Lesson S38: PreAnesthetic Assessment Of the Patient With Acute Ischemic Stroke—Part 2

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Professional Gaps

Most anesthesiologists are aware that it is essential to treat victims of acute ischemic stroke (AIS) as quickly as possible. The structure of a stroke care center and the involvement of the anesthesiologist in the stroke service is new information. This 2-part series discusses the pathophysiology of AIS and the treatments for stroke. Current guidelines for the accreditation and designation of a stroke center, diagnostic protocols, and treatment options for AIS are reviewed. Literature pertaining to the controversy of using general anesthesia versus sedation for the anesthetic management of AIS patients undergoing endovascular treatment is presented.

In Part 1, the 3 levels of stroke hospital designation are described. The signs and early diagnosis of AIS are reviewed, and thrombolysis with fibrinolytic agents explained.

Part 2 reviews endovascular therapy, the involvement of the anesthetic care provider, and the controversies surrounding anesthetic management of AIS.

Learning Objectives

At the completion of the activity, the reader will be able to:

1. Explain the different options for fibrinolytic therapy of AIS.
2. List the four devices approved for endovascular clot extraction.
3. Recognize the methods the FDA uses to approve medical devices.
4. Distinguish the different classes of FDA medical devices.
5. Understand the anesthetic implications of blood pressure control as it relates to patient outcome in AIS.
6. Assess the risk factors for poor outcome in the management of stroke patients under general anesthesia.
7. Critique the outcome data in patients receiving conscious sedation versus general anesthesia.
8. Evaluate the connection between end-tidal carbon dioxide (ETCO2) and patient outcome after anesthesia for Acute Ischemic Stroke.

9. Compare the different endovascular treatment options

10. Interpret the evidence behind the newly promulgated guidelines by SNACC for the Anesthetic Management of Endovascular Treatment for Acute Ischemic Stroke.

Case

A 79-year-old woman was brought to the emergency department after she was found on the floor of her apartment following activation of an elder protection electronic alert. A relative reported that the patient had a history of high blood pressure, type 2 diabetes mellitus, and chronic obstructive pulmonary disease (COPD). Vital signs included blood pressure 175/87 mm Hg, pulse of 76, respiratory rate of 17, and SpO₂ of 93% on 2 L O₂ via nasal cannula. In the emergency room, the patient had right-sided hemiplegia and was aphasic. Within 1 hour of arrival, she received IV recombinant tissue plasminogen activator (rtPA). Her neurologic condition did not improve, and after 3 hours from the onset of symptoms repeat computed tomography (CT) revealed no hemorrhage. The neuroradiologist wanted to perform a thrombectomy and called for an anesthetic consult. The patient had become agitated and did not follow commands.

Endovascular Therapy

The endovascular treatment for ischemic stroke includes intra-arterial injection of fibrinolytic agents, clot retrieval by suctioning a thrombus from a large intracranial vessel, or deployment of stent retrievers. Intra-arterial fibrinolysis was first studied using r-pro-urokinase in the PROACT II study. PROACT II was a phase III randomized trial to test the effectiveness of intra-arterial r-pro-urokinase with heparin in middle cerebral artery (MCA) strokes versus heparin alone. The study enrolled 180 patients with acute ischemic stroke (AIS) less than 6 hours old caused by occlusion of the MCA, confirmed by angiography, without either hemorrhage or evidence of early infarction on imaging. The primary outcome analysis was a 90 day modified Rankin Scale (mRS) of 0-2. Researchers also performed a secondary analysis of the rate of MCA recanalization, intracerebral hemorrhage, neurologic deterioration and death. The patients who received treatment had higher rates of a positive outcome (40% vs. 25%) with similar mortality (25% vs. 27%) and higher rates of recanalization of the middle cerebral artery (66% vs. 18%).

A study known as the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) also studied urokinase. This Japanese trial was stopped prematurely when intravenous recombinant tissue plasminogen activator – rtPA - was approved for treatment. The trial did not randomize enough patients to reach a conclusion. Secondary analysis of the data seemed to indicate the same outcome as that seen in the PROACT II trial.

Intra-arterial fibrinolysis has been shown in small studies to be better than IV rtPA in recanalizing large intracerebral vessels. Thus, patients who have larger thrombi - i.e. large neurologic deficits - may be candidates for this therapy. However, with invasive methods, any delay in treatment may counterbalance the benefits. Rapid IV thrombolysis has increased effectiveness when administered concomitantly with intra-arterial (IA) rtPA. A series of pilot studies evaluated the combined treatment of IV rtPA and IA rtPA. Thirty five patients were randomly assigned to IV/IA rtPA or placebo/IA rtPA for the management of patients undergoing endovascular therapy for AIS.
groups. The primary outcome was improvement of the National Institute of Health Stroke Scale (NIHSS) score at 7-10 days. There was no difference in outcome between the two groups either at 7-10 days or at 90 days.

These pilot studies were followed by larger studies, including the Interventional Management of Stroke (IMS).\textsuperscript{13} The first IMS study enrolled 80 patients with NIHSS score $\geq 10$ who received rtPA within 3 hours of stroke onset. Patients also received IA rtPA if there was persistent vessel occlusion. A positive clinical outcome was seen in 43% of cases and reperfusion was seen in 56% of cases. Intracranial hemorrhage (ICH) was seen in 6.3% of cases, similar to the National Institute of Neurological Disorders and Stroke (NINDS) IV rtPA study (which reported 6.6%). Three month mortality was 16%, similar to both arms of the NINDS trial (placebo 24% and rtPA 21%).

A second IMS study was commissioned, known as IMS II, which added low energy trans-cranial ultrasound to the IV/IA rtPA. There were 81 patients enrolled.\textsuperscript{14} Trans-cranial ultrasound of the occluded large cerebral vessel as a treatment for AIS is an emerging therapy that has very limited data supporting its use. Positive outcomes were seen in 46% of cases, reperfusion was seen in 61% of cases, ICH in 9.9%. Mortality was 16%.

A third IMS study, IMS III,\textsuperscript{15} was initiated but stopped prematurely after it showed no improvements when IV rtPA and endovascular therapy was compared to IV rtPA alone. Results based on the accumulated data are pending. Again, as seen in the IV rtPA only studies, the time interval to definitive treatment is crucial to patient outcome. The mode of vessel recanalization may actually matter less.

Because few patients with treatable AIS are eligible for IV rtPA, (unknown stroke onset time, recent surgery or anticoagulation, particularly with oral drugs whose effect cannot be monitored), mechanical thrombectomy remains the only treatment modality for many patients. Even though there is no evidence that vessel recanalization is equivalent to brain tissue reperfusion, IV rtPA versus mechanical thrombectomy trials are underway. The results will hopefully eliminate the ambiguity of the current data, as mechanical thrombectomy has only been studied as a rescue modality when IV rtPA is contraindicated or has failed.

Four FDA-approved devices for clot extraction (mechanical thrombectomy): the Merci Retriever, the Penumbra System, the Solitaire Flow Restoration Device, and the Trevo Retriever. The Merci system is a memory-shaped nitinol (nickel titanium) wire with helical loops. This wire is deployed, pushed through the clot and the whole assembly with the clot is removed. The FDA approved the Merci Retriever in 2004 after a single arm prospective study. One hundred and fifty one patients, who presented up to 8 hours after AIS and were ineligible for IV rtPA, were enrolled.\textsuperscript{16} The device successfully recanalized 46% of the occluded vessels. Recanalization was accompanied by good neurological outcome in about half the patients. If the vessel was not recanalized only 10% of the patients had a good outcome. These results paved the way for the use of mechanical thrombectomy in AIS.

The Penumbra System vacuums the thrombus through an intracerebral micro-catheter. The system was studied in 2007 enrolling 125 patients with NIHSS score greater than 8 who were within 8 hours of stroke onset.\textsuperscript{17} Partial or complete recanalization was seen in 82% of patients with 25% of patients having a good outcome and the rate of ICH was not increased.

A new class of recanalization devices is called “stentriever.” The Solitaire Flow Restoration Device and
Trevo Retriever (Fig.1) are both deployable stents that incorporate the thrombus into the mesh of the stent. The deployed open stent with embedded clot fragments is then withdrawn. The Solitaire was tested against the Merci system.\textsuperscript{18} One hundred and thirteen patients with moderate to severe stroke who were within 8 hours of stroke onset and were either refractory to or ineligible for IV rtPA were studied. Recanalization was better versus the Merci arm (61\% vs. 24\%), as was 90 day outcome (58\% vs. 33\%), and 90 day mortality was lower (17\% vs. 38\%). The TREVO 2 study was also designed as a non-inferiority trial against the Merci retriever.\textsuperscript{19} In 178 patients the Trevo Retriever had better recanalization rates (86\% vs. 60\%), better 90 day outcomes (40\% vs. 20\%), and similar mortality (33\% vs. 24\%).

**Figure 1.** Solitaire Flow Restoration device after removing a clot from a patient.

Stent retrievers are much more effective at achieving recanalization of large occluded intracranial vessels (MCA, internal carotid artery terminus) than either IV rtPA or the first/second generation devices. Much work is being done in establishing their place in the comprehensive treatment of AIS patients in terms of both efficacy and patient selection.

The United States Food and Drug Administration is tasked to protect the public health by making sure that medical devices intended for human use are safe and effective. Within the FDA is a separate Center for Devices and Radiological Health (CDRH) that regulates medical devices and devices that emit radiation. The oversight that is given by CDRH to each device before it can be marketed depends on
the device classification. Regulations increase from class I to class III. Class I devices are low risk devices such as dental floss; class II devices are higher risk such as condoms; and class III are devices considered to have substantial risk, such as heart valves. Class III devices need to be approved before use. Devices that do not confer substantial risk to the patient can be approved quickly. There are two ways to obtain approval for a medical device with a substantial risk to the patient. The manufacturer can submit a device Pre-Marketing Application or the manufacturer can apply for a 510(k) exemption. The 510(k) exemption is given to devices that are substantially equivalent to other devices already on the market. None of the mechanical thrombectomy devices have had, to date, a head to head trial with IV rtPA even though the history of the FDA clearance for mechanical thrombectomy devices dates to 1976. There is an unbroken line of 510(k) clearances beginning from one device grandfathered in on May 28, 1976. The MERCI retriever gained FDA 510(k) clearance as being equivalent to its predecessor, the Concentric Retriever that, in turn, received FDA clearance in 2001. This device then gained clearance because it was felt to be equivalent to the Target Therapeutics Attracter Endovascular Snare and the Microvena Corporation Amplatz Goose Neck Microsnare, both of which were believed to be equivalent to other “predicate” devices. While this method of device approval lowers the monetary burden to enter the device market, clinical efficacy in comparison to proven treatments remains unknown for a long time.

Anesthetic Management

The ideal anesthetic technique for endovascular thrombolysis in acute ischemic stroke is mired in controversy. There are two competing goals. The patient must be kept immobile to ensure the best possible imaging quality so that recanalization can be done quickly; and there is a need for hemodynamic stability, patient cooperation and serial neurological examination. These goals result in different approaches to anesthetic care. Some centers use general anesthesia exclusively, others use general anesthesia only when sedation has failed. Anesthesiologists do not routinely participate in AIS endovascular treatment in most centers. With this in mind, what is reported in the literature as “general anesthesia” is also sometimes referred to as “the intubated state,” indicating that some patients might have required airway protection or agitation control without involvement of an anesthetic care team.

In a study published in 2010, Abou-Chebl et al took a retrospective look at 980 patients treated for AIS in 12 stroke centers. They identified seven independent predictors of poor outcome: age, NIHSS score, degree of vessel recanalization, ICH, carotid terminus occlusion, and general anesthesia. The patients who had general anesthesia were at higher risk for poor outcome. They were more likely to have carotid terminus occlusion (25% vs. 15%) and higher NIHSS scores (17 ± 5 vs. 16 ± 6). In the secondary analysis, only those patients who had an isolated middle cerebral artery occlusion (M1 segment) and had either general or local anesthesia with or without sedation were compared. Using binary logistic-regression modeling they found that patients placed under general anesthesia had a higher risk of poor outcome.

Another study by Davis et al reviewed the charts of 96 patients treated for stroke in one center between January 2003 and September 2009. This group had neurological outcome data (mRS) at 90 days and received either general anesthesia or sedation/local anesthesia. At this center, the anesthesiologists were involved sporadically. Some patients required intubation because of pre-intervention aspiration, airway obstruction or decreased consciousness. Otherwise, the method of anesthesia was determined collectively by the physicians involved. This study also found general anesthesia during stroke intervention was a risk factor for poor outcome. The authors found that
having a single systolic blood pressure reading of less than 140 mmHg and general anesthesia were predictors of a poor outcome. Ninety six percent of patients who received general anesthesia had at least one reading of a systolic blood pressure lower than 140 mmHg whereas only 40% of patients who received local anesthesia had this level of hypotension. Davis et al found that low baseline stroke severity, lowest systolic blood pressure above the arbitrary cutoff of 140 mmHg systolic, and the use of light sedation or local anesthesia were independent risk factors for good neurologic outcome.

Although the NIHSS score at the time of the intervention identifies sicker patients, events such as those listed in Table 1 can significantly contribute to a negative outcome even in AIS patients with better scores. These events occurred more often in the general anesthesia group. It was therefore hypothesized that a baseline stroke severity, which would incorporate these general medical complications, could be the sole predictor of the outcome of therapy. The results are also consistent with the hypothesis that hypotension and blood pressure variability caused by induction of general anesthesia worsens the ischemic damage caused by stroke.

Ahmed et al studied blood pressure values at baseline, 2 hours and 24 hours after AIS was treated with IV rtPA. The study was a retrospective analysis of the Safe Implementation of Thrombolysis in Stroke – International Stroke Thrombolysis Register. Included in this study were 11,080 patients with AIS who were divided into 4 groups.

- Group 1: hypertensive patients treated with medication
- Group 2: hypertensive patients not treated for hypertension after stroke
- Group 3: patients who did not have a diagnosis of hypertension and who were treated with anti-hypertensive medication after stroke
- Group 4: non-hypertensive patients who were not treated for hypertension after stroke

The outcomes evaluated were: symptomatic intracerebral hemorrhage either after 24 hours or after 7 days, death at 3 months, and functional independence at 3 months. The study found that patients with high systolic blood pressure (averaged over time) had a higher incidence of symptomatic intracerebral hemorrhage at 2 and 24 hours after stroke onset. When evaluating mortality and independent living, the relationship to blood pressure had a U shaped distribution, with the best outcomes occurring in patients who had systolic blood pressures between 141-150 mmHg and poor outcomes occurring in patients with both hypertension and hypotension. This study concluded that treatment of hypertension after IV rtPA is important to improve outcome. The same is probably true of blood pressure management after endovascular recanalization in AIS. Hence, after successful mechanical thrombectomy, systolic BP is customarily maintained at or below 140 mm Hg.

A recent article retrospectively analyzed 89 patients who received general anesthesia while undergoing endovascular treatment for AIS. The goal of this study was to find a physiologic variable that would correlate with a 90 day mRS outcome. The mean arterial blood pressure (MAP), end tidal carbon dioxide (EtCO$_2$), use of a warming device, and procedure length were studied. During anesthesia, the
MAP was calculated from the systolic and diastolic pressures averaged in each 15 minute period. The authors did not find any statistical correlation between any of the blood pressure parameters and 90 day AIS outcome. The EtCO\textsubscript{2} was averaged every 30 minutes during the case. The authors noted that the 60 minute average and the 90 minute average values for EtCO\textsubscript{2} did correlate with patient outcome. The EtCO\textsubscript{2} values at both time points were higher in patients with good outcomes: 35.2 versus 32.2 mm Hg at 60 minutes and 34.9 versus 31.9 mm Hg at 90 minutes.\textsuperscript{25} The authors attribute the lack of correlation between blood pressure and outcome to a difference in statistical methodology from that used by Davis et al. The putative mechanism of worsened ischemic brain damage related to low EtCO\textsubscript{2} is hypothesized to involve hypocapnic cerebral vasoconstriction.

Management of the Case Presented

The female patient in the case presented was confused, unable to respond to any questions and could not follow commands. She required general anesthesia to limit movement to allow the neuroradiologists to perform the endovascular thrombectomy. Her family reported that she took medications for blood pressure but did not know the names or doses. They knew she had breakfast that morning but they had not seen her for the rest of the day. The patient was moved onto the interventional table and the monitors were applied. A 20g IV placed in the emergency room was functional. While the patient was being made ready for the intervention (urinary catheter insertion and groin area shaving), a radial arterial line was placed. After pre-oxygenation, general anesthesia was induced with propofol 50mg, fentanyl 50mcg, and succinylcholine 140mg. On direct laryngoscopy, there were bloody secretions in her upper airway. Endotracheal intubation was accomplished without complications. Anesthesia was maintained with sevoflurane. In order to maintain systolic blood pressure over 140 mm Hg, a phenylephrine infusion at 50mcg/min was begun. It was discontinued immediately after recanalization. Within one hour of entry into the room, the neuroradiologist successfully deployed a stentriever and removed the thrombus from the M1 segment of the MCA. The anesthetic was discontinued. Since the patient did not follow commands before general anesthesia, it was not expected that she would be fully responsive. She was extubated after she opened her eyes spontaneously and had a gag response. She was then transferred to the Stroke Unit. The next day she was alert, feeding herself with some minimal strength deficit in the left arm and was able to walk with minimal assistance.

Conclusion

Anesthesiologists face difficult decisions when treating acute ischemic stroke patients as they are not medically optimized and any delay in treatment will harm the patient. The decision to use sedation or general anesthesia is patient specific. General anesthesia is a necessary option if the patient cannot protect his airway or cannot remain still for the procedure. The safety of general anesthesia has been called into question in small, retrospective studies. It is possible that hypotension - often associated with general anesthesia, especially on induction - is detrimental to brain perfusion. Avoiding hypertension is important to minimize the risk of hemorrhagic complications after treatment. Specific damage from inhalational anesthetics and other drugs as well as physiologic derangements such as inadvertent hyperventilation, untreated hyperglycemia or hyperthermia may be significant contributors to poorer outcomes under general anesthesia. The time to treatment, recanalization and presumably reperfusion is of utmost importance. Some have invoked the advantage of local anesthesia with or without sedation as preventing delays related to the initiation of general anesthesia. It is important to recognize that AIS is a major public health concern, that the indications for interventional treatment for stroke are being actively defined and that there is a major role for anesthesiologists in
pro-actively shaping the emergency care of these acutely ill patients with multiple comorbidities. While a dedicated stroke team with an assigned anesthesiologist would be ideal in all hospitals, such a situation is not feasible. Therefore, all anesthesiologists should be aware of the urgency that surrounds these cases, the techniques involved and how anesthetic care can best be given.

The Society for Neuroscience in Anesthesiology and Critical Care (SNACC) published a consensus statement on the anesthetic management of endovascular AIS treatment in April 2014. This statement reiterates the management steps conforming to the 2013 AHA/ASA guidelines. Specific anesthetic management recommendations are based on expert opinion, as data comes from retrospective studies. Questions relating to anesthetic technique safety, risks and benefits need to be answered through future, prospective studies.

Dr. Elizabeth A.M. Frost, who is the editor of this continuing medical education series, is clinical professor of anesthesiology at The Mount Sinai School of Medicine in New York City. She is the author of Clinical Anesthesia in Neurosurgery (Butterworth-Heinemann, Boston) and numerous articles. Dr. Frost is past president of the Anesthesia History Association and former editor of the journal of the New York State Society of Anesthesiologists, Sphere. She is also editor of the book series based on this CME program, Preanesthetic Assessment, Volumes 1 through 3 (Birkhäuser, Boston) and 4 through 6 (McMahon Publishing, New York City).
REFERENCES


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**Post-test**

1. Which of the following is a deployable stent used for recanalization?
   a. IA rtPA
   b. MERCI retriever
   c. Penumbra system
   d. Solitaire flow restoration device

2. What was the result of the Japanese MELT trial?
   a. Streptokinase is too dangerous to use on humans
   b. It was closed due to the approval of IV rtPA
   c. IV rtPA can be used safely in humans up to 6 hours from stroke onset
   d. Urokinase can be given up to 3 hours after stroke onset

3. The Interventional Management of Stroke trials validated that:
   a. IV rtPA is more efficient at recanalization than IA rtPA
   b. IV rtPA was efficacious after 8 hours of stroke onset
   c. The time interval to definitive treatment is crucial to patient outcome
   d. Mode of vessel recanalization is crucial to patient outcome

4. Abou-Chebl found that high risk of poor outcome was associated with:
   a. General anesthesia
   b. Intracranial hemorrhage
   c. Difficult airway
   d. Lower NIHSS scores

5. Risk factors for a negative outcome after IV rtPA do NOT include:
   a. Hypotension
   b. Arrhythmia
   c. Intracerebral hemorrhage
   d. Obesity
6. Recanalization of large occluded vessels is most effectively achieved with:
   a. Trevo retriever
   b. IV rtPA
   c. Merci retriever
   d. Trans-cranial ultrasound

7. What is the goal SYSTOLIC blood pressure after endovascular recanalization of AIS?
   a. It is not a factor
   b. 141-150
   c. 160-180
   d. Depends on the interventionalist’s preference

8. What therapy was studied in the PROACT II trial?
   a. The efficacy of IV rtPA during a 3-4.5 hour window
   b. Intra-arterial rtPA and heparin versus heparin alone
   c. MCA recanalization with endovascular thrombectomy
   d. Blood pressure management after IV rtPA

9. In the study performed by Davis et al, which is associated with poor outcome?
   a. Low NIHSS score at baseline before stroke treatment
   b. Blood pressure below 140 mm Hg
   c. Light sedation used for endovascular stroke treatment
   d. Co-morbid conditions such as obesity and diabetes

10. Which of the follow factors will disqualify an AIS patient from IV rtPA treatment?
    a. Stroke onset time 90 minutes prior
    b. Hypertension with atrial fibrillation
    c. History of sleep apnea
    d. Long term anticoagulation therapy