



## **Stroke Pathophysiology**

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### **Introduction**

The two major mechanisms causing brain damage in stroke are, ischemia and hemorrhage. In ischemic stroke, which represents about 80% of all strokes, decreased or absent circulating blood deprives neurons of necessary substrates. The effects of ischemia are fairly rapid because the brain does not store glucose, the chief energy substrate and is incapable of anaerobic metabolism.<sup>1</sup> Non-traumatic intracerebral hemorrhage represents approximately 10% to 15% of all strokes. Intracerebral hemorrhage originates from deep penetrating vessels and causes injury to brain tissue by disrupting connecting pathways and causing localized pressure injury. In either case, destructive biochemical substances released from a variety of sources play an important role in tissue destruction.

### **Focal Ischemic Injury**

A thrombus or an embolus can occlude a cerebral artery and cause ischemia in the affected vascular territory. It is often not possible to distinguish between a lesion caused by a thrombus and one caused by an embolus. Thrombosis of a vessel can result in artery-to-artery embolism. Mechanisms of neuronal injury at the cellular level are governed by hypoxia or anoxia from any cause that is reviewed below.

At a gross tissue level, the vascular compromise leading to acute stroke is a dynamic process that evolves over time. The progression and the extent of ischemic injury is influenced by many factors.<sup>2-5</sup>

Rate of onset and duration: the brain better tolerates an ischemic event of short duration or one with slow onset.

Collateral circulation: the impact of ischemic injury is greatly influenced by the state of collateral circulation in the affected area of the brain. A good collateral circulation is associated with a better outcome.

Health of systemic circulation: Constant cerebral perfusion pressure depends on adequate systemic blood pressure. Systemic hypotension from any reason can result in global cerebral ischemia.

Hematological factors: a hypercoagulable state increases the progression and extent of microscopic thrombi, exacerbating vascular occlusion.

Temperature: elevated body temperature is associated with greater cerebral ischemic injury.

Glucose metabolism: hyper- hypoglycemia can adversely influence the size of an infarct.

### **Cerebral Blood Flow**

Normal cerebral blood flow (CBF) is approximately 50-to 60 ml/100g/ Min and varies in different parts of the brain. In response to ischemia, the cerebral autoregulatory mechanisms compensate for a reduction in CBF by local vasodilatation, opening the collaterals, and increasing the extraction of oxygen and glucose from the blood. However, when the CBF is reduced to below 20 ml/100g/min, an electrical silence ensues and synaptic activity is greatly diminished in an attempt to preserve energy stores. CBF of less than 10ml/100g/min results in irreversible neuronal injury.<sup>1,6-11</sup>

### **Mechanisms of neuronal injury**

Formation of microscopic thrombi responsible for impairment of microcirculation in the cerebral arterioles and capillaries is a complex phenomenon. Formation of a micro thrombus is triggered by ischemia-induced activation of destructive vasoactive enzymes that are released by endothelium, leucocytes, platelets and other neuronal cells. Mechanical “plugging” by leucocytes, erythrocytes, platelets and fibrin ensues.<sup>12</sup>

At a molecular level, the development of hypoxic- ischemic neuronal injury is greatly influenced by “overreaction” of certain neurotransmitters, primarily glutamate and aspartate. This process called “excitotoxicity” is triggered by depletion of cellular energy stores. Glutamate, which is normally stored inside the synaptic terminals, is cleared from the extracellular space by an energy dependent process. The greatly increased concentration of glutamate (and aspartate) in the extracellular space in a depleted energy state results in the opening of calcium channels associated with N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors. Persistent membrane depolarization causes influx of calcium, sodium, and chloride ions and efflux of potassium ions.<sup>13-24</sup>

Intracellular calcium is responsible for activation of a series of destructive enzymes such as proteases, lipases, and endonucleases that allow release of cytokines and other mediators, resulting in the loss of cellular integrity.<sup>15-19</sup>

Inflammatory response to tissue injury is initiated by the rapid production of many different inflammatory mediators, tumor necrosis factor being one of the key agents. Leukocyte recruitment to the ischemic areas occurs as early as thirty minutes after ischemia and reperfusion. In addition to contributing to mechanical obstruction of microcirculation, the leucocytes also activate vasoactive substances such as oxygen free radicals, arachidonic acid metabolites (cytokines), and nitric acid. The cellular effects of these mediators include vasodilatation, vasoconstriction, increased permeability, increased platelets aggregation, increased leukocyte adherence to the endothelial wall, and immunoregulation.

Endothelial cells are one of the first cell types to respond to hypoxia. This response occurs at morphological, biochemical and immunological levels, causing a variety of physiological and pharmacological effects. Morphologically, endothelial cells swell and

form “microvilli” at the luminal surface of the cell. This results in a reduction in the luminal patency of the capillary vessel. Mechanical plugging by erythrocytes, leukocytes, and platelets ensues. At a biochemical level, endothelial cells mediate the effects of vasoactive agents such as endothelin peptides, eicosanoids, and smooth muscle relaxant (probably nitric acid), which in part modulate the vascular tone of the microcirculation. Activation of endothelial adhesion molecules promotes leukocyte adherence to the endothelial wall, a key process in the initiation of the inflammatory process.<sup>13-24</sup>

### **Ischemic Penumbra (IP)**

Within an hour of hypoxic- ischemic insult, there is a core of infarction surrounded by an oligemic zone called the ischemic penumbra (IP) where autoregulation is ineffective. The critical time period during which this volume of brain tissue is at risk is referred to as the “window of opportunity” since the neurological deficits created by ischemia can be partly or completely reversed by reperfusion of the ischemic yet viable brain tissue within a critical time period (2 to 4 hours?).<sup>1,6-8,10,11,23-25</sup>

IP is characterized by some preservation of energy metabolism because the CBF in this area is 25% to 50% of normal. Cellular integrity and function are preserved in this area of limited ischemia for variable periods of time. The pathophysiology of IP is closely linked to generation of spontaneous waves of depolarization (SWD). SWD can originate from multiple foci; some from the ischemic core and others from ischemic foci within the peri-infarct zone (penumbra). Sustained increases of synaptic glutamate and extracellular potassium ions are closely associated with the development of SWD. Glutamate receptor antagonists that block transmembrane calcium flux and prevent intracellular calcium accumulation are known to suppress SWD. Hypoxic or rapid depolarizations eventually supervene just before irreversible neuronal death.<sup>26-34</sup>

### **Neuronal death**

The two processes by which injured neurons are known to die are coagulation necrosis and apoptosis.

Coagulation necrosis (CN) refers to a process in which individual cells die among living neighbor cells without eliciting an inflammatory response. This type of cell death is attributed to the effects of physical, chemical, or osmotic damage to the plasma membrane. This is in contrast to liquefaction necrosis, which occurs when cells die, leaving behind a space filled by “inflammatory response” or pus.

In CN, the cell initially swells then shrinks and undergoes pyknosis – a term used to describe marked nuclear chromatin condensation. This process evolves over 6 to 12 hours. By 24 hours extensive chromatolysis occurs resulting in pan-necrosis. Astrocytes swell and fragment, myelin sheaths degenerate. Irreversible cellular injury as demonstrated by eosinophilic cytoplasm and shrunken nuclei are seen between 8 to 12

hours after arterial occlusion (91). The morphology of dying cells in coagulation necrosis is different than that of cell death due to apoptosis.<sup>10,11,15,17,35</sup>

The term apoptosis is derived from the study of plant life wherein deciduous trees shed their leaves in the fall. This is also called “programmed cell death”, because the leaves are programmed to die in response to seasonal conditions. Similarly, cerebral neurons are “programmed” to die under certain conditions, such as ischemia. During apoptosis, nuclear damage occurs first. The integrity of the plasma and the mitochondrial membrane is maintained until late in the process. Ischemia activates latent “suicide” proteins in the nuclei, which starts an autolytic process resulting in cell death. This autolytic process is mediated by DNA cleavage.<sup>36,37</sup>

Apoptotic mechanisms begin within 1 hour after ischemic injury whereas CN begins by 6 hours after arterial occlusion. This observation has an important bearing on future directions of research. The manner by which apoptosis evolves is a focus of much research, because, hypothetically, neuronal death can be prevented by modifying the process of DNA cleavage that seems to be responsible for apoptosis.

### **Ischemic Stroke**

The three main mechanisms causing ischemic strokes are: (a) thrombosis, (2) embolism and (3) global ischemia (hypotensive) stroke. All ischemic strokes do not neatly fall into these categories and the list of entities responsible for unusual stroke syndromes is very long. However, strokes caused by vasospasm (migraine, following SAH, hypertensive encephalopathy) and some form of “arteritis” stand out among the more infrequent causes of stroke.

### **Thrombosis**

Atherosclerosis is the most common pathological feature of vascular obstruction resulting in thrombotic stroke.<sup>38</sup> Atherosclerotic plaques can undergo pathological changes such as ulcerations, thrombosis, calcifications, and intra-plaque hemorrhage. The susceptibility of the plaque to disrupt, fracture or disrupt or ulcerate depends on the structure of the plaque, and its composition and consistency. Disruption of endothelium that can occur in the setting of any of these pathological changes initiates a complicated process that activates many destructive vasoactive enzymes. Platelet adherence and aggregation to the vascular wall follow, forming small nidi of platelets and fibrin. Leucocytes that are present at the site within 1 hour of the ictus mediate an inflammatory response.<sup>38-43</sup>

In addition to atherosclerosis, other pathological conditions that cause thrombotic occlusion of a vessel include clot formation due to hypercoagulable state, fibromuscular dysplasia, arteritis (Giant cell and Takayasu), and dissection of a vessel wall.

In contrast to the occlusion of large atherosclerotic vessels, lacunar infarcts occur as a result of occlusion of deep penetrating arteries that are 100 to 400  $\mu$ m in diameter and originate for the cerebral arteries. The putamen and pallidum, followed by pons,

thalamus, caudate nucleus, and internal capsule are the most frequently affected sites. The size of a lacunar infarct is only about 20 mm in diameter. The incidence of lacunar infarcts is 10% to 30% of all strokes depending on race and preexisting hypertension and diabetes mellitus. The small arteriole, most frequently as a result of chronic hypertension lengthens, becomes tortuous and develops subintimal dissections and micro-aneurysms rendering the arteriole susceptible to occlusion from micro-thrombi. Fibrin deposition resulting in lipohyalinosis is considered to be the underlying pathological mechanism.<sup>44,45</sup>

### **Embolism**

Embolic stroke (ES) can result from embolization of an artery in the central circulation from a variety of sources. Besides clot, fibrin, and pieces of atheromatous plaque, materials known to embolize into the central circulation include fat, air, tumor or metastasis, bacterial clumps, and foreign bodies. Superficial branches of cerebral and cerebellar arteries are the most frequent targets of emboli. Most emboli lodge in the middle cerebral artery distribution because 80% of the blood carried by the large neck arteries flow through the middle cerebral arteries.<sup>43</sup>

The two most common sources of emboli are: the left sided cardiac chambers and large arteries, (e.g. “artery to artery” emboli that result from detachment of a thrombus from the internal carotid artery at the site of an ulcerated plaque).

The neurological outcome from an ES depends not only on the occluded vascular territory but also on the ability of the embolus to cause vasospasm by acting as a vascular irritant. The vasospasm can occur in the vascular segment where the embolus lodges or can involve the entire arterial tree. Vasospasm tends to occur in younger patients, probably because the vessels are more pliable and less atherosclerotic.

Many embolic strokes become “hemorrhagic” causing hemorrhagic infarction (HI). Hemorrhagic infarct (used here synonymously with hemorrhagic transformation of an ischemic infarct) is an ischemic infarct in which bleeding develops within the necrotizing cerebral tissue. The pathogenesis of hemorrhagic transformation of a pale infarct is a complex phenomenon.

The two common explanations that are advanced to explain the pathogenesis of HI in embolic strokes are: (1) Hemorrhagic transformation occurs because ischemic tissue is often reperfused when the embolus lyses spontaneously and blood flow is restored to a previously ischemic area. An initial vascular obstruction is likely to occur at a bifurcation of a major vessel. The occlusion may obstruct one or both of the branches, producing ischemia of the distal tissue. Blood vessels as well as brain tissue are rendered fragile and injured. When the occluding embolus either lyses spontaneously or breaks apart and migrates distally, CBF is restored to the “injured or ischemic” microcirculation. This can result in a hemorrhagic or “red infarct” in what had previously been a bloodless field. The areas that continue to be poorly perfused are referred to as “pale” or “anemic infarcts.” (2) Hemorrhagic transformation is also known to occur with persistent occlusion of the parent artery proximally, indicating that hemorrhagic transformation is not always

associated with migration of embolic material. HI on the periphery of infarcts in presence of persistent arterial occlusion is caused by reperfusion from leptomeningeal vessels that provide collateral circulation. In patients with ES, it is not unusual to see HI side-by-side with ischemic infarction.

The three main factors associated with “red infarcts” or hemorrhagic infarctions include the size of the infarct, richness of collateral circulation, and the use of anticoagulants and interventional therapy with thrombolytic agents. Large cerebral infarctions are associated with a higher incidence of hemorrhagic transformation. Hypertension is not considered to be an independent risk factor for hemorrhagic transformation of an ischemic infarct.<sup>46-49</sup>

### **Global – Ischemic or Hypotensive stroke**

Profound reduction in systemic blood pressure due to any reason is responsible for “hypotensive stroke.” Some neurons are more susceptible to ischemia than others. These include the pyramidal cell layer of the hippocampus and the Purkinje cell layer of the cerebellar cortex. Cerebral gray matter is also particularly vulnerable. Abundance of glutamate in these neurons renders them more susceptible to global ischemia.

Global ischemia causes the greatest damage to areas between the territories of the major cerebral and cerebellar arteries known as the “boundary zone” or “watershed area.” The parietal-temporal-occipital triangle at the junction of the anterior, middle, and posterior cerebral arteries is most commonly affected. Watershed infarction in this area causes a clinical syndrome consisting of paralysis and sensory loss predominantly involving the arm; the face is not affected and speech is spared. Watershed infarcts make up approximately 10% of all ischemic strokes and almost 40% of these occur in patients with carotid stenosis or occlusion.<sup>50</sup>

## **Pathophysiology of Stroke**

### **Reference List**

1. Jones TH, Morawetz RB, Crowell RM, et al. Thresholds of focal ischemia in awake monkeys. *J Neurosurg.* 1981; 54:773-782.
2. Wass CT, Lanier WL,. Glucose modulation of ischemic brain injury: review and clinical recommendations. *Mayo Clin Proc.* 1996;71:801-812.
3. Bruno A, Biller J, Adams HP Jr, et al. Acute blood glucose level and outcome from ischemic stroke. *Neurology.* 1999;52:280-284.
4. Reith J, Jorgensen HS, Pedersen PM, et al. Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome. *Lancet.* 1996;347:422-425.
5. Schwab S, Spranger M, Aschoff A, et al. Brain temperature monitoring and modulation in patients with severe MCA infarction. *Neurology.* 1997;48:762-767.
6. Pulsinelli WA. The ischemic penumbra in stroke. *Sci Med.* 1995;1:16-25.
7. Hakim AM. Ischemic penumbra, the therapeutic window. *Neurology.* 1998;51(Suppl 3):S44-S46.
8. Astrup J, Seisjo BK, Symon L. Thresholds in cerebral ischemia – the ischemic penumbra. *Stroke.* 1981;12:723-725.
9. Zivin JA, Choi DW. Stroke therapy. *Sci Med.* 1991;265:56-53.
10. Wise RJ, Bernardi S, Frackowiak RS, Legg NJ, Jones T. Serial observations on the pathophysiology of acute stroke: the transition from ischaemia to infarction as reflected in regional oxygen extraction. *Brain.* 1983;106 (Pt 1):197-222.
11. Heros R. Stroke: early pathophysiology and treatment. *Stroke.* 1994;25:1877-1881.
12. Garcia JH, Liu K, Yoshida Y et al. Brain microvessels:factors altering their patency after the occlusion of a middle cerebral artery (Wistar rat). *Am J Pathol* 1994; 145:728-40.
13. Siesjo BK Free radicals and brain damage. *Cerebrovasc Brain Metab Rev.* 1989; 1:165-211

14. Del Zoppo GJ, Schmidt-Schonbein GW, Mori E. et al. Polymorphonuclear leukocytes occlude capillaries following middle cerebral artery occlusion and reperfusion. *Stroke*. 1991; 22:1276-1283
15. Siesjö BK: Cell damage in the brain: a speculative synthesis. *J Cereb Blood Flow Metab*.1981; 1:115-185
16. Rothman SM, Olney JW Excitotoxicity and the NMDA receptors. *Trends Neurosci*. 1987; 10:299-302
17. Becker KJ. Inflammation and acute stroke. *Curr Opin Neurol*. 1998;11:45-49.
18. Hademenos GJ, Massoud TF. Biophysical mechanisms of stroke. *Stroke*. 1997;28:2067-77
19. DeGraba TJ. The role of inflammation after acute stroke, utility of pursuing anti-adhesion molecule therapy. *Neurology*. 1998;(Suppl 3):S62-S68.
20. Kroemer G, Pepit P, Zamzami N et al. The biochemistry of programmed cell death. *FASEB J*. 1995; 1277-1287
21. Adams DH, Shaw S. Leukocyte-endothelial interactions and regulation of leukocyte migration. *Lancet* 1994; 343: 831-836
22. Schor K, Braun M. Platelets as a source of vasoactive mediators. *Stroke*. 199; 21:IV32-IV35
23. Garcia JH, Liu K, Yoshida Y et al. Influx of leukocytes and platelets in an evolving brain infarct (Wistar rat). *Am J Pathol* 1994; 144: 188-199.
24. Garcia JH, Yoshida Y, Chen H et al. Progression from ischemic injury to infarct following middle cerebral artery occlusion in the rat. *Am J Pathol* 1993; 142:623-635
25. Hossmann YA. Viability thresholds and the penumbra of focal ischemia. *Ann Neuro*. 1994;36:557-565.
26. Nedergaard M. Mechanisms of brain damage in focal cerebral ischemia. *Acta Neurol Scand* 1988; 77 (supp):1-24.
27. Takagi K, Ginsberg MD, Globus MY-T, et al. Changes in amino acid neurotransmitters and cerebral blood flow in the ischemic penumbral region following middle cerebral artery occlusion in the rat: correlation with histopathology. *J Cereb Blood Flow Metab* 1993; 13: 575-585.

28. Leao AAP. Spreading depression of activity in the cerebral cortex. *Neurophysiolo* 1944; 7: 359-390
29. Back T, Ginsberg MD, Dietrich WD, Watson BD. Induction of spreading depression in the ischemic hemisphere following experimental middle cerebral artery occlusion: effect on infarct morphology. *J Cereb Blood Flow Metab* 1996; 16: 202-213
30. Dereski MO, Chopp M, Knight RA et al. The heterogeneous temporal evolution of focal ischemic neuronal damage in the rat. *Acta Neuropathol* 1993; 85: 32-333
31. Busch E, Gyngell ML, Ris M, et al. Potassium induced cortical spreading depression during focal cerebral ischemia in rats: contribution to lesion growth assessed by diffusion-weighted NMR and biochemical imaging. *J Cereb Blood Flow Metab* 1997; 17(suppl)
32. Nedergaard M, Hansen AJ. Characterization of cortical depolarizations evoked in focal cerebral ischemia. *J Cereb Blood Flow Metab* 1993; 13:568-74.
33. Graf R, Saito R, Hubel K et al. Spreading depression-like negativations turn into terminal depolarizations after prolonged focal ischemia in rats. *J Cereb Blood Flow Metab* 1995; 15(suppl 1):S15
34. Hansen AJ. Effects of anoxia on ion distribution in the brain. *Physiol Rev* 1985; 65: 101-148
35. Garcia JH. Morphology of global cerebral ischemia: a review. *Crit Care Med*. 1988; 16:979.
36. Choi DW. Ischemia-induced neural apoptosis. *Curr Opin Neurobiol*. 1996;6:667-672.
37. Kajstra J, Cheng W, Reiss K et al. Apoptotic and necrotic myocyte cell deaths are independent of variables to infarct size in rats. *Lab Invest*. 1996; 74:86-1
38. Challa V. Atherosclerosis of the Cervicocranial arteries. In Toole JF (ed) *Cerebrovascular disorders*. 5<sup>th</sup> edition. Lippincott Williams and Wilkins, Philadelphia, 1999.
39. Fuster V, Stein B, Amboose JA et al. Atherosclerotic plaque rupture and thrombosis: evolving concepts. *Circulation* 1990; 82(suppl II); 47-59.
40. Glagov S, Zarins CB. What are the determinants of plaque instability and its consequences? *J Vasc Surg* 198; 9: 389-390.

41. Falk E. Why do plaques rupture? *Circulation* 1992; 86:30-42.
42. Zamir M, Silver MD. Hemorrhagic and microvascular phenomenon within the arterial wall. *Can J Cardiol* 1992;8:981-84.
43. Garcia JH, Ho Khang-Loon, Pantoni L. Pathology in Barnett, Henry JM, Mohr JP, Stein BM, Yatsu FM (eds), *Stroke Pathophysiology, Diagnosis and Management*. Third edition, Philadelphia, PA: Churchill Livingstone; 1998.
44. Pullicino PM Pathogenesis of lacunar infarcts and small deep infarcts. 1993. *Adv Neurol* 62: 125-140.
45. Yu R, McNeil JJ, O Malley HM, Davis SM, Donnan GA Risk factors for lacunar infarction syndromes. *Neurology* 1995;45: 1483-87.
46. Lyden PD, Zivin JA. Hemorrhagic transformation after cerebral ischemia: Mechanisms and incidence. *Cerebrovasc Brain Metab Rev.* 1993; 5:1-16.
47. Toni D, Fiorelli M, Bastianello S, Et al. Hemorrhagic transformation of brain infarct: predictability in the first five hours from stroke onset and influence on clinical outcome. *Neurology*. 1996;46:341-345.
48. Fagan SC, Garcia JH. Reperfusion hemorrhage after middle cerebral artery occlusion in the rat. *Neurology* 1996;46:A195.
49. Hart RG, Easton JH. Hemorrhagic infarcts. *Stroke* 1986;17: 586-89
50. Garcia JH, Anderson ML: Circulatory disorders and their effects on the brain. pp 715-822. In Davis RL, Robertson DM (eds): *Textbook of Neuropathology*, 3<sup>rd</sup> edition. Williams & Wilkins, Baltimore 1997

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### Annotated Bibliography

1. **Barnett, Henry JM, Mohr JP, Stein BM, Yatsu FM (eds), Stroke Pathophysiology, Diagnosis and Management. Third edition, Philadelphia, PA: Churchill Livingstone; 1998**

This is one of the most exhaustive sources of all aspects of stroke. A voluminous book of over 1400 pages is divided into 5 sections. The section of pathophysiology has an excellent review of neurochemistry and molecular biology. Two very useful chapters dedicated to functional MRI and PET scans reference recent works which validate hypotheses regarding cerebral blood flow and oxygen/glucose metabolisms.

2. **Toole JF. Brain Infarction: Pathophysiology, Clinical Feature and Management Cerebrovascular disorders. In: Toole JF (Editor) 5<sup>th</sup> edition. Philadelphia, PA: Lippincott Williams & Wilkins; 1999**

This chapter is particularly well written. The author explains the basic concepts of pathophysiology without excessive detail. Separate chapters review cerebral embolism, intracerebral and subarachnoid hemorrhage. This is an excellent choice for a concise review of the various types of strokes.

3. **Hakim AM: Ischemic penumbra, the therapeutic window. Neurology. 1998;51(supp 3):S44-46**

Hakim presents a concise but very informative review of ischemic penumbra. He stresses that despite the knowledge of penumbra, we have yet to translate this knowledge into clinical practice. The neuronal death in the penubral tissue is now believed to be due to apoptosis. Research towards interrupting the apoptosis may allow greater viability of the penubral brain tissue.

4. **Choi DW. Ischemia-induced neural apoptosis. Curr Opin Neurobiol. 1996;6:667-72**

Choi distinguishes the traditional concept of hypoxic neuronal death due to necrosis from that of apoptosis. The process of apoptosis is also considered to be distinct from ischemia induced excitotoxicity. Apoptosis is now known to occur in both global and focal ischemic insults. This is a good review of apoptosis.

## Pathophysiology of Stroke

### Questions

- 1. Conditions that adversely influence progression and extent of ischemic injury include all of the following except:**
  - a. Systemic hypotension
  - b. Rapid development of an ischemic event
  - c. Hypercoaguable states
  - d. Prolonged ischemia
  - e. Subnormal normal body temperature
  - f. Hypo or hyperglycemia
  - g. State of collateral circulation
  
- 2. Features of ischemic stroke due to global reduction in cerebral blood flow (Hypotensive stroke) include all the following except:**
  - a. Hippocampus and Purkinje cell layer of the cerebral cortex are most vulnerable to a reduction in cerebral blood flow
  - b. Speech difficulties typify victims of Hypotensive stroke who recover
  - c. Uncontrolled release of excitatory amino acids primarily glutamate and aspartate cause calcium channels to open up which ultimately leads to cell death
  - d. Sites affected by critically low cerebral blood flow are located at the end of an arterial territory, the so called watershed areas
  
- 3. The true statement with regards to ischemic penumbra (IP) is**
  - a. IP is an area of massive neuronal death that results from a global reduction in cerebral blood flow (CBF)
  - b. CBF in the IP is usually above the 50% of the norm
  - c. Auto regulatory mechanisms are preserved in the IP
  - d. IP is a potentially salvageable area of marginal blood flow that surrounds a core of ischemic brain tissue
  
- 4. All of the following are true except**
  - a. Reperfusion hemorrhage results when 'fragile' ischemic or injured vessels rupture after sudden restoration of blood flow
  - b. Hemorrhagic transformation of an ischemic infarct generally occurs in what had previously been a blood-less field
  - c. Hypertensives are more likely to suffer from reperfusion hemorrhage
  - d. Thrombolytic therapy increases the likelihood of reperfusion hemorrhage

## **Pathophysiology of Stroke**

### **Answers**

**1. Answer e.**

Several studies have shown that hypothermia is actually beneficial in attenuating effects of brain ischemia.

**2. Answer b.**

A common site of a watershed infarction is the border zone between the anterior and middle cerebral arteries that extends over the frontomotor homunculi at approximately the level of the cortical representation of the arm. The resulting clinical syndrome consists of paralysis and sensory loss, predominantly involving the arm. Face is not affected and speech is spared.

The watershed infarct involving the anterior, middle and posterior cerebral arteries occurs in parietal occipital region causing homonymous hemianopia with visual agnosia, disorientation in space, apraxia, dysgraphia and dyslexia. Speech difficulties are more commonly seen with a stroke involving the vascular territory of middle cerebral artery.

**3. Answer d.**

Cerebral blood flow in the ischemic penumbra (IP) is approximately 25% to 50% of normal. Cellular integrity and function are preserved in this area of limited ischemia for variable periods of time. This makes IP a potentially salvageable area.

**4. Answer c.**

The hemorrhagic transformation of an ischemic infarct - the so-called reperfusion hemorrhage is a complex phenomenon. The three main factors associated with this include the size of the infarct, richness of collateral circulation, and the use of anticoagulants and thrombolytic agents. Interestingly hypertension is not considered to a risk factor for reperfusion hemorrhage unlike hemorrhagic stroke that is more common in patients with hypertension.