Review Article

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Time-Dependent Neuroprotection and Precision Interventions in Acute Ischemic Stroke in the Reperfusion Era

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ABSTRACT

Acute ischemic stroke (AIS) ranks as the second leading cause of mortality among noncommunicable diseases globally. Although recent advancements in intravenous thrombolysis and endovascular thrombectomy have markedly increased recanalization rates in patients with large vessel occlusion, improvements in clinical outcomes have not been consistently observed. Accumulating evidence demonstrates that successful recanalization does not necessarily translate into effective tissue reperfusion. Accordingly, the concept of neuroprotection has evolved from a traditional focus on mitigating cellular necrosis toward a strategy aimed at delaying the progression of ischemic penumbra and preserving salvageable brain tissue. This review summarizes the dynamic processes underlying reperfusion injury, microcirculatory dysfunction, neurovascular unit disruption, and associated neuroprotective mechanisms. Particular emphasis is placed on reversible changes within penumbra, reperfusion-induced injury amplification, and emerging imaging-guided approaches and molecular biomarkers for precision interventions. These insights provide a framework for developing spatiotemporally coordinated, individualized neuroprotective strategies.

Key words: acute ischemic stroke; neuroprotection; reperfusion; penumbra; brain imaging technology; precision medicine

INTRODUCTION

Over the past two decades, acute ischemic stroke (AIS) reperfusion therapy has advanced substantially. The combined application of intravenous thrombolysis and endovascular thrombectomy has markedly enhanced recanalization rates. Nevertheless, a considerable proportion of patients still experience neurological deterioration or infarct progression despite successful angiographic recanalization[1,2]. This discrepancy underscores a fundamental limitation of current reperfusion therapies. While recanalization is necessary, it is not sufficient to ensure tissue salvage. In some cases, reperfusion itself may induce additional injury through oxidative stress, heightened inflammation, microcirculatory dysfunction, and disruption of the blood-brain barrier (BBB). Clinical imaging studies indicated that 20%–30% of patients had a reperfusion mismatch, in which restored large vessel patency failed to re-establish adequate tissue perfusion, implicating microvascular dysfunction as a major determinant of poor outcomes[3].

Accumulating experimental and clinical evidence indicates that once neurons surpass key bioenergetic and calcium-dependent thresholds, the true reversal of cell death remains biologically limited, particularly within the narrow time window of acute stroke intervention[4]. In contrast, delaying the progression of penumbra—a region of metabolically compromised but structurally intact tissue—offer a more feasible therapeutic target. Preserving neurovascular unit (NVU) integrity and slowing the conversion of penumbra to infarct core have thus emerged as central goals[5]. This conceptual shift moves the therapeutic focus from res-

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cuing irreversibly injured neurons to stabilizating salvageable tissue. In response, contemporary neuroprotection has shifted from an isolated therapeutic approach to a synergistic reperfusion strategy that prioritizes delaying ischemic progression to extend the therapeutic window and enhance reperfusion benefit[6]. Advances in multimodal imaging and molecular biology have progressively elucidated the temporal sensitivity and reperfusion-dependent mechanisms underlying neuroprotection. These insights establish a refined theoretical foundation for developing precision, individualized stroke interventions.

In this context, this review synthesizes current understanding of the spatiotemporal biology of ischemia-reperfusion injury in AIS. It examines the formation and dynamic evolution of the ischemic penumbra and highlights the central role of the NVU in modulating tissue vulnerability and injury reversibility. Based on these concepts, the review summarizes the major pathological mechanisms underlying reperfusion injury and outlines emerging strategies that integrate neuroprotection with reperfusion therapy, including the regulatory role of collateral circulation and pharmacological and non-pharmacological interventions targeting reperfusion related injury. In addition, it emphasizes the potential of advanced imaging techniques and biomarker-based stratification to identify salvageable tissue and facilitate individualized treatment strategies.

THE ISCHEMIC PENUMBRA AND NVU: A DYNAMIC CORE OF REVERSIBLE INJURY

Formation and dynamic evolution of the penumbra

Following AIS, tissue injury develops dynamically along gradients of cerebral blood flow (CBF), cell metabolic demand, and inflammatory activity. Upon vessel occlusion, the cessation of CBF results in the formation of an infarct core surrounded by the ischemic penumbra (**Fig. 1**). The ischemic penumbra is defined as the region between the infarct core and normal perfused tissue, where cells are functionally silenced but remain structurally viable[7]. This view has moved the stroke therapeutic strategy in AIS from a purely time-centered model toward one focused on tissue pathophysiology and salvageability. When CBF declines to approximately 20%—30% of baseline, neural tissue enters a state of metabolic stress with suppressed electrical activity but preserved cellular integrity[7]. Sustained hypoperfusion, however, triggers a cascade of calcium overload, mitochondrial dysfunction, oxidative stress, and inflammatory amplification, driving progressive collapse of penumbra and its conversion to infarction[8]. The rate of this conversion defines the effective therapeutic window and serves as a critical determinant of reperfusion efficacy[7,9].

Emerging evidence indicates that penumbral fate is modulated by genetic and metabolic programs. For instance, networks of circular RNAs (circRNA), such as circ. 7225 and circ. 5415, have been implicated in the regulation of synaptic signaling and inflammatory pathways during ischemia reperfusion[10]. Notably, circOGDH, derived from oxoglutarate dehydrogenase gene, correlates with penumbral volume, partly through extracellular vesicle-mediated communication within the NVU[11]. These findings suggest that circRNA-mediated competing endogenous RNA (ceRNA) networks may represent novel therapeutic targets[10]. Nevertheless, current evidence remains largely preclinical or associative, and circRNAs should be regarded as mechanistically informative but not yet clinically actionable regulators. Ischemic preconditioning under chronic hypoperfusion further induces metabolic reprogramming that enhances tolerance to energy stress[12]. Collectively, these findings illustrate that the penumbra represents a genetically and metabolically regulated microenvironment, extending beyond perfusion deficits alone.

The NVU and its selective vulnerability

The NVU encompasses a functionally integrated system of neurons, astrocytes, endothelial cells, smooth muscle cells, and pericytes, which together maintain dynamic coupling between CBF and neuronal activity[7,13]. In the early ischemic phase, NVU injury manifests as astrocytic calcium dysregulation and loss of aquaporin 4 polarity, degradation of endothelial tight junction proteins, pericyte-mediated capillary constriction, and impaired microvascular blood flow[14,15]. During reperfusion or sustained hypoperfusion, oxidative stress, complement activation, and leukocyte infiltration disrupt the endothelial basement membrane interface, leading to BBB breakdown and initiating a self-amplifying cycle of structural and functional deterioration[15] (**Fig. 1**).

NVU components exhibit distinct vulnerability to ischemia reperfusion injury[7]. Neurons are the most sensitive due to their high metabolic demand and

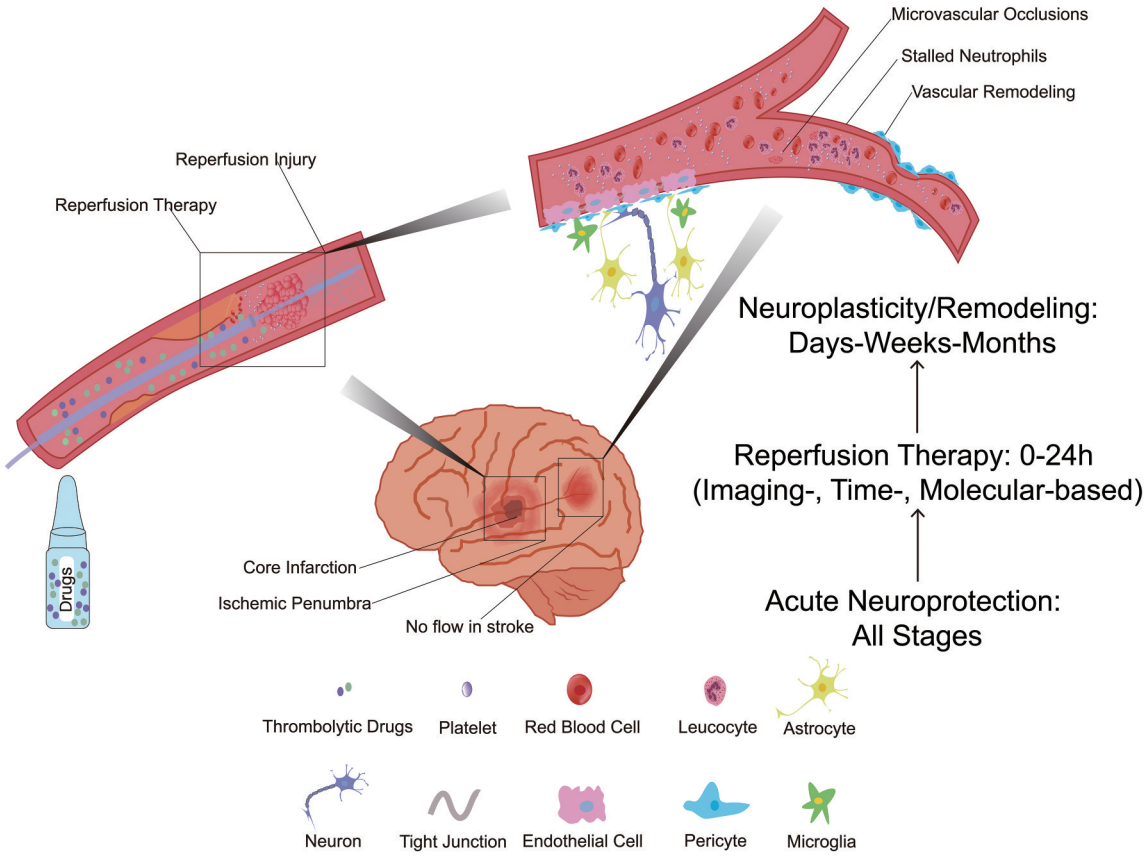

Figure 1. Spatiotemporal cascade of ischemia reperfusion injury and neurovascular unit (NVU) dysfunction in acute ischemic stroke.

The schematic illustrates the progression from arterial occlusion to reperfusion and its downstream effects on the NVU. Following vessel occlusion, cerebral blood flow cessation leads to the formation of an infarct core surrounded by the ischemic penumbra, where tissue viability is temporally preserved. Reperfusion therapy restores macrovascular flow but may trigger reperfusion injury, characterized by excessive production of reactive oxygen and nitrogen species endothelial activation, and blood-brain barrier disruption. At the microvascular level, neutrophil stalling, platelet aggregation, endothelial swelling, and pericyte-mediated capillary constriction contribute to microvascular occlusions and the no-reflow phenomenon, thereby limiting effective tissue reperfusion. Within the NVU, dynamic interactions among neurons, astrocytes, microglia, endothelial cells, pericytes, and tight junction proteins mediate excitotoxicity, inflammation, oxidative stress, and vascular remodeling. The distribution of circulating drugs is influenced by the blood-brain barrier permeability and microcirculatory patency, highlighting the importance of timing-dependent and mechanism-guided neuroprotective strategies integrated with reperfusion therapy.

complex synaptic architecture, while astrocytes, endothelial cells, and pericytes display greater metabolic buffering capacity[14]. These mechanistic insights have positioned NVU protection as a central paradigm in modern neuroprotection. Pharmacological agents such as 3K3A-activated protein C (3K3A-APC), cilostazol, and, edaravone-dexborneol have demonstrated antioxidant, anti-inflammatory, and barrier-stabilizing effects in preclinical models, promoting microvascular repair and delaying penumbral conversion[16]. This system-level approach establishes a conceptual foundation for integrated regulation of CBF, metabolic homeostasis, and neuroimmune interactions in future therapeutic strategies[6].

From the time window to the tissue window and molecular window

For decades, AIS treatment has relied on a fixed time window from symptom onset to treatment. However, accumulating evidence demonstrates that the critical determinant of tissue salvageability is not merely the elapsed time since onset, but rather the current perfusion status, metabolic activity, and cellular viability of the affected brain tissue[17]. These insights have given rise to the tissue window concept, which emphasizes that, even beyond conventional time limits, subsets of patients may retain structurally intact but functionally impaired penumbral tissue with the potential for recovery[18,19]. Multimodal neuroimaging enables the identification of such tissue by integrated assessment of perfusion – diffusion mismatch, collateral flow, and

metabolic indicators, thereby supporting tissue-based rather than time-based precision intervention strategies. Clinical trials such as WAKE-UP, EXTEND, DAWN, and DEFUSE-3 have validated this paradigm[17,20-22], demonstrating that imaging-defined tissue viability can safely extend the benefit of reperfusion therapies well beyond traditional temporal boundaries[5].

Beyond imaging, the emergence of circulating and molecular biomarkers has further expanded the therapeutic window concept to molecular window. Unlike the tissue window, which primarily reflects macroscopic perfusion and metabolism, the molecular window focuses on reversible cellular and molecular stress states within the ischemic penumbra, capturing biological processes that precede irreversible cell death[5,23]. Integration of these indicators allows for dynamic, molecular-level monitoring of penumbral evolution. A multimodal hierarchical framework incorporating imaging and molecular omics thus supports the transition from time-driven to tissue-driven precision interventions in AIS[23].

KEY PATHOLOGICAL MECHANISMS OF REPERFUSION INJURY

Energy metabolic imbalance and excitotoxicity

Within seconds of ischemia onset, the interruption of oxygen and glucose delivery to brain tissue precipitates a rapid reduction in ATP production and subsequent failure of the Na^+/K^+-ATPase pump[15,24]. This energetic failure induces membrane depolarization and excessive glutamate release. The accumulated extracellular glutamate overactivates N-methyl-D-aspartate receptors (NMDARs) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), leading to excessive Ca^{2+} influx. The ensuing calcium overload promotes opening of the mitochondrial permeability transition pore (mPTP) and triggers bursts of free radical generation, ultimately engaging both necrotic and apoptotic pathways (**Fig. 2**). The ensuing energy crisis disrupts neuronal membrane potential and propagates spreading depolarization waves, further amplifying excitotoxic cascades[25,26]. Elevated glutamate levels correlate with infarct expansion and neurological deterioration, supporting its role as a biomarker of excitotoxic burden.

Excitotoxicity may also be reinitiated during reperfusion. Restored oxygen and glucose supply enhance phosphorylation of NMDAR subunits (GluN2A/GluN2B) and calpain-mediated cleavage of NR2A/NR2B, facilitating the reassembly of the PSD95-nNOS complex. This assembly upregulates nitric oxide (NO) production and drives excessive peroxynitrite ($ONOO^-$) formation, resulting in combined oxidative and nitrative stress[26]. The postsynaptic density protein 95 (PSD-95)-nNOS signaling axis is now recognized as a central mediator of reperfusion injury. Circulating NR2-derived peptides and NR2A/NR2B autoantibodies reflect pathological NMDAR activation and provide a mechanistic basis for patient stratification, as exemplified by the PSD-95 inhibitory peptide nerinetide, which has shown neuroprotective signals in Phase Ⅱ clinical trials[27,28].

Excitotoxic injury is tightly linked to early, potentially reversible apoptotic signaling within the ischemic penumbra, where activation of caspase-1, caspase-3, and caspase-8 has been detected within 24 hours after ischemia[29,30]. While sustained caspase activation marks irreversible cell death, transient activation during early reperfusion may reflect salvageable neuronal populations, highlighting a potential molecular window for intervention[31]. Excitotoxicity is further intertwined with disturbances in excitatory and inhibitory neurotransmission. Ischemia reduces γ -aminobutyric acid (GABA) synthesis, impairs vesicular release, and downregulates GABA receptor subunits[32]. Concurrently, astrocytic stress markers such as S100B and axonal injury markers such as neurofilament light chain (NfL) are frequently elevated, reflecting NVU dysfunction. While acute excitotoxicity exacerbates neuronal injury, sustained excessive GABAergic signaling may impair synaptic plasticity. Emerging agents such as ZL006-05 concurrently suppress PSD95-nNOS signaling and augment GABAergic transmission, significantly improving functional recovery in animal models and highlighting new avenues toward stage-specific neuroprotection[32].

Reperfusion-induced oxidative stress and multi-mechanism cascade reactions

Although reperfusion restores CBF and alleviates the ischemic energy crisis, it simultaneously triggers an excessive oxidative burst. Reverse electron transport at mitochondrial complex Ⅰ generates large quantities of superoxide anions (O_2^-), particularly in penumbral tissue, which react with NO to form $ONOO^-$, leading to lipid peroxidation, protein nitration, and nuclear DNA fragmentation. During ischemia, endogenous antioxidant systems, including glutathione, superoxide dis-

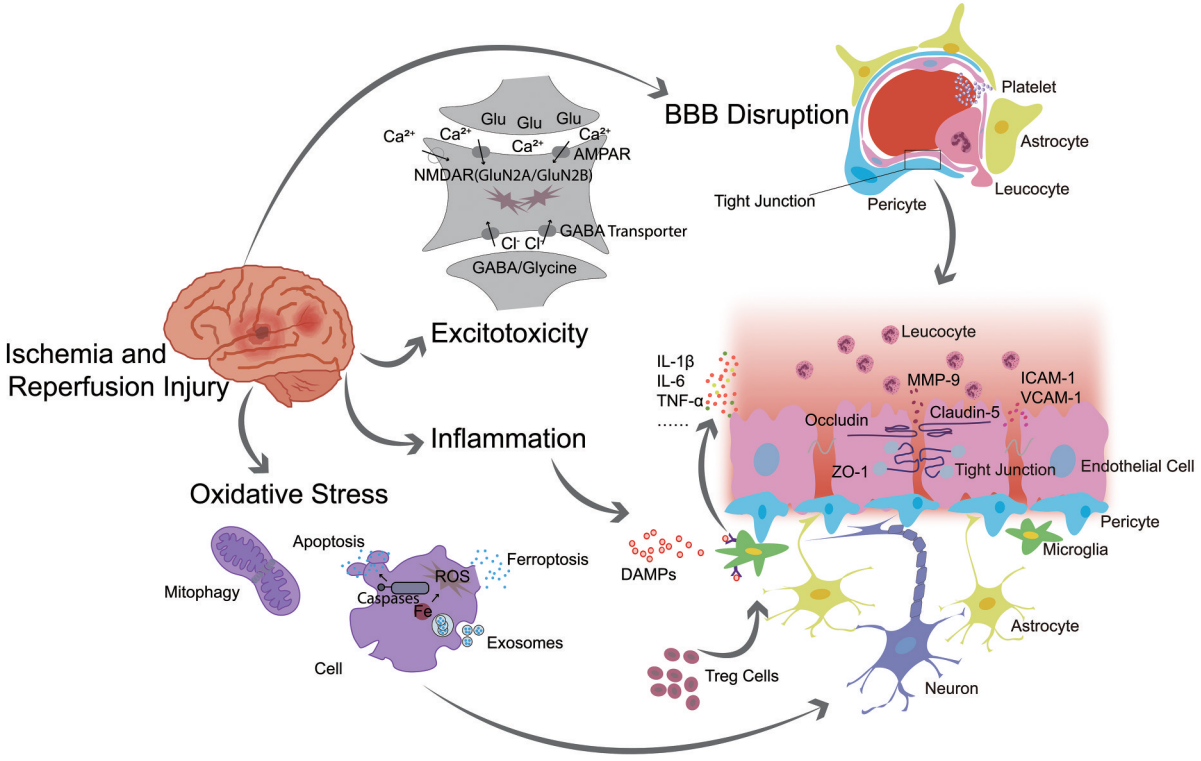

Figure 2. Schematic overview of key pathological mechanisms underlying ischemia reperfusion injury and post-ischemic microenvironmental remodeling.

Ischemia initiates rapid metabolic failure that triggers excitotoxic signaling, mitochondrial dysfunction, and oxidative stress in neurons and glia. Concurrent endothelial injury disrupts BBB integrity and impairs microvascular perfusion. Although reperfusion restores microvascular flow, it amplifies inflammatory responses and redox imbalance, thereby exacerbating neurovascular unit injury. The schematic highlights the bidirectional crosstalk among neurons, glia, endothelium, and immune cells, emphasizing that penumbral fate is determined by the temporal interaction of ischemic and reperfusion-associated mechanisms, rather than by a single dominant pathway. BBB: blood-brain barrier; Glu: glutamate; NMDAR: N-methyl-D-aspartate receptor; GluN2A/GluN2B: glutamate Ionotropic receptor NMDA type subunit 2A/2B; AMPAR: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GABA: γ -aminobutyric acid; ROS: reactive oxygen species; DAMPs: damage-associated molecular patterns; Treg cells: regulatory T cells; IL-1β: interleukin-1 beta; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha; MMP-9: matrix metalloproteinase-9; ICAM-1: intercellular adhesion molecule-1; VCAM-1: vascular cell adhesion molecule-1; ZO-1: zonula occludens-1.

mutase, and catalase, are markedly depleted, resulting in accumulation of oxidative stress markers such as malondialdehyde, 8-iso-prostaglandin F2α, and oxidized glutathione. This depletion impairs the clearance of oxygen radicals upon reperfusion, resulting in extensive mitochondrial and membrane damage[33,34].

Beyond reactive oxygen species (ROS), dysregulated iron metabolism and ferroptosis critically amplify reperfusion injury. Following reperfusion, increased Fe^{2+} reacts with polyunsaturated fatty acid-rich phospholipids on cell membranes, a process associated with elevated circulating ferritin, transferrin saturation, and lipid peroxidation products, initiating lipid peroxidation and propagating a lipid-iron-coupled oxidative cascade that drives cell death[35]. In animal study, iron chelators such as deferoxamine attenuate ferroptosis-related damage and improve neurological outcomes[36]. In parallel, inhibition of NADPH oxidase (NOX) reduces both ROS generation and lipid peroxidation; the NOX1/4 inhibitor GKT137831 suppresses iron-dependent lipid oxidation in multiple stroke models[37].

Mitophagy also exhibits a biphasic role in reperfusion injury. Moderate activation of the PINK1/Parkin pathway removes dysfunctional mitochondria, suppresses ROS accumulation, and maintains metabolic homeostasis, thereby promoting neuronal survival[38]. However, sustained hyperactivation of mitophagy reduces mitochondrial mass, limits ATP synthesis, and induces apoptosis and synaptic impairment. These findings support the concept that mitochondrial stress responses during reperfusion span a reversible-irreversible spectrum, consistent with a molecular window. Recent evidence indicates that methylthiamine mitigates post-stroke cognitive impairment by restraining excessive mi-

tophagy and preserving synaptic plasticity[39].

Clinical strategies targeting oxidative stress provide a translational basis for modulating mitochondrial homeostasis. Edaravone and edaravone-dexborneol not only scavenge hydroxyl radicals and activate the Nrf2/HO-1 pathway but also stabilize the BBB and mitochondrial membrane integrity[40,41]. These agents slow penumbra progression by improving microvascular oxygen supply and metabolic efficiency, supporting combined antioxidant and metabolic approaches.

Amplification of inflammation and immune responses

In ischemia reperfusion injury, sterile inflammation triggered by damage-associated molecular patterns (DAMPs) acts as a major amplifier of secondary neuronal damage. During early ischemia, DAMPs released from necrotic cells, such as high mobility group box 1 (HMGB1) and ATP, activate Toll-like receptors (TLR2/TLR4) and downstream NF-κB signaling, driving microglial polarization toward a pro-inflammatory M1 phenotype and promoting release of cytokines including interleukin-6, interleukin-1β, and tumor necrosis factor-α (**Fig. 2**). These cytokines are detectable in plasma or cerebrospinal fluid and reflect the intensity of innate immune activation[42,43]. Concurrently, endothelial upregulation of adhesion molecules such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 facilitates leukocyte infiltration across the BBB, aggravating oxidative stress, microvascular obstruction, and barrier disruption, ultimately forming a self-reinforcing cycle of injury[44,45] (**Fig. 2**).

Upon reperfusion, oxygen re-entry, complement activation, and persistent DAMP signaling further amplify inflammation, resulting in extensive leukocyte adhesion and aggregation within microvessels, therby exacerbating the no-reflow phenomenon[44]. Elevated circulating levels of matrix metalloproteinase-9 (MMP-9), tumor necrosis factor-α, and interleukin-6 during this phase are consistently associated with worse neurological outcomes and reflect active microvascular inflammation. The TLR4 antagonist ApTOLL selectively suppresses DAMP-TLR4-NF-κB signaling and downstream cytokine release, whereas the anti-α4 integrin monoclonal antibody natalizumab limits immune cell trafficking across the BBB[45].

The post-ischemic immune response exhibits a biphasic temporal pattern. Following the acute destructive phase, immune signaling may transition toward tissue repair, characterized by the emergence of pro-regenerative microglial subsets and the expansion of regulatory T cells that facilitate debris clearance, vascular remodeling, and synaptic recovery[46]. Endogenous anti-inflammatory mediators such as APC, acting through protease-activated receptor-1, exert neuroprotective, vasculoprotective, and anti-apoptotic effects within the NVU, partly by inhibiting p53-mediated endothelial cell death[47]. Recent single-cell and spatial omics studies have mapped these dynamic microglial population shifts with high resolution, supporting the concept of specific phase immune modulation[48]. These cross-mechanistic interactions underscore the need for multi-target interventions.

BBB disruption and microcirculatory impairment

BBB plays a central role in maintaining neural microenvironmental homeostasis, with its integrity primarily dependent on tight junction proteins, including claudin-5, occludin, and ZO-1, between cerebral endothelial cells (**Fig. 2**). During cerebral ischemia, excessive activation of MMP-2 and MMP-9 degrades these tight junction components, resulting in structural breakdown of the BBB[49,50]. Accordingly, elevated circulating MMP-9 levels serve as a surrogate marker of BBB proteolytic injury[47]. This disruption promotes plasma extravasation, contributes to vasogenic edema, and intensifies neuroinflammatory cascades. Upon reperfusion, increased shear stress and surges in ROS further injure endothelial cells, leading to sustained increases in BBB permeability. These changes not only facilitate inflammatory cell infiltration but also impede effective delivery of neuroprotective agents to brain tissue[51].

At the microcirculatory level, the no-reflow phenomenon represents a critical barrier to achieving full reperfusion benefit. Despite successful macrovascular recanalization, persistent hypoperfusion may occur downstream due to neutrophil accumulation, pericyte-mediated capillary constriction, microvascular spasm, and microthrombus formation[3,51]. High-resolution magnetic resonance imaging (MRI) and optical microvascular imaging have demonstrated a strong correlation between microcirculatory obstruction and unfavorable clinical outcomes[52]. Therapeutic strategies aimed at restoring microvascular patency, such as vasodilators, antiplatelet agents, and endothelial-protective therapies, including 3K3A-APC, have shown efficacy in reducing non-perfused territories and may enhance targeted delivery of neu-

roprotective agents in preclinical models[53].

The integrity of the NVU is further influenced by systemic hemodynamic patterns during the peri-reperfusion period. A secondary analysis of the ENCHANTED trial revealed that for patients receiving thrombolysis, a rapid reduction in systolic blood pressure (SBP) within the first hour was significantly associated with a decreased risk of severe cerebral edema, likely by reducing the hydrostatic pressure gradient across a compromised BBB[54]. However, this physical protection must be balanced against tissue perfusion requirements. The ENCHANTED-MT trial demonstrated that intensive SBP control (< 120 mmHg) following successful endovascular thrombectomy actually led to worse functional outcomes and early neurological deterioration. This highlights a critical paradox in reperfusion injury: while excessive SBP variability and pressure spikes can exacerbate BBB disruption and vasogenic edema through shear stress and MMP activation, aggressive hypotension may impair microcirculatory patency in the setting of distal no-reflow, where cerebral autoregulation is already dysfunctional[55]. Taken together, these interrelated mechanisms converge to dynamically reshape the post-stroke microenvironment during ischemia and reperfusion (**Fig. 2**).

NEUROPROTECTION AND SYNCHRONIZED REPERFUSION STRATEGIES

Regulatory role of collateral circulation

Collateral circulation is a critical physiological determinant of penumbra viability and directly influences the therapeutic window for neuroprotective interventions. Adequate collateral flow compensates for reduced cerebral perfusion following large vessel occlusion by sustaining residual oxygen and glucose delivery to ischemic tissue, thereby delaying infarct core expansion[56]. The pial collateral network, which comprises anastomoses between distal branches of the anterior, middle, and posterior cerebral arteries, supports retrograde perfusion from adjacent territories and serves three major protective functions: extending the salvageable tissue window (> 6 hours in well-developed collaterals), reducing infarct volume (a 10% increase in collateral flow reduces infarct size by 20%), and lowering the risk of hemorrhagic transformation through preservation of microvascular integrity[57].

Quantitative collateral grading using computed tomography angiography and computed tomography perfusion (CTP) parameters, such as the Tan score and ASITN/SIR scale, strongly correlates with post-reperfusion functional outcomes[58]. In rapid progressors, insufficient collateralization accelerates CBF decline and promotes swift penumbra-to-core transition, yielding a narrow therapeutic window even when recanalization is timely. In contrast, slow progressors with robust collateral perfusion maintain metabolic stability for prolonged periods, enabling early neuroprotective treatment to preserve reversible tissue prior to reperfusion[2].

In addition to sustaining basal perfusion, enhanced collateral flow increases vascular shear stress and promotes NO-mediated vasodilation as well as upregulation of angiogenic factors such as vascular endothelial growth factor and angiopoietin 2, producing a dual vascular metabolic protective effect. These findings support the emerging concept of collateral-augmented neuroprotection, integrating pharmacological (e.g., NO donors, calcium channel blockers, and cilostazol) and physiological approaches (e. g., induced hypertension and controlled ventilation) with neuroprotective agents to expand the treatment window and improve tissue survivability[56].

Pharmacological and non-pharmacological strategies targeting reperfusion injury

In the reperfusion era, pharmacological neuroprotection is increasingly being repositioned as an adjunct strategy aimed at modulating reperfusion injury rather than reversing established infarction. Current investigational agents can be broadly categorized according to their principal mechanisms: inhibition of excitotoxic signaling (e. g., nerinetide targeting PSD95-nNOS coupling), attenuation of oxidative stress and mitochondrial dysfunction (e.g., edaravone-dexborneol and nelonemdaz), suppression of inflammatory and immune amplification (e. g., 3K3A-APC and natalizumab), and stabilization of the BBB and microvascular integrity (e.g., imatinib and butylphthalide) [59]. This categorization reflects a transition from single pathway blockade toward integrated modulation of the NVU. However, clinical benefit appears highly dependent on reperfusion status, treatment timing, and drug interactions with thrombolytics. Despite favorable safety profiles and modest efficacy signals in selected populations, overall effect sizes remain limited, highlighting ongoing challenges in timing, patient stratification, and biological heterogeneity[2].

Among non-pharmacological approaches, normobaric hyperoxia may enhance oxygen diffusion within the penumbra and transiently stabilize endothelial integrity before recanalization. However, its effects are highly time- and dose-dependent, and delayed administration after reperfusion may aggravate oxidative stress[60]. Targeted temperature management, including systemic or selective hypothermia, reduces metabolic demand and secondary injury cascades in experimental models, but clinical efficacy remains unproven, and selective brain cooling techniques are still investigational[60,61]. Remote ischemic conditioning applied before reperfusion may activate endogenous protective signaling pathways, whereas peri-reperfusion benefits are often difficult to distinguish from the effects of successful recanalization, and delayed use may exert longer-term vascular and immune modulation[62,63]. Neuromodulatory approaches, such as transcranial direct current stimulation and vagus nerve stimulation, leverage a post-ischemic window of heightened plasticity to facilitate network reorganization rather than acute tissue preservation[64]. Overall, non-pharmacological strategies offer biologically plausible multitarget modulation but are limited by logistical complexity and systemic risks. Future progress will require precise temporal synchronization with individual pathophysiological stages to achieve meaningful neurovascular protection.

Temporal synergy in neuroprotection

Neuroprotection should be implemented continuously across the pre-, intra-, and post-reperfusion phases rather than solely after recanalization. Traditional clinical trials frequently administer neuroprotective agents only post-reperfusion, thereby missing the critical ischemic cascade in which damage pathways are initiated[16]. The "continuation of intra-ischemic injury" hypothesis posits that reperfusion injury is an amplification of processes initiated during ischemia, including inflammation and oxidative stress[65].

Preclinical models show neuroprotective therapies yield greater benefits when reperfusion is achieved, indicating that their efficacy depends on perfusion restoration to deliver drugs to injured tissue[17]. Clinically, neuroprotection should therefore be regarded as a synergistic adjunct to reperfusion rather than a standalone alternative. When reperfusion occurs rapidly, the therapeutic window is narrow; when recanalization is delayed or incomplete, neuroprotection mitigates progression; if reperfusion fails, neuroprotection may slow but cannot prevent infarction[2].

Clinical evidence further demonstrates that neuroprotection is effective primarily in patients who achieve successful reperfusion[66]. In the ESCAPE-NA1 trial, nerinetide improved outcomes in endovascular thrombectomy patients who did not receive concomitant alteplase but lost efficacy in thrombolysis-treated patients due to enzymatic drug degradation, highlighting the dependence of therapeutic benefit on metabolic and reperfusion conditions[67]. Thus, reperfusion restores blood flow, while neuroprotection stabilizes the cellular environment and mitigates reperfusion-driven secondary injury.

Imaging-based stratification and identification of salvageable tissue

Advances in multimodal imaging have transformed penumbra assessment from static anatomical inference to quantitative, treatment-guiding stratification of ischemic core and salvageable tissue. In current clinical practice, ischemic core is defined by irreversible cellular injury, typically identified by diffusion restriction on MRI with an apparent diffusion coefficient (ADC) $< 0.62 \times 10^{-3}$ mm^2/s, or by severe hypoperfusion on CT perfusion indicated by CBF < 30% of the contralateral hemisphere. In contrast, ischemic penumbra is characterized by critical hypoperfusion with preserved diffusion, most commonly operationalized as Tmax > 6 seconds on perfusion imaging without corresponding ADC reduction[68]. Combined perfusion metrics further refine tissue classification: reduced CBF with preserved or mildly increased cerebral blood volume reflects compensatory vasodilation and metabolically viable penumbra, whereas concurrent reductions in CBF and cerebral blood volume indicate irreversible infarct core formation[69]. MRI-defined DWI-FLAIR and DWI-PWI mismatch has been validated by randomized trials to identify salvageable penumbra beyond fixed time windows, enabling tissue-based thrombolysis selection[17,68,70].

Collateral status exhibits a quantifiable relationship with penumbra duration. Arterial spin labeling (ASL) enables noninvasive assessment of regional perfusion and arterial transit time, revealing marked spatial variability in ischemic progression rates[56]. Positron emission tomography (PET) and CTP studies confirm that slow-progressing patients with robust collaterals may retain viable penumbra ⩾ 12 hours post-onset,

whereas fast-progressing patients exhibit rapid core expansion within hours[22]. Radiomics-based integration of ASL and CTP further enhances penumbra detection and enables temporal monitoring of ischemic evolution[71]. With the adoption of machine learning, imaging now supports automated prediction of infarct growth, penumbra persistence, and functional outcomes, facilitating individualized treatment-guiding tissue window modeling[72]. Additionally, the hypoperfusion-hypodensity mismatch model additionally identifies salvageable tissue without relying on automated perfusion software, thereby expanding clinical utility[73].

Metabolic imaging provides complementary physiological validation. Oxygen extraction fraction (OEF) -based imaging, using OEF-MRI or PET, identifies viable penumbral tissue by detecting elevated OEF and a relatively preserved cerebral metabolic rate of oxygen ($CMRO_2$), with PET studies suggesting a critical $CMRO_2$ threshold of approximately $\geqslant$ 1.4 mL/(100 g·min), below which tissue recovery is unlikely[9]. Comparative studies show OEF improves precision beyond perfusion mismatch alone[74]. Moreover, Fe-GA catalytic polymers applied in middle cerebral artery occlusion models reduce ROS accumulation and restore Akt and Nrf2/HO-1 signaling, demonstrating real-time imaging-guided antioxidant neuroprotection[75]. Deep learning integrated across multimodal datasets now enables automated segmentation, prediction, and outcome modeling, translating radiographic features into clinically actionable decision support for timing and strategy selection in precision neuroprotection[76].

CONCLUSION

In the reperfusion era, the clinical value of neuroprotective therapies lies not in reversing ischemic injury alone, but in delaying ischemic progression, expanding the volume of tissue amenable to reperfusion, and achieving spatiotemporally coordinated protection of the NVU. AIS is characterized by marked temporal dynamics and spatial heterogeneity, in which the viability of the ischemic penumbra determines both therapeutic plasticity and the duration of the intervention window. Accumulating evidence indicates that the effectiveness of neuroprotection is governed by two interdependent dimensions: time dependence and reperfusion dependence. Meaningful clinical benefit arises only when agents preserve metabolic activity in salvageable tissue while acting across both pre-reperfusion and post-reperfusion pathological phases.

Future therapeutic goals should shift from broad, nonspecific neuroprotection to precision potentiation. Neuroprotective interventions must be integrated into a comprehensive stroke care paradigm, forming a continuous and synergistic treatment chain. Early intervention during ischemia can slow penumbra collapse and extend the window for recanalization, whereas sustained treatment following reperfusion mitigates oxidative and inflammatory cascades, promotes NVU repair, and facilitates true effective reperfusion. The ischemic penumbra represents a molecularly regulated and potentially reversible state, giving rise to a molecular window of therapeutic plasticity that complements and extends traditional imaging-based definitions. Nevertheless, several translational barriers remain substantial. The development of multi-target neuroprotective agents is intrinsically challenging, given the need to modulate multiple, temporally overlapping injury pathways without introducing off-target toxicity or compromising physiological repair processes. Although biomarkers are increasingly identified, the feasibility of real-time biomarker detection in AIS remains limited by assay speed, standardization, and integration with urgent treatment decision-making.

The convergence of advanced imaging and multi-omics technologies is emerging as a key driver of precision neuroprotection. Techniques such as MR perfusion imaging, ASL, DWI-FLAIR mismatch, and collateral assessment enable quantitative, real-time evaluation of tissue viability and metabolic reserve. However, their effective integration with circulating or molecular biomarkers requires validation and further refinement to achieve accurate patient stratification. Meanwhile, artificial intelligence-based multimodal fusion models allow individualized predictions of ischemic progression and therapeutic response. As contemporary stroke science increasingly emphasizes, the goal is not simply to prevent neuronal death, but to deliver the right intervention to the right patient at the right time. Such a paradigm redefines the role of neuroprotection within the modern stroke treatment continuum and lays a foundation for truly personalized, dynamic, and mechanism-guided patient care.

ARTICLE INFORMATION

Conflict of interests

The authors declare no conflicts of interests.

Authors' contributions

Shi FN: conceptualization, investigation, software, writing - original draft, and writing - review & editing. Yu ZD and Wang XN: writing-original draft and writing-review & editing. Zhang ZC: review, editing, and supervision. All authors have reviewed and approved the final version of the manuscript.

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综述

在再灌注时代急性缺血性卒中的时间依赖性神经保护与精准干预

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摘要

急性缺血性卒中是全球非传染性疾病中第二大死亡原因。尽管静脉溶栓和血管内取栓术显著提高了闭塞大血管的再通率，然而患者的临床结局并未相应改善。研究表明，单纯实现血管再通并非意味着有效的组织再灌注。因此，神经保护策略的重心也就由单纯减少神经细胞坏死，转为延缓缺血半暗带进展，最大化保护可挽救脑组织。本文系统综述了急性缺血性卒中再灌注损伤、微循环障碍、神经血管单元破坏和神经保护机制的时相演变。重点探讨了可逆性半暗带的演变过程、再灌注诱发的损伤放大效应，以及基于脑成像技术引导和分子生物标志物的精准干预策略。这些进展为构建时空协调、个体化的神经保护策略奠定了理论基础。

关键词：急性缺血性卒中；神经保护；再灌注；半暗带；脑成像技术；精准医学

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