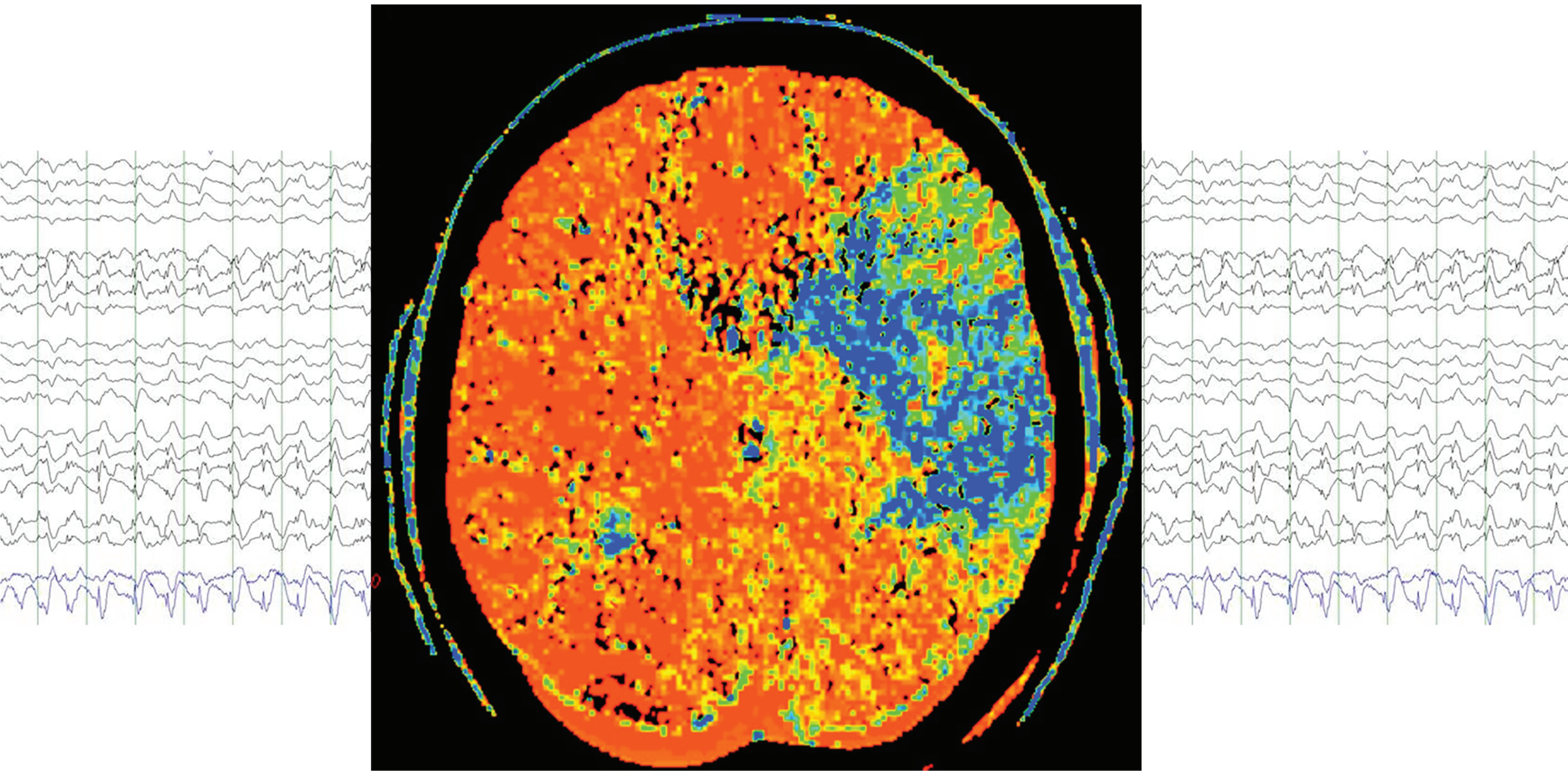
THE PRACTICE OF NEUROCRITICAL CARE



by the
Neurocritical Care Society

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THE PRACTICE OF NEUROCRITICAL CARE

by the

NEUROCRITICAL CARE SOCIETY

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This book is dedicated to the patients we serve.

ISBN-13: 978-0-9909917-4-8

Library of Congress Control Number: 2015939357

Cover Design by Jenni Wheeler
Typeset by Mary K. Ross

Printed in the United States of America

FOREWORD

A principal mission of the Neurocritical Care Society (NCS) is to promote "*Quality Patient Care* by identifying and implementing best medical practices for acute neurological disorders that are consistent with current scientific knowledge, and that promote compassionate care and respect for patient-centered values." Ever since 2007, NCS has held a session at its annual meeting focusing on practical education regarding current neurocritical care and general critical care topics. This began principally as a board review course to prepare physicians who were taking the UCNS Neurocritical Care certification examination. However, we quickly realized that most of the attendees were actually not taking the certification test. Instead they were fellows, nurses, pharmacists, and practicing physicians who were looking for an update regarding best practices in neurocritical care. Two things quickly became clear: there is a strong need for practical education in clinical neurocritical care and NCS is in a unique position to provide this service. It is out of the evolution of those NCS annual meeting courses that this textbook arises.

As neurocritical care has grown, there has been an expansion in the number of textbooks and educational offerings related to neurocritical care topics. Numerous texts have been written, many by NCS members, and published by commercial publishers. So what are we doing here? Well *The Practice of Neurocritical Care, by the Neurocritical Care Society* aims to be a little different. We have brought together topics presented at the 2011 and 2013 NCS annual meetings, updated their content, and taken on the publishing role ourselves, as the Neurocritical Care Society. Each of the 25 topics in this text starts with a clinical case, includes practical clinical information to be used at the bedside, and finishes with a set of questions (and answers). This text can certainly be used to prepare for the neurocritical care certification examination, or for the neurocritical care portion of the boards for neurology, neurosurgery, or other critical care specialties. However, we believe it is valuable to any practitioner interested in a current update on Neurocritical Care from experts in the field.

This book also represents the Neurocritical Care Society's first effort at publishing. We did this for several reasons. First, by keeping the creation of the monograph "in house" we have been able to turn around the material into a widely available offering in about one-third the time of a typical publishing house textbook. Also importantly, proceeds from the sale of this book are brought back to NCS to use for research program funding, rather than becoming income for a commercial publisher. We see this effort as leveraging education for the scientific advancement of the field.

Production of this text has been a labor of love. We are grateful to the hard work of the authors, the direction of the NCS Publications Committee in getting this project to fruition, and the support of the NCS executive office for helping make it happen. This product is certainly not as slick as many other commercial print textbooks available in the market. You will probably notice that the formatting may not be perfect and you may even find some errors in grammar or spelling along the way. Don't hesitate to let us know. That's ok, because our main goal is to provide quality and reliable content, distribute it widely, and help advance neurocritical care education worldwide while learning how to do so independently of for profit commercial entities. We hope you and your patients benefit from this textbook. And we welcome your feedback as we hope that this will be the first of many similar educational offerings to come from the Neurocritical Care Society.

Claude Hemphill, Alejandro Rabinstein, and Owen Samuels
on behalf of the Neurocritical Care Society
January 2015

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CONTENTS

Chapter 1

ACUTE ISCHEMIC STROKE

Nerissa Ko and Wade Smith

CLINICAL CASE

A 62 year-old woman with hypertension and hyperlipidemia was last seen normal after going to bed around midnight. Her husband awoke when he heard a loud sound in the bathroom at 3:00 am. She was unable to speak but was nodding appropriately. She could not move her right side. Her husband called 911 and paramedics brought her to the ED where a code stroke was activated. Her initial blood pressure was 190/110 mmHg. On examination, she had a right homonymous hemianopia, leftward gaze preference, and a dense right hemiparesis. She was unable to speak, but nodded appropriately to simple questions. Her NIHSS was 20. A CT scan of the head was obtained, and did not show any evidence of hemorrhage. There was a hyperdensity noted in the proximal left middle cerebral artery, with blurring of her insular ribbon on that side.

Given that it was 4 hours since she was last seen normal, her husband was consented for IV t-PA within the extended time window of 4.5 hours. Per her husband, she was taking baby aspirin as her only antithrombotic agent. Her D-stick glucose was 110 mg/dl. Her blood pressure was lowered to <185/110 mmHg with 2 doses of IV labetalol prior to IV t-PA administration. Her admission laboratory studies eventually showed normal CBC, INR and glucose levels.

Given the likelihood of large vessel occlusion, additional interventions were considered. Her husband consented for possible endovascular therapy and she was brought to the Neurointerventional radiology suite. A cerebral angiogram showed occlusion of the left M1 segment with collateral flow to the distal middle cerebral artery (MCA) territory. An embolectomy device of the generation-type available at the time she was treated was deployed, with successful removal of thrombus at 6 hours after symptom onset (Figure 1-1).

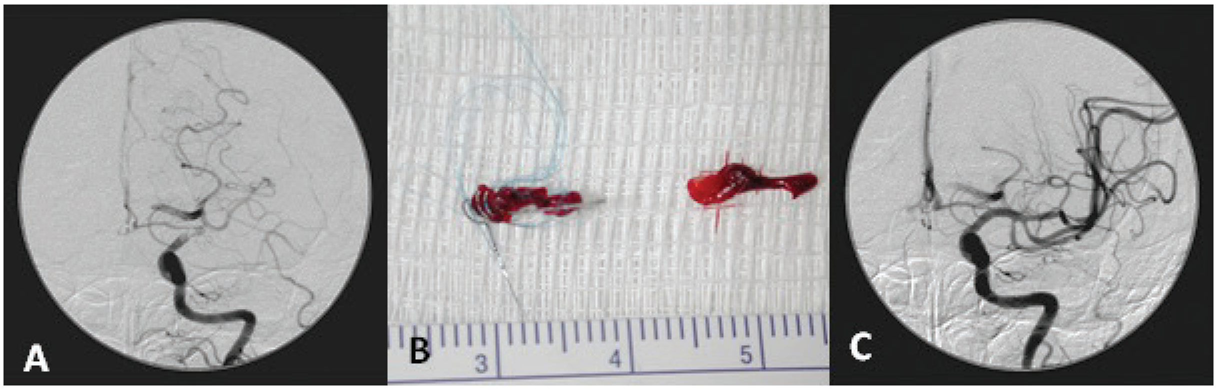

Figure 1-1. Cerebral angiogram showing a left carotid injection and a proximal L middle cerebral artery (MCA) occlusion (a), followed by successful mechanical embolectomy using the Merci retriever device (b), and follow-up angiogram with revascularization of the L MCA territory (c).

The patient was subsequently transferred to the Neurointensive Care Unit for further management. She remained intubated after the procedure. Her hypertension required further control with nicardipine drip to maintain her blood pressure <180/105 mmHg. After 24 hours, she was extubated and weaned off the nicardipine drip with institution of oral antihypertensive medications. She was noted to be in atrial fibrillation on cardiac monitoring. Her CT after 24 hours showed a distal embolic stroke and no hemorrhage. She was eventually discharged to acute rehabilitation able to walk but with moderate hemiparesis and mild expressive aphasia.

OVERVIEW

Acute ischemic stroke (AIS) is a treatable neurological emergency. This chapter will cover the acute management of AIS relevant for in-hospital treatment. The literature on AIS is extensive and well summarized by several references. The most recent and comprehensive review that includes guidelines for AIS management is essential reading for neurointensivists [1]. Other reviews focus on the anatomy and clinical work-up of AIS [2]. Statements within this chapter are cited extensively in the guidelines reference and not reproduced here for brevity.

EPIDEMIOLOGY

Stroke is the fourth leading cause of death and a leading cause of long-term disability in the United States. Approximately 87% of strokes are ischemic. Non-modifiable risk factors for AIS include increasing age, gender, and race/ethnicity. Modifiable risk factors include hypertension, diabetes mellitus, atrial fibrillation, carotid artery disease, smoking, and hypercholesterolemia. More recently, physical inactivity, sleep apnea, and chronic kidney disease have been identified as risk factors for stroke [3].

PATHOPHYSIOLOGY

Ischemic stroke is caused by a reduction in blood flow to a region of brain sufficient to cause ischemic infarction of brain tissue. Within the central nervous system of humans and many other mammals, this ischemic threshold is between 18 and 20 ml/100 mg tissue/min [4]. Although the ischemic cascade is complex, a few important processes are worth special mention. Focal cerebral infarction occurs via two distinct pathways: a necrotic pathway in which cellular cytoskeletal breakdown is rapid, due principally to energy failure of the cell, and an apoptotic pathway in which cells become programmed to die. Ischemia produces necrosis by starving neurons of glucose, which in turn results in failure of mitochondria to produce ATP. Without ATP, membrane ion pumps stop functioning and neurons depolarize, allowing intracellular calcium to rise. Cellular depolarization also causes glutamate release from synaptic terminals; excess extracellular glutamate produces neurotoxicity by activating postsynaptic glutamate receptors that increase neuronal calcium influx. Free radicals are produced by membrane lipid degradation and mitochondrial dysfunction. Free radicals cause catalytic destruction of membranes and likely damage other vital functions of cells. Lesser degrees of ischemia, as are seen within the ischemic penumbra, favor apoptotic cellular death causing cells to die days to weeks later.

Time-dependency for Brain Infarction

Brain tissue with cerebral blood flow levels lower than the ischemic threshold will infarct at increasing rate depending on the magnitude of this blood flow reduction. *Focal ischemia* of brain (as is the case with AIS) is to be distinguished from *global ischemia* (cardiac arrest) in that blood flow to brain tissue rarely goes to zero for any brain region, even the tissue at the core of the brain infarct. In focal ischemia, there are typically extensive collateral sources of blood flow, chiefly via the circle of Willis and through pial-pial anastomosis of arterioles. So, even within the central zone of blood flow reduction (the *core infarct*), perfusion is rarely completely absent. Because of this important detail, brain tissue in AIS can last substantially longer allowing one to intervene with revascularization therapies (thrombolysis and mechanical thrombectomy). In global ischemia, cardiac arrest in excess of 10 to 20 minutes causes significant brain infarction, while in focal ischemia revascularization can prevent infarction within several hours of stroke onset.

The *ischemic penumbra* is a region within brain tissue where cerebral perfusion is lowered but not low enough to cause immediate infarction. The size of the core and penumbra is time-dependent. Several lines of evidence show that if the occluded cerebral vessel remains occluded and all other physiological processes remain constant, the volume of core infraction will expand centripetally to consume the penumbra. The rate of this process is variable in humans but is in the order of hours. Core infarcts are not salvageable with acute stroke therapies, but prevention of penumbral tissue infarction is mitigated with reperfusion therapies. *Salvage of penumbral tissue is the chief goal in revascularization therapy.* Measurement of the penumbra in any given patient at the time of presentation to the hospital is a major focus of investigational imaging-based techniques (see below).

Mitigation of Cerebral Ischemia

Rapid restoration of cerebral blood flow to levels exceeding the ischemic threshold is the main method for preventing or limiting brain infarction. This can be achieved by re-opening the occluded brain blood vessel, either by use of thrombolytic drugs or endovascular mechanical means. Each of those strategies is discussed in the treatment section below. Both hypoglycemia and hyperglycemia have been shown to increase infarct size in animal experiments, and hyperglycemia has been shown to be associated with increased mortality in AIS patients. Despite this epidemiological evidence however, tight control of serum glucose during AIS has not been shown to reduce stroke mortality. Hyperthermia has also been shown to increase infarct volume in animal models and is associated with worse outcome in AIS. Treating the underlying cause of fever is standard practice among neurointensivists; adjuvant prescription of antipyretics seems prudent although it is often ineffective. Use of more advanced methods to achieve euthermia or induce hypothermia (endovascular means or surface cooling) requires further clinical study. An extensive search for compounds that protect the brain during ischemia, so called "neuroprotectant drugs", has produced numerous potential drugs that reduce stroke volume in animals. Despite this, no compound has been found effective in human stroke. At present, no pharmacological agents with putative neuroprotective actions have demonstrated efficacy in improving outcomes after ischemic stroke, and use of any specific neuroprotective agents is not currently recommended.

CLINICAL FEATURES

AIS is the sudden onset of neurological signs and symptoms explainable by a vascular cause. Clinically, if symptoms resolve within 24 hours, this is called a transient ischemic attack (TIA). Recently, this definition has changed to exclude from the TIA diagnosis any patient who has an observable infarct on brain imaging even if their symptoms have resolved within 24 hours- the so called *tissue based definition* [5,6]. Stroke is a clinical diagnosis and has several mimics including migraine, hypoglycemia, liver failure, post-ictal Todd paralysis and infection/sepsis (which may unmask a previously asymptomatic brain infarct). Since the standard of care for treating AIS with t-PA is based on the clinical exam, and a non-contrast CT scan excluding hemorrhage. The practice of treating AIS is one of the few examples in medicine where a doctor is performing a life-threatening procedure based solely on their clinical exam without a laboratory confirmation of their diagnosis. Because time is critical, the use of standardized neurological examinations that can be performed quickly is uniformly recommended. Stroke assessment tools, such the National Institutes of Health Stroke Scale (NIHSS), can quantify the clinical deficit, facilitate communication, and select patients for appropriate interventions.

DIAGNOSIS

Nearly all AIS patients undergo cross-sectional brain imaging when available. The main utility is to distinguish ischemic stroke from hemorrhagic stroke because the treatment and secondary prevention are typically different. In most cases, a non-enhanced head CT will be the most useful test in identifying hemorrhagic stroke and detecting subtle early ischemic changes important in the acute management of AIS. MRI diffusion-weighted imaging has a far better sensitivity and specificity for acute infarct compared to CT. Despite C. Miller Fisher's description of lacunar syndromes that showed small vessel strokes were clinically distinct from large vessel strokes, some large vessel brain occlusions can mimic classic lacunar syndromes. In addition, large vessel disease is present in many AIS patients with lacunar strokes. Therefore, many stroke centers are combining acute cross-sectional imaging (either CT or MR) with angiography to allow for better pathophysiological classification of the stroke (which drives secondary prevention) and decision support for acute intervention (i.e. endovascular techniques). These multi-modality imaging protocols are simple to apply and have the advantage of imaging the entire cerebrovascular axis from heart, through neck, and intracranial in one imaging epoch.

However, the treating physician must keep in mind that the decision to give IV t-PA is based on clinical examination and non-contrast CT imaging alone. Since cerebral ischemia worsens with time, one should not allow the acquisition of angiographic or perfusion data to slow the administration of t-PA [1,7]. Imaging-guided patient selection for treatment is one of the most active areas in stroke research to guide our ability to treat with IV t-PA at time intervals beyond 3 hours, and select for patients who will benefit from more aggressive endovascular therapies. In a recent clinical trial, a favorable penumbral pattern on neuroimaging did not identify patients that would benefit from endovascular therapy [8]. Effective use of these techniques (MRI perfusion-diffusion mismatch or CT perfusion-blood volume mismatch) is still under investigation. An example of a stroke CT imaging protocol with use of CTA and CT perfusion is shown in Figure 1-2 in an acute stroke patient treated with IV t-PA.

TREATMENT

Acute Management

Airway

As with any neurocritical care patient, the patient's airway should be assessed and tracheal intubation considered in stuporous or comatose patients. Patients undergoing invasive procedures require monitoring throughout the procedure because airway status is dynamic depending on administration of sedative drugs and progression of stoke signs. Patients with AIS typically do not have neurogenic pulmonary edema, but because of frequent concomitant cardiac disease or pulmonary disease (mostly COPD) tracheal intubation may be necessary for pulmonary failure. Rapid sequence intubation is often indicated. Oxygenation should be optimized to maintain >94% saturation.

Blood pressure

In general, acute arterial hypertension typically wanes on its own over the first day. Arterial hypertension should not be treated acutely after AIS with few exceptions. If the patient is a candidate for IV t-PA, blood pressure needs to be lowered to less than 185/110 mmHg prior to administration of t-PA, and maintained at <180/105 mmHg for 24 hours after treatment. Lowering blood pressure is recommended in malignant hypertension causing other organ ischemia (myocardial infarct, renal failure). Newer guideline recommendations suggest lowering blood pressure by 15% if it exceeds 220/120 mmHg even if no end-organ failure is occurring. It is commonly accepted, but not proven that lowering blood pressure simply because it is elevated may threaten penumbral perfusion and exacerbate brain ischemia. Both high and low blood pressures have adverse effects on outcome. Current studies have shown mixed results, and the most recent acute blood pressure lowering trial did not change outcome [9]. Results of ongoing studies testing the safety and efficacy of acute blood pressure lowering will improve the science of this recommendation. Initiation of antihypertensive medications after 24 hours is considered safe in most patients who remain hypertensive, especially if they have a prior history of hypertension.

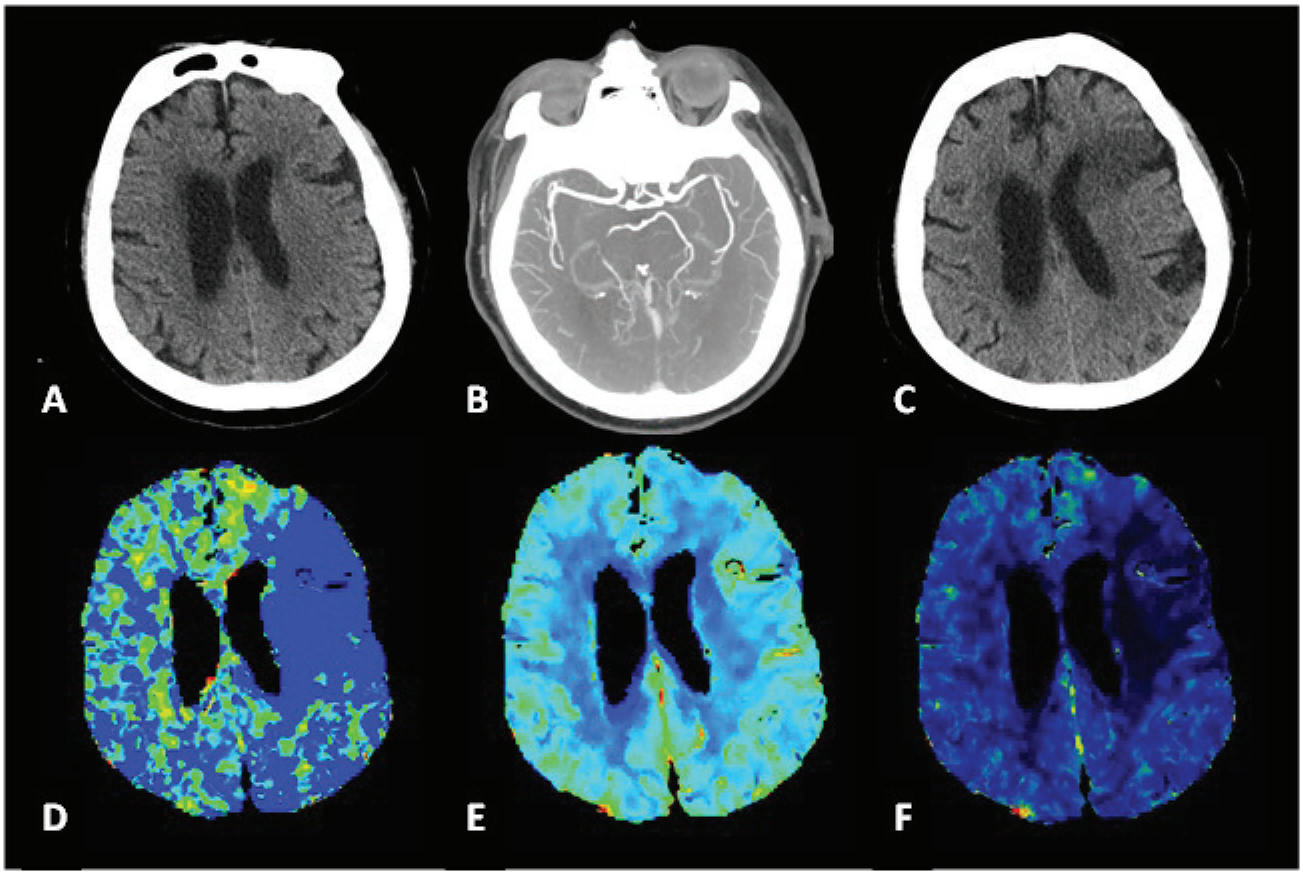

Figure 1-2. 80 year-old woman presented to the ED with sudden onset aphasia, right gaze preference and facial droop. Non-contrast CT (a) showed no evidence of hemorrhage. CTA showed partial occlusion of the distal left MCA (b). She was treated with IV t-PA within 53 minutes of symptom onset. Her repeat head CT 24 hours later showed a partial left anterior MCA infarct and no hemorrhage (c). CT perfusion images consisting of mean transit time [MTT] (d), cerebral blood volume [CBV] (e), and cerebral blood flow [CBF] (f) were consistent with a mismatch between a larger territory at risk on the MTT images compared to the region with decreased CBV. The CBV correlated well with the final area of infarct on CT (c).

Choice of blood pressure agent is similar to their use in other neurocritical care patients. Labetalol IV or nicardipine infusion is typically first-line because of the short-acting nature of these agents. If a patient's exam declines with blood pressure lowering, it is generally felt that the previous blood pressure should be restored. Hypotension, or relative hypotension, should be treated by stopping the administration/infusion of any blood pressure lowering drug, giving a fluid bolus of normal saline, and keeping the patient flat or in Trendelenberg position until the blood pressure rises. Use of vasopressors may be necessary if these treatments are ineffective.

Revascularization Therapy

Intravenous t-PA

IV t-PA was approved for label change to include AIS in 1996 in the United States. It was subsequently approved in Canada and Europe and in several Asian nations and it is currently considered standard of care across the world. Extensive review of IV t-PA treatment can be found elsewhere [1]. Briefly summarized here however, there are two major trials that one should know. The first is the NINDS rt-PA trial published in 1995 [10]. In that trial, use of rt-PA at a dose of 0.9 mg/kg, given as a 10% bolus and the remainder over 1 hour, was shown effective at reducing stroke morbidity (functional outcome) at 3 months. Most recently the ECASS-III trial [11] showed that similar administration of rt-PA in the 3.0-4.5 hour time window is also effective, although less so. The ECASS-III study limited eligibility to patients between 18 and 80 years, and did not enroll patients with diabetes and prior stroke. Additional exclusion for extended window IV t-PA included any use of oral anticoagulants and NIHSS >25. Meta analysis of all enrolled patients in IV t-PA trials have shown a consistent benefit for patients treated within 4.5 hours and beyond this time mortality appears to rise principally from intracerebral hemorrhage [12].

This section will review the steps necessary to safely administer IV t-PA treatment. The goal of the emergency evaluation of patient with AIS is to deliver treatment within 60 minutes of arrival. Eligibility and administration of t-PA is reviewed in Table 1-1. The essential steps are (a) defining the onset of stroke, (b) checking for inclusion and exclusion criteria, (c) performing and interpreting the brain imaging study, (d) administering t-PA, and (e) providing medical management of the stroke patient overall.

Stroke Onset Time

The onset of stroke is defined as the time the patient can reliably tell you that the first symptoms of stroke began, or if they do not know, the last time the patient was seen normal by an observer. If a patient goes to sleep normal and awakens with stroke symptoms, the time of onset is when they went to sleep. The onset time of stroke symptoms starts the 3-hour window in which t-PA needs to be started. It is considered good quality care to administer t-PA within 1 hour of hospital arrival (“door-to-needle-time”). Similar to the emergency response in trauma and acute coronary syndromes, the ‘golden hour’ for intervention in AIS requires similar systems to deliver timely care and improve outcomes.

In pooled analysis of multiple trials of IV t-PA, the time of treatment may be extended beyond 3 hours safely, but the efficacy declines. It is clear that IV t-PA given to otherwise unselected patients is associated with an exponential risk in intracranial hemorrhage rates. Currently, IV t-PA is approved for use only within 3 hours in the United States, with increasing use of the extended time window within 4.5 hours in selected cases. Imaging selection will most likely help guide use beyond these time windows in the future. If the onset of the stroke is unclear, t-PA should not be administered.

Table 1-1. Indications and contraindications for use of intravenous tissue-type plasminogen activator (t-PA) for acute ischemic stroke within 3 hours of symptom onset

Indication	Contraindication
Clinical diagnosis of stroke	Sustained blood pressure >185/110 mmHg
Onset of symptoms to time of drug administration < 3 hours	Glucose <50 or >400 mg/dL
	Platelets <100,000/mL; hematocrit <25%
Computed tomography (or MRI) scan showing no hemorrhage	Use of heparin within 48 hours and prolonged APTT, or oral anticoagulants elevated INR (>1.7)
Age ≥ 18 y	Current use of target specific anticoagulants
	CT > 1/3 of MCA territory with hypodensity
	Prior stroke or head injury within 3 months
	Prior intracranial hemorrhage
	Myocardial infarction within 3 months
	Major surgery in preceding 14 days
	Arterial puncture at a non-compressible site within 7 days
	Minor or rapidly improving symptoms
	Pregnancy
	Gastrointestinal or urinary bleeding in preceding 21 days
	Seizure
For t-PA use within 3-4.5 hours, additional exclusions include:	Age >80, any anticoagulant use, NIHSS >25, and history of stroke and DM

APTT, activated partial thromboplastin time; *INR;* international normalized ratio

Inclusion/Exclusion Criteria

Exclusions are similar to those of thrombolytics in acute myocardial infarction or pulmonary embolus. t-PA will lyse clot, unlike aspirin or heparin which simply prevents further clot deposition. Therefore, t-PA should not be administered to a patient who could bleed into or around a site that would be life threatening. Femoral artery catheterization is not contraindicated but the groin should be scrutinized following t-PA administration and serial hemoglobin concentration followed; groin site hemorrhages can be fatal if not recognized early. Recent placement of intravenous access in the neck or subclavian vessels is a relative contraindication. If the patient is intubated the risk of losing an airway from a neck hematoma is minor; conversely, obtaining an airway in a patient with a large neck hematoma can be very difficult so this eventuality should be anticipated. It is up to physician discretion what major surgery means, but most centers will not treat a patient who has had an abdominal operation, a craniotomy, or other invasive procedure that could produce significant bleeding. Blood glucose is the only laboratory value required before initiation of t-PA under 3 hours. Platelet count and INR should be obtained and decision to continue t-PA infusion should be made based on the results. For t-PA use within 3-4.5 hours, additional exclusions include: age >80, any anticoagulant use, NIHSS >25, and history of stroke and diabetes mellitus (DM), (see Table 1-1) [11].