Research Progress in Defining Ischemic Penumbra in Acute Stroke Based on Magnetic Resonance Metabolic Techniques

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Abstract-The onset time window of ischemic stroke patients is often unclear. Whether they can benefit from reperfusion therapies such as thrombolysis or thrombectomy depends on the presence of an ischemic penumbra (IP). Therefore, for stroke patients where every minute counts, the identification of IP must be not only rapid and accurate but also easy for clinicians to understand. A large number of studies have shown that IP defined based on perfusion thresholds is insufficiently accurate. The true IP is a dynamically evolving process, referring to tissues whose cellular structure has not been destroyed and can be salvaged. Its inner and outer boundaries can only be truly and accurately reflected at the molecular level of cellular metabolism.To this end, emerging magnetic resonance metabolic detection technologies have focused on various metabolic parameters in stroke patients, such as tissue pH value, oxygen extraction fraction (OEF), lactate (Lac), phosphocreatine (PCr), etc. Amide proton transfer imaging (APTw) is used to accurately detect changes in tissue pH values to understand tissue metabolic information. Magnetic resonance quantitative susceptibility mapping (QSM, CAT-QQ) can detect OEF to assess tissue oxygen metabolic status. Fast high-resolution magnetic resonance spectroscopic imaging (MRSI) combined with SPICE (SPectroscopic Imaging by exploiting spatiospectral CorrElation) technology enables in vivo, non-invasive multi-molecular synchronous imaging, making tissue metabolic conditions clear at a glance. Additionally, high-field multinuclear magnetic resonance technology can observe substances such as sodium ions and glucose, providing more accurate and detailed physiological and metabolic information at the molecular level. This article reviews the research status of the above physiological and metabolic parameters in defining IP.

Keywords: Metabolic Magnetic Resonance; Ischemic Penumbra; Artificial Intelligence

1. Introduction

According to the latest clinical data, approximately 3.94 million new stroke patients are diagnosed annually in China, with ischemic stroke being the most common type [1]. The key to treating acute ischemic stroke (AIS) lies in determining whether salvageable brain tissue, known as the ischemic penumbra (IP), exists within the ischemic region. The early dual-threshold model (electrical failure and membrane failure), a clinical model guiding stroke management, defines IP as an area with electrical failure (neuronal dysfunction) but without cellular energy failure (structural loss) [2]. Based on this theory, subsequent studies further defined IP as brain tissue that can be salvaged after reperfusion, though this definition remains inaccurate for IP [3].When an ischemic event occurs, cerebral blood flow (CBF) drops sharply, leading to local ischemia and hypoxia, which in turn disrupts cellular aerobic metabolism. Cells then switch to anaerobic metabolism, causing lactate (Lac) accumulation and increased phosphocreatine (PCr) consumption. These factors result in cellular acidosis and pH decline, ultimately inhibiting protein synthesis [4-6]. In the early stage of CBF decline in AIS patients, besides changes in pH and Lac, the body activates compensatory mechanisms to maintain the cerebral metabolic rate of oxygen ($CMRO_2$), which is achieved through an increase in the oxygen extraction fraction (OEF). Thus, OEF rises first in the early ischemic stage. As CBF continues to decline below the electrical failure threshold, the body's compensatory mechanisms can no longer meet energy demands, and both OEF and $CMRO_2$

begin to decrease until cell death occurs [7-8]. Therefore, from the perspective of tissue metabolism, defining IP as the mismatched area between the tissue acidosis (pH decline) region and the adenosine triphosphate (ATP) reduction region is more rigorous [9]. Meanwhile, the expression of endogenous proteins such as hypoxia-inducible factor-1, erythropoietin, transforming growth factor, and interferon regulatory factors increases as part of the body's compensatory mechanisms to delay the progression of IP to infarct. From the physiological evolution of stroke described above, using parameters related to tissue acidosis caused by anaerobic metabolism (such as pH, Lac) or certain thresholds corresponding to tissue hypoxia regions (such as OEF, $CMRO_2$) to identify IP [10-11] represents a breakthrough for benefiting more stroke patients. In particular, visualization imaging techniques for IP not only help clinicians understand the ischemic region, formulate personalized treatment plans, predict prognosis, and evaluate treatment efficacy but also benefit AIS patients at different stages of[12-13]. Scholar Richard Leigh et al. [3] believe that such visualization methods can assess both tissue physiology/metabolism and hemodynamic status.Thus distinguishing the penumbra region (which may progress to infarction) requires rapid and accurate imaging from the perspective of physiological imaging parameters, while eliminating contrast differences between white and gray matter. This can only be achieved by tapping into key entry points among metabolic parameters (CMRGlc, sodium/potassium ions, OEF, Lac, pH, PCr, ATP), and apparent diffusion coefficient (ADC). Therefore, this review discusses in-depth research on these physiological and metabolic parameters using magnetic resonance metabolic imaging techniques.

2. Technical Status of Reflecting Inner and Outer Boundaries of IP Based on pH or Lac

2.1 Amide Proton Transfer Imaging (APT)

IP is a dynamic pathophysiological process. After stroke, abrupt reduction in local cerebral blood flow (CBF) disrupts the tricarboxylic acid cycle and oxidative phosphorylation that maintain physiological functions through aerobic metabolism within IP. Cells activate anaerobic glycolysis for survival, where glucose is decomposed into lactate under anaerobic conditions, leading to intracellular lactate accumulation and pH decline. As CBF further decreases, ATP-dependent ion pump dysfunction disrupts intracellular ion balance, causing massive influx of sodium and calcium ions and efflux of potassium ions. Sodium influx induces cellular edema, which further compresses surrounding neural tissues (neurons and nerve fibers) and microvasculature (arterioles, venules, capillary networks), exacerbating brain tissue damage [14-16]. Therefore, early detection of pH decline or Lac elevation in stroke patients can salvage reversible brain regions. Notably, pH remains normal in benign hypoperfusion areas [17].Amide proton transfer-weighted (APTw) imaging is a pH-sensitive technique [18]. It uses specific radiofrequency pulses to selectively saturate and label amide protons on protein and polypeptide chains. The labeled amide protons transfer to free water via chemical exchange, causing free water proton saturation, reduced magnetization, and attenuated water signals. APTw imaging indirectly converts exchange rate information into images by detecting pre- and post-exchange water signal changes, facilitating clinical interpretation [19-20]. Notably, the exchange rate is influenced not only by intracellular pH but also by protein/peptide concentration and type. In APTw imaging, low pH regions appear as hypointense areas, with APTw values decreasing significantly as acidosis worsens . That is, more pronounced acidosis in hyperacute/early stroke correlates with stronger APTw signals. In the subacute phase, necrosis absorption, reactive gliosis, and partial reperfusion may shift acidosis to alkalosis in the infarct core (IC), increasing pH, weakening APTw signal intensity, and elevating APTw values . Thus, APTw imaging shows great potential in delineating irreversible IC, reversible IP, and benign hypoperfusion areas .

Studies by Jiang Yuhan , Wang Yanting , and Cao Guanjie consistently showed that hyperacute and acute stroke patients exhibit marked acidosis and pH decline, with APTw values in all IP regions higher than those in IC. In the subacute phase, IC APTw values become higher than normal areas due to acidosis-to-alkalosis transition. These findings align with the pathophysiological evolution of stroke and DWI changes at corresponding stages. IP exists not only in hyperacute/acute phases but also in the subacute phase. However,APTw signal sources

are complex, influenced by lesion/sequence intrinsic factors (e.g., magnetic field strength [B0, B1], direct water saturation [DS] effect, magnetization transfer contrast [MTC] effect, nuclear Overhauser effect [NOEs], imaging parameters) and manufacturer variations . Researchers have implemented improvements: using magnetization transfer ratio asymmetry (MTR asym) to reduce DS/MTC effects; optimizing pulse sequences with continuous-wave RF saturation or parameter-adjusted pulse trains (total RF saturation time = 2s, B1 selection); applying spectral presaturation by inversion recovery (SPIR) for fat suppression; performing second-order shimming of B0 field and multi-acquisition at ± 3.5ppm to enhance APTw SNR; and using MTRasym (3.5ppm) matrices, rainbow color scales, and storing pseudocolor/grayscale images during data processing.In the current imaging landscape (where CTP/PDM are inaccurate for IP detection and PET is time-consuming/expensive), the combined use of APTw and DWI-based ADC imaging will soon enable rapid, accurate, and standardized acquisition of IP/IC images for whole-volume assessment of ischemic brain tissue.

2.2 Magnetic Resonance Spectroscopy (MRS)

Magnetic resonance spectroscopy (MRS) is a technique that evaluates tissue metabolic status by analyzing specific peaks of different metabolites in imaging. For example, the N-acetyl-aspartate (NAA) peak typically appears at ~2.02 ppm, choline (Cho) at ~3.22 ppm, creatine (Cr) at ~3.03 ppm, and lactate (Lac) at ~1.33 ppm. Analyzing these peaks reveals metabolic conditions within tissues. Zhuo Lihua et al. used ^{1}H magnetic resonance spectroscopy (^{1}H-MRS) combined with DWI and 3D-ASL to assess ischemic penumbra in acute cerebral infarction patients, demonstrating dynamic infarct processes through metabolic changes measured by ^{1}H-MRS. Results showed Lac levels increased during acute ischemia/hypoxia, peaking in the infarct core (IC), with lower Lac concentrations in IP than IC. Normal brain tissue had low Lac levels, which only rose significantly under ischemic/hypoxic conditions due to increased anaerobic metabolism. The most severe acidosis occurred in IC, with milder acidosis closer to normal tissue, consistent with metabolic characteristics of IP and IC in AIS patients. NAA levels decreased within hours after infarction, with lower concentrations in IC than IP and normal surrounding areas; NAA peaks in IP matched normal regions in some patients. As NAA primarily resides in neurons and serves as a neuronal marker, this indicates preserved neuronal function in hyperacute/acute phases, aligning with the concept of IP (salvageable, undamaged neuronal tissue). Cho concentrations were lower in IC than IP but similar to normal tissue, suggesting disrupted cell membranes in IC (since Cho is mainly membrane-associated) versus intact membranes in IP and normal regions. Cr concentrations followed a gradient: IC < IP < normal tissue, indicating that Cr — critical for rapid energy replenishment at axon terminals and presynaptic membranes — was more abundant in severely ischemic/hypoxic areas with pronounced acidosis. This study noninvasively visualized metabolic changes through MRS, uncovering IP's metabolic characteristics and evolution at the tissue level. Xing Yingying et al. further concluded that higher pre-treatment IP detection rates via MRS combined with DWI-based ADC imaging correlated with better therapeutic outcomes by observing Cho concentration changes.

Compared to spectral peak interpretation, color-coded images are more intuitive. The latest fast high-resolution 3D-MRS (MRSI) combined with SPICE (SPectroscopic Imaging by Exploiting Spatiospectral CorrElation) enables in vivo, noninvasive, contrast-free multi-molecular imaging, rapidly acquiring multi-metabolite concentration data in a single scan without motion artifacts. Lin et al. validated SPICE's sensitivity to stroke onset time by analyzing whole-brain spectra from 73 ischemic stroke patients across hyperacute (0 – 24 hours), acute (24 hours – 1 week), and subacute (1 – 2 weeks) phases. They found declines in neuronal metabolites (NAA) and energy metabolites (Cr) in lesions correlated significantly with onset time, while NAA reduction and Lac elevation were strongly linked to infarct volume. By fusing SPICE-derived multi-metabolite imaging targets, this approach improves prediction of stroke onset time, offering expanded imaging options for patients with unknown onset times and providing visual support for rapid IP identification. However, the technique requires validation through larger datasets and

longitudinal studies.

3. Technical Status of Reflecting IP Outer Boundary Based on Oxygen Extraction Fraction (OEF)

Richard Leigh et al. proposed that OEF begins to increase when CBF drops to 50% of baseline. This is because OEF changes depend on blood oxygen levels: in stroke patients, arterial occlusion reduces CBF and arterial oxygenation, leading to compensatory OEF elevation. As blood flows from arteries to veins, oxygen is fully consumed by brain tissue, decreasing venous oxygenation, which is visualized in T2 and T2*-weighted imaging.Typically,there are multiparametric quantitative BOLD (qBOLD), quantitative susceptibility mapping (QSM), and the QSM+qBOLD combined model (CAT-QQ).The qBOLD technique signal differences due to deoxyhemoglobin (dHb) at different echo times and derives OEF values by fitting experimental curves, enabling regional OEF quantification. However, qBOLD models have complex parameter couplings, introducing uncertainties and inevitable errors during multiparameter fitting; even minor noise compromises accuracy , limiting its clinical utility. Early quantitative susceptibility mapping (QSM) identified correlations between susceptibility changes in ischemic regions and tissue damage/blood component alterations but saw limited clinical use due to poor image resolution and accuracy. With technological improvements, Kreisler A et al. [48] analysis showed that compared with the contralateral normal tissue (OEF = 25.5% ± 3.1%), OEF was elevated in hemispheres with large DWI-PWI mismatch (traditional IP regions) and lower in non-perfused or DWI-PWI matched areas (infarct core), indicating compensatory OEF increase with CBF reduction — consistent with the physiological evolution of IP outer boundaries based on oxygenation. This provides new insights into stroke pathophysiology and oxygen metabolic changes during recovery, though the technique still requires optimization, standardized analysis protocols, and clinical guidelines to enhance IP delineation accuracy and practicality.

Zhang Shun et al. used phase/amplitude information from QSM sequences to measure arteriovenous susceptibility differences, combined with CBF from 3D-ASL to estimate cerebral oxygen metabolism parameters, and employed the CAT-QQ method (QSM+qBOLD with multi-echo amplitude signal clustering analysis) to calculate OEF. Results showed slightly decreased OEF in IC compared to normal tissue, higher OEF in CBF-DWI mismatch regions (potential IP), and reduced CMRO2 in both IC and IP. OEF trended downward in IC with longer symptom onset-to-MRI times, while contralateral OEF remained stable. This technique enables voxel-level OEF quantification without gas inhalation or respiratory control, avoiding risks of invasive procedures and overcoming parameter assumptions in standalone QSM/qBOLD. By integrating OEF with other MRI parameters, it more accurately reflects cerebral oxygen metabolism, enhancing clinical feasibility. But the technical implementation is currently quite difficult.

4. Multinuclear Magnetic Resonance Techniques

Under normal circumstances, conventional magnetic resonance imaging (MRI) primarily uses hydrogen protons (^{1}H) due to the high water and hydrocarbon content in human tissues, as well as the high gyromagnetic ratio and strong signal of ^{1}H nuclei . In addition to traditional ^{1}H MRI, multinuclear MRI using non-hydrogen nuclei such as sodium (^{23}Na), deuterium (^{2}H), and carbon (^{13}C) has emerged and is rapidly developing in the field of medical imaging. At low magnetic field strengths, multinuclear MRI suffers from low signal-to-noise ratios, making clear signal acquisition difficult; detectable signals are only achievable at ultra-high field strengths or in hyperpolarized states.Jones SC et al. confirmed linear sodium concentration increases in ischemic core regions using ^{23}Na-MRI, which not only enables estimation of ischemic areas and prediction of stroke onset time but also lays a foundation for expanding the thrombolysis time window in stroke patients. Boada FE et al. further proposed that total cellular sodium concentration (TSC) measured by MRI is a potential biomarker for assessing post-stroke brain tissue viability. Weerling et al. used ^{23}Na-MRI to show significantly reduced sodium signals in penumbral tissue during the acute phase and linear sodium signal increases in the infarct core. These studies demonstrate the feasibility of ^{23}Na-MRI for identifying potential

IP and IC regions and providing objective evidence for determining stroke onset time and guiding thrombolysis decisions .

Although ^{31} phosphorus MRI (^{31}P-MRI) remains in the exploratory and clinical trial phase, Pinggera D et al. observed different changes in PCr/ATP ratio, PCr/Pi ratio, and individual PCr/ATP levels between acute and subacute phases in severe traumatic brain injury using ^{31}P-MRS. While this study focused on ATP and PCr metabolism in traumatic brain injury, it provides insights for applying ^{31}P-MRI to investigate and treat ischemic brain injury at different stages. Stephanie Alice Treichl et al. found that in ischemic stroke with acidosis, ^{31}P-MRS/MRSI revealed significantly increased relative signal intensity of inorganic phosphate (Pi) and decreased α -ATP/ β -ATP signals. Brain pH in ischemic tissue correlated positively with PCr signal intensity/PCr index and negatively with Pi signal intensity, indicating a link between high-energy phosphate metabolism and brain pH during ischemic acidosis. This aligns with the pathophysiological evolution of stroke, suggesting that ^{31}P-MRI—especially in hyperpolarized states — may provide more precise metabolic information for defining IP in ischemic brain diseases, with promising future applications in IP research.

For cerebral metabolic rate of glucose (CMRGlc), deuterium (^{2}H)—a stable isotope of hydrogen with similar chemical properties and slightly different physical characteristics — has been studied. Meerwaldt et al. used deuterium metabolic imaging (DMI), which visualizes tissue metabolism via injected/ingested ^{2}H-labeled glucose and its downstream products (e.g., ketones, acetate), combined with fluorodeoxyglucose (FDG)-PET to investigate post-ischemic reperfusion metabolism. FDG-PET showed reduced glucose uptake in the ipsilateral middle cerebral artery region at 48 hours post-stroke, with recovery by day 11. DMI revealed time-dependent changes in active glucose metabolism, including increased lactate production and reduced glutamate/glutamine synthesis at 48 hours, followed by further declines in oxidative metabolism at day 11. This indicates that stroke severity modulates brain metabolic changes, with DMI imaging depicting metabolic states during ischemic tissue injury. After De Feyter HM et al. first achieved human ^{2}H metabolic imaging in 2018 to visualize glucose uptake and other metabolic processes (e.g., aerobic glycolysis (Warburg effect) in tumors), Kaggie et al. and Niess et al. applied DMI to 3.0T clinical MRI systems, demonstrating its feasibility under broad clinical conditions. However, DMI currently faces challenges in sensitivity, hardware, and data processing/analysis, requiring extensive clinical trials to validate its efficacy and safety for disease diagnosis and treatment monitoring, limiting its current clinical utility.

According to the varying metabolite contents across brain regions and the significant correlations among multiple metabolites — particularly the abnormal oxygen and energy metabolism in ischemic/hypoxic lesion areas of stroke patients — labeling corresponding metabolites (such as glucose, pyruvate) as substrates for ^{13}C magnetic resonance (^{13}C-MRI) can reflect tissue metabolic status. This method of accurately measuring metabolic damage improves disease detection and diagnosis, and developing new treatment approaches holds significant importance for challenging diseases . Although ^{13}C-MRI has not yet been applied to diagnose cerebral ischemic diseases, Uthayakumar et al. used hyperpolarized ^{13}C-MRI to measure whole-brain metabolism in healthy individuals of different ages and found significant differences in lactate and bicarbonate levels across brain regions. Viswanath et al. employed hyperpolarized ^{13}C-glucose MRI to show that lactate levels and lactate/pyruvate ratios were lower in radiation necrosis lesions than in tumor foci in rats. Park et al. and Miloushev et al. [68] further validated the feasibility of this technique for assessing human brain metabolism using hyperpolarized ^{13}C-pyruvate MRI. Collectively, these findings indicate that ^{13}C-MRI can detect metabolic changes in various neurological diseases to evaluate metabolic damage. However, the high cost of ^{13}C hyperpolarization equipment and the short maintenance time of hyperpolarized states limit its clinical application. Developing fast imaging techniques to maximize signal acquisition and analysis will facilitate its clinical translation.

5. Artificial Intelligence

In recent years, with the rapid development of

artificial intelligence (AI) technology, AI has been successfully applied in automatic diagnosis of ischemic stroke, lesion segmentation, treatment plan selection, and prognosis prediction, demonstrating broad application prospects. Altman et al. compared deep learning-accelerated MRI (3 minutes 4 seconds) with conventional MRI (14 minutes 18 seconds) for the same sequence and found consistent diagnostic performance in AIS patients, with significantly shortened scanning time using deep learning. Duan et al. achieved 8-fold acceleration for susceptibility-weighted imaging (SWI) sequences via deep learning, shortening the entire examination process while maintaining image quality and improving SWI success rates. This technology was further validated in Duan Qi et al.'s study , showing that accelerated SWI maintains key imaging features comparable to non-accelerated SWI while reducing examination time. Notably, such acceleration techniques can be applied to other imaging sequences, effectively addressing the core challenge of long MRI scan times and facilitating preoperative precise navigation.In image segmentation, cascaded stroke segmentation models have been shown to fuse and segment multi-sequence MRI images of ischemic stroke. Improved methods like nnU-Net and depthwise separable convolutional networks excel in differentiating stroke types and achieving fine-grained segmentation of small regions. Convolutional neural networks (CNNs), in particular, have demonstrated significant superiority in ischemic stroke imaging diagnosis, far outperforming manual interpretation in efficiency. Integrating AI with MRI techniques such as APTw, QSM, or MRSI may enable rapid and precise visualization of IP inner/outer boundaries in the near future, warranting promotion in MRI examinations for AIS patients.

6.Conclusions and Prospects

Current expert consensus on clinical assessment and treatment of IP in AIS patients recommends CT scans within <4.5 hours or 24 hours of symptom onset to exclude hemorrhage and initiate thrombolysis promptly, discouraging multimodal imaging from delaying thrombolysis. For patients with unknown onset times or >4.5 hours since last normal status, MRI is recommended to identify potential thrombolysis responders. In practice, however, most AIS patients have unclear onset times. According to the American Heart Association (AHA), IP assessment and DWI imaging must be completed within 20 minutes of admission, alongside vascular hemorrhage and patency evaluations—requirements uniquely balanced by MRI in terms of time and image quality.Considering time, cost, and accuracy, 3D-APT technology stands out among current MR metabolic techniques, offering new opportunities for stroke patients across different time windows and advancing personalized treatment for those previously limited by strict time frames. The integration of AI further optimizes MR metabolic imaging, enhancing its accuracy and clinical utility.Notably, AIS pathophysiology primarily stems from ischemia/hypoxia. Studies show that long-term high-altitude residents — characterized by chronic hypoxia — exhibit distinct cerebral oxygen metabolism compared to lowlanders. High-altitude stroke patients face "double stress" from preexisting cerebrovascular hypoxia and high-altitude hypoxic environments, leading to more severe hypoxia and complex pathogenesis. Therefore, investigating the specificity of IP and IC in high-altitude ischemic stroke is critical to refining prevention strategies and improving outcomes across diverse environments.

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