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No-reflow phenomenon following stroke recanalization therapy: Clinical assessment advances: A narrative review

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Abstract:

The no-reflow phenomenon (NRP) after successful vascular recanalization in acute ischemic stroke (AIS) has become a major cause of poor clinical prognosis and ineffective recanalization. However, there is currently no clear definition or unified clinical assessment method for the NRP. Therefore, it is urgent to clarify the clinical evaluation criteria for the NRP and develop new no-reflow evaluation techniques so that remedial treatment can be applied to AIS patients suffering from the NRP. In this brief review, a variety of NRP assessment methods and defining criteria for clinical practice are presented.

Keywords:

Angiography, arterial spin labelling, no-reflow phenomenon, perfusion imaging, transcranial Doppler

Introduction

Acute ischemic stroke (AIS) is primarily caused by the occlusion of the cerebral arteries.[1] A growing number of researchers have found that some ischemic stroke patients who have undergone vascular recanalization therapy have relieved large vessel blockages and achieved complete vascular recanalization. However, despite this achievement, the brain tissue within the affected blood supply area does not fully and effectively restore blood perfusion. This phenomenon is commonly referred to as the "no-reflow phenomenon" (NRP).[2] Currently, there is no unified standard for diagnosing and evaluating the NRP in clinical patients to guide its prevention and treatment. Therefore, this review examined the existing clinical strategies for assessing the NRP.

The No-Reflow Phenomenon

The NRP was initially described by Ames *et al*. in a rabbit stroke model in 1968.[3] They reported that despite relief from vessel obstruction, cerebral blood flow (CBF) was not fully restored. Subsequently, the NRP has been extensively studied in the context of reperfusion treatment for myocardial infarction.[4] Some patients who undergo successful vascular recanalization after percutaneous coronary intervention (PCI) experience insufficient BF perfusion in the damaged myocardium. Research indicates that postoperative mortality rates are significantly higher in patients who exhibit the NRP after PCI for myocardial infarction.[5]

In stroke, the NRP refers to a situation in which severe tissue perfusion deficiency persists despite complete reopening of the previously occluded area. An increasing number of studies have recognized the NRP after thrombectomy in ischemic stroke, which is common after acute cerebral infarction vascular recanalization. Moreover, the presence of the NRP has been identified as a primary factor contributing

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to poor functional recovery or ineffective recanalization in stroke patients. Furthermore, studies have linked poor prognosis in patients with successful vascular recanalization to the NRP.[6] Notably, in cases of AIS resulting from large vessel occlusions, endovascular treatment achieves recanalization rates exceeding 85% or even 90%.[7] Despite this, the disability-free survival rate for patients remains around 30%, with a mortality rate exceeding 15%.[8]

As emergency recanalization technology for AIS becomes more widespread, the NRP has garnered increased attention in research. Several clinical studies have revealed that 25%–42% of patients who achieve successful large-vessel recanalization following mechanical thrombectomy still exhibit the NRP, as detected through cerebral perfusion imaging.[9] This phenomenon is closely associated with a larger final cerebral infarction volume and poor clinical prognosis. In 2012, Dalkara and Arsava noted that existing clinical studies showed an incidence rate of at least 25% for the NRP in patients with successful cerebral vascular recanalization. They also highlighted that the severity of brain tissue damage and clinical outcomes depends more on successful reperfusion than on responsible vascular recanalization.[10]

Similar mechanisms underlie both the brain and coronary NRPs, including blood component stasis (e.g., red blood cells, white blood cells, and platelets), which can lead to microvascular bed embolism, as well as endothelial cell contraction or edema.[11,12] However, the brain NRP differs from the coronary NRP in that other components unique to the brain tissue, such as the neurovascular unit, also contribute to NRP development. In addition, ischemia-induced swelling of astrocyte endfeet may obstruct microcirculation,[13,14] whereas brain interstitial edema resulting from blood–brain barrier disruption may compress the brain microvascular bed and inflammation-or free-radical-induced pericyte contraction may hinder capillary return. In addition, pericyte edema may lead to further perfusion obstacles.[14,15] Moreover, the inhibition of cortical spreading may cause vascular nerve uncoupling, resulting in impaired cerebrovascular regulation, which in turn leads to cerebral microvascular bed contraction and contributes to NRP onset.[12] These findings highlight the need for additional research to better understand the mechanisms underlying the brain NRP.

Clinical Assessment of the No-Reflow Phenomenon

Currently, clinical evaluation of the NRP relies predominantly on imaging techniques. Earlier studies used transcranial Doppler (TCD) to assess large vessel recanalization and single-photon emission tomography to evaluate the NRP.[15] In recent years, angiography and perfusion imaging techniques have been widely used to assess vascular reperfusion. Various imaging techniques have emerged to evaluate brain tissue perfusion, including positron emission tomography, single-photon emission computed tomography, xenon-enhanced computed tomography, computed tomography perfusion (CTP) imaging, and dynamic susceptibility contrast-enhanced magnetic resonance perfusion imaging. These methods depend on different digital imaging techniques to visualize various tracers, allowing for the acquisition of information such as CBF and brain tissue volume to evaluate the perfusion status. The following table compares the characteristics of the assessment methods used in this study [Table 1].

Research has demonstrated that adverse outcomes after vascular recanalization in patients with AIS are significantly associated with larger baseline diffusion-weighted imaging (DWI) lesion volumes. Consequently, a larger baseline core infarct area, rather than the NRP, may be the primary factor contributing to ineffective recanalization.[22] Studies have found that regions with high DWI signals before thrombectomy, which are indicative of severe hypoperfusion, are more likely to exhibit the NRP on perfusion-weighted imaging (PWI) following thrombectomy.[23,24] Therefore, baseline DWI images also offer predictive value for the occurrence of the NRP.

The NRP is responsible for poor prognosis in patients with AIS after embolectomy. Therefore, it is important to recognize the NRP in a timely manner and administer remedial therapy according to the location of the NRP and the severity of hypoperfusion as reflected by the diagnostic modalities introduced in this article, such as the regional application of vasodilators in the hypoperfusion area. It is critical to relieve the inflammation caused by reperfusion injury to restore blood perfusion in the infarction area in time[25] and improve the neurological function of patients.

Angiography

Similar to the grading of arterial occlusive lesions (AOLs), reperfusion status has also been graded to evaluate the recovery of BF in the microcirculation downstream of the occluded cerebral artery. Owing to the shared characteristics between AIS and acute myocardial infarction, the thrombolysis in myocardial infarction (TIMI) vascular perfusion grading system for acute myocardial infarction was initially employed for the angiographic evaluation of AIS.[26] AIS and acute myocardial infarction share a similar pathogenesis and response to vascular recanalization therapy and both exhibit the NRP after vascular

Table 1: Contract of clinical assessments methods for no-reflow phenomenon assessment

Assessments methods	Principle	NRP recognition	Deficits	Advantages and prospective
TICI vascular perfusion grading system	Grade based on the blood flow velocity of the target vessel and the degree of contrast agent filling in the blood supply area of the target vessel		The existing no-reflow assessment systems using angiography always rely on humans to determine the grading with poor quantitative accuracy	The Mori and Qureshi grading systems for multi-factor evaluation and qTICI based on artificial intelligence may offer a powerful diagnostic tool for cerebral no-reflow in future[16]
CIS	CIS can assess the adequacy of collateral compensation by evaluating the redness of capillaries in ischemic areas, thus determining the reperfusion status	There are two manifestations of ischemic area: The area lacking positive flow in the brain tissue, but receiving blood supply in a retrograde manner through the pia mater or receiving its blood supply in an anterograde manner, but having a significant delay due to the proximal partial recanalization of clots[17]	CIS is only applicable for internal carotid artery or middle cerebral artery blockage situations	CIS can be used as a supplementary indicator alongside other standards for recognition of NRP
CBV, CBF	Low perfusion areas exhibit a decrease in CBF, while CBV may be normal or mildly increased but decreased in severe situations[18]	CBV or CBF demonstrating a difference of over 15% compared to the corresponding area of the contralateral cerebral hemisphere indicates NRP[6]	While Tmax is often delayed in some patients, CBV and CBF are normal	
Tmax	Tmax represents the time it takes for the iodine contrast agent to reach all tissues, serving as a sensitive indicator of tissue perfusion changes and brain tissue infarction	A delay in Tmax after recanalization of thrombectomy vessels in ischemic stroke implies a substantial hypoperfusion area or NRP		
MTT	MTT refers to the time needed for the contrast agent to travel from the arterial side to the venous side of the brain	An extended MTT indicates the presence of cerebral tissue hypoperfusion		MTT serves as a potential indicator for defining the NRP
ASL	ASL provides quantitative perfusion mapping of the brain without requiring an injection of contrast agents			Allowing for quantitative perfusion mapping of the brain without limitations from contrast agents[19]
TCD	TCD can evaluate hemodynamic changes following arterial blood supply reconstruction, and it is widely used to evaluate cerebrovascular reactivity and its autoregulation function	The rise of the TCD pulsatility index indicates the increased microvascular resistance, suggesting that the pulsatility index could be a readily available clinical biomarker for the NRP[20]	TCD is heavily influenced by the operator's skill level and there are various factors affecting its parameters	TCD offers the benefits of low cost and ease of operation, and doppler ultrasound-based contrast-enhanced ultrasound technology is a promising technique for NRP assessment[21]

TICI: Thrombolysis in cerebral infarction, qTICI: Quantitative TICI, CIS: Capillary index score, CBV: Cerebral blood volume, CBF: Cerebral blood flow, NRP: No-reflow phenomenon, Tmax: Time to maximum, MTT: Mean transit time, ASL: Arterial spin labeling, TCD: Transcranial Doppler

recanalization. However, owing to the different physiological characteristics of the heart and brain tissue, Yoshihara *et al*. upgraded the TIMI system to the thrombolysis in cerebral infarction (TICI) system for cerebral vascular perfusion grading,[27] a system that has been widely adopted. This grading mainly considers the BF velocity of the target vessel and the degree of contrast medium filling the target vessel's blood supply area. Notably, during thrombectomy, a contrast medium is injected and can be transferred through the site of vascular blockage. The grading is then completed by evaluating the extent to which the contrast medium can reach into the distal vasculature of the blockage and assessing the perfusion velocity throughout the radiography procedure.[28]

In the Interventional Management of Stroke I and Interventional Management of Stroke II studies, recombinant tissue type plasminogen activator thrombolysis was used to open occluded large cerebral vessels. The AOL score was used to assess the recanalization of large vessels after thrombolysis, whereas the TICI scale was used to evaluate the presence of the NRP. The findings revealed a discrepancy between AOL and TICI scores, signifying that recanalization did not equate to reperfusion. The TICI is a superior

predictor of clinical prognosis.[29] A 2020 meta-analysis suggested that the expanded TICI vascular perfusion grading system better assesses perfusion status after intravascular recanalization therapy and predicts clinical prognosis compared to TICI.[30] Subsequently, the Mori and Qureshi grading systems for multi-factor evaluation were developed.[31] Nonetheless, current no-reflow assessment systems using angiography depend on human judgment to determine the grading based on BF velocity after major vessel recanalization and the degree of contrast agent filling in the supply area (speed and range), resulting in poor quantitative accuracy. Moreover, the quantitative TICI (qTICI) scales developed based on artificial intelligence in 2020 may offer a powerful diagnostic tool for cerebral no-reflow in future.[16]

In addition to the modified TICI (mTICI) vascular perfusion grading system, the capillary index score (CIS) on digital subtraction angiography is a novel indicator for evaluating the reperfusion status of capillaries in ischemic regions and may potentially identify the NRP. On cerebral angiography, fine and uniform redness of the capillaries serves as a marker of normal brain tissue.[32] Ischemic areas exhibit two manifestations: Areas with no positive flow in the brain tissue but receiving retrograde blood supply through the pia mater, or areas receiving anterograde blood supply but experiencing significant delay due to proximal partial recanalization of clots. CIS can assess the adequacy of collateral compensation by evaluating the redness of capillaries in ischemic areas, thus determining the reperfusion status.[17] Notably, CIS is only applicable to internal carotid artery or middle cerebral artery (MCA) blockages. However, research indicates that a higher CIS after recanalization is a strong predictor of a favorable prognosis.[33] By using the CIS as a supplementary indicator alongside other standards, the NRP after recanalization treatment can be identified, ultimately optimizing patient selection for recanalization treatment.[34]

Computed tomography perfusion and perfusion-weighted imaging

CTP imaging and PWI are traditional methods of perfusion evaluation and are widely employed in the clinical assessment of the NRP. Notably, studies have demonstrated no significant difference in the reliability of CTP and PWI maps when evaluating perfusion status.[35] However, these methods have limitations, including high cost, complex inspection processes, inability to be repeatedly conducted, and lack of real-time monitoring capabilities.

CTP and PWI are functional imaging techniques that involve multiple continuous scans of a selected layer during intravenous contrast agent injection, allowing the acquisition of the time-density curve of each pixel within that layer. Using this curve, various mathematical models have been applied to calculate the BF, blood volume (BV), mean transit time (MTT), and time to peak of the contrast agent.[36] These parameters are essential for evaluating the perfusion status of the brain tissue following vascular recanalization.

Cerebral blood volume and cerebral blood flow

Cerebral BV (CBV) represents the amount of blood in every 100 g of brain tissue, whereas CBF refers to the volume of BF (in ml) per minute per every 100 g of brain tissue. By employing functional perfusion software and deconvolution algorithms to analyze CTP or PWI images, the CBV and CBF can be calculated. These values can change as early as 30 min after the onset of stroke symptoms. In low-perfusion areas, there is a decrease in CBF, whereas the CBV may appear normal or mildly increased, although it may be decreased in severe situations.[18]

The widely accepted definition of the NRP is a persistent hypoperfusion area visible on the relative CBV or CBF map of CTP or PWI in the infarcted area 24 h after successful recanalization of the responsible vessel. When compared to the corresponding area of the contralateral cerebral hemisphere, the CBV and CBF tend to demonstrate a difference of over 15%.[6] A 2020 study revealed that among all patients with successful large blood vessel recanalization (TICI ≥2b), 52.9% exhibited hypoperfusion based on CBV and CBF evaluations using CTP. Further analysis indicated that hypoperfusion in patients after major vessel recanalization was an independent risk factor for early neurological improvement within 24 h (defined as a decrease of ≥8 points or reaching ≤2 within 24 h compared to baseline National Institute of Health stroke scale) and poor prognosis after 90 days (mRS ≥3). In addition, hypoperfusion was significantly associated with hemorrhagic conversion after major vessel recanalization. This study also found that some patients experienced delayed recovery. Moreover, an insufficient perfusion volume of >3.5 ml, as observed on CTP, can be used to identify patient subgroups with poor clinical prognosis and differentiate them from patients with delayed recovery.[37]

Time-to-maximum

Time-to-maximum (Tmax) is a perfusion parameter utilized in both computed tomography (CT) and magnetic resonance imaging (MRI) perfusion. This parameter reflects the time delay between the arrival of the contrast bolus in the proximal large-vessel arterial circulation (arterial input function) and the brain parenchyma. The use of CTP or PWI for CBV and CBF assessment has the following limitations: CBV and CBF

are normal in most patients, and Tmax is often delayed. Additionally, Tmax represents the time taken for the iodine contrast agent to reach all tissues, indicating the moment when the brain tissue blood storage reaches its maximum value, serving as a sensitive indicator of changes in tissue perfusion and brain tissue infarction. A Tmax >6 s is considered the identification standard for the ischemic penumbra.[38] Even in cases of lacunar infarction, significant elongation of Tmax in the lesion area on DWI has been associated with neurological deterioration.[39] Consequently, a delay in Tmax after recanalization of thrombectomy vessels in ischemic stroke implies a substantial hypoperfusion area or the NRP. Some studies have used MRI to determine the final infarct volume, and the results indicated a strong correlation between delayed Tmax and large final infarct volume. Therefore, while the accuracy of CBV and CBF in identifying the NRP was superior compared to the final mTICI score, it was less accurate than Tmax.[40]

Studies have assessed the microcirculation reperfusion status after revascularization using tissue optimal reperfusion (TOR), defined as a Tmax difference >6 s between baseline and early follow-up, resulting in a 90% reduction in lesion volume. TOR is closely associated with favorable functional prognosis after mechanical thrombectomy, and its correlation with prognosis is stronger than the mTICI score.[24]

Mean transit time

The MTT refers to the time required for the contrast agent to travel from the arterial to the venous side of the brain, representing the average of all transit times.[41] As a result, an extended MTT indicates the presence of cerebral tissue hypoperfusion. It is widely accepted that the MTT of the ischemic penumbra is >1.45 times the MTT in contralateral normal areas.[38]

Studies have defined reperfusion as a reduction in MTT of 75% or more and confirmed that patients with an MTT reduction of more than 75% exhibit a smaller final infarct volume compared to patients achieving simple vascular recanalization.[42] Consequently, the MTT serves as a potential indicator for defining the NRP.

Arterial spin labeling

Arterial spin labeling (ASL) is a widely used technique for assessing the NRP. This nonenhanced MRI perfusion imaging method does not require the injection of contrast agents, allowing for quantitative perfusion mapping of the brain without limitations from contrast agents. It is based on magnetically labeling arterial blood protons as the natural endogenous tracer to estimate tissue perfusion,[43] and its effectiveness has been demonstrated in healthy control groups and patients with AIS.[19] ASL research has determined that a 40% reduction in CBF compared to the corresponding regions of the contralateral hemisphere is most effective in identifying severe hypoperfusion or no-reflow. However, the incidence of NRP according to this criterion is low, although many cases of mild cortical hypoperfusion have been identified.[22]

In a recent study, ischemic stroke patients underwent ASL and DWI examinations within 24 h of vascular recanalization treatment. Additionally, the study developed an ASL-based automatic reperfusion scoring system (auto-RPS) using the Alberta Stroke Program Early CT Score (ASPECTS) system. Compared with manual reperfusion scoring and DWI-ASPECTS, this scoring system can accurately identify the NRP and predict patient functional outcomes.[44]

In another study, researchers explored the potential reduction in cerebral no-reflow following cardiac arrest by inhibiting lipid peroxidation through the use of deferoxamine (DFO) during ischemia-reperfusion injury, in which ASL was used to continuously measure cerebral perfusion. The findings revealed that DFO significantly increased cerebral perfusion after resuscitation, reduced the incidence of no-reflow, and markedly improved neurological deficit scores in patients receiving DFO treatment.[45]

Transcranial Doppler

TCD is a safe and effective method for examining hemodynamic changes following carotid arterial blood supply reconstruction. TCD allows for the measurement of BF velocity, and a decrease in velocity is indicative of inadequate reperfusion. Additionally, an increase in the pulse index, which reflects vascular resistance, can suggest the presence of the NRP.[46]

TCD has been widely used to evaluate cerebrovascular reactivity and autoregulation functions, which can serve as clinical markers for the NRP. Previous studies have assessed reperfusion status after carotid arterial blood revascularization.[47] Specifically, studies have found that when the average BF velocity in the MCA is increased compared to preoperative levels, the risk of reperfusion syndrome increases. A prospective single-center observational study found that TCD detected an increased average BF velocity in the recanalized MCA within the first 6 h postintravascular recanalization, which was correlated with an increased final infarct volume at 3 months and poor functional prognoses. Additionally, higher maximum TCD and ΔTCD in subarachnoid hemorrhages were linked to worse clinical outcomes 3 months after onset, highlighting the value of TCD in evaluating BF status and predicting prognosis in cerebrovascular diseases.[48]

TCD has been increasingly used in ischemic stroke research for cerebral microvascular assessments, such as when evaluating cerebral vascular resistance using the pulsatility index (PI) to predict white matter injury and lacunar infarction-related cognitive dysfunction.[49] Even when recanalization is achieved and the cerebral infarction volume is small, a significant increase in cerebral microvascular resistance in the ischemic area still supports the existence of the NRP in the microcirculation after recanalization.[2] Moreover, the increase in the TCD PI after recanalization indicates that increased microvascular resistance in the ischemic region often occurs after successful recanalization, suggesting that the PI could be a readily available clinical biomarker for the NRP.[20] In 2022, a study demonstrated that an increased MCA PI in patients with AIS after thrombectomy, as measured using TCD ultrasound, was associated with a poor prognosis.[50] Therefore, an increased PI is potentially linked to higher cerebrovascular resistance and the occurrence of the NRP.[20,51]

Compared with previous methods for cerebral perfusion imaging after recanalization therapy, TCD offers the benefits of low cost and ease of operation. However, it has the limitation of low accuracy, as TCD is heavily influenced by the operator's skill level and the various factors that affect its parameters. Recently, new TCD parameters reflecting cerebral vascular tension regulation have been proposed, with promising applications in no-reflow evaluation.[49,52] Additionally, contrast-enhanced ultrasonography technology has also recently been developed.[21] This new cerebral perfusion evaluation technology provides low-cost portability, real-time monitoring, safety, and the ability to perform repeated examinations. It also allows bedside real-time patient monitoring, making it a promising tool for clinical application.[53]

Perspectives and Prospective Techniques

In response to the various limitations of current diagnostic modalities, researchers have developed advanced no-reflow assessment techniques, including ultrasound contrast, artificial intelligence-based qTICI, and ASL-based auto-RPS. Additionally, multimodal electroencephalography monitoring based on the bispectral index has been applied to identify the NRP after cerebral infarction based on research on coronary occlusive diseases.[54] These innovative diagnostic techniques show promise but require further clinical validation.

Recent studies have investigated the effects of various interventions on clinical outcomes, such as hypothermia before thrombectomy,[55] different anesthesia schemes during thrombectomy,[56] and ischemic preconditioning after stroke.[57] However, these studies raised the question of whether the observed differences in outcomes can be attributed to variations in the NRP.

In clinical practice, shortening the door-to-puncture time, using thrombus aspiration if necessary to reduce thrombus burden, avoiding repeated thrombectomy operations, and controlling blood pressure, blood sugar, and so on can prevent the NRP by reducing brain tissue injury.[2] Once the NRP is identified by the above monitoring methods, remedial occupational therapy options should be applied as soon as possible, such as by administering adenosine to reduce the resistance of small arteries, platelet glycoprotein IIb/IIIa receptor antagonists to inhibit platelet aggregation, and vasodilator drugs to dilate the responsible vessels.[58] These interventions aim to enhance patient recovery and improve long-term prognosis.

Conclusion

The NRP is a significant concern in the treatment of AIS, particularly after vascular recanalization. Currently, various techniques are used in clinical practice to identify the NRP. Notably, CTP and PWI are the most widely used examinations for evaluating cerebral perfusion, as these methods are more accurate than TCD in evaluating CBF and are easier to implement compared to angiography and other techniques for NRP assessment.

To comprehensively evaluate the NRP, we recommend a combination of approaches, including a cerebral vascular perfusion grading system, perfusion imaging, TCD, ASL, and consideration of symptom relief in patients. This multi-modal approach improves diagnostic accuracy, reduces the risk of misdiagnosis or missed diagnoses, and provides a comprehensive evaluation of the NRP. In addition, as animal experiments primarily use labeling techniques or tracers to assess the NRP, these techniques are expected to be applied in clinical studies in the future. However, these mainstream evaluation methods present certain challenges, including high examination costs, complex operations, and limited accuracy. Therefore, several key objectives should be addressed in future studies. First, the diagnostic criteria for the NRP must be clarified to improve the accuracy and reliability of the evaluations. Second, the development of more advanced identification technologies is essential to enhance detection and diagnosis. Third, early identification of AIS patients at high risk for the NRP is crucial to enable timely remedial measures and improve patient prognosis.

Ethical statement

Not applicable.

Data availability statement

Data sharing not applicable to this article as no datasets were analyzed during the current study.

Authors' contributions

YK: Concepts, Design, Literature search, Manuscript preparation and Manuscript editing. SL, BZ, YD: Concepts, Design and Manuscript editing. WZ: Concepts, Design, Definition of intellectual content, Manuscript editing, Manuscript review and Guarantor. XJ: Concepts, Design, Definition of intellectual content, Manuscript review and Guarantor.

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Conflicts of interest

Dr. Xunming Ji is Editor-in-Chief, Dr. 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 them and their research groups.

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