2 branches, and the proximal ACA segments is to assess patients on a case-by-case basis and to offer MT only if deficits are disabling and the occlusion can be reached safely using available equipment.

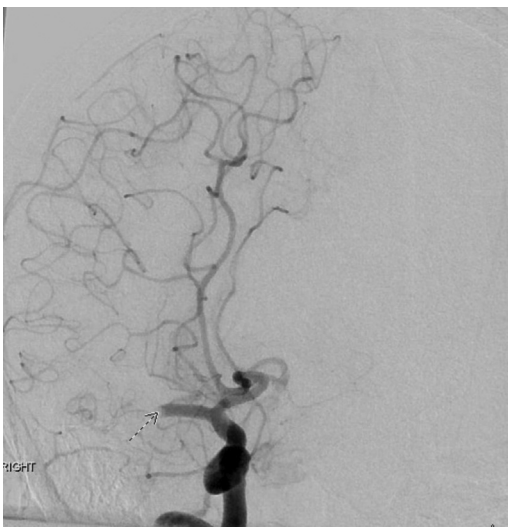

Fig. 2. Arrow points to right MCA proximal M1 segment occlusion.

Presentation 6 Hours or Less from Last Known Well (Early Window)

Six clinical trials published in 2015 compared MT with stent retrievers with intravenous rtPA alone or best medical therapy. These trials established the superiority of MT in patients presenting within 6 hours with a number needed to treat (NNT) to achieve functional independence ranging from 3 in the EXTEND-IA[22] trial to NNT of 7.5 in MR CLEAN trial.[23] A pooled meta-analysis of 5 of the clinical trials was performed by the HERMES collaboration and revealed an NNT of 2.6 to reduce disability by at least 1 grade on mRS. Patient's eligibility for MT mainly depends on the Alberta Stroke Program Early CT Score (ASPECTS). This is a 10-point score of the extent of infarction in the MCA territory on axial CT head or diffusion-weighted MRI. A score of 10 indicates no signs of early ischemia in the MCA territory, whereas a score of 0 indicates complete MCA early ischemic changes. Good outcome with mechanical thrombectomy was seen in patients with ASPECTS of greater than or equal to 6. Patients with ASPECTS less than 6 have less benefit and increased risk from mechanical thrombectomy, although it is not clear that the benefit of MT in low ASPECTS patients is not clinically meaningful. It is important that the ASPECTS be considered in the overall clinical context with the age of the patient, baseline level of independence, and patient/family preferences regarding goals of care in the setting of certain disability.

Presentation 6 to 24 Hours from Last Known Well (Late Window)

The AHA/ASA time window recommendations for MT were expanded to 16 hours after the results of the DEFUSE trial were published[24] and to 24 hours after the results of the DAWN[25] trial were published. Both DEFFUSE and DAWN selected patients for MT by using advanced imaging with CTP or MR perfusion. Both trials used the concept of infarct core (IC) to penumbra mismatch on perfusion imaging measured by automated software. Core infarct was defined equally in both trials as cerebral blood flow (CBF) less than 30% of the contralateral normal hemisphere CBF, whereas the penumbra was defined by a Tmax greater than 6 seconds, which is a region of reduced perfusion that was not yet included in the infarct core (Fig. 3).

DEFFUSE 3 enrolled patients up to 90 years of age with NIHSS greater than or equal to 6 and presenting within 6 to 16 hours of last known well. The trial required that the IC volume be less than 70 mL and an IC:penumbra

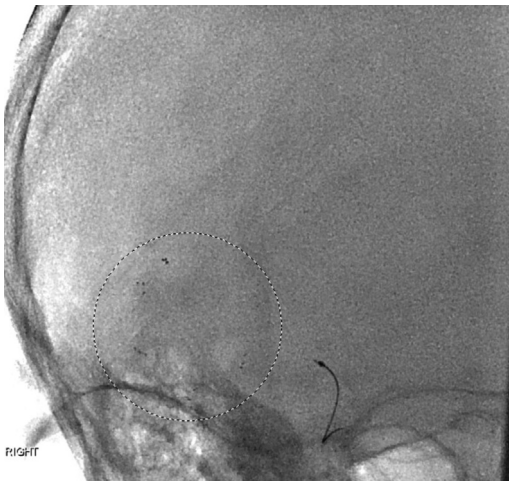

Fig. 3. Circle showing stent retriever deployed in the right middle cerebral artery.

mismatch of greater than 1.8. The trial was stopped early after enrollment of 182 patients due to efficacy of the treatment arm. Functional independence defined as mRS of 0 to 2 at 90 days was achieved in 44.6% in the mechanical thrombectomy arm compared with 16.7% in the medical treatment arm with ($P < .001$). The number NNT to achieve functional independence was 3.6.

The DAWN trial enrolled 206 patients between 6 and 24 hours from stroke onset with a more complex clinical and radiographic mismatch criteria. Penumbra was not directly assessed but was inferred based on clinical:IC mismatch: patients were categorized into 3 groups:

Group A: patients aged 80 years and older with NIHSS greater than or equal to 10 and infarct volume less than 21 mL.

Group B: patients younger than 80 years with NIHSS greater than or equal to 10 and infarct volume less than 31 mL.

Group C: patients younger than 80 years with NIHSS greater than or equal to 20 and infarct volume 31 to 51 mL.

Functional independence defined as mRS of 0 to 2 at 90 days was achieved in 49% in the MT arm compared with 13% in the medical arm. The NNT was 3. The rate of symptomatic ICH was not significantly different (6% with MT vs 3% with medical treatment, $P = .5$). These 2 trials have significantly changed the paradigm of acute stroke management in the late window. Mechanical thrombectomy outside the strict criteria set by DEFFUSE 3 and DAWN trials in the late window is considered experimental. Furthermore, some have questioned the need for such strict imaging criteria, which can delay and restrict the number of patients treated; to address this issue there are several RCTs that are assessing the benefit of MT in patients with larger IC or ASPECT less than 6.

POSTERIOR CIRCULATION LARGE VESSEL OCCLUSION

The incidence of LVO in the posterior circulation including the VA, BA, or posterior cerebral arteries is much lower than in the anterior circulation. On the other hand, acute BA occlusion carries a higher risk of severe neurologic deficit and death. The randomized trials of MT did not include this patient population and as such the AHA/ASA guidelines did not support MT with the same level of vigor as in the anterior circulation. Recently the first international RCT comparing MT with standard medical treatment in BA occlusion (BASICS) was completed with disappointing results. MT performed within 6 hours of stroke onset showed no significant benefit compared with standard medical therapy for 90-day disability. However, the confidence intervals were very wide due to underrecruitment, and a substantial benefit of mechanical thrombectomy cannot be excluded based on this trial. On subgroup analysis there was a signal of benefit with MT for patients presenting with an NIHSS greater than or equal to 10.[26] The optimal patient selection and time window for mechanical thrombectomy in BA occlusion remain unclear. One of the major challenges is that imaging of the neural structures of the posterior circulation is limited by bony artifacts with conventional CT. MRI is far superior for the detection of acute ischemia but is time-consuming and may not be readily available. Another limitation of posterior circulation MT trials is that there is a higher prevalence of atherosclerotic occlusion as the cause of the LVO compared with anterior circulation trials that may be associated with less desirable angiographic outcomes and a higher rate of reocclusion with MT performed without angioplasty and stenting. Our current practice is to offer MT to patients with significant disability or NIHSS greater than 10 who do not have evidence of extensive pontine, midbrain, or thalamic infarction. If possible, we will perform a limited MRI, so called "wake-up MRI protocol," for patients presenting beyond 6 hours to rule out irreversible infarction of the brain stem before revascularization. Further studies with larger number of subjects are needed.

REPERFUSION AND FIRST PASS EFFECT

The main goal in acute stroke treatment is to achieve complete reperfusion to the affected area of the brain as soon as possible. The modified Thrombolysis in Cerebral Infarction (mTICI) score (Table 2) is the most widely used score across all MT trials that quantify reperfusion angiographically. TICI score is proved to predict outcomes. TICI 2b and higher is considered adequate reperfusion that is associated with improved outcomes in most of the clinical trials, although more recently it is recognized that the goal of MT should be TICI 2c or 3. In some cases, multiple passes of the stent retriever are needed to achieve reperfusion, and this is associated with higher rates of complications and futility. Achievement of reperfusion after a single stent retriever pass is associated with significantly better outcomes and is known as the first pass effect. The usage of balloon guide catheters (BGC) during MT is associated with increased first pass effect.[27]

Table 2
Modified thrombolysis in cerebral infarction (mTICI) score

mTICI 0	No recanalization
mTICI 1	Minimal recanalization
mTICI 2a	Partial recanalization and perfusion of $<$ 50% of the vessel territory
mTICI 2b	Partial recanalization perfusion of $>$ 50% of the vessel territory
mTICI 2c	Near-complete perfusion except for slow flow in a few distal cortical vessels or presence of small distal cortical emboli
mTICI 3	Complete reperfusion

STENT RETRIEVER VERSUS SUCTION THROMBECTOMY (THE COMPASS TRIAL)

MT can be performed using second-generation stent retrievers, distal aspiration catheters, or both together. The COMPASS trial randomized 270 patients with anterior circulation LVO to MT using catheter aspiration (AKA contact aspiration) only or stent retriever as first-line treatment. There was no difference in good functional outcomes at 90 days between the 2 groups with similar recanalization rates, indicating noninferiority of aspiration thrombectomy. Achievement of TICI 3 within 45 minutes was better with aspiration technique (34% vs 23%, $P = .05$), and time to groin puncture was shorter compared with patients treated with a stent retriever (25 minutes vs 35 minutes, $P = .03$).[28] However, a minority of the stent retriever procedures were performed with BGC catheters, which casts doubt on the validity of the comparison. There were no significant differences in rates of ICH, all-cause mortality, or overall safety. More recently the ASTER 2 trial conducted in France[29] showed that contact aspiration combined with a stent retriever had similar rates of TICI 2c/3 and clinical outcomes to stent retrievers with BGC catheter. The current AHA/ASA guidelines acknowledge noninferiority of contact aspiration. Our approach is to use stent retrievers and BGC catheters as first-line treatment except in cases of severe cervical tortuosity, dissection, or stenosis that may preclude distal placement of the BGC, in which case we use contact aspiration along with a stent retriever.

GENERAL ANESTHESIA VERSUS CONSCIOUS SEDATION

Mechanical thrombectomy can be performed under general anesthesia (GA) or conscious sedation (CS). Several retrospective studies have shown that CS may be associated with better outcomes and lower mortality than GA.[30,31] Although GA leads to better control over patient movements, making it more comfortable for both patient and operator, it may add to the time of procedure initiation, carries the risk of significantly dropping blood pressure during induction, and masks the pain response associated with cerebral vessel stretching, vasospasm, and injury. On the other hand, CS may be associated with a higher risk of aspiration in some patients. Three small sample size randomized single-center trials (AnSTROKE, SIESTA, and GOLIATH) have shown noninferiority of GA compared with CS in clinical outcomes.[32–34] Because of the discrepancy between the very large retrospective analyses and the smaller RCTs, larger RCTs are being conducted. Until further conclusive evidence is available, we recommend individualizing anesthesia choice based on a patient's status. GA is preferred for severely agitated patients or those who are comatose and unable to maintain their airway. It is critical that drops in blood pressure be avoided during induction and maintenance of GA or CS.

BLOOD PRESSURE MANAGEMENT POSTMECHANICAL THROMBECTOMY

Hypertension is a well-known physiologic response to brain ischemia as part of cerebral autoregulation, which can maximize CBF via collaterals despite LVO. Blood pressure (BP) goals before and during MT should be to maintain BP at baseline unless it is very high (systolic BP $>$ 220 mm Hg) or low ($<$130 mm Hg). BP goals after MT have been a topic of controversy. Good evidence data from RCTs are not yet available. The best available evidence comes from a multicenter retrospective study showing a higher likelihood of good outcome and lower odds of hemicraniectomy in the group of patients with systolic blood pressure less than 140 mm Hg after successful recanalization.[35] Very elevated BP after MT has been associated with poor outcomes but so has very low BP resulting in a U-shaped curve.[36,37] Higher SBP targets can be considered on a case-by-case basis in patients who achieve partial recanalization in order to maintain perfusion to the tissue at risk. Regardless of BP goal, close observation in dedicated stroke units or neurologic critical care units by dedicated nurses and physicians is essential and has been associated with improved neurologic outcomes.[38]

DISCLOSURE

O. Alsrouji has nothing to disclose. A. Chebl has received (minor) honoraria for consulting work from Medtronic Inc, Cerenovus Inc.

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