

Reperfusion injury in the age of revascularization

Significant advancements over the past several years in the endovascular treatment of acute ischemic stroke have substantially improved patient outcomes. The efficacy of mechanical thrombectomy within 6 h was first established following several clinical trials^[1-5] and has recently been proven to be efficacious for up to 24 h following the onset of ischemia.^[6,7] The primary initial goal of endovascular intervention, recanalization of the occluded artery and reperfusion of downstream vessels, tends to be observed in approximately 80% of patients undergoing intervention. The success of this treatment modality in selected patients far exceeds the 20%–40% recanalization rate seen following tissue plasminogen activator alone.^[8,9]

While recanalization is the initial primary objective following an ischemic event and is essential for salvaging ischemic penumbra, reperfusion carries many deleterious effects as well. In many patients, despite robust restoration of perfusion, progressive stroke can still be observed despite maintaining vessel patency, due to secondary reperfusion injury. Several preclinical studies have directly observed this phenomenon with serial magnetic resonance imaging, in which the apparent diffusion coefficient was decreased at the end of a transient ischemic event, improved for several hours during reperfusion, and finally decreasing in a delayed fashion during secondary ischemic and inflammatory injury.^[10]

Numerous mechanisms underlying ischemia/reperfusion injury have been defined, with three stages of reperfusion injury occurring in succession following successful recanalization.^[11] The first stage is driven by increased metabolic demand, resulting in hyperemia with a loss of cerebral autoregulation and increased blood–brain barrier (BBB) permeability. Hemorrhagic transformation, if it occurs, tends to arise in this early stage of reperfusion. The second stage of reperfusion injury is marked by hypoperfusion, termed the “no-reflow effect.” Hypoperfusion and secondary occlusion have been attributed to metabolic depression, microvascular obstruction, and endothelial cell swelling and activation. This precipitates further ischemic injury and BBB breakdown and leads to the third stage, a marked inflammatory reaction and increased paracellular permeability, clinically resulting in cerebral edema.

Endothelial activation during ischemia generates a thromboinflammatory environment with profound

microvascular dysfunction. Ischemic damage to the endothelial surface triggers a cascade of pro-inflammatory markers, promoting microvascular thrombosis. Following ischemia, an upregulation in the surface expression of P-selectin has been identified in both endothelial cells and platelets as early as 1 h following reperfusion.^[12] P-selectin binds GPIIb/IIIa, a glycoprotein that serves as the focal point of platelet adhesion, aggregation, and thrombus propagation.^[13] During acute ischemic stroke and during hyperemic reperfusion, platelets tether to the vessel wall through interactions between GPIIb/IIIa and von Willebrand factor, promoting a prothrombotic intraluminal environment.^[12] These interactions between endothelial cells, platelets, and leukocytes underlie the environment of thromboinflammation, serving to exacerbate secondary infarct growth following the initial ischemic insult. Further impeding microcirculatory flow, ischemia induces sustained pericyte contraction of microvessels downstream from the occluded parent vessel, despite successful reperfusion.^[14] Sustained pericyte contraction and microthrombi in distal microvasculature impede flow following ischemia/reperfusion injury, ultimately leading to the “no-reflow effect.”

In addition to microvascular thrombosis, cerebral ischemia generates a strong inflammatory response. Upregulation of endothelial surface adhesion molecules and increased cytokine production during ischemia promotes lymphocyte, polymorphonuclear leukocyte, monocyte, and macrophage infiltration following reperfusion.^[14] Reperfusion is also well known to enhance immune system activation in response to cell death programs triggered during ischemia in response to both necrotic tissues and apoptotic cells. Largely T-cell mediated, both antigen-specific and antigen-independent mechanisms have been found to play a significant role in continued cell death in the days following initial reperfusion.^[14] Genetic and pharmacologic interventions have been shown to ameliorate this deleterious inflammatory response, providing robust neuroprotection.

In addition, reactive oxygen species and oxygen-free radical production increase dramatically during reperfusion. This impairs neuronal survival within ischemic tissues and penumbra and worsens functional recovery due to secondary injury. Several studies have evaluated the use of nitroxide radicals and other free radical scavengers in preclinical models, demonstrating

neuroprotective function.^[15] Treatment with free radical scavengers may be aided in part by increased BBB permeability and ease of passage into damaged parenchymal tissue.

BBB disruption is a common underlying factor in reperfusion injury, hemorrhagic transformation, and cerebral edema following an ischemic event. Starting during cerebral ischemia, reperfusion has been identified as the strongest predictor of early BBB disruption.^[16] BBB disruption is frequently observed clinically, and can be radiographically visualized as delayed gadolinium or contrast enhancement in cerebrospinal fluid spaces. The loss of BBB permeability is detrimental in numerous ways, leading to increased vasogenic edema, a more robust inflammatory response, and endothelial cell swelling.

Although reperfusion induces numerous detrimental effects, early reperfusion is clearly needed to salvage remaining viable neurons within the ischemic core and peri-ischemic penumbra. In addition to protecting viable neurons, early reperfusion has also been shown to enhance survival of endothelial cells and pericytes in the ischemic core, promoting fibrosis and astrogliosis.^[17] This has been shown to improve neuronal reorganization and functional recovery following stroke.

While approximately 80% of patients experience revascularization of an occluded vessel following endovascular treatment, only 40% of patients will achieve a good functional outcome following rehabilitation. Reperfusion of major intracranial arteries through thrombolysis or endovascular mechanical thrombectomy is clearly necessary to salvage brain tissue; however, simple restoration of cerebral flow is not solely adequate to prevent secondary infarct growth. Given the increasing number of patients being treated with endovascular thrombectomy at extended time windows, more patients are experiencing recanalization, and reperfusion injury will be observed with increasing frequency in patients following acute ischemic stroke. While reperfusion of ischemic brain tissue and penumbra undoubtedly generates improved clinical outcomes, finding new ways to mitigate the deleterious effects of reperfusion injury will continue to improve stroke outcomes.

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Conflicts of interest

There are no conflicts of interest.

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