Role of Anesthesia for Endovascular Treatment of Ischemic Stroke
Do We Need Neurophysiological Monitoring?

Laxmi P. Dhakal, MBBS; José L. Díaz-Gómez, MD; William D. Freeman, MD

The use of acute endovascular stroke intervention was called into question after the results of 2 negative stroke endovascular trials (Interventional Management of Stroke 3 [IMS-3] and Systemic Thrombolysis for Acute Ischemic Stroke per the Stroke Center registry [SYNTHESIS]). However, the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial compared patients with acute stroke with proximal anterior circulation artery occlusions with usual stroke care, including intravenous tissue-type plasminogen activator (tPA). The study demonstrated a favorable shift in outcomes in the intervention group by modified Rankin Scale (mRS) by 90 days (odds ratio [OR], 1.67; 95% confidence interval [CI], 1.21–2.30). Improvement in mRS was noted for all categories except for death. General anesthesia (GA) was used in 38% of the patients in the intervention group of MR CLEAN. In contrast, 9% of the patients in the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial received GA. The rate of functional independence (mRS, 0–2 by 90 days) was higher in the intervention group (53.0% versus 29.3%; P<0.01). Furthermore, lower mortality rate was seen in intervention group (10.4 versus 19.0; P=0.04). A recent meta-analysis by Fargen included MR CLEAN and the prior endovascular stroke trials and suggested a favorable shift outcome (mRS, 0–2; good outcome by 90 days; OR, 1.67; 95% CI, 1.29–1.16; P=0.0001) for patients with large-vessel occlusions who receive interventional therapy. In a post hoc analysis of MR CLEAN for use of GA, Berkhemer reported at the International Stroke Conference in Nashville, TN, a favorable effect when non-GA was used instead of GA (mRS, 0–2 at 90 days 38% versus 23%; P=0.013). Also, GA was associated with delayed initiation of interventional therapy in comparison with conscious sedation (CS; 162±69 versus 134±60 minutes). Moreover, conversion from non-GA to GA was 6 of 137 (4.4%). Interestingly, there was no significant difference in time to revascularization as well as procedural duration. Thus, the authors proposed not using GA for faster interventional treatment initiation. The purpose of this article is to review the literature on the implications of anesthesia during acute stroke intervention based on recent trials and provide evidence about potential neurophysiological monitoring techniques to monitor such acute stroke intervention patients during GA.

To Sleep or Not To Sleep? GA or CS?
Do patients with acute stroke requiring endovascular intervention who receive GA far better than those who receive CS or monitored anesthesia care? The available literature suggests that patients who receive GA actually do worse than those who receive CS or monitored anesthesia care. However, it should be recognized that the majority of the retrospective studies report a higher stroke severity in the GA-treated group of patients compared with non-GA patients as measured by the National Institutes of Health Stroke Scale (NIHSS). Initial NIHSS severity, however, was adjusted for between GA and non-GA groups in the post hoc MR CLEAN analysis, and the prospective study still found worse overall outcomes and time delays in the GA-treated group. Before MR CLEAN, a recent meta-analysis and systematic review by Brinjikji et al also evaluated this issue and compared those receiving CS versus GA for acute stroke intervention. The meta-analysis analyzed 9 studies with a total of 1956 patients (814 with GA and 1142 with CS). The data showed that patients undergoing GA had higher odds of death (OR, 2.59; 95% CI, 1.87–3.58), lower odds of good functional outcome (OR, 0.43; 95% CI, 0.35–0.53) and pulmonary complications (OR, 2.09; 95% CI, 1.36–3.23), with no difference in procedure time (P=0.28). However, the preinterventional NIHSS was higher on average in those receiving GA compared with CS. Therefore, given the retrospective nature of the studies, causality cannot be ascribed to GA alone because the patients had higher average NIHSS. The data nonetheless raise concerns about use of GA in endovascular stroke trials until a prospective and ideally randomized trial can delineate cause and effect.

Why, then, do patients with acute stroke receiving endovascular intervention still undergo GA? Many factors influence the decision to use GA over CS; they should be considered on an individual basis and be related to patient need or procedural
Recent surveys of stroke interventionists\(^2\) suggest that GA was the most common preference, followed by monitored anesthesia care\(^3\) and local sedation/CS.\(^2\) However, these preferences for GA by interventionalists seem to be based on perceived greater efficiency and the increased safety of having a controlled scenario for airway management for a patient who is motionless or being to deteriorate. Patients with stroke with cortical hemispatial neglect maybe relatively hyperactive on one side of their body or have psychomotor agitation and not lie still during the procedure. Other patients with stroke with aphasia may be verbally unresponsive or fail to follow verbal commands during the procedure. This is especially important when considering that intracranial guide wires or stent-retriever devices are being placed through relatively small (eg, middle cerebral artery–1st segment diameter is \(3\) mm) and occluded intracranial arteries. However, time delays of IMS\(^2\) and a post hoc analysis of MR CLEAN\(^1\) showing worse outcomes in GA patients need to be carefully considered against individual preferences. Furthermore, a pooled analysis of the GA utilization rates in the most recent prospective acute stroke intervention trials is shown in Table 1, as well as the initial NIHSS severity and outcomes (if reported).

Despite the method used, the pros and cons of either GA or non-GA anesthesia used during endovascular stroke therapy should be carefully considered (Figure). For CS, potential benefits include a minimal effect on systemic blood pressure (BP), level of consciousness, and neurological examination. Drawbacks include potential conversion to GA and intubation if the patient deteriorates. Also, patients who start as CS who cannot remain motionless to allow safe and effective intervention need to be converted to GA and may have subsequent time delays. For GA, potential benefits include a secure airway if patient is at risk for vomiting, emesis, and aspiration (eg, high NIHSS >20) and immobilization of the patient for the interventionalist. Drawbacks to GA include anesthetic induction causing hypotension and loss of standard neurological examination or the ability to assess NIHSS score during a procedure.

Prospective trials are planned to help answer this question, including ANSTROKE, Sedation Versus General Anesthesia for Endovascular Therapy in Acute Stroke–Impact on Neurological Outcome (Sweden),\(^2\) and GOLIATH, General or Local Anesthesia in Intra-Arterial Therapy (Denmark),\(^2\) which will analyze the associated outcome of CS versus GA and the BP variation in patients receiving endovascular intervention.

### Other Risks Associated With Anesthesia: To Intubate or Not To Intubate?

A recent review by Takahashi et al\(^1\) outlines other theoretical risks of GA, including delays in the endovascular procedure because of time devoted to the anesthetic induction and intubation (ie, longer door-to-needle times), as well as hypoxemia (vasoconstriction mediated) or hypotension-related injury to a vulnerable vascular penumbra. The authors also note the rate of GA used in the IMS-3 trial was 33.9%, which is similar to the aforementioned 37.8% in the MR CLEAN trial. The groups were fairly matched, except for a slight difference in NIHSS between groups (average NIHSS=16 in the local anesthesia group versus NIHSS=18 in the GA group). However, in the SYNTHESIS trial, 22 of 165 (13%) patients underwent GA.\(^2\) One of the main considerations in IMS-3 trial is that patients who received GA had higher baseline NIHSS compared with CS (18 versus 16). Furthermore, GA was less likely to achieve a good outcome (respiratory rate, 0.64; 95% CI, 0.49–0.84) and had a greater risk of inhospital death (respiratory rate, 3.11; 95% CI, 1.86–5.20).\(^2\) Also, an analysis of the IMS-1 and IMS-2 trials by Nichols et al\(^2\) demonstrated a 10% decrease in the chance of a good outcome for every 30 minutes of case delay. Therefore, the dogma that brain may trump other factors when considering GA, especially if hemodynamics and other factors are controlled. The post hoc analysis of GA versus non-GA by MR CLEAN also showed time delay in the GA group, which was associated with worse outcomes versus non-GA group.

Conversely, there are risks for not performing GA in patients with stroke with obtundation or who are at risk for airway compromise, severe psychomotor agitation that jeopardizes the expediency or safety of the procedure, or increases the risk of aspiration pneumonia and hypoxia. Therefore, the anesthesiologist plays a critical role in assessing the level of consciousness, discussing the need for GA with the neurointerventionalist, and monitoring hemodynamic changes during

### Table 1. Pooled Comparison of General Anesthesia Use in Major Recent Prospective Acute Endovascular Intervention Trials

<table>
<thead>
<tr>
<th>Stroke Interventional Trial</th>
<th>GA Utilization Rate, NIHSS Comparison With Non-GA, or Outcomes</th>
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<tbody>
<tr>
<td>ESCAPE (Goyal et al(^4))</td>
<td>9.1%, comparison NIHSS (GA vs non-GA) and outcomes not reported</td>
</tr>
<tr>
<td>MR CLEAN (Berkhemer et al(^5,18,19))</td>
<td>37.8%, GA vs non-GA patients (NIHSS adjusted) fared worse; (P=0.013)</td>
</tr>
<tr>
<td>EXTEND-IA (Campbell et al(^1))</td>
<td>36%, comparison NIHSS (GA vs non-GA) and outcomes not reported</td>
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<tr>
<td>SWIFT-PRIME(^2,25)</td>
<td>37% but no outcome differences reported as yet</td>
</tr>
<tr>
<td>REVASCAT(^2)</td>
<td>6.7% GA utilization rates, with no report on outcomes vs non-GA group</td>
</tr>
<tr>
<td>IMS(^24,28)</td>
<td>33.9%, baseline NIHSS were slightly lower in the CS group vs GA (median 16 vs 18). The GA group was less likely to achieve a good outcome (RR, 0.64; 95% CI, 0.49–0.84; (P=0.001)) and had a greater risk of inhospital death (RR, 3.11; 95% CI, 1.86–5.20; (P&lt;0.0001))</td>
</tr>
<tr>
<td>SYNTHESIS(^2)</td>
<td>12.1%, comparison NIHSS (GA vs non-GA) and outcomes not reported</td>
</tr>
</tbody>
</table>

\(P\) indicates confidence interval; ESCAPE, Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial; GA, general anesthesia; IMS, Interventional Management of Stroke; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; NIHSS, National Institutes of Health Stroke Scale; REVASCAT, Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy; RR, respiratory rate; SWIFT-PRIME, Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke; and SYNTHESIS, Systemic Thrombolysis for Acute Ischemic Stroke per the Stroke Center registry.
Anesthesia and Stroke Intervention

...the procedure. After the procedure, we would suggest management by anesthesiologists, neuroanesthesiologists, similarly stroke-trained intensivists, and neurointensivists who are competent or credentialed in the management of patients with acute stroke. Currently, American Heart Association guidelines for acute stroke do not provide recommendations for the type of anesthesia to use in acute endovascular therapy. However, the Society for Neuroscience and Anesthesiology and Critical Care provided best practice information for the perioperative management of patients with acute ischemic stroke undergoing interventional therapy, which are outlined in Table 2. We suggest medical providers be proficient in providing GA within these guidelines and in neurological monitoring and managing patients with acute stroke during and after endovascular interventions.

Anesthetic Induction, Relative Hypotension, and Anesthetic Drug Selection

Hemodynamic and BP monitoring are extremely important during anesthetic induction and the perioperative management of patients with acute stroke. BP guidelines are recommended within the first 24 hours of acute ischemic stroke to determine whether intravenous tPA is given. Typically, systolic BP is kept <185 mmHg within the first 24 hours after intravenous tPA, per Society for Neuroscience and Anesthesiology and Critical Care guidelines, similar to endovascular intervention (Table 2). In stroke, cerebrovascular autoregulation is lost because of cerebrovascular reactivity becoming constant. In other words, cerebral blood flow becomes linearly dependent on cerebral perfusion pressure. Therefore, the optimal sweet spot for BP optimization (not too high, not too low) should be individualized, and the patient’s history of pre-existing hypertension, the severity of neurological injury, volume of ischemic brain and potential penumbra, the duration of ischemic time, and risk factors for hemorrhagic transformation should all be taken in account when managing such patients. Some anesthetic agents such as volatile gas agents (eg, isoflurane and sevoflurane) and intravenous barbiturates such as thiopental, ketamine, and propofol have purported neuroprotective effects perhaps because of the reduction in cerebral metabolic consumption of oxygen (CMRO₂). However, any potential neuroprotective effect would seem to be more theoretical, given the negative results of the 9-study meta-analysis comparing GA versus CS by Brinjikji et al. As mentioned above in Table 2, Society for Neuroscience and Anesthesiology and Critical Care recommendations suggest that the anesthetic agent be individualized based on the characteristics of patient with stroke.

Neuromonitoring at postoperative recovery and neurointensive care unit or equivalent

Neurophysiological Monitoring During GA: To Monitor or Not To Monitor?

Patients receiving CS can perform an intermittent focused neurological examination (clinical monitoring) as needed during the neuroendovascular procedure. Dramatic neurological improvement (ie, NIHSS, ≥10) is reported after some MCA recanalization cases and patients may spontaneously speak or move the previously hemiparetic side. In those cases, the neurological examination and NIHSS correlate with volume of brain salvaged and, in most cases, improved functional neurological outcome. However, patients with acute stroke under GA will not be able to perform a neurological examination, which creates a dilemma for a clinical outcome–based disease. Neumonitoring (NM) methods outside of the angiographic information during endovascular intervention or standard GA monitoring includes transcranial Doppler (TCD), electroencephalography, somatosensory-evoked potentials (SSEP), and near-infrared spectroscopy (NIRS). The type of NM method used depends on the availability, expertise, and clinical question to be answered during the procedure. For the following NM techniques described below, the potential delay in door-to-intervention times should be considered a major limitation,
delays in starting the stroke endovascular intervention are associated with worse outcomes. 24

Transcranial Doppler
TCD estimates cerebral blood flow velocities of proximal segments of the medial (middle cerebral artery–1st segment), anterior (anterior cerebral artery–1st segment), and posterior cerebral arteries. 36 The main advantage of TCD is that it can provide real-time measurement of large intracranial artery blood flow, blood vessel patency, microemboli, and recanalization status. Furthermore, TCD can also potentially augment the thrombolytic effects of intravenous tPA, known as sonothrombolysis to disrupt an intracranial arterial thrombus. 37,38 In MCA stroke as compared with conventional angiography, TCD is ≈91% sensitive and 93% specific. 39 TCD can also monitor the effects of intravenous or intra-arterial thrombolytic therapy for recoclusion and hyperemia. 40 Many limitations exist for use of TCD as a NM tool during an acute neuroendovascular procedure with GA. The main limitation is the concern for time delays and the 24/7 availability and technical adequacy of the personnel performing these exams. Also, the TCD probe itself might interfere with the digital subtraction angiogram images. Also, the angiogram itself can visualize proximal and distal MCA segments, unlike TCD. Therefore, the use of TCD during the acute GA-treated stroke endovascular intervention is questionable because of these significant limitations.

Brain Oxygenation Methods
Jugular venous oxygen saturation (SjvO₂) measures the hemispheric brain mixed arteriovenous oxygenation but has fallen out of favor because of the development of noninvasive techniques such as NIRS. 36 Measurement of SjvO₂ requires the insertion of a jugular venous catheter in patients, potentially with intravenous tPA, which not only delays the neuroendovascular procedure itself but can also be associated with complications such as internal carotid artery injury, immediate venous puncture bleeding or later thrombosis, and infection. NIRS uses near-infrared light between 600 and 1000 nm in length to penetrate the human scalp, skull, and brain tissue to 2.5 cm below the skin level. Hence, NIRS provides noninvasive information of mixed arteriovenous oxygenation. Most NIRS monitors are placed above the eyebrows to sample frontal ACA-MCA vascular territories. Although relative desaturations in regional saturation of oxygen (rSO₂) values are described during carotid occlusion and carotid endarterectomy (CEA) clamping, 41 there are no large prospective data to recommend this NM technique routinely during GA for patients with acute ischemic stroke undergoing neuroendovascular therapy.

Electroencephalography and Quantitative Electroencephalography Techniques
An electroencephalogram typically uses at least 18 electrodes circumferentially around the head and has the ability to detect reduced cerebral blood flow when compared with positron emission tomography. 32 The usefulness of electroencephalography has been demonstrated during NM monitoring of surgical treatment of cerebral aneurysm clipping, 43 carotid artery clamping, and during CEA. 44 In patients undergoing CEA, major electroencephalography changes occur with marked electric attenuation and slowing with cerebral blood flow values <10 mL/100 g per minute, with the critical level defined as 15 mL/100 g per minute. 34,46

Although quantitative electroencephalography methods have emerged using Fast Fourier Transformation to provide surrogate cerebral ischemia information, 47,48 there are many
limitations of this technique in the acute stroke endovascular setting. The main limitation is related to 24/7 availability of technical staff to place electroencephalography electrodes and 24/7 neurological expertise in reading electroencephalography to provide real-time feedback during the neuroendovascular procedure. Another limitation is electroencephalography sensitivity being limited by GA itself with deeper levels of sedation and anesthesia which reduce cerebral blood flow (globally). Also, electroencephalography electrodes themselves or their wires may interfere with the digital subtraction angiographic images. Therefore, we do not recommend the routine use of electroencephalography during acute stroke endovascular therapy until larger data sets show evidence of its benefit.

SSEP and Brain Stem Auditory Evoked Potentials
Intraoperative SSEP recording has been used as a warning of impending ischemic injury during CEA.49 Rowed et al49 compared simultaneous SSEP, TCD, and electroencephalography during CEA. Cortically generated P25 amplitude of median SSEP was the most reliable method. Median SSEP generates electric shocks at either median nerve location with recording electrodes at the elbow, Erb’s point, cervical spine, and scalp. Brain stem auditory evoked potentials are primarily used in neurosurgery involving monitoring of the brain stem or cranial nerves. There are no reports of using SSEP or brain stem auditory evoked potential intraoperatively for acute stroke neuroendovascular intervention under GA. Therefore, we cannot recommend these NM methods for monitoring acute endovascular stroke therapy patients because MR CLEAN, ESCAPE, and Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial (EXTEND-IA) do not mention these methods being used for monitoring their patients under GA.

Discussion on Endovascular Trials: The Pendulum Swings Toward Intervention
The MR CLEAN trial demonstrated an absolute difference of 13.5 percentage points in the rate of functional independence (modified Rankin Scale, 0–2) in favor of the endovascular intervention (32.6% versus 19.1%). The study mentioned GA use in 37.8% of cases of endovascular-treated patients.1 Data presented by Berkhemer et al8 at ISC 2015 Nashville, TN, and a post hoc analysis of use of GA on MR CLEAN showed a difference toward better outcome (mRS 0 to 2 [good outcome] at 90 days was better in local anesthesia/CS versus GA group [38% versus 23%; P=0.026]). However, conversion from CS to GA was necessary in 6 of 137 (4.4%). In EXTEND-IA,17 the use of CS or GA for endovascular treatment was at the discretion of the neurointerventionalist. Although 12 of 33 (36%) patients received GA, they did not report the associated outcome to GA nor the NIHSS comparison between those who received GA versus without GA to determine whether stroke severity and concerns about airway protection were the prime reason for GA. Furthermore, Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke50 (SWIFT-PRIME) investigators presented data at ISC 2015 Nashville, TN. The study was stopped on February 4, 2015, because of favorable results with interventional treatment. To date, no data are available on the effect of GA in patients treated with endovascular intervention. In fact, the results were just published,25,26 as well as the recently terminated Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy (REVASCAT) trial,27 which was stopped due to ethical considerations about the control arm of IV tPA–treated patients given these other recent major interventional trials. The REVASCAT trial utilized GA in 6.7% of cases but outcomes of those cases versus non-GA are not yet reported. The main disadvantage of endovascular therapy is the delay in time of treatment because of the time required to mobilize the interventional team and, in many cases, the need to transfer the patient to another hospital. Current American Heart Association guidelines32 do not recommend a preference for CS, monitored anesthesia care, or GA for acute ischemic stroke undergoing endovascular treatment; rather, they recommend timely, rapid, and coordinated intervention among the systems of care.32 We suggest an individualized approach to decide whether to use GA or CS in this clinical setting (Figure).

Conclusions
GA use varies between ≈6.7% and 44% depending on the study reviewed for acute stroke intervention and is associated with worse outcomes compared to non-GA treated patients in both prospective and retrospective trials. Whether this is because of higher initial stroke severity, delays in intervention start time (eg, IMS-3 every 30-minute delay was associated with a 10% reduction in good outcomes),39 or other mechanisms such as comorbidities or effects of anesthesia on the brain the results will hopefully be addressed in 2 ongoing trials: GOLIATH and ANSTROKE.29,30 Therefore, until compelling evidence emerges for neuromonitoring during GA, given its potential time delays, we do not recommend advanced neuromonitoring (eg, TCD, electroencephalography, and NIRS) during GA for acute endovascular intervention. We recognize the value of direct angiographic and anesthesia monitoring during the procedure, as well as clinical examination before and after the procedure. Moreover, the cerebral angiogram itself during endovascular intervention provides valuable information about collaterals, recanalization, and cerebral blood flow. We suggest medical providers appropriately experienced or credentialed in stroke neurology, anesthesia/neuroanesthesia, intensive care, and neurocritical care be involved in the care of such complex endovascular stroke patients.

Disclosures
None.

References


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