Brain Attack

Strategies in the Management of Acute Ischemic Stroke:
Neuroscience Clerkship
Stroke is a common and devastating disorder

• Third leading antecedent of death in American men, and second among women
• Thirty day death rate after infarction ranges from 15% to 33%
• 750,000 new cases annually
• 3.89 million survivors of stroke in 1994
• Annual cost to society 41 billion dollars in 1997
Neurologists alone cannot manage a public health problem of this size

- Presently, the only effective therapies must be used in the first six hours after the onset of stroke
- Physicians who may encounter patients in the early hours after stroke must know what to do:
  - Emergency room physicians, primary care physicians, internists, obstetricians
  - Interventionalists (cardiac, neuroradiology), cardio-thoracic surgeons
Acute ischemic stroke

- The brain, like all organs of the body, depends on blood supply.
- If a portion of the brain loses blood supply, it stops functioning.
- If blood supply is not promptly restored, tissue begins to die.
- Brain tissue does not regrow.
In this example, intravascular clot, formed in heart in the context of atrial fibrillation, broke away, and moved through major arteries until it lodged at the bifurcation of the right middle cerebral artery. The ischemic tissue is portrayed as darkened. Survival of the tissue is dependent on collateral flow over the surface of the brain, not easily seen here.
Pathogenesis of ischemic stroke

• Embolism
  – Especially cardioembolic stroke

• Occlusive Disease, with or without artery to artery embolization
  – Most significant site is carotid bifurcation

• Intrinsic disease of small penetrating arteries
  – The etiology of lacunar infarction
Cardioembolic Stroke

- Emboli lodge at predictable sites, usually where vessels divide, and the resulting occlusion gives rise to characteristic clinical findings.
- Onset is typically abrupt, but symptoms may change as blood pressure fluctuates.
- Outcome is critically dependent on collateral circulation over the surface of the forebrain.
- The risk of immediate, recurrent embolization is often difficult to estimate.
In the setting of intermittent or chronic atrial fibrillation, blood clots may form in the left atrium, break away and then embolize to the arterial circulation. Typically, clot lodges at vessel bifurcations. The resulting clinical deficit often is abrupt.
Cardiac abnormalities associated with increased risk of stroke

• Rhythm disturbances
  – Atrial fibrillation, sick sinus syndrome

• Structural abnormalities
  – Valve stenosis, prosthetic valves, dyskinetic wall motion, mural thrombus, atrial septal aneurysm, dilated cardiomyopathy

• Stroke associated with cardiac surgery

• Patent foramen ovale or atrial septal defect
Loss of function in embolic stroke

- The embolism occludes a vessel (often a bifurcation).
- If the occlusion results in sufficient loss of blood supply, affected brain tissue stops functioning.
- The patient experiences the consequences of focal loss of function: weakness, altered sensation, altered language, altered vision.
Altered strength and/or sensation in face and arm

Loss of speech output

Loss of language comprehension
Outcome in embolic stroke

- The effect of an occlusion in the vessels surrounding the brain (anterior, middle, and posterior cerebral arteries, up to the second set of branches) is critically dependent on collateral flow over the surface of the brain.
- While there is evidence that arteries over the surface of the brain can change diameter, at present we have no direct control over their caliber, and we do not know how to influence collateral flow other than to maintain perfusion pressure.
Embolic occlusion of left middle cerebral artery

Contralateral filling into left middle cerebral artery territory

Collaterals from the anterior cerebral artery extend into the territory of the occluded middle cerebral artery
Extracranial occlusive vascular disease

• Preferential sites of atheromatous disease
  – Carotid bifurcation
  – Vertebral artery, distal to PICA
  – Mid-basilar artery

• Outcome critically dependent on collateral circulation through the Circle of Willis

• Internal carotid or vertebral dissection very important in younger patients
Atheromatous disease is not uniformly distributed in precerebral and cerebral vessels. Clinically, the most significant sites of atheromatous disease include the bifurcation of the carotid artery, the distal vertebral artery just before the origin of the basilar artery, and the mid-portion of the basilar artery. Surgical endarterectomy is appropriate for the carotid. We are just exploring the feasibility of angioplasty and/or stenting in the vertebral and basilar arteries.
Consequences of atheromatous disease

- Atherosclerotic narrowing of the pre-cerebral arteries (the internal carotid and the vertebral arteries) leads to focal ischemic stroke in two ways. First, clot formed at the site of the atheromatous narrowing can break away, and embolize. Second, there may be occlusion at the site of the atheromatous narrowing, causing insufficient perfusion distally, ischemia and stroke.
In this instance of artery-to-artery embolization, clot formed just distal to the stenosis breaks off and embolizes, lodging at the bifurcation of the left middle cerebral artery.

If the carotid stenosis is very severe, perfusion pressure drops across the stenotic segment, and perfusion pressure available to drive collateral circulation (over the surface of the brain) may be quite low distal to the carotid stenosis.
Carotid and vertebral occlusion

- In the second pattern of stroke caused by atheromatous disease, a large pre-cerebral vessel becomes occluded, often by clot formation. There may be insufficient blood supply distally, and ischemia in a ‘watershed’ distribution. Outcome depends on whether there is sufficient collateral blood supply through the Circle of Willis.
Intrinsic disease of small penetrating arteries: lacunar infarction

• The occlusive process is different from atherosclerosis, and may not involve clot formation

• The vessels usually do not have collaterals

• Before age 65, nearly 80% of intrinsic disease is associated with diabetes and/or hypertension

• May be mimicked by occlusion at the origin of the penetrating artery
At present, it is uncertain whether thrombolysis or heparin anticoagulation will interrupt the process of small vessel occlusion. The best course is prevention, with treatment of hypertension and diabetes mellitus.
Initial evaluation of acute ischemic stroke

- Neurological exam designed to localize ischemic tissue
- Pertinent history: time and pace of onset, change in severity or quality of deficit, history of vascular disease

- EKG, monitor
- Oxygenation
- Intravenous access
- CBC, PT, PTT, electrolytes, glucose (immediate)
- Stool for occult blood
- Cranial CT scan
Initial therapy for hypertension

• Blood pressure commonly is elevated in acute ischemic stroke, and often will return to usual range spontaneously

• Do not treat in the absence of myocardial infarction/ischemia or arterial dissection

• If diastolic is >140, use nitroprusside

• If systolic is >220 or diastolic is 121-140, use labetalol 10mg IV over 1-2 minutes

• Goal for thrombolysis is systolic <185 and diastolic <110
Avoid treating hypertension in ignorance

• As an illustration of the complexities of treating hypertension in the setting of acute ischemic stroke, consider the following patient:

• A 74 year old woman developed weakness of the right hand and mild expressive aphasia, lasting about 30 minutes. Her blood pressure was 220/110. Should the elevated blood pressure be treated?
Injection of the right carotid artery shows normal vessels, and filling of the contralateral anterior cerebral artery.

Injection of the left carotid artery reveals normal vessels, though the anterior cerebral is somewhat faint.
The severe stenosis (at least 80%) of the left internal carotid causes a reduction in perfusion pressure distally.

Pressure: 220/110

Much less

Right Carotid

Left Carotid
Imaging acute stroke

- Cranial CT scan is useful for detecting hemorrhage and early signs of infarction and mass effect
- Diffusion MRI detects evidence of ischemia sufficient to injure cells
- Perfusion MRI detects intracranial ischemia
- MRA detects dissections and occlusions
CT scan obtained within a few hours of the onset of right-sided weakness and aphasia.

This area has subtle loss of gray-white boundaries and early low density, suggestive of ischemic damage.
Patient RP - 5 Hours Post Onset Right Hemiparesis and Aphasia

Conventional MRI
T2-weighted Images

Echo-planar Diffusion-weighted Images

Echo-planar Perfusion Images
Therapy in the first hours

• Presently, the only effective therapy for acute ischemic stroke is thrombolysis: dissolution of the clot that has occluded the vessel.

• In general, the earlier blood supply is re-established, the greater the chance for recovery.

• The risk of cerebral hemorrhage due to thrombolysis increases with increasing duration of ischemia.

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Exogenous tissue plasminogen activator (tPA) catalyzes the formation of plasmin from plasminogen adsorbed to the clot. The plasmin then cleaves fibrin, and the clot may fall apart, allowing restoration of arterial flow.
Decisions about thrombolysis

• Current guidelines for thrombolytic therapy are intended to decrease the likelihood of complication.
  • Incorrect diagnosis
    – Cerebral or subarachnoid hemorrhage
    – Seizure
  • Potential for systemic bleeding
  • Potential for intracerebral hemorrhage
Decisions about thrombolysis

- Duration of deficit; time from last known normal function
- Rapid improvement
- Cranial CT scan evidence of early infarction or hemorrhage
- PT >15, or platelets <100,000
- Recent surgery (14 days)
- Stroke or head trauma in previous 3 months
- Hemoptysis, GI or GU hemorrhage 21 days
- Seizure
- Severe deficit in aged
How can lysis of the clot save brain?

• Key to this is rate at which tissue is killed--how long do we have to re-perfuse?
• Next key is whether available agents in fact dissolve clots in cerebral circulation?
• Finally, does the frequency of adverse effects mitigate against reperfusion therapy?
A ligature was used to occlude the middle cerebral artery, and then released to restore cerebral blood flow.

If cerebral blood flow was reduced to this level, tissue would survive even if restoration of blood flow was delayed for 4 hours.

If cerebral blood flow was reduced to this level, tissue would survive only if restoration of blood flow occurred in less than 2.5 hours.
Intravenous Therapy with Thromblytic Agents Does Lyse Intravascular Clots

- Del Zoppo and colleagues performed cerebral angiography before and after intravenous therapy with tPA, and found clear evidence of clot dissolution
  - Ann Neurol 32: 78-86, 1992
Intravenous Therapy with tPA in the First Three Hours Improves Neurological Function at 3 Months

Patterns of Thrombolytic Therapy

- Intravenous, in the first three hours after onset; this is the only FDA-approved approach
- Intravenous followed by intra-arterial in the first three hours, especially when occlusive or tandem disease suspected; preferred at UHC
- Intra-arterial, preferred between three and six hours after onset
Advantages of intra-arterial therapy

• Precision in diagnosis: the angiogram allows one to determine if the patient has persisting clot in the cerebral or pre-cerebral circulation. It is possible to avoid treatment in patients without persisting clot, and thus avoid unnecessary morbidity in patients who could not benefit.

• Because the dissolution of clot can be viewed, one uses only as much thrombolytic agent as necessary.

• Take advantage of concentration, and mechanical aids.
Intra-arterial Thrombolysis
Pre and post thrombolysis with intra-arterial therapy

Stroke is an Emergency!
Comparison of IA thrombolysis over 6 hours with IV thrombolysis in the initial three hours

**IA UK**
- Placebo: 48, 13, 15, 24
- r-tPA: 50, 16, 17, 17
- IA UK: 38, 23, 18, 21

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The mortality in the IA population reflects the disease severity

An appropriate comparison is with the PROACT I study. Patients were examined angiographically to identify those with middle cerebral artery occlusions. Some were randomized to no thrombolysis, and re-studied an hour later. The mortality in this “placebo” group was 42.9%. Of those treated with pro-Urokinase, the mortality was 26.9%.
Cerebral hemorrhage complicating thrombolysis

• The most important problem is hemorrhage into infarction. Small arteries damaged by severe ischemia rupture when arterial perfusion is restored.

• Less important is hemorrhagic infarction. In moderately injured tissue, capillaries and post-capillary venules lose tight junction integrity and red cells leak into the surrounding brain.
This patient had an internal carotid artery dissection and embolic occlusion of the left middle cerebral artery.
Decrease in cerebral blood flow, and rate of brain destruction, are not uniform in the setting of acute ischemic stroke.
Symptomatic Hemorrhage

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Patterns of Thrombolytic Therapy

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Severity, Time and Outcome

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Time is Brain!

• In instances of ischemic stroke, the most important predictors of outcome are duration and severity of ischemia. In general, physicians cannot directly modify the severity of the ischemia, except for clot lysis. However, we can work on the problem of duration. This requires patient education, and systematic efforts to eliminate delay in emergency evaluation.
Global Outcome (mRS 0-1, BI 95-100, NIHSS 0-1) at Day 90

Adjusted odds ratio with 95% confidence interval by stroke onset to treatment time (OTT) ITT population (N=2776)
Care after thrombolysis

- Intensive care unit, with frequent exams and continuous EKG monitoring
- Maintain blood pressure
- Early transfusion for hemorrhage, to avoid loss of oxygen carrying capacity
- Cranial CT scan if abrupt change
- Infarcted tissue will swell
Anticoagulation and thrombolysis

- Current guidelines for intravenous therapy withhold heparin for 24 hours
- After intra-arterial therapy, do not use heparin if the lesion enhances or there is hemorrhage
- Potential value of heparin is in preventing reformation of the partially digested embolus or recurrent embolization
Further Reading

• The chapters dealing with cerebrovascular disease in Harrison’s Textbook of Medicine are well-written. They don’t lay out the three patterns of pathogenesis (embolic, occlusive, and small vessel), but they are excellent in describing the clinical effects of occlusion of particular arteries. See Chapter 366, pages 2328-2336, 14th Edition.
### Severity, Time and Outcome
**UHC (1998-2002*)**

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Carotid Artery Stenting

Pre-Stenting

Post-Stenting

Stroke is Preventable

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