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Impacts of futile reperfusion and reperfusion injury in acute ischemic stroke

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Abstract:

Acute ischemic stroke (AIS) remains to be a challenging cerebrovascular disease. The mainstay of AIS management is endovascular reperfusion therapy, including thrombectomy and thrombolysis. However, ineffective (futile) reperfusion (FR) or reperfusion injury (RI) can be seen in a significant number of patients undergoing reperfusion strategy. In this article, we discuss two clinically relevant concepts known as "time window" and "tissue window" that can impact the clinical outcome of reperfusion therapy. We also explore patient risk factors, leading to FR and RI as well as an emerging concept of "no-reflow phenomenon" seen in ineffective reperfusion. These fundamental concepts provide insight into the clinical management of AIS patients and provide references for future research.

Keywords:

Endovascular reperfusion therapy, ineffective (futile) reperfusion, no-reflow phenomenon, thrombectomy, thrombolysis, time window, tissue window

Acute ischemic stroke (AIS) remains as one of the most prevalent cerebrovascular diseases, leading to significant morbidities and mortalities worldwide. According to the American Heart Association, nearly half the deaths attributable to cerebrovascular disease worldwide was related to AIS.[1] AIS manifest as a large vessel occlusion causing an interruption of blood flow to part of the brain resulting in neurological deficits and long-term disabilities when not properly treated.[2] Endovascular reperfusion therapy, encompassing intravenous thrombolysis and mechanical thrombectomy (MT), is an established best practice treatment modality associated with improved 90-day clinical outcome in AIS patients.[3,4] Thrombectomy is a mechanical procedure to remove the clot, whereas thrombolysis involves dissolving the clot chemically. The aim of reperfusion strategy is to restore cerebral blood flow in ischemic stroke patients and prevent clinical complications. However, despite successful and timely-administered reperfusion therapy, nearly half of patients with AIS do not have favorable clinical outcomes at 90 days.[5] This concept of successful, prompt reperfusion without clinical benefit is known as "futile reperfusion" (FR) which is categorized as treatment failure.[6] Another phenomenon that can occur with reperfusion strategy is paradoxical neurological damage resulting in debilitating complications known as "reperfusion injury" (RI).[7] While treatments of AIS continue to emerge, there are still significant risks associated with them, notably FR and RI. Ineffective FR refers to the failure to adequately restore blood flow to the ischemic brain tissue after thrombectomy or thrombolysis, resulting in continued ischemic damage. In contrast, RI is a harmful process triggered by the restoration of blood flow, causing additional damage beyond the initial ischemic injury.[8,9] It is therefore crucial to understand the determinants that result in clinically effective reperfusion without any associated damages [Figure 1].

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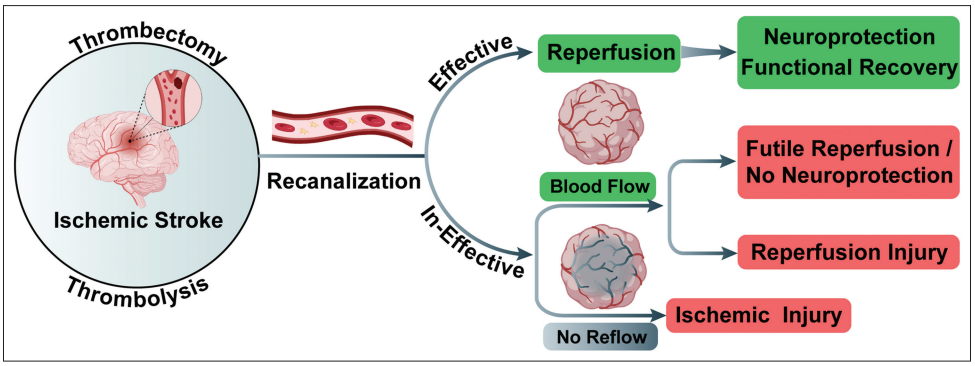

Figure 1: This diagram illustrates the therapeutic pathways and outcomes for ischemic stroke. At the onset of stroke, two primary interventions, the thrombectomy and thrombolysis, can be considered, while both aimed at recanalization of the occluded blood vessel. If recanalization is effective, it leads to reperfusion, restoring blood flow to the affected brain region. A successful reperfusion can result in neuroprotection and functional recovery. However, if recanalization is not effective, it can lead to three possible outcomes: (1) Reperfusion that may occur but too late does not rescue brain issue; and/or (2) Reperfusion occurs but causes reperfusion injury, leading to additional brain damage; (3) Persistence of no blood flow resulting in brain injury

As clinicians encounter patients with AIS, it is essential to understand the stroke risk factors as well as patient characteristics associated with FR.[10] Moreover, there is a need for objective tests measuring the degree of reperfusion as well as clinical outcomes following endovascular thrombectomy (EVT) treatment. It is widely accepted that successful reperfusion postthrombectomy is defined as a score of ≥2b on the modified thrombolysis in cerebral infarction (mTICI).[6] Furthermore, the modified Rankin Scale (mRS) is a broadly utilized global outcome rating scale to categorize the extent of functional independence in poststroke patients. A 90-day mRS score of 0–2 indicates a good clinical outcome.[6] In a recent study conducted by Sun *et al*., data gathered from 297 patients who underwent EVT across three academic stroke treatment centers in China were analyzed. This included age, sex, mRS, National Institute of Health Stroke Scale (NIHSS), Alberta Stroke Program early CT score, time to treatment, risk factors, and comorbidities. Patients were included if they presented to the center within 24 h of the onset of stroke symptoms, exhibited prestroke independent functioning (mRS <2), and achieved successful final reperfusion (mTICI) >2b/3. The study endpoint was to measure the association of these patient characteristics with FR; also known as reperfusion without functional independence (RFI). The authors defined RFI as successful reperfusion defined as mTICI ≥2b without functional independence at 90 days (mRS ≥3). The study analysis revealed that advanced age, chronic kidney disease, a higher 24-h NIHSS score, and incomplete reperfusion (mTICI score of <3) were the independent predictors of FR. Another study referred to this phenomenon as clinically ineffective reperfusion (CIR).[5] In their research, the authors explored the potential causes of CIR. These findings indicated that the size of the pretreatment ischemic core is the most important predictive factor for CIR post-EVT. Another notable cause of CIR is a phenomenon known as no-reflow, wherein there is a clinically significant reperfusion deficiency due to obstructed microvasculature blood flow, unlike the hypoperfusion caused by upstream arterial occlusion.[11] Jia *et al*. further demonstrated various modifiable and nonmodifiable risk factors for CIR. These factors include female sex, older age, history of hypertension, diabetes, higher NIHSS score, and the location of the arterial occlusion. These different studies consistently identified risk factors for FR, including age, hypertension, diabetes, higher NIHSS score as well as the potential causes of FR such as the size of the pretreatment ischemic core. These insights into risk factors and clinical findings may serve as basis for potential interventions that can improve the functional outcomes postreperfusion in AIS patients. Such interventions may include neuroprotective or pharmacological treatments,[12] particularly in cases where recanalization is likely to yield less favorable outcomes.[13]

Another challenge in AIS patients is the prevention of RI.[14] This is a devastating complication of EVT that can potentially be fatal. Many changes occur because of AIS. Some of these changes include increased permeability of the blood–brain barrier[15] and may contribute to cerebral edema (CE) and hemorrhagic transformation.[16] They are often associated with secondary injuries and even mortality.[3] Other changes seen in AIS include reduced blood supply, oxygen, and nutrients.[3] There also appears to be hindered metabolic waste removal, resulting in the accumulation of free radicals such as superoxide and peroxynitrite.[14] In addition to the above changes resulting from reduced cerebral blood flow, disturbed inflammatory processes and programmed cell death (apoptosis) may occur.[17] Therefore, abrupt cerebral blood flow restoration may overwhelm an already damaged system resulting in CE and cell extravasation.[18] In a recent study by Flottmann *et al*., the authors developed imaging techniques aimed at assessing the cerebral injury growth within the

reperfusion regions. The team developed the concept of radiological observed RI by studying the changes in the lesion area after MT. Serial computed tomography CT and magnetic resonance imaging (MRI) scans were started at baseline before recanalization, immediately after, and 24 h after to explore the expansion of the infarct. The CT and MRI studies were compared to ensure consistency in findings. In this study, radiological imaging of the brain within the first 24 h that detected radiological observed RI was associated with poor outcomes despite successful reperfusion. Other publications highlighted that reperfusion could aggravate brain edema and may even lead to abnormal blood flow and microvascular legions within the area of reperfusion.[19]

The primary causes and mechanisms of ineffective reperfusion, the FR, after EVT are closely linked to the extent of initial tissue damage before recanalization.[5] One critical factor is the volume of the pretreatment ischemic core, which significantly influences the effectiveness of reperfusion after EVT. This is where the concepts of "time window" and "tissue window" become crucial.[6] "Time window" refers to the interval between the onset of stroke symptoms and the initiation of treatment.[18] The effectiveness of EVT is highly time-sensitive; the sooner the treatment is administered after stroke onset, the better the chances of salvaging the penumbral tissue (the area around the ischemic core that is at risk but not yet infarcted). Hence, it is widely accepted that assessing clinical outcomes in AIS patients involves measuring time intervals such as door-to-puncture and door-to-reperfusion.[20] Treatment delays increase the likelihood of ischemic core expansion, reducing the potential benefits of reperfusion.[20] The "tissue window" is a critical concept that relates to the state and viability of brain tissue at the time of treatment for stroke.[7] This window relates to the factors such as the size of the ischemic core – the area of the brain that has already suffered irreversible damage due to the lack of blood flow – moreover, the presence of a salvageable penumbra, which is the surrounding area at risk but not yet irreversibly damaged.[18] Patients with a large ischemic core and a small or nonexistent penumbra are less likely to benefit from effective reperfusion. In such cases, a sizable portion of brain tissue may already be irreversibly damaged, leaving limited scope for recovery even after restoring blood flow. It is important to note that even within the same time frame from the onset of stroke symptoms (the same "time window"), the brain's response to ischemia can vary significantly among patients.[13] This variation leads to different levels of tolerance to the ischemic insult. As a result, two patients treated at the same interval poststroke onset might exhibit different extents of brain damage. These individual differences in ischemic tolerance mean that the "tissue window" is not uniformly applicable across all patients.[3] Therefore, it must be assessed on a case-by-case basis using advanced imaging and other potential techniques.[12]

The variability in brain tissue response to ischemia, important in determining the "tissue window," is influenced by several factors, including age, overall health status, medical conditions (such as diabetes or hypertension), as well as the efficiency of collateral blood flow – The alternative vascular pathways that supply blood to the brain when primary routes are obstructed.[18] In addition to these factors, we speculate that certain key molecular signaling mechanisms might act like a "tap" or "valve," influencing the tissue's fate when it reaches a critical threshold of ischemic stress. These molecular pathways could determine whether brain tissue remains viable and salvageable or progresses to irreversible damage. Identifying and understanding these molecular factors could be pivotal in advancing stroke diagnosis and treatment. Taken together, a personalized assessment, which considers individual variability in response to ischemic insult, is crucial for determining the potential for successful reperfusion. By considering the unique characteristics of each patient, health-care professionals are better able to guide the decision-making process in stroke treatment. This approach aims to optimize the outcomes by tailoring interventions to individual patient profiles, thereby enhancing the efficacy of treatments such as EVT and improving overall recovery prospects.

In summary, AIS presents a formidable challenge to medical practitioners due to its strong association with severe morbidity and mortality. Despite advancements in treatments for AIS, they carry fundamental risks, including FR and RI, complicating patient recovery. FR occurs when attempts to re-establish blood flow to the ischemic brain regions through thrombectomy or thrombolysis fail, thereby prolonging the ischemic damage. On the other hand, RI involves additional damage caused by the restoration of blood flow, exacerbating the original ischemic harm. These complications highlight the complexities involved in effectively managing stroke, demanding a practical approach by health-care providers in evaluating patient-specific risk factors and interpreting diagnostic imaging. The goal is to ensure that treatments not only achieve the intended therapeutic effects but also mitigate the likelihood of adverse outcomes.

Author contributions

A.E. analyzed and summarized comprehensively current findings on the reperfusion after ischemic stroke. H.W. revised the manuscript and drew Figure 1. Y.D. designed the study and revised the manuscript.

Ethical statement
Not applicable.

Data availability statement
Data sharing not applicable to this article as no datasets were generated and/or analyzed during the current study.

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Conflicts of interest
Prof. Yuchuan Ding is an Associate Editor of Brain Circulation. The article was subject to the journal's standard procedures, with peer review handled independently of this editor and their research groups.

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