



Module 1. Introduction to Stroke and Stroke Prevention

Objectives for Module 1

Knowledge

- Compare and contrast ischemic stroke and transient ischemic attack (TIA)
- Distinguish ischemic from hemorrhagic stroke
- Describe 3 major mechanisms that can produce an ischemic stroke
- Name the most common causes of (1) non-traumatic subarachnoid hemorrhage and of (2) intraparenchymal (intracerebral) hemorrhage

Clinical Applications and Reasoning

- Describe what would typically be seen in non-contrast CT scans showing the brain of a patient with acute intracranial hemorrhage
- List at least 4 common symptoms of stroke that a layperson might report
- Explain why an individual who has recently had a myocardial infarction or has recently been diagnosed with atrial fibrillation is at increased risk for having a stroke
- Provide at least 2 reasons why immediate follow-up testing for a patient believed to have experienced a TIA is essential

Clinical Applications to Patient Education

- Develop 3 points that you would use in explaining what a stroke or a TIA is *to a patient*

Overview

A stroke is an episode of rapid-onset neurologic dysfunction resulting from injury to the brain, spinal cord or retina (CNS) that is caused by interruption of blood flow (ischemia) leading to focal infarction, or by bleeding into or around the brain (hemorrhage).

Permanent disabilities that are commonly produced by a stroke include:

- Some weakness or paralysis on one side of the body
- Inability to walk without some assistance
- Cognitive deficits
- Difficulty in talking or in understanding what is being said
- Visual impairment
- Depressed mood
- Dependence on others to carry out activities of daily living (ADLs)

Stroke-related brain injury

A stroke can be triggered by one or a series of sudden vascular events that may last only a few minutes. The resulting damage to some brain cells initiates a cascade of chemical and cellular events injuring additional brain tissue that was not initially involved. In some strokes, it may be possible to abort these events and “rescue” much if not all of the brain. However, such a successful rescue requires medical or interventional therapies during the initial minutes and hours after the patient’s signs and symptoms first appear. Types of acute therapies and guidelines for their use have changed dramatically in the past 5 years, although much still remains to be learned. The brain continues to respond to its injury over a period that may last a few days or more, but at this later time the goal of therapy is preventing complications and further injury.

A stroke may kill the patient or produce permanent brain damage. If an individual survives a stroke, his or her specific long-term neurologic deficits will depend on many interacting factors including: the type and size of stroke, the specific parts of the brain that are involved, the effectiveness of any early medical treatment or interventions, continuing treatment and rehabilitation, and characteristics of both the individual and his or her family/caregivers.

STROKE FACTS – All data for the United States (2020)

- About 795,000 people experience a new or recurrent stroke each year.
- All told, about 7.0 million adults \geq 20 years old report having had a stroke.
- The age-adjusted incidence of first ischemic stroke per 1000 was 0.88 for whites, 1.91 for blacks, and 1.49 for Hispanics (1993-97 data).
- Stroke is the fifth leading cause of death in the U.S., behind heart disease, cancer, unintentional injuries, and chronic lower respiratory diseases. Worldwide, stroke is the second most common cause of death after ischemic heart disease.
- From 2007 to 2017 the age-adjusted number of stroke deaths declined by 13.6 percent among all racial/ethnic groups, but remained highest among nonHispanic blacks. However, the lifetime risk of stroke is increasing, due in part to the aging population.
- Each year more females than males have a stroke and die of stroke.
- The prevalence of stroke increases with age in both males and females; however 10% of all strokes occur in individuals 18 to 50 years of age.
- Stroke is a leading cause of serious, long-term disability.
- The estimated direct and indirect cost of stroke in 2014-2015 was \$45.5 billion.

Based on American Heart Association 2020 Statistical Update

Death soon after a stroke is caused by brain-related or medical complications

The brain swelling that occurs after a stroke increases intracranial pressure. If there has been hemorrhage, the added volume of blood contributes to the increased pressure. The skull cannot expand. Thus when intracranial pressure (ICP) increases, “relief” can only be obtained by displacing brain tissue into a different compartment within the skull where the pressure is lower. This is referred to as brain “herniation.” If the forebrain is swollen, its displacement downward can produce compression of the brainstem. A stroke involving the brainstem itself (or the cerebellum) may also cause swelling and compression. If the reticular formation of the brainstem is involved, its dysfunction may result in irreversible coma, or in death because of respiratory arrest or circulatory failure. Measures to lower ICP and prevent a herniation can include raising the head of the bed, IV mannitol, or surgical measures such as temporary removal of the skull overlying the swollen brain region.

Medical complications following a stroke can include pulmonary embolus due to deep venous thrombosis, pneumonia, or myocardial infarction to name just three. The recent decrease in the number of stroke deaths in the U.S. reflects improved acute stroke care and prevention of the medical complications of stroke. However improvement in the detection and treatment of hypertension beginning in the 1970s appears to have had the most substantial influence on the recent decline in stroke mortality.

Aggressive prevention can reduce a patient’s risk of having a first stroke

Individuals can decrease their risk of stroke and stroke mortality first and foremost by controlling blood pressure, as chronic hypertension is a powerful determinant of risk for both ischemic stroke and intracranial hemorrhage. Other important measures often associated with significant stroke risk reduction include abstaining from cigarette smoking, increasing physical activity, maintaining a normal BMI, managing blood lipid levels, and, if appropriate participating in treatment of diabetes mellitus, cardiovascular disease, and atrial fibrillation. Additional medical or surgical treatment can reduce the chances of strokes in individuals who are at particularly high risk, including those who have had a recent TIA (a warning sign of stroke) or myocardial infarction, or those with atrial fibrillation. Additional potentially modifiable risk factors for stroke continue to be actively studied.

Therapies administered during an acute ischemic stroke can sometimes reverse or limit brain injury

In certain patients, both thrombolytic and thrombus-extracting treatments may entirely reverse the course of an acute ischemic stroke or limit the permanent brain injury that it produces. However, their use requires recognizing that the patient is experiencing one or more warning signs of stroke, and acting immediately (by calling 9-1-1 or emergency medical services) so the patient reaches the hospital within the first 1-2 hours after symptoms began. The benefits of both therapies is time dependent, with earlier treatment associated with greater benefits. Studies suggest that at best only about one-third of those who have a stroke will access the ED in less than 2 hours.

Warning Signs/Symptoms of Stroke
<ul style="list-style-type: none">▪ Sudden NUMBNESS or weakness of face, arm or leg, especially on one side of the body▪ Sudden CONFUSION, trouble speaking or understanding speech▪ Sudden TROUBLE SEEING in one or both eyes▪ Sudden TROUBLE WALKING, dizziness, loss of balance or coordination▪ Sudden, SEVERE HEADACHE with no known cause <p>(as described in patient education literature of the American Stroke Association)</p>

The American Stroke Association has adopted **F.A.S.T.** to help patients and witnesses easily remember the most common signs and symptoms of stroke and how they should respond:

- F** – Face Drooping
- A** – Arm Weakness
- S** – Speech Difficulty
- T** – Time to call 9-1-1 (emergency medical services)

Ongoing research should provide future physicians with additional ways to limit brain damage once the “triggering” vascular event has occurred, and to select the patients who are likely to benefit from these therapies. There are also exciting advances in the area of stroke rehabilitation.

At present, physicians are more successful at reducing the chances that a stroke will occur in the first place, than at reversing ongoing tissue injury or improving post-stroke function.

Strokes can be caused by either blockage or rupture of an artery

About 87% of strokes are ischemic – due to arterial occlusion. The resulting inadequate blood flow (ischemia) deprives the brain of oxygen and glucose, and slows the removal of metabolic wastes. The parts of the brain that the occluded artery can no longer adequately supply very rapidly begin to function abnormally or cease to function. If ischemia persists, brain cells die. The term “infarct” is commonly used to describe such a region of dead tissue. The brain is at special risk for ischemia because there is often not enough redundancy in its arterial supply to maintain adequate blood flow if one artery is suddenly occluded.

About 13% of strokes are hemorrhagic – due to arterial rupture. Bleeding can initially occur *within* the brain. Such intraparenchymal or intracerebral hemorrhages account for about 10% of strokes. Bleeding can also initially occur *around* the brain, in the subarachnoid space. Subarachnoid hemorrhage accounts for about 3% of strokes. A hemorrhage can produce injury by distorting, compressing, and tearing brain tissue, (including its blood vessels), by the toxic effects of the blood itself, or by increasing intracranial pressure.

“Large” arteries and “small” arteries are both involved in stroke

The arteries that supply the central nervous system originate from the aorta or other great vessels. **“Large” arteries** are defined as the extracranial portions of the carotid and vertebral arteries and their large intracranial branches, which lie in the subarachnoid space *on the surface of the forebrain and brainstem*. These large arteries in turn give rise to “small” arteries.

“Small” arteries are the vessels that actually *enter brain tissue* and ultimately branch to form the capillary beds where oxygen exchange occurs. Some small arteries are short branches that supply superficial regions. However other small arteries are long branches that penetrate deep into the brain parenchyma to supply structures including the basal ganglia, internal capsule, thalamus, as well as parts of the brainstem and cerebellum.

Ischemic strokes most frequently involve narrowing or blockage of large arteries. Hemorrhagic strokes are more equally divided between the large and small arteries.

Strokes affect the forebrain most often, the brainstem or cerebellum less often, and the spinal cord rarely. This presumably reflects differences in the volume of tissue, and also in the sizes and arrangement of the arteries that supply these regions.

Introduction to Ischemic Stroke

In **StrokeSTOP** we will focus on ischemic strokes that occur if blood flow is blocked in an artery supplying the brain, producing focal ischemia. We will not discuss the severe widespread brain injury caused by failure of the entire circulation that affects all organs (systemic hypotension).

PREVIEW: The Three Major Types of Ischemic Stroke

Type of Stroke	Pathophysiology
1. Large Artery (arteries in neck or on brain surface)	Severe stenosis or occlusion caused by atherosclerotic thickening of wall. Often local thrombus formed on ulcerated atherosclerotic plaque may suddenly block the artery completely and trigger the ischemic event.
2. Small Artery (arteries that penetrate brain)	Occlusion may be by atherothrombosis, but more commonly lipohyalinosis in deeply penetrating small arteries (initiated by chronic hypertension) leads to the subsequent collapse of their walls and occlusion.
3. Embolic	Arterial occlusion (often at bifurcations or narrowed regions) caused by emboli from a cardiac source or from any of the large arteries supplying the brain, especially the carotid artery in the neck.

A little more about each major type of ischemic stroke:

1. Large Arteries can be occluded by atherosclerotic plaque, often accompanied by local thrombosis

Atherosclerosis often develops at the branch points or curving portions of both the extracranial and intracranial large arteries. These are locations where blood flow is slowed and more turbulent. The internal carotid artery is particularly at risk, although exactly where along its course the disease tends to occur and how quickly it progresses apparently reflects environmental and genetic factors, as well as the presence of additional risk factors that may stimulate plaque growth, such as hypertension and cigarette smoking.

Atherosclerosis involves focal accumulations of lipid, smooth muscle cells, foamy macrophages, and eventually cholesterol crystals, under the surface lining (endothelium) of the artery. With time these accumulations can form elevated plaques that protrude into the vessel's lumen and significantly reduce blood flow. Perhaps the analogy of a kitchen drainpipe becoming gradually plugged with cooking grease and sludge will help you visualize what is happening.

If occluding the vascular lumen weren't bad enough, plaques can do a number of additional things that further compromise the brain's circulation. For instance, a plaque can ulcerate (break open), and the resulting damage to its endothelial lining stimulates the development of thrombus (blood clot), which even further narrows the vessel. What's more, pieces of thrombus or plaque core can be swept along by the blood flowing through the vessel, becoming emboli (see Embolic stroke below)

A thrombus is a solid mass of platelets and/or fibrin (and other components of blood) that is formed locally in a vessel or the heart. Thrombi form when the clotting mechanism gets turned on. This is supposed to happen when you are injured. However, it can also occur at the site of an ulcerated atherosclerotic plaque, or whenever the endothelial cells that line the inner surface of an artery have been damaged. Thrombus formation may also occur in places where blood flow is sluggish, enabling clotting factors to activate and giving platelets more opportunity to stick together. Disorders of blood cells or blood proteins can increase the chance of thrombus formation, and therefore contribute to the risk of ischemic stroke.

2. Small Arteries can be occluded by pathology associated with hypertension, diabetes, and aging.

Blood flow in small arteries of the brain may be blocked by emboli or thrombus in the large arteries from which they originate. However, there are several additional kinds of pathology that uniquely affect the walls of small arteries, leading to their collapse and blockage of blood flow.

“Small” artery strokes preferentially involve *long penetrating* arteries and arterioles that supply deep central forebrain structures including the basal ganglia, internal capsule, thalamus, and deep cerebral white matter, as well as central regions of the pons and cerebellum. These slender penetrating vessels may be particularly affected by **hypertension** because many branch off them directly from large high-flow, high-pressure arteries at nearly right angles and in addition have thin muscular walls. Sustained high blood pressure is believed to initiate a degenerative process called **lipohyalinosis**, in which the walls of affected small vessels become stuffed with glassy “hyaline” material consisting largely of lipoproteins. This can eventually lead to weakening of the wall and progressive occlusion of the lumen.

A second different process that can also occlude small vessels is the formation of **microatheroma**, which is basically the same atherosclerotic process that affects larger caliber extra and intracranial vessels. Commonly microatheroma formation, like lipohyalinosis, affects the long penetrating vessels, although microatheroma may also affect short superficial vessels supplying the cortical surface. Patients with hypertension and diabetes appear to be especially susceptible to the formation of microatheroma in small brain arteries.

Elderly individuals in particular may have strokes due to narrowing or occlusion of short arteries and arterioles supplying the cerebral cortex caused by **amyloid angiopathy**. The underlying pathology does not seem to be associated with high blood pressure or diabetes, but rather is caused by accumulation of beta amyloid protein in vessel walls, progressively weakening them and eventually leading to severe luminal narrowing or occlusion. Beta amyloid is also one of the major abnormal proteins present in Alzheimer’s disease, and amyloid angiopathy may add superficial cortical ischemic strokes to the already-devastating degenerative effects of Alzheimer’s disease.

Occlusion of small arteries supplying brain structures causes **small-vessel strokes**. These are also called **lacunar strokes** because the area that is infarcted takes the form of a small lacune or cavity (usually less than 15mm in diameter). Although the area infarcted by a small vessel stroke may be small, it can lead to major neurologic deficits. A much larger infarct may actually produce a less extensive (or intrusive) neurologic deficit for the patient. This is because the deficits after stroke depend on exactly what structures are involved.

3. Emboli carried by the bloodstream can occlude both large and small arteries

An embolus is most often a piece of a thrombus that has broken free and is carried toward the brain by the bloodstream. You’ll often encounter the term **thromboembolus** because it turns out that most emboli arise from thrombi, although bits of plaque, fat, air bubbles, and other material also qualify as emboli. Presumably an embolus floats along with the flowing blood until it encounters a narrowing in the artery through which it cannot pass (for instance a bifurcation or a region of elevated plaque). When the embolus gets stuck it blocks the artery, reducing blood flow to downstream tissues and thus rendering them ischemic.

Two Key Sources of Emboli to the Brain

- **Cardiac:** Cardiac disease is the most common cause of cerebral embolism. Atrial fibrillation leads to blood pooling in the left atrium or atrial appendage and therefore increased thrombus formation. Thrombus can also form on damaged or prosthetic mitral or aortic valves, or in the left ventricle if the pumping action of the heart is suboptimal because of a myocardial infarction. Fragments of these thrombi can enter the systemic circulation and travel to any organ, including the brain.
- **Arteries Supplying the Brain -- Artery-to-Artery Embolism:** Ulcerated atherosclerotic plaque at the carotid bifurcation or nearby regions of the internal carotid artery is the most common source of artery-to-artery emboli. Bits of thrombus that have formed on the damaged endothelium or fragments of the plaque core itself can break off and then be carried distally in the carotid circulation to reach the brain or retina. Atherosclerosis can potentially develop in any of the extra- or intracranial parts of large arteries supplying the brain, providing additional sources of emboli.

The diameters and branching patterns of the large arteries have a lot to do with where embolic material tends to travel, and where it tends to ultimately lodge. For instance, the large diameter, gently curving course, and rapid blood flow in the middle cerebral artery put it at particular risk for embolism – and therefore the regions of brain that it supplies at risk for embolic stroke. The smaller anterior cerebral artery, which originates from the internal carotid at a sharper angle, captures emboli less often – emboli apparently don't corner well!

Ischemic strokes may be preceded by Transient Ischemic Attacks (TIAs)

A TIA is a brief episode in which neurological deficits suddenly occur and then disappear, caused by focal brain, spinal cord, or retinal ischemia. Most of these events last only a few minutes to an hour or so, although the classic definition includes events that persist up to 24 hours before they fade. Unlike a stroke, the neurologic exam demonstrates no remaining functional deficits once the TIA has ended. However while their clinical symptoms may have resolved, as many as one-third of patients who experience a TIA will have new (acute) infarctions (regions of cell death in the CNS attributable to ischemia) visualized by diffusion-weighted magnetic resonance imaging (MRI).

Some strokes occur “out of the blue” but a number of ischemic strokes are preceded by one or more TIAs. Sometimes the symptoms produced by recurrent TIAs are exactly the same each time they occur. Other times the symptoms are different, and can even occur on the other side of the body. Remember that a TIA occurs when an artery is temporarily blocked. If the same region of one artery is being blocked each time, this would produce the same symptoms. How would you explain TIAs that produce different symptoms? (*Answer: a different region of the same artery or another artery altogether is being blocked.*)

A TIA is an important warning sign of stroke. A TIA is an important warning sign that the stage is set for an ischemic stroke, because it demonstrates that enough vascular and/or cardiac pathology is present to produce neurologic symptoms. Patients with possible TIAs require urgent evaluation, determination of stroke risk, and initiation of appropriate stroke prevention therapy. Treatments that specifically target these underlying disorders and risk factors can significantly reduce the chances that patients who have experienced TIAs will later have a stroke (permanent neurological deficits). We will discuss some of them in later modules.

TIA FACTS – Data for the United States (2020)

- About 12% of all strokes are preceded by a TIA, based on retrospective patient reports.
- Many patients who experience TIA-like symptoms fail to inform their healthcare providers.
- The incidence of TIA increases with age, and is higher in males, blacks and Mexican-Americans than in their female and nonHispanic white counterparts.
- Short-term risk of stroke and other vascular events following a TIA has historically been reported as high as 10% at 2 days, and as high as 17% at 90 days. However at least one more recent study reports much lower rates, perhaps reflecting better and faster evaluation of acute TIA and implementation of secondary stroke prevention strategies in the study population.

The term ‘**mini-stroke**’ is sometimes used in describing a TIA to emphasize the severity of the event and the importance of obtaining immediate medical attention, even though the episode of impaired neurological function may last only a few minutes. The risk of a stroke that produces lasting neurologic deficits in the hours or days following a TIA is substantial, but may be significantly reduced when it is treated on an urgent basis.

During a Transient Ischemic Attack an artery is *temporarily* blocked.

One mechanism explaining what happens during a TIA is embolization of platelet aggregates, small thrombi or plaque debris from the extracranial vessels supplying the brain or from the diseased heart. This material travels into a brain or retinal artery and briefly plugs it up, reducing blood flow to a specific downstream region and causing its dysfunction. However if the embolic material quickly fragments and passes distally, then circulation through that part of the artery is re-established and normal function returns. Since little if any tissue has actually died, the patient has no permanent neurologic deficit. A second mechanism sometimes proposed to explain TIAs is a low perfusion state, usually thought to result from carotid artery stenosis. However this would require a large drop in blood pressure and is now thought to be a less common mechanism of TIA.

There is really no such thing as a transient *hemorrhagic* attack. It would be very unusual for hemorrhage *into brain tissue* to cause transient, focal neurological deficits because the signs/symptoms can be reversed only when the blood has been removed -- a process that takes weeks or months, not minutes. Major hemorrhages *into the subarachnoid space* caused by aneurysm rupture are sometimes preceded by a warning leak, more formally called a sentinel bleed. Again, this does not usually produce transient focal (specific) deficits, but rather a headache that lasts several days. (See the next section for more about Hemorrhagic Strokes)

If patients don't tell you about symptoms consistent with a TIA, or if you fail to recognize that they could be describing a TIA, you will miss an opportunity to intervene and perhaps prevent a major stroke!

Introduction to Hemorrhagic Stroke

Intraparenchymal (also called Intracerebral) Hemorrhage is bleeding directly into the brain and ventricles. This is the most common type of intracranial hemorrhage. **Hypertensive intraparenchymal hemorrhage** is usually caused by spontaneous rupture of a small penetrating artery deep in the brain. The most common sites are the basal ganglia (especially the putamen), internal capsule and deep white matter of hemisphere, thalamus, and central regions of the pons and cerebellum), As discussed when we talked about ischemic strokes, the small arteries supplying these regions are particularly susceptible to chronic untreated hypertension, which apparently initiates lipohyalinosis. This pathology alters the normal wall structure of small penetrating arteries and arterioles. Classic teaching links lipohyalinosis to the formation of microaneurysms (Charcot-Bouchard aneurysms) that may subsequently rupture.

In the extremely elderly, the walls of small “short” arteries and arterioles supplying the *superficial* regions of the cerebral hemispheres may develop deposits of amyloid protein (**cerebral amyloid angiopathy**), also discussed with small- vessel ischemic stroke. These weakened walls can rupture causing hemorrhages in the superficial regions of the hemispheres. The resultant hemorrhages are referred to as **lobar hemorrhages**, presumably because they involve outer portions of the various lobes of the brain. Recall that they often occur in elderly individuals who have had normal blood pressure throughout their lives, and appear to be more closely associated with the presence of Alzheimer’s disease than with hypertension.

Non-traumatic **subarachnoid hemorrhage** (bleeding around the brain) is most commonly caused by rupture of **saccular (berry) aneurysms**. These aneurysms are thought to be a consequence of developmental abnormality, and get their name because they typically include a protruding neck and a thin-walled dome. They commonly form at the branch points of large or medium-sized intracranial arteries in or near the Circle of Willis, and most often involve arteries of the anterior (carotid) circulation. Aneurysms rupture into the subarachnoid space, usually in the basal cisterns, but hemorrhage may extend secondarily into the adjacent brain tissue as well. Aneurysms usually announce their presence only when they rupture. Less often, they may reveal themselves by compressing neighboring structures and producing neurologic symptoms. Sometimes aneurysms may bleed just a little prior to a more massive rupture. A warning like a sudden unexplained headache or other neurological disturbance may make it possible to identify the problem, and to initiate surgical or endovascular intervention if it is indicated.

The neurologic deficits produced by hemorrhagic strokes can reflect damage to regions of the brain *remote* from the affected artery. There are several reasons for this: (1) When an artery ruptures, blood under arterial pressure is forcefully shot into the brain and can travel a long distance (2) Increased intracranial pressure due to the sudden addition of hemorrhaging blood can compress and distort brain tissue located at some distance from the site of arterial rupture.

What CT scans can show about ischemic and hemorrhagic stroke

A Head CT (Computed Tomography) scan *without contrast* is usually the first radiologic test used when a patient presents with neurologic symptoms suggesting a stroke or TIA.

When there is acute hemorrhage into the brain, the accumulated hemoglobin makes the area look bright (hyperdense) in CT images. Very early ischemic strokes are NOT detected on routine CT scans. Thus a non-contrast CT scan in the first hours of symptom onset is used to *exclude* hemorrhagic stroke, not to confirm ischemic stroke. Contrast material is not used, because the normal presence of hyperdense contrast material in blood vessels and meninges could mask a small hemorrhage. Identifying the cause of stroke is essential if the administration of thrombolytic drugs is being considered to restore cerebral perfusion. Diffusion-weighted imaging (DWI) is far more sensitive for directly visualizing very early ischemic infarction than is either CT or standard MRI.