

# Research progress of imaging technologies for ischemic cerebrovascular diseases

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## Abstract

Cerebrovascular diseases mainly affect the blood supply of the brain, which has a high demand for oxygen and glucose for the nerve tissues to perform its nerve functions. Ischemic cerebrovascular disease can not only cause stroke, but is also associated with a high incidence of asymptomatic infarction and minimal bleeding that can lead to cognitive and behavioral changes. These changes ultimately manifest as vascular dementia or cognitive impairment. In clinical settings, ischemic cerebrovascular disease can be classified as a transient ischemic attack, reversible ischemic neurological deficit, progressive stroke, complete stroke, marginal infarction, or lacunar infarction. In this review, the research progress of imaging technologies for ischemic cerebrovascular diseases was reviewed, with an aim to provide evidence for clinical practitioners.

## Keywords

Cerebrovascular disease, imaging method, diagnosis, treatment, computed tomography, positron emission tomography, magnetic resonance imaging, angiography

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## Introduction

Cerebrovascular diseases are the main cause of disability and the second leading cause of mortality, secondary to ischemic heart disease.<sup>1</sup> The incidence of ischemic cerebrovascular diseases may be related to vascular wall lesions, changes in blood components, and hemodynamic changes. Hypertension, diabetes mellitus, hyperlipidemia, smoking, and genetic factors have all been

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demonstrated to play a pivotal role in accelerating the occurrence of ischemic brain disease.<sup>2</sup>

The diagnosis of ischemic brain disease is usually confirmed by a patient's medical history and signs, imaging examinations, laboratory examinations, and etiological typing. Of these techniques, imaging examination is an important reference index. At present, imaging examinations for ischemic cerebrovascular diseases mainly include electronic computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and transcranial Doppler ultrasound. These methods are used to detect cerebral ischemic damage, such as the location, scope, hemodynamic changes, and cerebral metabolic changes of infarction.<sup>3</sup> Furthermore, digital subtraction angiography (DSA), magnetic resonance angiography, and CT angiography (CTA) are used to identify the causes of cerebral ischemia, such as intracranial or extracranial artery stenosis, thrombosis, embolism, or cerebral arteriosclerosis. A wide array of molecular imaging techniques, including permeability imaging, have also been gradually applied in clinical practice. These techniques assist physicians in neurosurgery and provide a deeper understanding of the pathophysiological changes that occur in nervous system diseases. In this narrative review, we summarize the role and research progress of imaging examinations in ischemic cerebrovascular diseases.

### **Physiological changes in ischemic cerebrovascular diseases**

Ischemic cerebrovascular diseases involve a series of metabolic and molecular changes caused by interruption or severe damage of the cerebral blood supply, which leads to brain dysfunction and morphological damage. Changes in cerebral hemodynamics

are the basis of a wide range of ischemic cerebrovascular diseases. The brain of a healthy person contains approximately 130 billion neurons and accounts for just 2% of the total mass of the human body, whereas it accounts for 20% of the total blood oxygen consumption and 15% of the cardiac blood output.<sup>4</sup> Oxygen consumption by the brain occurs almost entirely through glucose oxidation metabolism. Under normal physiological conditions, glucose is the single substrate for brain energy metabolism.<sup>5</sup> The metabolism of glucose in neuronal cells mainly functions to provide energy for cellular nutrition and clearance functions. Increases in glucose consumption caused by functional activation are limited to synapse-rich areas. Approximately 59% of the total energy consumption of the brain is used for synaptic processes, while 21% is used for action potential propagation, and just 20% is used to maintain cell resting potentials.<sup>6</sup>

Cerebral blood volume (CBV) refers to blood in the arteries, capillaries, and veins. In the human body, approximately 30% of CBV is in the arteries, and 63% to 70% is in the veins and capillaries. The average cerebral blood flow (CBF) of the normal whole brain is approximately 50 mL/100 g/minute.<sup>3</sup> Blood flow to gray matter is relatively high (up to 80 mL/100 g/minute), whereas blood flow to white matter is lower (20 mL/100 g/minute, on average). The cerebral metabolic rate of oxygen (CMRO<sub>2</sub>) in the brain is approximately 3.2 mL/100 g/minute on average, of which gray matter consumes 6 mL/100 g/minute and white matter consumes 2 mL/100 g/minute.<sup>3</sup> Thus, the difference in normal arteriovenous oxygen content is approximately 6.4 vol% for individuals with normal hemoglobin concentrations. Glucose is the main energy substrate consumed by the brain, accounting for approximately 25% of the total glucose consumption of the human body. In

healthy volunteers,  $^{18}\text{F}$ -fluorodeoxyglucose PET has been used to demonstrate that the average glucose consumption of the brain is 29 to 32  $\mu\text{mol}/100\text{ g}/\text{minute}$ , which is consistent with the whole brain metabolic rate provided by the Kety–Schmidt method.<sup>7</sup> The functional anatomy of the brain is reflected by metabolic activities in individual regions. Glucose consumption in the visual cortex is 45 to 50  $\mu\text{mol}/100\text{ g}/\text{minute}$ , while in the striatum it is 42 to 46  $\mu\text{mol}/100\text{ g}/\text{minute}$ . The other regions of the cerebral cortex and basal ganglia have glucose consumptions of 35 to 42  $\mu\text{mol}/100\text{ g}/\text{minute}$ , while the gray matter structure of the posterior cranial fossa consumes 25 to 30  $\mu\text{mol}/100\text{ g}/\text{minute}$ . The metabolic rate of glucose in white matter is the lowest, at 15 to 22  $\mu\text{mol}/100\text{ g}/\text{minute}$ .<sup>8</sup> Up to 92% of adenosine triphosphate in the brain originates from glucose oxidation metabolism, which provides 12 mmol/100 g/minute of adenosine triphosphate; the total brain reserves of adenosine triphosphate and creatine phosphate are only 8 mmol/kg, which can last for less than 1 minute. Under anaerobic conditions, the anaerobic glycolysis of glucose and glycogen can only provide another 15 mmol/100 g/minute of adenosine triphosphate. Thus, a loss of consciousness occurs when the partial pressure of oxygen in the brain declines to 15 to 25 mmHg. To maintain a sufficient supply of blood, oxygen, and glucose to nerve tissue, cerebral circulation is strictly regulated by several stable mechanisms: low metabolic coupling (functional requirement coupled to tissue),  $\text{CO}_2$  vascular reactive partial pressure ( $\text{CO}_2$  partial pressure), cerebral vasodilation caused by hypoxemia, and automatic regulation of oxygen (blood pressure and cerebral perfusion pressure). Monitoring the blood supply to the brain plays an important role in the diagnosis and treatment of ischemic cerebrovascular diseases.

## Application of CT and PET in ischemic cerebrovascular diseases

Multidetector-row computed tomography can rapidly deliver thin-layer and large-scale scanning, and has promoted the development of CT perfusion (CTP) and CTA. Although MRI is the preferred method for imaging old blood samples, CT can identify the signs of fresh hemorrhage. CT and MRI scans have similar performances in terms of describing the follow-up of infarction, but CT scans are also capable of displaying contrast-enhanced margins from 2 to 4 weeks after stroke events. PET has high sensitivity, thus offering additional information regarding the secondary inactivation of brain regions that are not directly damaged. Early PET studies have revealed differences in glucose uptake among ischemic areas, suggesting the existence of anaerobic glycolysis in these regions. By measuring the oxygen extraction rate, researchers can track the progression of infarction within 48 hours.<sup>9</sup>

CTA can be employed to illustrate the morphology of carotid plaques and to predict the presence of carotid intraplaque hemorrhage (IPH),<sup>10</sup> although MR-IPH technology is widely recognized as the gold standard method. CTA plaque ulcers can be used as an alternative marker for IPH, and can therefore be used as an alternative risk factor for stroke. However, the sensitivity of single-layer CTA in detecting plaque ulcers has been questioned. With the emergence of multi-layer technology and improvements in resolution, CTA may now show better diagnostic performance.<sup>11</sup> Walker et al.<sup>11</sup> reported that the application of CTA for measuring Hounsfield units of plaque components has low reliability for predicting the quantities of lipids, fibrous tissue, or bleeding components within a single plaque. This insufficient performance of CTA may be partially explained by the

marked heterogeneity that is observed in the histological examination of a single plaque. A small number of studies have demonstrated that low-density plaques on CTA often consist of hemorrhagic components.<sup>12</sup> However, the low density observed on CTA fails to directly measure the CT attenuation of hemorrhage, but rather reflects the presence of large necrotic lipid nuclei in the plaques. CTA has high accuracy in the detection of plaque ulcers. We have identified a high consistency between observers when analyzing CT scans of plaque ulcers.<sup>13</sup> In addition, multifunctional CT scans can distinguish tissue that has increased or decreased attenuation, thereby allowing the nature of carotid plaques to be explored. This method contributes to characterizing the tissue composition of plaques by expanding the potential of CTA in plaque assessment.<sup>14</sup>

Cerebral sinovenous thrombosis (CSVT) is a common type of venous sinus and cerebral venous disease.<sup>15</sup> CT scans can be used to detect CSVT, evaluate the features of CSVT, and identify CSVT in both nonenhanced and enhanced phases. However, CSVT cannot be diagnosed by CT scan, and the severity of sinus involvement and venous infarction is underestimated in 40% of patients.<sup>16</sup> Certain conditions in nonenhanced CT scans can simulate CSVT. In particular, a subarachnoid hemorrhage at the tentorial margin of the cerebellum can be mistakenly identified as CSVT.<sup>17</sup> For spontaneous atherosclerotic internal carotid artery occlusion, the symmetry of the venous sinus in CT scans is associated with the impairment of cerebral reserve function.<sup>18</sup> A previous study has proposed that venous drainage can also affect cerebral perfusion and the lateral tributaries.<sup>19</sup> Thus, CTP is suitable for the assessment of cerebrovascular physiology. Compared with MRI, CTP can prolong the reperfusion window.<sup>20</sup> CTP can also improve the diagnostic performance of

stroke, and provides useful additional information for relatively inexperienced physicians compared with nonenhanced CT and CTA.<sup>21</sup> CTP images can be obtained by monitoring the first passage of contrast agent through the cerebrovascular system. A linear relationship model between the concentration of contrast agent and the attenuation in Hounsfield units is established for the subsequent evaluation.<sup>22</sup> Parsons et al.<sup>23</sup> have reported that the early evaluation of intracranial and extracranial vascular systems using CT/CTA can predict the recurrence of stroke. Moreover, CTP has been used to define the ischemic penumbra and infarction core, to select patients eligible for receiving tenecteplase therapy.<sup>23</sup> CTP can also be used to detect high-perfusion areas after the incidence of ischemic cerebrovascular diseases.<sup>24</sup> In the event of stroke, high-perfusion areas in the brain parenchyma should not be abnormally interpreted as contralateral low-perfusion areas or acute infarction areas.<sup>25</sup> CTP is able to provide effective information about cerebrovascular physiology, thus increasing diagnostic performance for ischemic cerebral diseases.

### **Application of MRI in ischemic cerebrovascular diseases**

Compared with CT, MRI has multiple advantages. It has a higher discrimination ability for distinguishing cerebrovascular events from acute focal neurological diseases induced by other causes, and a higher sensitivity for identifying early-stage acute ischemic lesions.<sup>26</sup> Thus, MRI can be used as a prognostic tool for ischemic stroke. Research has revealed that, as a gold standard, MRI has more advantages in the qualitative and quantitative analysis of carotid plaque morphology than histological assessments of carotid artery resection specimens.<sup>27</sup> MRI can be used to

classify carotid plaques according to the histopathological classification of the American Heart Association. In addition, the existence of vulnerable features depicted by MRI *in vivo* has been demonstrated to be correlated with MRI findings. Nevertheless, researchers have attempted to focus on the identification of vulnerable plaques using CT scans. In principle, however, the most advanced MRI scheme can add useful evidence for the staging of tissue-level diseases and can provide information about the distribution and size of cerebral infarctions; it can thus be considered as the gold standard for evaluating hemodynamic damage. MRI can also replace the role of PET in detecting CBF, CBV, oxygen extraction rate, and CMRO<sub>2</sub>. In addition, MRI can replace the function of single-photon emission computed tomography in the detection of CBF and CBV. The diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) sequences of MRI are currently the most sensitive methods for differentiating between large and small or acute and subacute and chronic ischemic infarction. As the gold standard, DWI has a high diagnostic accuracy for distinguishing acute stroke, with a scanning time of less than 2 minutes.<sup>28</sup> In addition, perfusion MRI can be used to detect hemodynamic parameters, and has been widely applied in the diagnosis of chronic and ischemic cerebrovascular diseases.<sup>29</sup>

MRI features can be used as valuable predictors of histological prognosis. The most common information relating to histological prognosis that is obtained from MRI is the estimated initial range and volume of the ischemic injury. Conventional MRI sequences, such as T1, T2, and FLAIR, have limited sensitivity for ischemic changes after a net increase in the water content of brain tissue. Consequently, the incidence of ischemia can be detected within several hours after the onset of symptoms. Additionally, DWI is highly

sensitive to cytotoxic edema, thus providing an opportunity to determine the extent of ischemic injury within the initial few hours after ischemia onset. A study that evaluated the dynamics of lesion volume through a series of MRI examinations highlighted that DWI lesion volumes underestimate the infarction volume in a majority of patients; the estimated size of an ischemic lesion increases by 144% to 180%, on average, during subsequent follow-up.<sup>30</sup> A certain degree of DWI reversal can be observed in approximately 25% of affected individuals.<sup>31</sup>

When attempting to locate the affected tissue after ischemic injury, factors other than the degree of cytotoxic edema should also be considered. One of these main factors is low perfusion in the ischemic region, which can be evaluated by perfusion-weighted imaging (PWI) MRI. Although PWI cannot evaluate the actual CBF or determine tissue perfusion, it can provide clinically reliable perfusion measures related to gold-standard PET.<sup>32</sup> Brain tissue that is normal on DWI but has abnormal perfusion is considered a feasible ischemic region, and may evolve into the infarction within a period of time.<sup>33</sup> Furthermore, modification of the MRI algorithm can improve the accuracy of prediction outcomes for tissue. Magnetic resonance angiography has revealed that patients with large vessel occlusion are not only more likely to have diffuse perfusion mismatch, but are also more prone to lesion expansion.<sup>34</sup> More importantly, histological prognosis predictions are largely influenced by the degree of recanalization. Regardless of the perfusion parameters, brain tissue close to DWI lesions has a high risk of deteriorating into infarction, whereas low-perfusion tissue located adjacent to the mismatched regions is generally unaffected on subsequent DWI images.<sup>35</sup>

MRI can also be used to predict the clinical outcome of ischemic cerebrovascular

diseases. Lesion volume is an independent and major predictor of clinical outcome after ischemic stroke.<sup>36</sup> Regardless of MRI time, the correlation between lesion volume and clinical outcome is far from satisfactory. A main factor leading to inconsistent results is the lesion site. Lesions located in clinically important areas may have destructive results regardless of their size, whereas large lesions may exert minimal effects if they are located in sites of relatively low activity. Therefore, a novel prediction model is currently being developed that may be used to combine lesion volume and location information for such assessments.<sup>37</sup> Steady-state enhanced MRI is also a promising tool that is being developed and may be useful for evaluating the degree of angiogenesis.<sup>38</sup> In addition, MRI is an essential tool for assessing the risk of recurrence after ischemic stroke and transient ischemic attack. Combining this imaging information with effective clinical tools can significantly improve the prediction accuracy for the recurrence of early stroke in transient ischemic attack patients.<sup>39</sup>

MRI also plays an important role in therapeutic decision-making algorithms for ischemic cerebrovascular diseases. The current treatment of acute ischemic stroke relies on the successful recanalization of occluded arteries to establish reperfusion in the ischemic regions. It is therefore important to identify high-risk patients for recanalization/reperfusion therapy. Patients with a small infarction core and low-risk cerebral hemorrhage are target individuals. Therefore, the presence of small lesions on DWI and large DWI/PWI mismatches can be considered as imaging substitutes for this promising clinical scheme, in which thrombolytic therapy may be benign. This hypothesis has been verified in an observational study in which the patients received MRI 3 to 6 hours after the onset of symptoms, before receiving intravenous tissue plasminogen activator therapy.<sup>40</sup> Similarly,

small-scale observational studies have attempted to propose lesion volume thresholds to identify the potential benefits of intra-arterial thrombolysis, and recommend an initial lesion volume of 70 mL on DWI as a marker of unfavorable clinical prognosis.<sup>41</sup> However, although MRI has many advantages, it fails to provide all of the information needed for accurate predictions. An ideal prognosis-predicting model should therefore integrate both clinical and imaging data.

Prior to the development of arterial spin labeling (ASL), the techniques employed for determining CBF were relatively invasive and involved the use of exogenous contrast agents, such as the [<sup>15</sup>O]H<sub>2</sub>O radiotracer in PET. The principles behind ASL resemble those using exogenous contrast agents; however, ASL is completely noninvasive, with no use of injections, and the tracer is magnetically labeled water rather than radioactively labeled water. One notable limitation of ASL is that it takes a relatively long time to obtain a single image.

### **Application of DSA in ischemic cerebrovascular diseases**

DSA uses computerized X-ray imaging equipment for image acquisition and subtraction, and may provide substantial improvements for vascular imaging. Venous DSA provides a safe, accurate, and cost-effective approach for examining extracranial and intracranial vessels in both outpatients and inpatients. Intra-arterial DSA has better spatial resolution than intravenous DSA.<sup>42</sup> Cerebral vasospasm (CVS) is a common complication of aneurysmal subarachnoid hemorrhage, and is closely associated with neurological deterioration and delayed cerebral ischemia (DCI). DSA is the gold standard for the diagnosis of CVS, and allows for the

**Table 1.** Advantages and disadvantages of different imaging modalities for ischemic cerebrovascular diseases.

Imaging modality	Advantages	Disadvantages
CT scan	Can identify the signs of fresh hemorrhage. High sensitivity in early-stage acute ischemic lesions.	Low reliability for predicting the quantity of lipid, fibrous tissue. Image resolution is relatively low.
PET	High sensitivity. Offers additional information regarding secondary inactivation of brain regions that are not directly damaged.	High medical expense.
MRI	High discrimination ability for distinguishing cerebrovascular events from acute focal neurological diseases induced by other causes. High sensitivity in early-stage acute ischemic lesions.	Lacks certain information needed for accurate prediction. Detection time is relatively long.
DSA	Safe, accurate, and cost-effective for examining extracranial and intracranial vessels. Is the gold standard for the diagnosis of cerebral vasospasm.	Limited availability.

CT, computed tomography; PET, positron emission tomography; MRI, magnetic resonance imaging; DSA, digital subtraction angiography.

accurate quantitative assessment of the severity of CVS in each intracranial artery as well as for the administration of intravascular interventional therapy. Nevertheless, although transcranial Doppler ultrasound and CTA have lower sensitivity and specificity for CVS detection, these examinations are also used because of the limited availability of DSA.<sup>43</sup> Multiple physicians have attempted to screen for CVS in subarachnoid hemorrhage patients to conduct risk stratification and timely intervention, as well as to prevent DCI-related morbidity. A recent survey found that a majority of patients undergo a series of screening interventions within 5 to 10 days after admission, including transcranial Doppler ultrasound (70.1%), DSA (24.9%), and CTA (23.7%).<sup>44</sup> Moderate to severe CVS has been reported as relatively uncommon in asymptomatic patients (18%), and none of these patients subsequently developed the precise symptoms of DCI or cerebral infarction during their hospital stay,

regardless of whether CVS was identified on DSA.<sup>45</sup> As the gold standard for detecting CVS, DSA can not only provide an optimal evaluation of blood vessel caliber, but can also supplement temporal information related to flow mechanics.<sup>46</sup>

Studies have demonstrated that it is feasible to use micro-CT during DSA of the cerebrovascular system in mouse models, which allows for accurate and repeated measurements of blood vessel calibers and changes, and provides relevant information about blood flow *in vivo*.<sup>45,46</sup> Perfusion defects on CTP have higher sensitivity but lower specificity compared with vasospasm on DSA. However, the diagnostic accuracy of DSA in diagnosing DCI has rarely been reported. Cardioembolic infarction accounts for approximately one quarter of all cerebral infarctions. The hemorrhagic transformation of an ischemic infarct suggests a cardiac origin of the stroke. Up to 95% of hemorrhagic infarcts have a cardioembolic pathophysiological mechanism.<sup>47</sup>

These findings may be limited because all of the results came from an Asian population, but they can still provide certain reference values. Moreover, cardiac evaluation, artery biopsy, and other examinations are needed to make an appropriate etiological diagnosis in certain cases of acute ischemic stroke.<sup>48</sup> Diffusion tensor imaging is more accurate and sensitive for quantifying ischemic cerebrovascular alterations compared with other conventional magnetic resonance techniques. Diffusion tensor imaging serves as a promising tool to detect early ultrastructural cerebral changes. Grau Olivares et al. have applied voxel-based morphometry to analyze mild cognitive impairment, and provide support for an anatomical substrate of the mild cognitive impairment entity in patients with lacunar infarction. Both gray and white matter changes seem to contribute to the cognitive impairment of such patients.<sup>49</sup> The features of each imaging modality are shown in Table 1.

## Conclusion

MRI has high sensitivity in the early diagnosis of ischemic cerebrovascular diseases. In addition, it can resolve the relatively low sensitivity of CT scans. Neuroimaging is evolving toward the comprehensive application of multiple examinations and the integration of structure and function, with an aim to provide more data regarding morphology, hemodynamics, cerebral metabolism, and function. In patients with ischemic stroke, neuroimaging plays an increasingly pivotal role in the early and differential diagnosis, treatment selection, dynamic monitoring of pathological changes, assessment of clinical efficacy, and prediction of patient prognosis.


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The authors declare that there is no conflict of interest.

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