Imaging of Stroke: Part 2, Pathophysiology at the Molecular and Cellular Levels and Corresponding Imaging Changes

OBJECTIVE. Stroke is the third leading cause of death and the leading cause of severe disability. During the “decade of the brain” in the 1990s, the most promising development was the treatment of acute ischemic stroke. It is thought to result from a cascade of events from energy depletion to cell death. In the initial minutes to hour, clinical deficit does not necessarily reflect irreversible damage. The final outcome and residual deficit will be decided by how fast reperfusion is achieved, which in turn depends on how early the diagnosis is made. This article explains the pathophysiology of stroke at the molecular and cellular levels with corresponding changes on various imaging techniques.

CONCLUSION. The pathophysiology of stroke has several complex mechanisms. Understanding these mechanisms is essential to derive neuroprotective agents that limit neuronal damage after ischemia. Imaging and clinical strategies aimed at extending the therapeutic window for reperfusion treatment with mechanical and pharmacologic thrombolysis will add value to existing treatment strategies. Acute ischemic stroke is defined as abrupt neurologic dysfunction due to focal brain ischemia resulting in persistent neurologic deficit accompanied by characteristic abnormalities on brain imaging. Knowledge of the pathophysiologic mechanisms of neuronal injury in stroke is essential to target treatment. Neuroprotective and thrombolytic agents have been shown to improve clinical outcome. Physiologic imaging with diffusion-weighted imaging (DWI) and perfusion CT and MRI provide a pathophysiologic substrate of evolving ischemic stroke.

Keywords: brain imaging, diffusion-weighted imaging, neuroradiology, pathophysiology, perfusion imaging, stroke, venous infarction, watershed infarction

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CBF according to the central volume principle, which states that $MIT = CBV / CBF$ [3].

**Pathophysiology**

Brain damage after infarction is caused by a plethora of complex mechanisms that lead to the accumulation of toxic metabolites causing cellular and architectural damage of brain parenchyma. Within minutes of vascular occlusion, an ischemic cascade begins; it includes energy and sodium-potassium pump failure, an increase in intracellular calcium, depolarization, spreading depression, generation of free radicals, blood-brain barrier (BBB) disruption, inflammation, and apoptosis [4]. These events are not strictly in order but show overlap.

**Sodium-Potassium Pump**

CBF of less than 10 mL/100 g of brain tissue causes severe depletion of oxygen and glucose, leading to a severe decrease in adenosine triphosphate (ATP) at the cellular level. Normally ATP transports $3 Na^+$ ions out of the cell in exchange with 2 $K^+$ ions into the cell. This decrease in ATP leads to the failure of the sodium-potassium pump. This failure causes passive diffusion of $Na^+$ ions inside the cells along with large amounts of fluid, which leads to cytotoxic edema [4–8] (Fig. 1). These changes cause an increase in extracellular $K^+$ by approximately 60–70 mL with a decrease in the $Na^+$ concentration by approximately 50%.

**Calcium Pump**

Depolarization of the cells leads to a large release of excitotoxic amino acids, especially glutamate, into the extracellular compartment, which has been confirmed by microdialysis technique [4–8]. Besides its direct neurotoxicity, glutamate causes activation of glutamate receptors such as N-methyl-D-aspartate (NMDA), $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazole propionate acid receptor (AMPA), metabotropic glutamate, receptor-operated channels, voltage-gated calcium channels, and store-operated channels leading to a large influx of $Ca^{2+}$ into the cells. A high concentration of intracellular $Ca^{2+}$ is toxic and plays a unique role in damaging the intracellular organelles [8] (Fig. 2) through the activation of a variety of $Ca^{2+}$-dependent enzymes (protein kinase C, phospholipase A$_2$, phospholipase C, cyclooxygenase, calcium-dependent nitric oxide synthase, calpain, and various proteases and endonucleases), which leads to irreversible mitochondrial damage, inflammation, necrosis, and apoptosis [9, 10].

Oxygen radicals (superoxide $[O_2^-]$, hydrogen peroxide $[H_2O_2]$, and hydroxyl radicals $[-OH]$) are produced during enzymatic conversions, particularly after reperfusion, which leads to lipid peroxidation membrane damage, dysregulation of cellular processes, and mutations of the genome [4, 10, 11]. In addition, oxygen radicals trigger inflammation and apoptosis. These changes directly or indirectly promote tissue injury and disrupt the cellular powerhouse, mitochondria membranes, leading to mitochondrial burst and cell death [11, 12].

**Blood-Brain Barrier**

The efficacy of the BBB is critically dependent on endothelial-astrocyte-matrix interaction. The neurovascular matrix (basement membrane) is made up of collagen type IV, heparan sulfate proteoglycan, laminin, and fibrinectin. Disruption of this matrix leads to disruption of the cell-to-cell signaling that maintains neurovascular homeostasis. Plasminogen activator and matrix metalloproteinase (MMP) are two major protease systems that modulate the matrix in the brain [4, 10]. MMP levels have been shown to increase in experimental models after ischemia, hemorrhage, and trauma. The combination of hypoxic damage to the vascular endothelium, toxic damage of inflammatory molecules and free radicals, and destruction of the basal lamina by MMP damages the BBB. Proteolysis of the neurovascular matrix leading to disruption of the BBB is mainly seen after reperfusion. This destruction of the BBB leads to vasogenic edema, inflammation, and hemorrhagic transformation [4, 10].

**Infarctions and Inflammation**

Within hours of infarction, the endothelial cells express adhesion molecules such as intercellular adhesion molecule–1 or vascular cell adhesion molecule–1 that help leukocytes adhere to the endothelium and transmigrate from the blood into the brain parenchyma [13]. Activated leukocytes (granulocytes, monocytes or macrophages, lymphocytes) produce proinflammatory cytokines (tumor necrosis factor–alpha [TNF-\(\alpha\)], interleukin-1, and interleukin-6) and chemokines [10, 14]. During this phase of inflammation, inducible microglial cells—the primary immunoeffector cells of the CNS—also become activated and produce proinflammatory cytokines, free oxygen radicals, and the enzyme cathepsin. Microglial cells are also phagocytically active [15].

**Cell Death**

Three fundamental mechanisms [10] lead to cell death during ischemic brain injury: excitotoxicity and ionic imbalance, oxidative and nitrosative stresses, and apoptoticlike cell death. These mechanisms overlap. Excitotoxicity and ionic imbalance and oxidative and nitrosative stresses lead to the loss of membrane integrity; organelle failure; and, eventually, coagulation necrosis, the most prominent mechanism of cell death in the central core [10, 16]. Histopathology shows astrocyte swelling and fragmentation, myelin sheath degeneration, and shrunken nuclei. Selective cell death is a well-identified phenomenon after cerebral infarction. Neurons and oligodendrocytes are more vulnerable to cell death than astroglial or endothelial cells. Even among neurons, specific neurons such as cornu ammonis 1, hippocampal pyramidal neurons, layer 3 of the cortex, neurons in the dorsolateral striatum, and Purkinje cells of the cerebellum are more susceptible [4, 10]. Capillary endothelium is quite resistant compared with other CNS cells and damage to capillary endothelium begins 4–6 hours after infarction. Disruption of the capillary endothelium leads to a break in the BBB.

**Apoptoticlike Pathways**

Apoptosis starts hours after the onset of ischemia, lasts for days, and is mainly seen in the penumbral region. There is activation of intrinsic and extrinsic pathways within the cells [5, 9, 10, 17]. The intrinsic pathway leads to elevation of intracellular calcium, reactive oxygen species, glutamate, and DNA damage, whereas the extrinsic pathway acts through binding of TNF-\(\alpha\). Both pathways cause damage to mitochondrial membranes leading to the activation of caspases [5, 7, 18]. Caspases catalyze the destruction of the cell. This autolytic process is mediated by DNA cleavage [17]. During apoptosis, nuclear damage occurs first, whereas the integrity of the plasma and the mitochondrial membrane is maintained until late in the process.

**Stages of Stroke: Corresponding Pathology and Imaging Findings**

Hyperacute Stage: Less Than 12 Hours

With the advent of IV and intraarterial thrombolytic therapy, the definition of hyperacute stroke has gained significant importance. According to the results of various trials performed across the globe, a therapeutic window has been identified for the treatment of stroke, thus emphasizing the importance of early diagnosis. As described previously,
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Multiple events take place within the infarcted and surrounding parenchyma at the cellular level. Imaging findings in this stage are mainly due to diagnoses of cytotoxic edema by DWI—apparent diffusion coefficient (ADC) and of thrombus within the vessels.

CT—A decade ago, the diagnosis of a hyperacute stroke based on CT was difficult. Today, because of the higher resolution available with newer scanners and, most importantly, the ability to adjust the window width and level (window width and center level, ~8–10 and 30–35HU, respectively) on the PACS system, it is possible to suspect the diagnosis of hyperacute stroke on CT [19, 20]. Clinical history and physical examination findings are vital to increase the detection rate of stroke significantly.

CT and perfusion CT have a major role in the diagnosis and treatment of acute stroke for two main reasons: easy availability and fast acquisition. In addition, CT readily and reliably excludes hemorrhage. Early signs of stroke on CT are caused by an increase of the water content in the infarcted area that leads to obscuration of normal anatomic structures. These signs include loss of insular ribbon, obscuration of lentiform nucleus, loss of gray matter—white matter differentiation, and sulcal effacement [20, 21] (Fig. 3). Note that the early signs of stroke may not be seen on CT until 8 hours.

The hyperdense middle cerebral artery (MCA) sign (Fig. 4) is an indicator of proximal thromboembolism within the MCA (M1 segment) and is an indirect marker of acute infarction. This sign has a high specificity (~100%) but, unfortunately, is seen in only 17–50% of cases [20, 21]. This higher density is caused by an intraluminal clot with an attenuation value of 60–90HU. The hyperdense MCA sign is associated with a poor clinical outcome because of large territorial infarction and increased associated bleed. The differential diagnosis includes higher hematocrit value and vessel wall calcification, both of which are bilateral. When hyperdensity is seen in the MCA branches (M2, M3) within the Sylvian fissure, it is called the “MCA dot sign” and infarction is confined to the insular cortex and adjacent frontal cortex.

MRI—DWI has revolutionized the imaging of stroke by identifying cytotoxic edema within minutes of stroke [20–23]. Normally there is free motion of molecules within the extracellular space, called “brownian motion” [21–23] (Fig. 5). A decrease in ATP, failure of the sodium-potassium-ATPase pump, and anoxic depolarization lead to an intracellular shift of fluid causing cell swelling (cytotoxic edema) and contraction of the extracellular space (Fig. 5). These changes cause a decrease in brownian motion, which is seen on the DWI sequence as restricted diffusion (ADC). Cytotoxic edema is seen within minutes to hours on DWI with a sensitivity and specificity of 88–100% and 86–100%, respectively [22, 24]. This stage of infarction is reversible.

Perfusion imaging—The primary goal of perfusion imaging is to diagnose infarction and possibly to quantify the size of the core and penumbra—that is, to identify the mismatch between infarct core (irreversible brain tissue) and ischemic penumbra (potentially viable tissue if reperfused). CT angiography source images, CBV on perfusion CT, and DWI on perfusion MRI can be used to identify the infarct core [25].

The term “operationally defined penumbra” is used to describe the volume of tissue contained within the region of CBF-CBV mismatch on perfusion CT maps and of CBF-DWI mismatch on perfusion MRI maps. The region of CT-CBV or MR-DWI abnormality represents the core of infarcted tissue, and the CBF-CBV mismatch on CT (Fig. 6) and CBF-DWI mismatch on MRI represents the surrounding region of tissue that is hyperperfused but salvageable (penumbra). If these parameters match (CBF-CBV on CT and CBF-DWI on MRI), then it is called a “matched defect” (i.e., there is no penumbra to treat) (Fig. 7). Several studies have found that CBF is more useful than MTT in distinguishing different portions of the penumbra [26]. MTT maps are less helpful because they display circulatory derangements that do not necessarily reflect ischemic change including large- and small-vessel occlusion with collateralization, autoregulation, and reperfusion hyperemia after revascularization [27].

There is a region of “benign oligemia” within the region of CBF-CBV mismatch that is not expected to infarct even in the absence of reperfusion. Investigators have reported specific CBF thresholds for distinguishing between penumbra that is likely to infarct in the absence of early recanalization (nonviable penumbra, >68% reduction in mean CBF) and penumbra likely to survive despite persistent vascular occlusion (viable penumbra, <56% reduction in mean CBF) [28].

Penumbra is dynamic with factors such as collateral flow, admission glucose level, hematocrit level, blood pressure, and treatment influencing prediction of outcome. Despite these factors, the ultimate clinical outcome is strongly related to core lesion volume measured by DWI or CBV measured on CT. The degree of CBF reduction is also helpful in predicting the risk of hemorrhage. The clinical implications are that salvageable penumbra identified by CT or perfusion MRI has been proposed as a reason for extending the traditional therapeutic time window of 3 hours for IV thrombolysis, 6 hours for intraarterial thrombolysis of the anterior circulation, and 9 hours for intraarterial thrombolysis of the posterior circulation [29].

Acute Stage: 12–24 Hours

During the acute stage, there are further increases in the cytotoxic edema and intracellular Ca²⁺. Activation of a wide range of enzyme systems (proteases, lipases, and nucleases) and production of oxygen-free radicals lead to damage of cell membranes, DNA, and structural neuronal proteins ultimately leading to cell death. Increased tissue water results in prolongation of T1 and T2 relaxation times on MRI. T2 changes (seen after 6–8 hours) are more sensitive than T1: By 24 hours, 90% of patients show changes on T2-weighted imaging and only 50% show changes on T1-weighted imaging [19]. Increased tissue water results in effacement of convexity sulci and mild swelling of the gyri without mass effect. There may be associated subcortical hypointensity on T2-weighted imaging, which is due to free radicals sludging of deoxygenated RBC. In addition, thrombus may be seen as hypointensity within the vessel lumen (loss of normal signal void) [19, 21, 22].

Subacute Stage: 2 Days–2 Weeks

Because of a breakdown in the BBB and rupture of swollen cells, there is an increase in extracellular fluid (i.e., vasogenic edema) (Fig. 5). This takes about 18–24 hours to develop and becomes maximum by 48–72 hours [19, 20]. In this phase, imaging shows increased edema, mass effect, and possible herniation depending on the size and site of the infarct (Fig. 8). Gyral and parenchymal enhancement (Fig. 9) may be seen on contrast-enhanced T1-weighted imaging and is maximal at the end of the first week. Note that signal intensity in the infarcted area remains increased on DWI for almost 1 week and decreases thereafter, whereas reduced ADC values peak around 3–5 days, increase thereafter, and return to normal by 1–4 weeks [19, 21, 22].
Hemorrhagic transformation refers to hemorrhage in an infarcted area. The incidence of hemorrhagic transformation varies greatly between 10% and 43% (mean, 18%) [19] and is highest during the subacute stage. The severity of hemorrhage may range from a few petechiae to a large hematoma with mass effect. The pathophysiology of hemorrhagic transformation is not fully understood. Hemorrhagic transformation is thought to be due to a combination of vascular injury, reperfusion, and altered permeability. There is alteration in the integrins and disruption of basal lamina, collagen IV, and laminin by free radical and MMPs [10, 30, 31]. Exposure of this disrupted endothelium to the normal vascular pressure after clot lysis leads to reperfusion injury and extravasation of blood. This theory is called the “reperfusion theory.” However, investigators have documented that reperfusion of the occluded vessel is not a must for hemorrhagic transformation. Ogata et al. [32] documented that perfusion pressure from leptomeningeal collaterals on the surface of the brain is sufficient to cause damage and thus hemorrhage, challenging the reperfusion theory.

Hemorrhagic transformation is 2–3 times more likely in patients treated with thrombolysis [31, 33]. Major risk factors include the type, dose, and route of administration of the thrombolytic agent. Commonly used recombinant tissue plasminogen activator thrombolytic therapy may aggravate ischemia-induced microvascular damage by activation of the plasminogen-plasmin system with release of MMPs. Besides these risk factors, elevated glucose level, thrombocytopenia, and large infarct size show increased risk. As previously mentioned, the hyperdense MCA sign on unenhanced CT also is associated with an increased risk of hemorrhagic transformation. Although CT is commonly used for follow-up of stroke, MRI, especially susceptibility-weighted imaging such as gradient-recalled echo (GRE) imaging, is very sensitive in the diagnosis of early hemorrhagic transformation [34] (Fig. 10).

**Types of Stroke and Pathophysiology**

**Thromboembolic Infarction**

Thromboembolism and hemodynamic failure are two of the major causes of acute cerebral infarction. Thromboembolic infarctions are seen in all age groups. In elderly patients it is mainly due to atherosclerosis, whereas in pediatric patients and young adults it is mostly due to cardiac- or vasculopathic-hematologic causes. Thrombosis leading to vascular occlusion and subsequently to infarction is most commonly caused by atherosclerosis. The incidence of atherosclerotic infarction can vary from approximately 15% to 40%. The process of thrombus formation within the vessel is called “atherogenesis” [37]. A detailed discussion of the pathophysiology of atherogenesis is beyond the scope of this article and we suggest the following articles to interested readers: [37–39]. The pathogenesis of this process, in short, is illustrated in the schematic illustration in Figure 12. Carotid artery stenosis greater than 70% is related to a higher incidence of stroke; however, recent studies have shown that in addition to the degree of stenosis, the underlying morphology of plaque is an important predictor of stroke risk. Plaques with ulceration, hemorrhage, and fatty component are more prone for infarction than calcified, hard plaques. Depending on their composition and clinical significance, plaques are divided into hard plaques, which are collagen rich with barely detachable lipid, and soft plaque, which has a lipid-rich center and a fibrous cap. Soft plaques, called “vulnerable plaque,” are clinically significant because they are more prone for ulceration [38, 39] (Fig. 13).

Besides thrombosis, less common vascular diseases leading to vascular stenosis or occlusion of the vessels include arterial dissection; fibromuscular dysplasia; and vasospasm due to infection, drugs, or inflammatory causes. Vasculitis due to various causes such as systemic lupus erythematosus (SLE) and scleroderma can also lead to vascular occlusion and medium-to-large vessels infarctions. Multiple hematologic conditions such as a deficiency of protein C, protein S, or antithrombin III can lead to hyperviscosity and a hypercoagulable state leading to infarction. Other factors that can cause a hypercoagulable state are oral contraceptive use, pregnancy, postpartum period, paraneoplastic syndrome, and SLE.

Embolic material from either the heart or major vessels such as the carotid bifurcation can travel downstream and occlude the intracranial vessels. The most common site for plaque formation is the carotid bifurcation and in the first 2 cm of the internal carotid artery. Emboli may also originate from the aorta, vertebral arteries, or intracranial arteries. Embolic material in most cases is an atherosclerotic plaque composed of clot, platelets, or plaque debris. Atherosclerotic plaque accounts for 15–20% of all ischemic strokes, and the cardiac embolus is a source in 15–30% of all ischemic strokes. Cardiac conditions such as atrial fibrillation and flutter, myocardial infarction, ventricular aneurysm, prosthetic and rheumatic valves, and infective endocarditis are major risk factors for cardioembolism. Patients with atrial myxoma, congenital heart disease, or right-to-left shunt also have a higher incidence of cardioembolic stroke.

On imaging alone it is not easy to differentiate an embolic stroke from a thrombotic stroke. However, imaging findings that may favor an embolic cause are multiple, smaller subcortical strokes; involvement of the supra- and infratentorial compartment; multiple vascular distribution; and a hemorrhagic component at the time of presentation [19] (Fig. 14).

**Watershed Infarction**

Watershed infarctions are seen at the junction of the distal fields of the two nonanatominizing major cerebral arteries [19]. Watershed infarctions are classified into cortical watershed infarcts and internal watershed infarcts [40]. Cortical watershed infarcts
are further divided into anterior and posterior watershed infarctions. An anterior watershed infarction is between the anterior cerebral artery (ACA) and MCA territories, whereas a posterior watershed infarction develops between the ACA, MCA, and posterior cerebral artery junctional zones (Fig. 15).

On the basis of imaging, internal watershed infarcts can be further classified into confluent internal watershed infarction or partial internal watershed infarction [41]. Confluent internal watershed infarctions are confluent lesions running parallel to the lateral ventricle (Fig. 16). These lesions are usually unilateral, are due to extensive involvement of white matter, and typically present with stepwise onset of contralateral hemiplegia that recovers poorly. Partial internal watershed infarction appears as a single or multiple discrete rounded lesions in the same distribution as confluent internal watershed infarction and usually presents as episodes of brachiofacial sensory and motor deficit with good recovery [40, 41]. Although rare, watershed infarctions can also be seen in the posterior fossa between the superior cerebellar artery and the posteroinferior cerebellar artery (PICA) or between PICA, superior cerebellar artery, and anteroinferior cerebellar artery territories.

Despite much research, the pathogenesis of watershed infarction remains debatable and is thought to be multifactorial. A hemodynamic mechanism—which includes internal carotid stenosis or occlusion, systemic hypertension, and embolic events—is a major cause of watershed infarction [40–42]. The mechanisms of cortical watershed infarct and internal watershed infarct are presumed to be different. Cortical watershed infarcts are thought to be the result of microembolization either from carotid artery atherosclerosis or vulnerable plaque or from artery-to-artery emboli precipitated by an episode of systemic arterial hypotension (i.e., shock, cardiac arrest, or cardiopulmonary bypass surgery) [42, 43]. Internal watershed infarcts are caused by a combination of hypoperfusion of the internal border zone, severe carotid disease, and a hemodynamic event. Distal to the ICA occlusion, there is a reduction in the cerebral perfusion pressure (CPP) that responds by autoregulatory vasodilatation, leading to an increase in CBF and to prolonged MTT [44]. Elderly patients with impaired autoregulatory response and reduced luminal diameter are more vulnerable to even the slightest drop in systolic pressure. Any drop in the blood flow in such patients causes a decrease in oxygen tension and is responded to with an increase in oxygen extraction called “misery perfusion” [44]. Any further reduction of flow below the penumbra threshold leads to infarction.

In acute events, DWI is very sensitive for the diagnosis of both cortical watershed infarct and internal watershed infarct. Classically cortical watershed infarcts appear as fan- or wedge-shaped hyperintensities extending from the lateral margins of the lateral ventricle toward the cortex (Fig. 15), whereas internal watershed infarcts are seen as hyperintensities running parallel to the lateral ventricles, either confluent or focal, and may be unilateral or bilateral [19].

### Venous Infarction

La lacunes (“lacunes” = lake in French) are small-vessel deep infarcts less than 1.5 cm that usually cavitate [19]. For a long time, lacunar infarcts were thought to be caused by intrinsic disease of the small vessels, called “lipohyalinosis,” resulting from hypertension and diabetes. However, this hypothesis, called the “lacunar hypothesis,” does not explain why 50% of lacunar infarcts are seen in normotensive patients [45]. Lacunes are now thought to result from focal ischemic infarct caused by thrombi or emboli composed of platelets or fibrin (often with incorporated RBCs) in a background of diffuse atherosclerotic narrowing of small vessels [46]. Ipsilateral high-grade carotid stenosis and aortic arch atheroma have been shown to be risk factors for lacunar stroke. Although the outcome of lacunar stroke is substantially more favorable than other types of stroke, debate is ongoing within the neurology community about whether patients with lacunar infarcts need further workup to evaluate for the source of thrombosis.

Asymptomatic (“silent”) lacunar infarcts are at least five times more common than symptomatic infarcts [46]. When symptomatic, lacunar infarcts may present with classic lacunar syndromes: pure motor stroke, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, and dysarthria. MRI is more sensitive than CT for the diagnosis of acute and chronic lacunar infarcts [19, 46]. Acute lacunes show focal areas of restricted diffusion, most commonly in the deep white matter, whereas chronic lacunes are hyperintense on T2 and FLAIR images. A common differential diagnosis includes Virchow-Robin space, which follows CSF signal on all MRI sequences.

Cerebral venous thrombosis (CVT) accounts for 0.5% of all strokes [47]. New neuroimaging techniques—mainly MRI, MR venography, and CT venography—have revolutionized the diagnosis and therefore the treatment of CVT. Because the clinical presentation is nonspecific (e.g., isolated intracranial hypertension, focal deficit, seizures), the diagnosis of CVT on unenhanced CT can be challenging even for an experienced neuroradiologist. For early diagnosis of CVT, a high index of clinical suspicion with the use of appropriate imaging (MRI and MR venography) is a must.

The pathophysiology of venous infarction is multifactorial; venous infarction is mainly caused by pressure changes within the vascular tree [47–49]. Venous flow obstruction causes back pressure leading to a decrease in CBF. This decrease in CBF causes reduced CPP that, in turn, causes venous congestion, disruption of the BBB, and an increase in net capillary filtration leading to vasogenic edema. With the incorporation of DWI sequences in routine brain imaging, areas of restricted diffusion (cytotoxic edema) are seen within the infarcted region [49, 50]. When CBF is reduced below the penumbral level, failure of the sodium-potassium-ATP-dependent pump occurs and creates cytotoxic edema. Also investigators have proposed that increased pressure within the venous sinuses hinders the circulation of CSF from the subarachnoid space into the cerebral venous circulation, thereby leading to the development of intracranial hypertension, interstitial edema, and hydrocephalus [49–51].

A wide spectrum of parenchymal changes may be seen on imaging. On CT, venous infarction is seen as diffuse low-attenuating subcortical lesions adjacent to white matter with edematous overlying gyri in a nonarterial distribution. Areas of hemorrhage are seen in 40% of patients with venous infarction [49–51]. MRI is more sensitive and more specific than CT for the diagnosis of venous infarction. MRI shows a combination of vasogenic and cytotoxic edematous changes in the cortical and subcortical parenchyma with areas of hemorrhage (Fig. 17A). In contrast to arterial stroke, changes of cytotoxic edema in venous infarction are shown to be reversible on follow-up imaging. Even with extensive sinus thrombosis, parenchyma may not show an abnormality because mere thrombosis of the sinus is not sufficient to cause cerebral hypoperfusion. Occlusion of the bridging and cortical veins is necessary to prevent venous outflow, which induces parenchymal damage and infarction.

Direct signs of sinus thrombosis may be seen on CT or MRI. On CT, an acute blood clot
may be seen within the dual sinus (delta sign in the superior sagittal sinus), cortical veins (cord sign), or both [19, 52, 53]. On contrast-enhanced CT, nonenhancing thrombus with enhancement of the surrounding dura is called the empty delta sign. The appearance of signal suggestive of sinus thrombosis on MRI is variable and time dependent [47–53]. A thrombosed sinus appears isointense on T1 and hypointense on T2 during the first 3–5 days (deoxyhemoglobin). During the acute stage, hypointense thrombus on T2-weighted images may be mistaken for normal flow; a GRE sequence is more sensitive and shows hypointensity within the thrombosed sinus. On MR venography, the thrombosed sinus cannot be visualized (Fig. 17B). Between 5 and 20 days after thrombosis (methemoglobin), the thrombosed sinus is hyperintense on T1- and T2-weighted imaging. Approximately 1 month after thrombosis, the sinus shows areas of iso-intensity on T1- and T2-weighted imaging with partial or complete recanalization.

### Septic Infarction

Septic infarctions are caused by infected emboli that are most commonly due to an infected cardiac valve, sepsis, or IV drug abuse. The source is usually bacterial; however, in immunocompromised patients, the source can be fungal (e.g., aspergillosis) [19] (Fig. 18). Septic emboli can lead to cerebrovascular occlusion causing septic infarction, abscess, or septic aneurysm. Typically patients with septic infarction present with focal cerebral or cerebellar signs that do not resolve. Brain damage is caused by the release of inflammatory mediators such as lipopolysaccharide and endotoxin resulting in reduced CBF and reduced oxygen extraction, cerebral edema, disruption of the BBB, impaired astrocyte function, and neuronal death [54]. On imaging, hyperacute or acute septic infarctions cannot be distinguished from bland infarct. The late subacute stage may show increasing vasogenic edema with parenchymal and leptomeningeal enhancement [19] (Fig. 19). There may be changes of cerebritis or abscess formation that show restricted diffusion with hypointense on T2-weighted imaging. Approximately 1 month after thrombosis, the sinus shows areas of iso-intensity on T1- and T2-weighted imaging with partial or complete recanalization.

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**Fig. 1**—Schematic illustration of sodium-potassium pump failure: Decrease in adenosine triphosphate (ATP) at cellular level causes failure of sodium-potassium-ATP pump, which causes passive diffusion of Na and H₂O inside cell leading to intracellular (cytotoxic) edema. Higher level of extracellular K causes depolarization. ADP = adenosine diphosphate, Pi = proteinase inhibitor.

**Fig. 2**—Schematic illustration of calcium pump failure: Depolarization of cell after infarction leads to release of glutamate that, in turn, leads to opening of Ca channels and thus large influx of Ca inside cell. Higher levels of intracellular Ca cause mitochondrial damage and cellular rupture. ATP = adenosine triphosphate, ADP = adenosine diphosphate, Pi = proteinase inhibitor.

**Fig. 3**—61-year-old woman with left-sided weakness. Unenhanced CT scan of brain shows hypodensity in right middle cerebral artery territory (white arrow), effacement of convexity sulci, and loss of gray matter–white matter differentiation. There is obscuration of right caudate head (white arrowheads) and partial hypooptenuation of right putamen (black arrowhead). Note normal hyperdense insular ribbon (black arrows) on left side.
Fig. 4—Unenhanced CT scan of 61-year-old man with dense right hemiplegia reveals hyperdense thrombus in M1 segment (arrow) of left middle cerebral artery (MCA). This finding is referred to as dense MCA sign.

Fig. 5—Schematic illustrations of diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) basics.
A. Arrows show normal brownian motion in extracellular space with normal-size cells.
B. Failure of sodium-potassium-ATP pump leads to intracellular edema, swelling of cells (cytotoxic edema), decreased extracellular fluid, and hence decrease in brownian motion.
C. Large influx of Ca²⁺ inside cells leads to mitochondrial damage and cellular wall disruption, which in turn leads to cell rupture and increase in extracellular fluid (vasogenic edema).

Fig. 6—Hyperacute stroke with penumbra pattern in 56-year-old man.
A–C, Cerebral blood flow (CBF) (A), cerebral blood volume (CBV) (B), and mean transit time (MTT) (C) images from perfusion CT show area of mismatch between CBF and CBV, which is suggestive of penumbra. Area of reduced CBV (white oval, B) in left middle cerebral artery (MCA) territory is smaller than corresponding larger defect in CBF (arrowheads, A and C). Penumbra = CBF – CBV. There is viable tissue and patient will benefit from thrombolytic therapy.

(Fig. 6 continues on next page)
Fig. 6 (continued)—Hyperacute stroke with penumbra pattern in 56-year-old man.
D, Axial diffusion-weighted image obtained 24 hours after perfusion CT shows area of restricted diffusion limited to left lentiform nucleus and part of frontotemporal lobe.

Fig. 7—Hyperacute stroke without penumbra in 57-year-old man with left-sided weakness that began 3 hours earlier.
A and B, Axial diffusion-weighted (A) and cerebral blood flow (CBF) (B) images from perfusion MRI show area of restricted diffusion (arrowheads, A) in right frontal lobe with matched defect of decreased perfusion (arrows, B) on CBF—that is, there is no penumbra.

Fig. 8—Subacute infarction in 66-year-old man. Unenhanced CT scan of brain shows large hypodensity (arrowheads) in right middle cerebral artery (MCA) territory with loss of gray matter–white matter differentiation and effacement of convexity sulci with mass effect on surrounding brain parenchyma and ipsilateral lateral ventricle.
Fig. 9—Leptomeningeal and gyral enhancement in subacute stroke in two different patients.  
A, Axial T1-weighted contrast-enhanced image of 58-year-old woman shows leptomeningeal enhancement (arrows) in posterior parietal lobe.  
B, Axial T1-weighted contrast-enhanced image of 57-year-old man shows gyral enhancement (arrowheads) in frontoparietal lobes.

Fig. 10—67-year-old man who presented with right side weakness.  
A, Axial diffusion-weighted image shows acute stroke (arrows) in left posterior temporoparietal region.  
B, Axial gradient-recalled echo image from follow-up MR scan obtained 6 days after A shows dark signal intensity (arrowheads) within infarcted area due to bleed (hemorrhagic transformation).

Fig. 11—31-year-old man with movement disorder and learning disability with history of stroke.  
A, Axial diffusion-weighted image from MRI performed 1 year earlier shows acute stroke involving caudate head and putamen (arrows).  
B, Coronal T1 spoiled gradient-recalled image shows severe atrophy and cavitations of right caudate head (white arrow) and ex vacuo dilatation of right frontal horn. Note normal left caudate head (black arrow). Volume loss from prior stroke is also noted in right temporal cortex (arrowhead).
Pathophysiology of Stroke

**Fig. 12**—Schematic representation of atherogenesis. A–C, Atherogenesis is a decades-long process in which initial injury (A) is to endothelium, superficial or deep intima. This injury leads to migration of monocytes, macrophages, and endothelial cells (B). These cells, along with free radicals, low-density lipoprotein (LDL), and cholesterol form plaque (C). There is also foam cell and platelet deposition causing luminal narrowing.

**Fig. 13**—63-year-old man who presented with transient ischemic attack. A, Carotid Doppler image shows severe narrowing of lumen due to combination of soft and calcified plaque (arrow). B, Reformatted coronal image from CT angiogram of neck vessels shows plaque (arrowhead) causing severe stenosis.

**Fig. 14**—Embolic infarctions in 41-year-old woman with rheumatic heart disease. Multiple areas of restricted diffusion are seen involving right occipital, right putamen, and posterior limb of internal capsule and large left middle cerebral artery (MCA) territory.

**Fig. 15**—Cortical watershed infarction in 64-year-old man. Axial diffusion-weighted image shows areas of restricted diffusion in watershed areas (arrowheads) between anterior cerebral artery–middle cerebral artery (MCA) anteriorly and MCA–posterior cerebral artery (PCA) posteriorly that are suggestive of acute cortical watershed infarction.

**Fig. 16**—Bilateral internal watershed infarctions in 69-year-old man. Axial diffusion-weighted image shows linear areas of restricted diffusion (arrows) in subcortical white matter that are consistent with internal watershed infarction.
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Fig. 17—32-year-old woman who presented with headache and seizure. 
A, Axial T2-weighted image shows area of irregular hyperintensity in right parietal lobe (arrow). 
B, Sagittal MR venography image shows complete thrombosis of superior sagittal sinus (arrows).

Fig. 18—Acute infarction in 47-year-old man with CNS fungal infection. Contrast-enhanced CT scan of brain shows area of hypodensity (arrows) in right frontoparietal lobe with loss of gray matter–white matter differentiation; these findings are suggestive of acute stroke. Multiple rounded hypodensities (arrowheads) seen in cerebral parenchyma are fungal granulomas.

Fig. 19—Septic infarction from subacute bacterial endocarditis in 49-year-old man. 
A, Axial diffusion-weighted image shows area of restricted diffusion in frontal lobe (arrows) and caudate head (arrowhead). 
B, Contrast-enhanced T1-weighted image shows intense parenchymal enhancement (arrows) in infarcted area. Patient responded to antibiotic therapy.

**FOR YOUR INFORMATION**

This article is part of a self-assessment module (SAM). Please also refer to “Imaging of Stroke: Part 1, Perfusion CT—Overview of Imaging Technique, Interpretation Pearls, and Common Pitfalls,” which can be found on page 52.

Each SAM is composed of two journal articles along with questions, solutions, and references, which can be found online. You can access the two articles at www.ajronline.org, and the questions and solutions that comprise the Self-Assessment Module via http://www.arrs.org/Publications/AJR/index.aspx.

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