

## Ischemic Stroke Mechanisms, Prevention, and Treatment: The Anesthesiologist's Perspective

Myles R. McCrary<sup>1\*</sup>, Song Wang<sup>1,2\*</sup>, and Ling Wei<sup>1,2</sup>

### ABSTRACT

From <sup>1</sup>Department of Anesthesiology, Emory University School of Medicine, Atlanta, USA; <sup>2</sup>Department of Neurology and Laboratories of Stem Cell Biology and Regenerative Medicine, Neurological Disease Center and Experimental Research Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China.

\*Contributed equally to this work.

**Correspondence** to Dr. Ling Wei at [lwei7@emory.edu](mailto:lwei7@emory.edu).

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**Aim of review:** Stroke remains a leading cause of mortality and morbidity. After decades of extensive research, we have gained a detailed understanding of the cellular and molecular mechanisms governing stroke pathophysiology. Despite these advances, few novel and effective treatments have been discovered. Understanding the mechanisms that underlie ischemic brain damage may direct research on future therapies.

**Methods:** We reviewed the available literature pertaining to stroke pathology in the past decades and provided brief summaries of the important basic and clinical stroke findings.

**Recent findings:** This review provided an overview of basic stroke mechanisms and highlighted the main events and processes that lead to cellular demise. We concluded with stroke preventative measures and treatment, highlighting the role of anesthesiologists in preventing perioperative stroke.

**Summary:** An appreciation of our current understanding of stroke pathology may inform the development of new therapies or preventative measures for stroke, such as anesthetic preconditioning, and lead to optimal perioperative management of patients at high risk for stroke.

Stroke is one of the leading causes of death or long-term disability worldwide. According to the American Heart Association, stroke became the fifth leading cause of death in the United States in 2013 (1). Nearly 1 in 20 people in the United States die due to stroke. Fortunately, population trends for stroke are improving. Over the last decade, the relative rate of death from stroke has decreased by nearly a third, and the number of stroke deaths fell by 18.2%. Overall, stroke mortality has declined across sex, race, and age. Stroke death rates have decreased among people aged  $\geq 65$  years. Many of these improvements are attributed to improved preventative, perioperative, and manage-

ment guidelines, resulting in both reduced stroke incidence and lower stroke fatality rates (1- 4). However, despite these promising epidemiological trends, nearly 800,000 people encounter new or recurrent stroke yearly in the US alone, and few successful treatments have been developed to treat this disease (1).

### Stroke Types and Risk Factors

Most simply, stroke occurs when blood flow to the brain is blocked, resulting in cell death. There are two main types of stroke: hemorrhagic stroke, which results from blood vessel rupture, and ischemic stroke, which results from blood vessel occlusion. Hemorrhagic

strokes account for about 15% of total strokes (5). Blood from leaking vessels can enter the brain tissue (intracerebral hemorrhage, ICH), or the space below the arachnoid layer of the meninges (subarachnoid hemorrhage, SAH). ICH is more common than SAH. Over 80% of strokes are ischemic and can be categorized based on mechanism of blood vessel occlusion. The three primary ischemic stroke types are large artery atherosclerosis, cardiogenic embolism, and small vessel occlusion. The non-modifiable and potentially-modifiable risk factors for hemorrhagic and ischemic strokes are listed in the Table.

### Pathophysiology

Numerous mechanisms regarding ischemic stroke pathophysiology have been elucidated. Understanding the contribution of each mechanism can inform research and the development of novel treatments. Brain tissue is highly dependent on oxidative phosphorylation to provide energy, and thus requires high amounts of oxygen and glucose. It is estimated that the brain utilizes about 20% of the body's resting metabolism, and about half of that is used to maintain ion gradients (6). Impairment of cerebral blood flow cuts off the delivery of key nutrients and oxygen, compromising the energy consumption needed to maintain homeostasis. Many cells die as a direct result of ischemic stress. Ensuing biochemical and cellular events exacerbate brain damage after the initial hypoxic insult. Particularly, improper signaling due to ion imbalance after hypoxia plays a significant role in stroke progression. For this review, we will describe a series of temporal and spatial pathophysiological events that follow ischemic stroke. We also will provide a detailed discussion of the mechanisms that contribute to stroke pathology at each stage (Figure 1).

### Overview of Stroke Progression

The ischemic stroke region is comprised of two parts. In the core area of the ischemic territory, the perfusion deficit results in low ATP. Cellular energy homeostasis is disrupted and cell death develops within minutes. In the penumbra region, the area between unaffected and ischemic regions, partially preserved perfusion from non-

occluded collateral blood vessels allows for milder but still significant damage to occur (7). The core and penumbra regions are spatially and temporally dynamic. The penumbra comprises a large portion of the lesion volume during the initial stage of blood vessel occlusion (8). However, if left untreated, the penumbra region may become infarcted and the core territory can expand over the course of hours and days. It is believed that the core region of the stroke is unsalvageable, while the ischemic penumbra is at risk, but still rescuable if perfusion is restored (9). Recent literature has revealed that a select few cells can survive in the stroke core, suggesting that the core infarct region is not entirely unsalvageable (10). However, the majority of research is targeted at the peri-infarct area with apparent therapeutic opportunity. A cascade of harmful events, including excitotoxicity, spreading depolarization, oxidative and nitrosative stress, inflammation, and cell death are central to stroke pathology. Understanding the mechanisms that underlie brain damage in the stroke core and the ischemic penumbra may direct research on future treatments.

### Excitotoxicity, Calcium Dysregulation, and Ion Imbalance

Oxygen and glucose supply is impaired during the immediate perfusion deficit following stroke. This deficit compromises the energy supply required to maintain normal ionic gradients in neurons and glia. As a result, these cells can lose membrane potential resulting in depolarization events. Depolarization causes voltage-dependent calcium channel activation and excitatory amino acid (mainly glutamate) release into the extracellular space. Concurrently, presynaptic reuptake of glutamate is reduced due to the lack of energy needed to activate ion pumps, which further exacerbates the increased extracellular glutamate concentration. The excess glutamate binds AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and NMDA (N-methyl-D-aspartate) receptors to increase the influx of water, sodium, and calcium into neurons, inducing a host of signaling events that cause cell swelling, activation of catabolic activity, and eventual cell death (11, 12). Massive cal-

**Table. Comparison of Important Risk Factors for Hemorrhagic versus Ischemic Stroke.**

Risk factors	Hemorrhagic stroke	Ischemic stroke
<b>Non-modifiable</b>		
Sex	Females during and immediately after pregnancy	Male
Race/Ethnicity	Asian>African American>Hispanic>White	African American>Hispanic>White
<b>Modifiable</b>		
Blood pressure	Hypertension is a well-established risk factor for both types; strongest association with intracerebral hemorrhage	
Diabetes	Association not well-established; may negatively affect outcomes	Association well-established
Smoking	Associated with subarachnoid but not intracerebral hemorrhage	Association well-established
Atrial fibrillation	Not directly associated, however, anti-thrombotic (anti-coagulation>antiplatelet) use is strongly associated	Association well-established
BMI/Waist-to-hip ratio	High BMI/Waist-to-hip ratio is associated with both stroke types	
Diet (modified Alternate Healthy Eating Index)	High mAHEI is negatively associated with both stroke types	
Physical activity	Regular physical activity is negatively associated with both stroke types	
Alcohol consumption	Alcohol consumption is associated with both stroke types	

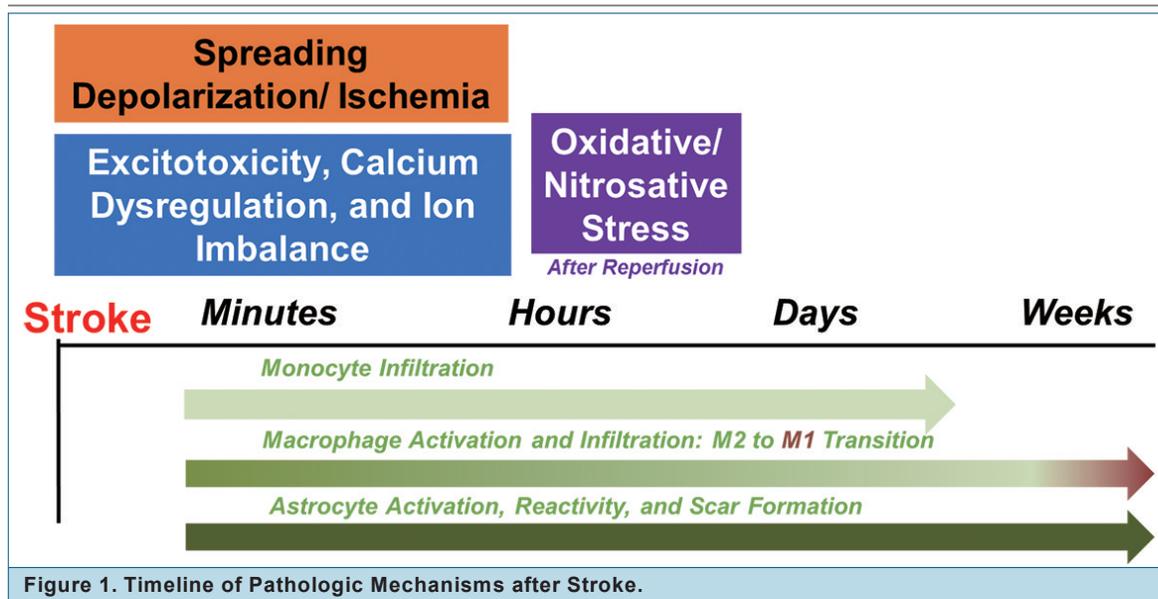
Note: This list is not exhaustive. See (2, 3, 5, 83, 97-101) for comprehensive lists of risk factors.

cium influx initiates a series of cytoplasmic, nuclear, and mitochondrial events that directly contribute to the development of tissue damage, for example, via activation of proteases (13). Uncontrolled activation of calcium-dependent enzymes leads to further ATP depletion and accelerates cell death. Acutely, calcium can activate phospholipase A2 to generate free radical species which cause membrane damage. Oxygen radicals can also contribute to inflammation and apoptosis, as will be discussed below. Calcium-induced activation of neuronal nitric-oxide synthase (nNOS) and other Ca<sup>2+</sup>-dependent enzymes causes nitric oxide (NO) and superoxide production, which further promote cell death and tissue damage. Mitochondria, an important source of reactive oxygen species (ROS), are also involved in acute cell toxicity (9, 14). Aside from damaging cell membranes and proteins, free radicals also arrest energy production, further disrupting energy homeostasis. Calcium release from the dysfunctional mitochondria further exacerbates intracellular calcium signaling. Cell to cell interactions may also contribute to the spread of excitotoxicity as indicated by the apparent role of gap junctions in NMDA receptor mediated neuronal death (15). While the glutamate toxicity hypothesis has been validated in laboratory settings, clinical trials targeting the NMDA and AMPA receptors have yielded negli-

gible results (16). It is likely that the cell death processes are far more complex than can be described by glutamate toxicity alone. The NMDA-AMPA pathway is only one player in the ion balance dysregulation following stroke. Indeed, many other ion channels have been implicated in calcium accumulation and toxicity. Sodium-calcium exchangers, gap junctions, volume-regulated anion channels, transient receptor potential channels, acid-sensing channels, and other non-selective cation channels contribute to ion imbalance (12, 17). There is ample space for research on the influence of specific receptors to ion imbalance after acute infarction, and how targeting these receptors may provide therapeutic benefits.

### Spreading Depolarization and Spreading Ischemia

As discussed above, ischemic neurons depolarize due to a lack of energy supply, and subsequently depolarize to release glutamate and potassium. Spreading depolarization describes a sustained depolarization of neurons, which is effectively a short circuit between neurons and the extracellular space (18). This depolarization is accompanied by cell swelling and dendritic spine distortion (19). Direct gap junction mediated connections between neurons may facilitate spreading of depolarization (18). Under pathological con-



ditions such as stroke, the normal hemodynamic response to depolarization, namely vasodilation associated with neurovascular coupling, can become inverted. Thus, rather than dilating, arterioles may constrict to reduce blood flow, termed spreading ischemia (18). Increases in extracellular cations (primarily potassium) and decreases in nitric oxide, augment vasoconstriction and reduces vasodilation. The ensuing spreading depolarization-induced ischemia creates a vicious cycle where supply of metabolic substrates is reduced and demand is simultaneously increased. Spreading depolarization is known to occur in the ischemic penumbra and may contribute to lesion progression (20, 21). Each successive spreading depolarization can cause enlargement of the stroke area (21). It has been suggested that targeting the inverse microvascular response to spreading repolarization may be a useful therapeutic intervention, since targeting depolarization has failed thus far (16, 18, 19, 22).

#### Oxidative and Nitrosative Stress

Oxidative and nitrosative stress also contribute to ischemic stroke pathology. Oxidative and nitrosative free radicals are byproducts of cellular metabolism and are normally removed by endogenous antioxidant enzymes and chemicals such as superoxide dismutase (SOD), glutathione peroxidase, catalase, ascorbic acid, and  $\alpha$ -tocopherol

(14). In the injured brain, radical species are extremely harmful since endogenous antioxidant enzymes and vitamin concentrations are not high enough to counteract excess radical formation (23). The brunt of mitochondrial ROS generation is believed to occur during reperfusion. Ischemia-induced post-translational modification of proteins in the oxidative phosphorylation pathway prime mitochondria for excessive activity upon the reintroduction of oxygen (24). This hyperactive state could lead to a surge of ROS during reperfusion, overwhelming endogenous protective mechanisms. Excess ROS can directly damage proteins, nucleic acids, lipids, and carbohydrates to promote cell death. ROS can also be generated via NMDA receptor induced NADPH oxidase activation (25). This pathway may be important acutely after ischemia during the excitotoxicity phase. Nitric oxide (NO) is a free radical and an important cellular signaling molecule involved in many physiological and pathological processes. However, excess NO can be directly and indirectly neurotoxic. Similar to ROS, reactive nitrogen species (RNS) are harmful to cellular components and can induce neuronal death (26). NO can react rapidly with superoxide to generate the strong oxidant peroxynitrite, which is extremely cytotoxic (27). NOS activity and NO production are increased in the ischemic brain, leading to increased peroxynitrite production and ensuing cellular damage. RNS are

known to contribute to breakdown of the blood brain barrier (BBB) via activation of matrix metalloproteinases (MMPs) (27, 28). Taken together, ROS and RNS are damaging neurotoxic agents that intensify ischemic damage after reperfusion. Targeting these reactive chemicals may be useful in reducing side effects after administration of tPA and the resulting reperfusion (27, 29).

### Inflammation after Stroke

Inflammation plays an important role in the pathogenesis of ischemic stroke. After an ischemic insult, several key transcriptional factors, such as hypoxia inducible factor 1 (HIF-1), nuclear factor- $\kappa$ B (NF- $\kappa$ B), interferon regulatory factor 1 (IRF1), and STAT3, are up-regulated via calcium-induced signaling pathways, increased oxygen free radicals, and hypoxia (30-32). These transcriptional factors induce the expression of numerous pro-inflammatory genes, including tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), interleukin 1 $\alpha$  (IL-1 $\alpha$ ) and 1 $\beta$  (IL-1 $\beta$ ), intercellular adhesion molecule 1 (ICAM-1), and selectins (11, 30, 33). Circulating leukocytes interact with these adhesion molecules to adhere to brain endothelium, transmigrate through the vascular wall, and enter the brain parenchyma. Neutrophils are thought to be the first leukocytes to infiltrate after ischemic stroke, and can be found as early as 30 minutes after focal ischemia (34). Peak infiltration is on the order of days (1-3 days), and may continue to remain in the ischemic area for weeks (35). This initial infiltrate amplifies the inflammatory response by releasing cytokines and chemokines, activating MMPs, and producing ROS. These effects are primarily negative and can result in BBB disruption, edema, neuronal death, and hemorrhagic transformation (30, 32-34, 36). However, at later stages, neutrophilic infiltration may promote recovery and regeneration, for example, via MMP-9 mediated neurovascular remodeling (30, 34, 36, 37).

Circulating macrophages and endogenous brain microglia also play dual roles in recovery by expressing anti- and pro-inflammatory mediators. Resident microglia respond initially (within hours following infarction), while blood-derived macrophages infiltrate later, by 3 days (34, 37,

38). They continue to accumulate over the course of weeks (34, 38). A number of studies suggest that the majority of macrophages in the ischemic brain are derived from resident microglia, and that the relative contribution of circulating versus resident macrophages needs further evaluation (34). Traditionally, microglia/macrophages have been thought to demonstrate two primary phenotypes: "classically activated" M1 (pro-inflammatory) and "alternatively activated" M2 (protective/trophic support) subtypes (38, 39). There is likely a significant overlap between these subtypes and a growing body of research indicates microglia/macrophages have an incredibly diverse range of biological functions following brain damage which is outside the scope of this review (34, 36, 38-42). The M2 phenotype is primarily restorative, and can promote processes such as neurogenesis, axon growth and remodeling, vessel growth and infiltration, and myelination processes (38). Initially after stroke, they are responsible for clearing cellular debris and infiltrating neutrophils (34). The M1 phenotype is primarily pro-inflammatory. For example, they can exert neurotoxic effects via the production and release of cytokines (i.e. IL-1 $\beta$ , IL-6, TNF- $\alpha$ ), ROS, and MMPs (38, 42, 43). Initially, the injury site is dominated by M2 macrophages; however, M1 macrophages dominate after about 1 week (38). This M2-to-M1 transition may create an unfavorable microenvironment for repair, and can last for weeks after injury (38).

Astrocytes are the most abundant cell type in the brain. Similar to other players in neuroinflammation, astrocytes play a dichotomous role in both damage and regeneration after stroke. They are able to form barriers between the CNS parenchyma and non-neural tissue, for example, along brain vasculature and the meninges (44). After stroke, astrocytic scars, formed mainly of newly proliferated astrocytes, create an interface between viable CNS parenchyma and the core infarct region (44-47). Within a couple days after ischemia, astrocytes become reactive, exhibiting stellate morphology and expression of GFAP (45, 46). The glial scar acts as a protective functional barrier that prevents the spreading of toxic inflammation (44). Early after stroke, astrocytes appear to play a primarily neuroprotective role (44, 47-49). Disruption of scar formation af-

ter stroke allows for the spread of neuroinflammation and results in greater loss of neurons, increased lesion size, and decreased function (44-48). However, during the recovery phase after ischemic insult, the astrocytic scar is thought to be inhibitory to axonal growth and is associated with reduced neural regeneration and functional recovery (47, 48, 50, 51). Contrary to this binary dogma, a growing body of research suggests the astrocyte scar can play a role in axonal recovery (52). Further research is needed to clarify the role of the glial scar in healing after stroke, and its relation to potential therapies.

The inflammatory mechanisms that occur in response to stroke are complex and exhibit dichotomies that can best be explained temporally. Detailed research is needed to tease apart the contributions of individual cell types across both time and space relative to infarction. Careful consideration of the cellular inflammatory responses must be accounted for in the development and evaluation of stroke treatments. Optimal treatment would attenuate the negative effects of neuroinflammation while preserving or accentuating the positive effects.

### Cell Death after Cerebral Ischemia

Cell death pathways are at the heart of stroke pathophysiology. Multiple modes of cell death are evident in stroke. Traditionally, these mechanisms were separated into apoptosis, or controlled cell death, and necrosis, or unregulated cell death (53). Apoptosis involves the organized dismantling of cells to minimize damage to neighboring cells, while necrosis leads to release of intracellular debris which can stimulate inflammatory responses and damage surrounding cells through various mechanisms, for example, by generating excess ROS (54, 55). We now understand there is considerable overlap between these pathways, and that necrotic cell death can be regulated (termed necroptosis, programmed necrosis, or caspase-independent programmed cell death) (11, 54-60). Autophagy, a lysosomal processes of cellular component recycling, is intimately associated with both cell death and survival mechanisms in ischemia (58, 59, 61-66). In fact, apoptosis, autophagy, programmed necrosis, and necrosis all occur in stroke, and some

cells even exhibit multiple mechanisms simultaneously (10, 60, 67). Recent literature suggests that after about 1 day post-stroke in the core region, around 70% of cells show signs of necrosis while 30% appear apoptotic, and autophagy is also concurrently activated in both of these cell death pathways (10).

There are two primary pathways of apoptosis in cerebral ischemia: 1) the intrinsic pathway, which initiates via mitochondrial release of cytochrome-C and activation of caspase-9, and 2) the extrinsic pathway, which commences with the activation of cell surface death receptors and caspase-8 (53, 54, 57). Both of these pathways eventually converge to activate the executioner proteases caspase-3 and -7 which drive proteolysis (53, 54, 57). Ultrastructural evidence indicates that during apoptosis, the nucleus and other cellular organelles are condensed and fragmented into smaller parts (53, 54). DNA is also hydrolyzed into many fragments. Finally, phagocytes ingest apoptotic bodies with minimal release of inflammatory cytokines (53, 57, 58). Necrosis is caused by overwhelming stress (i.e. acute hypoxia in stroke), resulting in unregulated cellular demise (11, 54, 57, 60, 68). Nuclei appear swollen, ROS are generated, and cellular membranes begin to disintegrate to allow the release of inflammatory cellular contents into the extracellular space (54, 55, 60, 63). Contrary to apoptosis and necrosis, programmed necrosis is highly regulated but occurs independently of caspase signaling, and is instead mediated via receptor-interacting protein1 (RIPK1) (56-58, 69). Activation of death receptors by TNF $\alpha$  and FasL are also involved in programmed necrosis (55-57, 69). In an evolutionary sense, programmed necrosis is believed to provide defense against intracellular pathogens that block apoptosis activation (57). Necroptosis has been documented in stroke, but its significance needs further study (12, 14, 54, 67, 70).

A number of morphological studies have elucidated the roles of apoptosis and necrosis after ischemic injury. Wei et al used a series of chemical and immunohistological methods, including 2,3,5-triphenyltetrazolium chloride (TTC) staining, hematoxylin-eosin (H&E) staining, terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL), and caspase-3 staining, and ultrastructural examination to study cell

death mechanisms in the ischemic cortex and non-ischemic thalamus after focal ischemia (60). They showed that the morphology of TUNEL+ cells in the ischemic core were primarily necrotic, whereas TUNEL+ cells in the thalamus and cortical penumbra exhibited both necrotic and apoptotic morphology (60). Isin et al also examined cell death patterns after transient and permanent focal ischemia to show that apoptosis and necrosis, or a mixed/hybrid phenotype, can occur in the same cells (67). They suggest that the ischemic neuronal cell death phenotype may be determined by the relative speed of apoptotic versus necrotic processes (67). Jiang et al performed a detailed analysis of the stroke core to show that apoptosis is a significant mechanism of cell death in the ischemic core, with up to 30% of cells undergoing programmed cell death (10). These findings need further clarification regarding the role of programmed necrosis in cellular demise.

Autophagy is a well-known player in cellular homeostasis. Superfluous or damaged proteins and organelles are packed into autophagosomes, which drain into lysosomes for degradation (58, 59, 70, 71). The role of autophagy in cell death, particularly in ischemic cell death, is controversial and under intense study. The effects of autophagy are likely context dependent. Numerous studies have demonstrated that autophagy is activated following ischemic insult (59, 62-64, 71-73). Whether autophagy is a driver of cell death in ischemia is still not clarified. Some experimental evidence suggests that reducing autophagy early after infarction can attenuate injury progression (71, 74-76). Conversely, other studies indicate that promoting autophagy may induce cells to undergo apoptotic rather than necrotic cell death, leading to reduced lesion sizes (71, 77, 78). Inadequate autophagy may also contribute to cell death in stroke (79). It is conceivable that a moderate amount of cellular component recycling, particularly in the acutely hypoxic stages of stroke, may provide neurons with a larger physiologic reserve thereby allowing the cells to sustain ischemic damage. It is equally conceivable that digesting valuable cellular components in response to hypoxic insult, when the cell needs them the most, can lead to cell demise. This view is consistent with observations that apoptosis and autophagy appear to predominate in the penumbra,

where cells may exhibit a physiologic reserve large enough to sustain the initial ischemic insult, and necrosis appears to predominate in the core region, where autophagy may be more associated with cell death (Figure 2) (10, 59, 62, 63, 65, 70, 80). Future research on autophagy and its role in ischemic cell death must place special consideration to location (i.e. infarct versus peri-infarct regions) and timing after stroke.

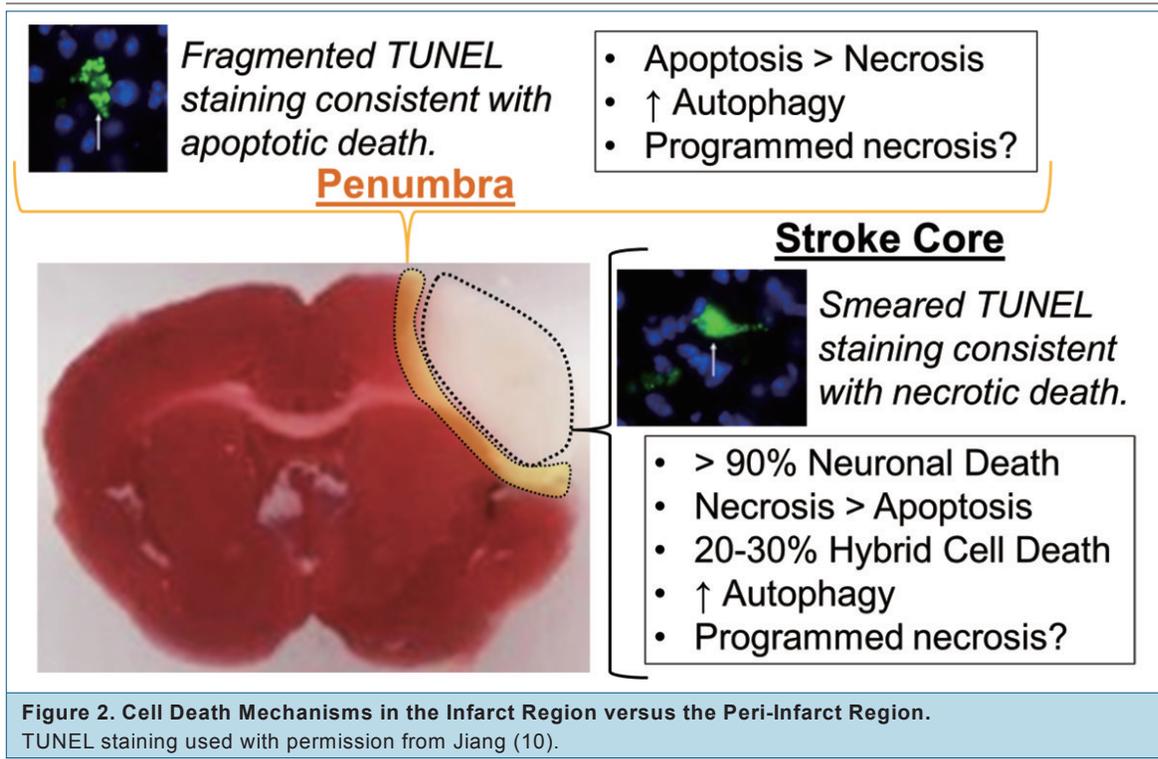
### Stroke Prevention and Treatment

Primary prevention is the optimal method for reducing stroke burden since nearly 80% of strokes are first events. Modifiable risk factors such as those listed in Table can be readily identified in stroke prone patients (3). The AHA/ASA guidelines for primary prevention of stroke provide detailed recommendations with special weight towards modifiable risk factors. They provide evidence based recommendations on physical activity, dyslipidemia, hypertension, obesity, diabetes, cigarette smoking, and other cardiovascular conditions (3).

For those who have already suffered ischemic stroke, rapid administration of tissue plasminogen activator (tPA) within 4.5 hours of stroke onset is the mainstay of treatment (81). tPA acts to dissolve the blood clot, directly improving blood flow to the perfusion-deficient area of the brain. There are benefits with earlier tPA administration (81, 82). Beyond this narrow time window, treatment with tPA is not effective and its side effects, primarily bleeding, outweigh the marginal benefits (81, 82). Mechanical thrombectomy within 6 hours of disease onset is another option for the treatment of acute ischemic stroke, and should be performed after treatment with tPA when indicated (81). As with tPA, earlier surgical treatment is associated with greater benefits. Secondary prevention of patients who have already experienced stroke is another important method to reduce stroke burden (83). Similar to primary prevention, secondary prevention focuses on control of risk factors, and special attention is paid to antiplatelet therapy (83).

### Perioperative Stroke: Anesthesiologist's Perspective

Surgical intervention is a significant and predict-



able risk for stroke. As such, guidelines for the perioperative prevention of stroke for high risk patients have been established (4, 84-86). Perioperative stroke is defined as 'brain infarction of ischemic or hemorrhagic etiology that occurs during surgery or within 30 days after surgery' (4). The most recent perioperative stroke guidelines for high risk patients published by the Society for Neuroscience in Anesthesiology and Critical Care, and associated studies, are summarized below.

Preoperative recommendations include screening patients for risk factors of perioperative stroke, and possibly delaying surgery in patients with recent stroke. Potentially modifiable risk factors for perioperative stroke include recent stroke, intraoperative cerebral hypoxia, hypotension, high thromboembolic risk, orthopedic joint replacement, and beta blockade (85). Ischemic stroke risk is a function of surgical procedure, and thus, suspicion for perioperative stroke should be based on procedure-specific incidences (85). Anti-coagulants and anti-platelets should be continued for patients with low risk of blood loss and discontinued for those with high risk of bleeding; bridging strategies should be implemented and therapy resumed between

1-3 days after surgery, depending on bleeding risk (4). Beta blockers and statins can be continued in patients already taking them (85). Outside of these guidelines, it has been theorized that pharmacological or ischemic preconditioning may enhance the brain's tolerance to ischemia thereby improving stroke outcomes (86).

Intraoperative recommendations suggest that neuraxial anesthesia techniques are associated with lower rates of perioperative stroke for hip and knee arthroplasty, but this has yet to be studied in other populations (4). There are no known associations between anesthetic type and risk for stroke; however, future clinical trials are needed to confirm the apparent lack of association (86-88). Intraoperative use of metoprolol may increase stroke risk, and the authors of the Consensus Statement suggest using short-acting beta blockers such as esmolol instead. There are currently no data to make recommendations on intraoperative ventilation techniques, however, it seems logical to avoid hypocapnia which causes reduction in cerebral blood flow (4, 85). Intraoperative hemorrhage is a risk factor for postoperative stroke, and as such, hemoglobin should be maintained >9.0 mg/dL for those already taking beta blockers. Glucose levels should

be monitored and maintained between 60-180 mg/dL to avoid hypo- and hyperglycemia. Intraoperative hypotension (measured by % reduction from baseline) should be avoided.

Postoperative stroke should be managed according to the AHA guidelines; specific recommendations include the production of an organized protocol for evaluation and treatment of suspected perioperative stroke (4). Use of a stroke rating scale and emergent brain imaging before therapy are recommended. If not contraindicated, tPA or thrombectomy should be considered, and hypertensive patients (systolic >180 mm Hg or diastolic >105 mm Hg) who receive tPA should still receive anti-hypertensive drugs. Supplemental oxygen, airway support, and ventilator assistance are recommended for patients with decreased consciousness or respiratory dysfunction (4).

A major point of future research should be how anesthetic technique may affect the risk or severity of perioperative stroke. Several clinical trials have been conducted on these matters (87-89). Stroke outcomes do not appear to be correlated with general anesthesia versus local anesthesia for patients undergoing carotid endarterectomy, and there is no apparent increased risk of stroke with nitrous oxide exposure (87, 88). Anesthetics can be neurotoxic if the local concentra-

tion becomes too high or if the patient is exposed for long durations; conversely, adequate anesthesia exposure may be neuroprotective (66). These effects may reflect the extent to which autophagy is induced. Excessive anesthetic exposure can disrupt calcium signaling, promote endoplasmic reticulum stress and severe autophagy, and result in apoptosis (66, 90, 91). Other studies show that brief exposure to anesthetics can precondition neurons by activating autophagy, leading to reduced cell death when later exposed to lethal anesthetic doses (66, 92, 93). Furthermore, anesthesia can alleviate microglial activation and improve neurological outcomes after stroke (94, 95). This raises an interesting implication: anesthetic preconditioning may be useful for perioperative stroke prevention and/or to improve stroke outcomes (86, 96). While promising pre-clinical studies have noted improvement in stroke outcomes in animals models after anesthetic preconditioning, no known clinical trials have yet been performed. Preconditioning methods may provide great utility for high risk patients, particularly perioperative patients who incur a predictable risk for stroke.

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