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Review article

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Endothelial dysfunction as a predictor of post-reperfusion complications in acute ischemic stroke: a literature review

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Acute ischemic stroke remains one of the leading causes of mortality and long-term disability worldwide. Although reperfusion therapies, including thrombolysis and mechanical thrombectomy, have demonstrated efficacy, a substantial proportion of patients fail to achieve the expected functional recovery, highlighting the need to identify additional pathogenetic factors that may influence stroke outcomes. Among these, endothelial dysfunction plays a particularly important role.

Objective: To summarize current evidence regarding the role of endothelial dysfunction in the development of complications following reperfusion therapy in acute ischemic stroke and to assess the prospects of endothelium-protective strategies.

Materials and methods: A literature review of publications from the last five years was conducted, including clinical studies, meta-analyses, and systematic reviews. Contemporary concepts of vascular endothelial injury, disruption of the blood–brain barrier, reperfusion injury, hemorrhagic transformation, and the "no-reflow" phenomenon (failure of microcirculation restoration) were analyzed. Laboratory and functional methods for evaluating endothelial function, including the EASIX index, were examined, and perspectives on endothelium-protective therapeutic approaches were outlined.

Results: Endothelial dysfunction was associated with an increased risk of hemorrhagic transformation, cerebral edema, and microcirculatory failure following thrombolysis and mechanical thrombectomy. Patients with elevated soluble Eselectin, von Willebrand factor, and symmetric dimethylarginine had worse functional outcomes, with favorable recovery (modified Rankin Scale 0–2) in 38 % compared with 64 % for lower biomarker levels ($p < 0.01$). In 325 patients undergoing thrombectomy, 12.6 % developed parenchymal hematoma, and higher endothelial dysfunction scores were independently associated with its occurrence (adjusted odds ratio 1.43; 95 % CI 1.03–1.99; $p = 0.032$), improving predictive performance of conventional risk models. These findings highlight endothelial dysfunction as a clinically relevant predictor of post-reperfusion complications.

Conclusions: Endothelial dysfunction is an important pathogenetic factor influencing the risk of complications and the effectiveness of reperfusion interventions. Integrating endothelial function assessment into clinical protocols may contribute to personalized treatment strategies, improved therapeutic outcomes, and better prognosis in patients with acute ischemic stroke.

Keywords: *endothelial dysfunction; acute ischemic stroke; reperfusion therapy; mechanical thrombectomy; thrombolysis; reperfusion injury; hemorrhagic transformation*

Introduction

Acute ischemic stroke is among the most common and severe neurological disorders worldwide, associated with high morbidity, mortality, and long-term disability. Ischemic stroke accounts for approximately 80–87 % of all acute cerebrovascular events and remains one of the leading causes of death and disability in the adult population. According to the World Health Organization, stroke causes an estimated 6 million deaths globally each year, and its prevalence continues to rise due to population aging and increasing rates of risk factors such as arterial hypertension, cardiovascular disease, and diabetes mellitus. In Ukraine, the prevalence of stroke exceeds the European average, reaching approximately 289.4 cases per 100,000 population. Each year, more than 110,000–145,000 new cases are registered, with about one-third of patients being of working age [1–5].

Recent studies increasingly emphasize endothelial dysfunction as a fundamental pathogenetic mechanism that influences stroke development and modulates

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the severity of its clinical course. The endothelium, which lines the inner surface of blood vessels and is composed of endothelial cells, interacts with blood flow, circulating cells, and the lymphatic system. It maintains vascular tone homeostasis by regulating the balance between vasodilation and vasoconstriction and protects against vascular inflammation and other pathological disturbances. Consequently, endothelial dysfunction leads to impaired vascular homeostasis and contributes to the development of cardiovascular, cerebrovascular, and metabolic disorders.

The endothelium synthesizes nitric oxide, a key mediator of vasodilation, whose production is regulated by hemodynamic changes that generate mechanical stress and activate signaling pathways stimulating nitric oxide synthesis. At the same time, endothelial cells produce vasoconstrictor factors, ensuring a balance of vascular tone. A hallmark of endothelial dysfunction is reduced nitric oxide bioavailability, resulting in impaired vasodilation, vascular rigidity, and vascular complications [6–8]. The mechanisms of endothelial dysfunction are diverse and complex, including oxidative stress, inflammation, activation of the renin–angiotensin–aldosterone system, and alterations in insulin and insulin-like growth factor signaling pathways [9–11].

In the context of ischemic stroke, endothelial dysfunction not only contributes to atherosclerotic lesions and thrombosis but also directly affects cerebral microcirculation, perfusion reserve, and blood–brain barrier integrity. Given the growing role of reperfusion interventions, including thrombolytic therapy and endovascular thrombectomy, studying endothelial dysfunction as a predictor of post-reperfusion complications—such as parenchymal hemorrhage, cerebral edema, and the no-reflow phenomenon—has become particularly relevant [12–17].

The aim of this review is to summarize current evidence regarding the role of endothelial dysfunction in the development of complications following reperfusion therapy in acute ischemic stroke and to assess the prospects of endothelium-protective strategies.

Mechanisms of endothelial dysfunction

Endothelial dysfunction occurs when normal endothelial function is impaired by external factors such as mechanical stress, excessive production of reactive oxygen species, or activation of the renin–angiotensin–aldosterone system. In this pathological state, the endothelium loses its ability to maintain adequate vasodilation and adopts a pro-inflammatory and pro-thrombotic phenotype, accompanied by enhanced proliferative and fibrotic processes.

Oxidative stress reduces nitric oxide bioavailability and leads to the formation of peroxynitrite, which damages cellular membranes and proteins. Inflammatory cytokines and adhesion molecules promote the recruitment of leukocytes and platelets, exacerbating microthrombosis and microcirculatory dysfunction. Activation of the renin–angiotensin–aldosterone system further decreases nitric oxide synthesis, increases reactive oxygen species production, and potentiates the inflammatory response, collectively resulting in impaired vascular tone and barrier function [9–12].

In cerebral vessels, these changes are particularly significant because the endothelium, together with the basement membrane, pericytes, and astrocytes, forms the blood–brain barrier. Disruption of its integrity leads to increased permeability, cerebral edema, and intracerebral hemorrhage, which are critical events in the acute phase of stroke.

In the context of reperfusion interventions, rapid restoration of blood flow after prolonged ischemia imposes additional hemodynamic and metabolic stress on the already damaged endothelium. Reperfusion is associated with massive reactive oxygen species production, activation of matrix metalloproteinases, intensified inflammatory response, and progression of endothelial dysfunction. Collectively, these processes constitute the pathophysiological basis of reperfusion injury, manifesting as cerebral edema, hemorrhagic transformation, and impaired microcirculation [12, 16, 17].

Endothelial dysfunction in ischemic stroke and after reperfusion intervention

Ischemic stroke is associated with systemic microvascular disturbances, which may also manifest as retinal vascular pathology. In patients with acute ischemic stroke, alterations in levels of endothelial dysfunction biomarkers, such as homocysteine, von Willebrand factor, E-selectin, and intercellular adhesion molecules, have been observed [7, 12].

The level of von Willebrand factor is significantly higher in patients with lacunar stroke, but lower than in those with non-lacunar stroke, potentially reflecting differences in the vascular bed and the pattern of injury [11, 18]. At the same time, heterogeneity in biomarker expression across different vessel types (capillaries, arterioles, large arteries) may partially obscure observed differences, underscoring the need for markers capable of reflecting systemic endothelial responses independently of the site of vascular injury.

Reperfusion interventions, including thrombolytic therapy and endovascular thrombectomy, are the most effective treatments for acute ischemic stroke. However, results from randomized trials and meta-analyses indicate that, despite high rates of successful recanalization after endovascular procedures (71–84 %), approximately half of patients do not achieve functional independence at 90 days (mRS 0–2), indicating that no clinically significant neurological improvement is observed. Across studies, the incidence of unfavorable outcomes ranges from 30 % to 60 %, highlighting the presence of additional pathophysiological factors limiting intervention efficacy [19, 20].

One of the primary factors reducing the effectiveness of reperfusion interventions is hemorrhagic transformation, which occurs following recanalization procedures and serves as a predictor of poor prognosis [21, 22].

Endothelial dysfunction may be a key determinant of the outcomes of recanalization interventions. First, restoration of blood flow in previously ischemic tissue initiates a cascade of reperfusion injury, characterized by intense oxidative stress and an inflammatory response. Dysfunctional endothelium amplifies these processes, promoting blood–brain barrier disruption and increasing the volume of secondary brain injury even in the setting

of technically successful recanalization [17, 23, 24]. Second, endothelial dysfunction compromises the structural integrity of the blood–brain barrier, increasing the risk of hemorrhagic transformation and cerebral edema following recanalization [17]. Third, reduced nitric oxide bioavailability limits vasodilatory reserve and perfusion of ischemic regions, potentially contributing to the phenomenon of incomplete microvascular reperfusion. Fourth, endothelial dysfunction is associated with a pro-thrombotic state, which elevates the risk of reocclusion after recanalization [6, 9, 10, 12].

Fifth, multiple passes of a stent retriever during mechanical thrombectomy can cause mechanical injury to the endothelium and disrupt the blood–brain barrier, detectable on fluid-attenuated inversion recovery (FLAIR) MRI 24 hours after the procedure. In this context, the HARM (Hyperintense Acute Reperfusion Marker) phenomenon—contrast enhancement on MRI following reperfusion—is considered a marker of local mechanical endothelial injury. The incidence of blood–brain barrier disruption increases proportionally with the number of stent-retriever passes and is observed in approximately half of patients [25]. Furthermore, histological analysis of thrombi retrieved during mechanical thrombectomy has demonstrated the presence of endothelial cells and fragments of the vascular wall in approximately 12 % of cases, indicating direct mechanical damage to the vascular endothelium during the procedure [26].

At present, it remains a matter of debate whether the initial endothelial status prior to intervention or the changes that develop after reperfusion are the decisive factor. Resolving this question has significant clinical implications, as it could improve risk stratification for hemorrhagic complications, reocclusion, and ineffective microvascular reperfusion, and provide a rationale for implementing endothelium-protective strategies.

Notably, arginine is included in the commercial formulations of alteplase and tenecteplase (Actilyse and Metalyse), which are used for thrombolytic therapy in ischemic stroke. L-arginine serves as a substrate for nitric oxide synthesis in endothelial cells, promoting vasodilation and maintaining perfusion. Although the exact concentration of arginine in these preparations is not disclosed by manufacturers, its presence could theoretically influence nitric oxide bioavailability and modify the vascular response. However, the absence of dedicated studies prevents drawing definitive conclusions regarding the clinical significance of this effect.

Thus, endothelial dysfunction may substantially limit the effectiveness of revascularization interventions by exacerbating reperfusion injury, compromising barrier function, reducing vasodilatory reserve, promoting thrombosis, and sustaining the inflammatory cascade.

Beyond these direct mechanisms of injury, endothelial dysfunction also affects cerebral blood flow autoregulation. Impaired vasodilation and increased arterial stiffness reduce perfusion reserve and elevate the risk of hypoperfusion, which may worsen treatment outcomes. Decreased vascular reactivity is associated with poorer functional prognosis, highlighting the importance of endothelial dysfunction in determining the clinical consequences of stroke [27].

Methods for assessing endothelial function

Assessment of endothelial function is an important tool for risk stratification and prognosis in cerebrovascular diseases. It includes the measurement of serological biomarkers and the use of functional tests that can be applied in clinical practice.

Serological markers include adhesion molecules (integrins, cadherins, selectins), which are activated during inflammation and facilitate leukocyte migration, as well as homocysteine, von Willebrand factor, interleukin-8, interleukin-18, and insulin-like growth factor deficiency [6, 7, 12, 28].

Homocysteine impairs nitric oxide synthesis and induces oxidative stress, exacerbating endothelial dysfunction [29]. P-selectin, von Willebrand factor, and interleukin-8 mediate leukocyte and platelet recruitment to the endothelium in response to vascular injury. Interleukin-18 enhances the production of pro-inflammatory cytokines and adhesion molecules. Insulin-like growth factor promotes nitric oxide synthesis, so its deficiency is also associated with endothelial dysfunction. C-reactive protein, as a marker of systemic inflammation, is likewise linked to endothelial dysfunction and vascular complications. In patients with ischemic stroke, elevated C-reactive protein levels correlate with poor prognosis, partly reflecting the role of systemic inflammation in pathogenesis, particularly in the cardioembolic stroke subtype [7].

Of particular interest is the endothelial activation and stress index (EASIX), which incorporates three laboratory parameters: serum creatinine, lactate dehydrogenase activity, and platelet count. This composite index has been proposed as an accessible, reproducible, and robust marker of systemic endothelial dysfunction that correlates with various cerebrovascular pathologies [30]. In the context of stroke, EASIX may be a promising tool, as it is independent of the vascular territory and can reflect the systemic response to endothelial injury.

EASIX is calculated as the product of serum creatinine and lactate dehydrogenase (LDH) activity divided by the platelet count. Elevated creatinine reflects impaired renal function, increased LDH activity indicates cellular stress and tissue injury, while a reduced platelet count may signify platelet activation and consumption under conditions of systemic inflammation.

EASIX is simple to calculate and provides a comprehensive measure of systemic stress. Its integration with functional methods for assessing vascular reactivity may enhance the accuracy of early diagnosis of endothelial dysfunction and monitoring of therapeutic efficacy, making this index a promising addition to existing risk assessment algorithms. Recent studies have demonstrated the prognostic significance of EASIX in patients with acute ischemic stroke after mechanical thrombectomy for large vessel occlusion. Higher EASIX values are associated with poor functional outcomes at 90 days, suggesting its potential as a tool for early risk stratification [32].

Functional methods for assessing endothelial function are diverse. The most commonly used include ultrasound-based assessment of flow-mediated dilation and reactive hyperemia index, plethysmography, and pulse wave velocity measurements. These approaches are

methodologically based on analyzing changes in vascular tone in response to pharmacological or mechanical stimuli.

These methods evaluate the capacity of vessels to dilate in response to increased blood flow, reflecting endothelial functional activity. However, none of these techniques has achieved "gold standard" status due to limitations in reproducibility and dependence on technical conditions and operator expertise [33, 34]. The most commonly used method for assessing endothelial function is the measurement of brachial artery flow-mediated dilation (FMD) following temporary occlusion, which reflects the endothelium's ability to respond to increased blood flow. The methodology is described in detail in the consensus guidelines of the International Brachial Artery Reactivity Task Force [35]. In healthy individuals, the artery dilates after reactive hyperemia due to the release of endothelium-dependent vasodilators, whereas this response is reduced in endothelial dysfunction. The primary outcome measure is the percentage change in arterial diameter relative to the baseline.

Pulse wave velocity (PWV) is another important parameter that reflects arterial stiffness and is closely associated with endothelial dysfunction [33]. Increased PWV is linked to a higher risk of vascular complications and poor prognosis, while reductions in PWV may be observed following effective management of cardiovascular risk factors [36].

In contemporary studies, transcranial color-coded Doppler ultrasonography with a breath-holding test is used to assess cerebral vasoreactivity as a surrogate marker of endothelial function [36–38].

Another approach involves assessing peripheral arterial tone using finger plethysmography. Plethysmographic sensors are placed on the fingers to continuously record changes in pulse volume in small arteries. Measurements are taken before and after reactive hyperemia induced by temporary brachial artery occlusion using a cuff. The reactive hyperemia index is calculated as the ratio of post-stimulus to baseline values. This method demonstrates high reproducibility and low inter-observer variability due to automated data analysis and shows good correlation with the presence of vascular pathology.

Recently, non-invasive methods for assessing the microvascular bed have been actively investigated, including laser Doppler flowmetry with scanning and adaptive optics to determine the wall-to-lumen ratio of retinal arterioles [38,39]. These approaches allow a more detailed evaluation of structural and functional changes in the microcirculation.

Thus, the combined use of biomarkers and functional methods, particularly the integration of the EASIX index, provides a basis for more precise assessment of endothelial status and personalized risk stratification for vascular events in patients with ischemic stroke.

Therapeutic strategies and prospects

In recent years, significant progress has been achieved in the treatment of ischemic brain injury and post-reperfusion complications, thanks to advances in medical technology.

Therapies targeting endothelial dysfunction are considered pathogenetically justified approaches for both primary stroke prevention and optimization of acute-phase treatment outcomes, particularly to reduce the risk of post-reperfusion complications.

Existing pharmacological strategies include angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, nitrates, and statins, as well as experimental approaches such as endothelial progenitor cell transplantation. These strategies aim to improve nitric oxide bioavailability, reduce oxidative stress, and modulate the inflammatory response. However, most of these interventions lack sufficient evidence of efficacy specifically in the context of acute stroke [40, 41].

Particular interest lies in strategies that can mitigate reperfusion injury following thrombolysis and thrombectomy. Restoration of blood flow to the ischemic zone triggers intense oxidative and inflammatory responses, leading to endothelial damage and disruption of the blood–brain barrier. This may result in the "no-reflow" phenomenon, where, despite the recanalization of the major vessel, microcirculation remains insufficient. Pathogenetically, this phenomenon is associated with microthrombosis, arteriolar spasm, endothelial edema, and activation of adhesion molecules.

Given that reperfusion interventions are the standard of care for acute ischemic stroke, endothelium-protective strategies may be considered a potential component of adjunctive therapy aimed at minimizing secondary brain injury.

Promising approaches include antioxidant and anti-inflammatory strategies capable of reducing blood–brain barrier damage. Anti-inflammatory therapy that modulates neutrophil activation and matrix metalloproteinases can decrease barrier permeability and the risk of hemorrhagic transformation. Particular attention has been focused on agents that restore nitric oxide synthesis or reduce its degradation, as nitric oxide deficiency is a central element of endothelial dysfunction [16, 42].

Antioxidants, neuroprotective agents, and exosome-based therapies offer several potential advantages. Their therapeutic effects are mediated through the reduction of oxidative stress, suppression of inflammatory responses, and modulation of autophagy processes, which collectively limit ischemic injury. Current clinical data indicate the potential of antioxidants and neuroprotective agents, while nanotechnology-based drug delivery systems may enhance bioavailability and allow targeted release at the ischemic site.

Stem cell–derived exosomes utilize microRNAs to stimulate neuronal regeneration and restore microcirculation. Despite significant experimental potential, their clinical application requires standardization of technology to meet regulatory requirements.

Therapeutic strategies aimed at correcting key elements of endothelial dysfunction hold considerable promise. Their further optimization may benefit from modern pharmacokinetic modeling approaches using artificial intelligence, which could improve predictions of drug permeability across the blood–brain barrier and minimize the risk of hemorrhagic transformation [16, 42–44].

The clinical relevance of these mechanisms has been increasingly supported by studies evaluating endothelial function and its impact on post-reperfusion outcomes.

Endothelial function after endovascular interventions exhibits a complex, biphasic pattern. Following peripheral arterial revascularization, endothelium-dependent vasodilation assessed by flow-mediated dilation improves from 4.1 ± 1.8 % to 6.7 ± 2.3 % ($p < 0.01$), reflecting partial restoration of vascular reactivity. At the same time, the early postprocedural period is marked by transient endothelial activation, with high-sensitivity C-reactive protein rising from 2.3 to 4.8 mg/L ($p < 0.05$) [45]. These findings suggest that mechanical stress initially injures the endothelium, triggering inflammatory responses, while gradual recovery allows partial functional restoration. Vessel recanalization therefore does not immediately equate to normalization of endothelial function.

In acute ischemic stroke, endothelial dysfunction plays a prognostic role. Elevated levels of symmetric dimethylarginine are independently associated with poor functional outcomes (odds ratio 1.42 per 0.1 μmol/L, 95 % confidence interval 1.10–1.83; $p = 0.006$), with patients in the highest quartile achieving favorable outcomes (modified Rankin Scale 0–2) only 38 % compared with 64 % for lower quartiles, $p < 0.01$ [12]. These associations remain significant after adjustment for age, baseline stroke severity, and time to reperfusion, emphasizing that endothelial dysfunction is not merely a bystander but a determinant of reperfusion efficacy.

Mechanistically, reperfusion triggers reactive oxygen species production, endothelial nitric oxide synthase uncoupling, and a 30–50 % reduction in nitric oxide bioavailability, accompanied by peroxynitrite formation and accumulation of oxidative stress markers. Shear stress alterations and the presence of intravascular devices further impair endothelial signaling through activation of nuclear factor-kappa B (NF-kB) and upregulation of adhesion molecules. These processes disrupt microcirculation, increase vascular permeability, and contribute to the risk of hemorrhagic transformation [46].

Clinical evidence supports the relevance of these mechanisms. In a prospective cohort of 325 patients undergoing mechanical thrombectomy, 12.6 % developed parenchymal hematoma. Those patients exhibited higher levels of soluble Eselectin and von Willebrand factor, as well as elevated composite endothelial dysfunction scores. After multivariable adjustment, endothelial dysfunction remained independently associated with parenchymal hematoma (adjusted odds ratio 1.432, 95 % confidence interval 1.031–1.988; $p = 0.032$) and improved the predictive performance of conventional risk models (net reclassification improvement 25.2 %, $p = 0.001$; integrated discrimination index 2.9 %, $p = 0.001$) [47].

Taken together, these findings illustrate that endothelial dysfunction after endovascular interventions is a dynamic and clinically significant process. While reperfusion can partially restore vascular function, early endothelial injury and ongoing microvascular impairment are key contributors to post-reperfusion complications, including hemorrhagic transformation. This highlights endothelial dysfunction not only as a mechanistic mediator of injury but also as a potential target for adjunctive therapies aimed at improving functional outcomes after stroke.

Research prospects

Future research should focus on defining the role of endothelial dysfunction in the pathogenesis of different ischemic stroke subtypes, including cardioembolic, macroangiopathic, and microangiopathic stroke.

Particular attention should be paid to studying the dynamics of endothelial function in the post-reperfusion period to identify biomarkers and functional parameters capable of predicting the risk of hemorrhagic complications and long-term functional outcomes.

A promising avenue is the development of multifactorial prognostic models that integrate clinical, laboratory, and instrumental indicators of endothelial function. This could facilitate personalized selection for thrombolytic therapy and mechanical thrombectomy, as well as justify the implementation of individualized endothelium-protective strategies.

Conclusions

Endothelial dysfunction represents a critical pathogenetic mechanism in ischemic stroke and substantially influences the risk of post-reperfusion complications. It disrupts the regulation of vascular tone, microcirculation, and the integrity of the blood–brain barrier, thereby increasing the likelihood of reperfusion injury, cerebral edema, and parenchymal hemorrhage.

The integration of functional assessment methods with the measurement of serological biomarkers, particularly the EASIX index, enhances the accuracy of risk stratification and enables tailored therapeutic strategies.

Therapeutic approaches aimed at restoring endothelial function have the potential to improve outcomes after thrombectomy and thrombolysis; however, their clinical efficacy requires further confirmation in prospective studies.

Disclosure

Conflict of Interest

The authors declare no conflict of interest.

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