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The imaging principle of IVIM and its value in the diagnosis and treatment of ischemic stroke

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Abstract: *Ischemic stroke (IS) is the most common cerebrovascular disease in clinical practice, with high morbidity, high mortality and high disability rate. It is the leading cause of death and disability among Chinese adults. Intravoxel incoherent motion (IVIM) enables simultaneous acquisition of tissue diffusion and perfusion information in a single scan. In 1988, Le Bihan first proposed the concept of IVIM. With the emergence of high-field MR and the improvement of computer post-processing speed,IVIM imaging technology has gradually developed and matured, and has been widely used in the diagnosis of various systemic diseases, especially in the application of IS.This article aims to review the imaging principle of IVIM and the value of IVIM in the diagnosis and treatment of ischemic stroke, and discuss the clinical application value and research prospect of IVIM in IS.*

Keywords: *Ischemic stroke, Intravoxel incoherent motion, Magnetic resonance imaging*

1. Overview of IS and its diagnosis and treatment dilemmas

IS is a general term for brain tissue necrosis caused by cerebral artery stenosis or occlusion and insufficient cerebral blood supply, which IS the most common cerebrovascular disease in clinical practice[1]. With the characteristics of high morbidity, high mortality and high disability rate, it has become the second leading cause of death and disability in the world[2]. More than 2/3 of stroke occurs in developing countries [3, 4], and stroke is the leading cause of death and disability among adults in China[5]. According to epidemiological studies, the age-standardized prevalence, incidence and mortality of stroke in China were 11148/100000, 246.8/100000 and 114.8/100000, respectively. Among them, ischemic stroke accounted for 77.8% of the patients and 69.6% of the new stroke patients each year. At present, the average annual increase of the incidence of first death among Chinese residents aged 40-74 years is 8.3%[6]. Ischemic stroke not only brings a heavy burden to the family and society, but also greatly consumes medical resources, so the prevention and treatment of stroke is particularly important. At present, MRI plays a great role in the diagnosis of IS [7]. Diffusion-weighted imaging (DWI) can improve the sensitivity of detecting the isothermal core in the early stage of stroke, and can detect the signal of acute cerebral infarction in the early stage of the disease. Perfusion Weighted Imaging (PWI) can eliminate the interference of non-ischemic stroke diseases and evaluate the ischemic penumbra and ischemic core, and distinguish the ischemic core and ischemic penumbra by the mismatch between PWI and DWI [8, 9]. PWI IS an important examination method for the diagnosis of IS[10] . The applications of PWI in the brain include dynamic susceptibility contrast (DSC) and arterial spin labeling (ASL). Intravoxel Incoherent motion (IVIM) is a new MR technique, which has the following advantages over DSC and ASL: 1.IVIM technology does not require the use of contrast medium, and is suitable for patients with liver and kidney insufficiency and allergy to contrast medium, without the problem of contrast medium deposition, while DSC requires the use of contrast medium. 2. IVIM signal is almost all derived from capillaries, which is not affected by large vessel signals, and does not directly depend on the influence of anterior cerebral effects such as carotid artery stenosis and cardiac output[11]. Arterial input function (AIF) is not selected for IVIM, and AIF must be used for DSC and ASL. Moreover, it is difficult to select an appropriate AIF, so IVIM does not have the shortcoming of inaccurate arterial input function[12-14]. 3. IVIM can obtain diffusion and perfusion information of tissues at the same time in a single scan, and the imaging time is short. DSC and ASL can only obtain perfusion information of tissues. Therefore, IVIM has attracted wide attention in the field of ischemic stroke diagnosis and treatment.

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2. Concept and parameter meaning of IVIM

The concept of IVIM was first proposed by Le Bihan[15]to explain the movement of blood flow in capillaries, and this movement is called pseudo-diffusion movement, which represents the perfusion of water molecules in blood vessels. This pseudo-diffusion movement is the process of water molecules flowing from one capillary segment to the next[15]. Refers to the movement of blood components within the microvascular system, rather than true Brownian motion. The movement form of water molecules in tissues is very complex, and its movement form has the following categories: 1. Brownian motion of water molecules in cells, intercellular Spaces and capillaries; 2. Water molecules are transported in and out of cells and blood vessels through aquaporins; 3. Perfusion of water molecules in blood vessels, that is, pseudo-diffusion motion.

The traditional DWI generally contains 2-3 b values (brain DWI b value is 0 and 1000s/mm²), and the ADC value is obtained by fitting two b values: $Sb/S0= e^{(-bADC)}$, where Sb represents the signal intensity when b is not 0S /mm², and S0 represents the signal intensity when b is 0S /mm². But DWI is a dispersion model, single index can only consider the water molecules in the movement of dispersion in the intercellular space, and at the same time assume the dispersion movement as gaussian distribution[16-18],namely water molecules diffuse absolute freedom, not affected by macromolecules such as protein, cell membrane barriers, so by DWI of ADC values can and can not accurately reflect the actual movement of the water molecules. The standard IVIM model is a biexponential model that considers both Brownian motion of water molecules in the intercellular space and perfusion of water molecules in blood vessels. The setting of b value is a key factor in IVIM imaging, and the size of b value affects the attenuation speed of tissue signal. The b value of conventional IVIM ranges from low to high, from 0-3500s/mm²[19]. The diffusion information and perfusion information of the tissue can be separated by post-processing with the double exponential equation of the standard two-compartment diffusion model: $Sb/S0= (1-f)\, e^{-bD} + fe^{-b\,(D^{*}+D)}$, where Sb represents the signal intensity when b is not 0S /mm², and S0 represents the signal intensity when b is 0s/mm². D is the slow diffusion coefficient, which represents the Brownian motion of water molecules in the intercellular space. D* is the pseudo-diffusion coefficient, representing the blood flow movement in the capillary segment; $D^{*}=lV/6$; V is the average blood flow velocity; l is the average capillary segment length [20]; f is the perfusion fraction, representing the ratio between the flowing blood and the water content of the overall tissue.

Since D* is much larger than D, the increase of b value on one hand will make the dispersion information more pure, on the other hand, the image quality will also decrease (the increase of b value will lead to more echo signal loss). The number of b values affects the accuracy of biexponential model fitting and imaging time. If the number of b values is too small, the imaging time is greatly reduced, but the accuracy of biexponential model fitting is also reduced. On the contrary, if the number of b values is too large, although the accuracy of the biexponential model fitting is greatly improved, the imaging time will also increase, which makes it difficult for patients to cooperate and increases the risk of motion artifacts. Images fitted with multiple b values are also theoretically better than images fitted with fewer b values. Up to now, the number and range of b values have not been standardized. Conklin [21]believes that the simplified combination of two non-zero b values can be used for IVIM imaging, and theoretically IVIM parameter information can be obtained. However, the reduction of b values reduces the accuracy of IVIM fitting map, so at least four non-zero b values are needed without degrading the image quality. At present, the b-value combination of 0, 50, 200 and 1000 proposed by Zhu[22]is the most consistent with Bland-Altman analysis, which is a method to examine the consistency test of data of two continuous numerical variables and has the characteristics of quantitative and qualitative research. Scholars have made unremitting efforts to find ways to improve the image quality of IVIM without increasing the imaging time. There are several ways to improve IVIM image quality: 1.MinJung Jang[23]proposed to use cNMF for automatic segmentation of IVIM images, and cNMF could well separate the low-irrigation areas due to dispersion reduction and perfusion reduction in IS. 2.Ivan I Maximov[24]improved the signal-to-noise ratio of IVIM images by applying 7T ultra-high field strength NMR equipment. Improve IVIM image quality 3. In addition, Bayesian estimation method[25], fusion bootstrap movement[26]and other methods can also improve the image quality of IVIM.

By evaluating these parameters with Firevoxel postprocessing software, we can not only obtain diffusion and perfusion information of the tissue, but also have a short imaging time and no problems such as contrast media allergy. In addition, signals obtained through IVIM are more accurate, because IVIM imaging avoids the influence of large blood vessels on microcirculation[11]. Thus, it has attracted wide attention in the field of IS diagnosis and treatment. IVIM can also assist BOLD in imaging and provide higher resolution, mainly because IVIM is more sensitive to capillary blood flow than BOLD

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[15, 27]. IVIM is also widely used in the classification of breast cancer[28-30]and the differentiation of high and low grade gliomas[31-34].

3. Application of IVIM in ischemic stroke

At present, PWI technology is commonly used in clinical practice to obtain perfusion parameters: Cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT) and other parameters can be used to evaluate the perfusion information of local tissues. If the IVIM parameters D, D*, F, fD* can reflect the real perfusion information of the tissue, it can be widely used in the diagnosis and treatment of IS, and become an alternative to DSC and ASL.

Initially, Le Bihan et al. discussed IVIM and PWI, and found that there was a certain relationship between the parameters of IVIM and PWI, and PWI perfusion parameters could be calculated by IVIM parameters[8, 20, 35]. F =CBV/fW, where fW is the volume fraction of visible water in capillaries[20], and F is the perfusion fraction, which represents the ratio of the flowing blood to the water content of the whole tissue. CBF=(6fw/Ll)fD*, L is the total length of capillaries[8, 15]. L is the average capillary segment length[20], D* is the pseudo diffusion coefficient, which represents the movement of blood flow in the capillary segment, MTT=Ll/6D*. This discovery makes IVIM parameters can be related to classical perfusion parameters, laying a certain foundation for the application of IVIM technology in clinical practice.

3.1 Application of IVIM in acute ischemic stroke

Many scholars have shown through studies that the IVIM parameters in the ischemic area are significantly lower than those in the contralateral area, and there is a good correlation between IVIM parameters and PWI perfusion parameters: In a retrospective analysis of the images of 101 patients with acute ischemic stroke (AIS), Suo et al.[36]found that among all pixels in the region of interest (ROI) of ischemic and normal areas, The parameter values D, f and fD* in the ischemic area were significantly lower than those in the contralateral side ($P<0.001$), and the differences were statistically significant, and the reduction of parameters D, f and fD* was consistent with the physiological and pathological significance of stroke. There was no significant difference between D* and contralateral region ($P=0.218$). This may be due to the poor repeatability of the measurement of parameter D*, which will be overestimated by 300%[37]. Yao performed IVIM and ASL imaging on 38 AIS patients and found that: The parameter values D, F, fD* and CBF in the ischemic area were significantly lower than those in the contralateral side ($P<0.001$), and the parameter values D* in the ischemic area were significantly lower than those in the contralateral side ($P=0.005$). The differences were statistically significant, and the decreases of parameters D, F, fD* and D* were consistent with the physiological and pathological significance of stroke. The results of Pearson correlation analysis showed that the parameter values f and fD* were correlated with the parameter values CBF ($r=0.472$ and $r=0.653$ respectively). Fei Chen[38] conducted experiments on 39 patients with ischemic stroke, and also found that the D, D*, f, fD* and ADC values of the healthy side were significantly lower than those of the contralateral side. The rD and rf values of the good recovery group were higher than those of the poor recovery group. In conclusion, IVIM parameters in ischemic area of stroke patients are significantly lower than those in normal area of contralateral area, and IVIM parameters have a good correlation with traditional PWI perfusion parameters, which can be used to evaluate the degree of ischemia in IS patients and reflect the real perfusion information of tissues.

In addition, compared with PWI, IVIM can also be used to separate the ischemic core from the ischemic penumbra. Zhu[8]et al, for the first time, took T_{max}>6S as the threshold, delineated the ischemic core, ischemic penumbra, non-ischemic zone and contralateral hemisphere on the basis of DWI and PWI images, measured the signal intensity and ischemic volume of IVIM on different ROIs, and then separated the ischemic core and ischemic penumbra through the mismatch between DWI and PWI parameter maps. Similar to PWI, IVIM separates the ischemic core and penumbra by the mismatch between DWI and F parameter map, which provides the imaging basis for endovascular mechanical thrombectomy (EMT) in patients with IS. Chen Qiong[39] conducted a retrospective analysis on 24 patients with chronic ischemic stroke and found that with the assistance of DKI, IVIM could better distinguish the ischemic core from the penumbra.

IVIM is also expected to be used to predict hemorrhagic transformation (HT). At present, intravenous thrombolytic therapy is the first choice of clinical treatment for AIS patients, but intravenous thrombolytic therapy will cause the risk of HT, and the prognosis of HT patients is very

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poor. Zhang Hua wen [40]divided AIS patients into HT group and non-HT group, and found that rD, rD* and rf of HT group were smaller than those of non-HT group, indicating that the degree of hypoperfusion of HT group was more serious. At present, domestic and foreign reports lack evidence on the correlation between IVIM parameters and HT in AIS patients. If future research can make a breakthrough in this direction, it will play a great role in improving the survival rate and disability rate of AIS patients.

IVIM can be applied to the detection of CCD in the crossed cerebellar diaschisis (CCD). Jianhong Ma[41] divided 74 patients with AIS into CCD negative group and CCD positive group, and found that the parameter values D, D* and F of the positive group were lower than those of the negative group, and the F value was lower, and the differences were statistically significant. D was positively correlated with CBF, and the difference was statistically significant ($r=0.515$, $P<0.01$), the area under the ROC curve AUG was 0.81. This shows that IVIM technology is feasible to detect CCD.

3.2 Application of IVIM in hyperacute ischemic stroke

Clinically, ischemic stroke cases within 6 hours of onset are usually classified as the hyperacute phase. At present, the application of IVIM in hyperacute ischemic stroke mainly focuses on assessing the dynamic changes of microvascular perfusion and measuring the quality of collateral blood flow in the penumbra: Qian et al. [42] constructed a dog model to simulate the physiological and pathological changes of dogs during hyperacute ischemic stroke. They found that the perfusion fraction f at 6h was significantly lower than the perfusion fraction f at 4.5h [42]. Therefore, parameter f can be used to evaluate the dynamic changes of microvascular perfusion during the development of hyperacute ischemic stroke. When Christian[43]analyzed parameter map f in IVIM, he followed up patients who showed penumbra injury in parameter map F. By comparing the difference between perfusion injury area and follow-up image, the quality of collateral circulation blood flow in penumbra could be measured.

3.3 Application of IVIM in chronic and subacute ischemic stroke

IVIM can assess cerebrovascular reactivity (CVR) in patients with chronic ischemic stroke, Ikuko Uwano[44] performed single-photon emission computed tomography (SPECT) and IVIM simultaneously on 47 patients with chronic ischemic stroke. The cerebral vascular reactivity to acetazolamide stimulation was measured, and the IVIM perfusion parameter F had high sensitivity and specificity (0.71 and 0.90, respectively) in evaluating CVR in patients with chronic ischemic stroke with unilateral carotid artery stenosis. This study shows that IVIM is a good method for evaluating CVR in patients with chronic ischemic stroke, and its biggest advantage over SPECT is that IVIM is a non-invasive imaging technique.

Zu Jinyan[45] analyzed the changes of cerebral blood flow perfusion parameters of IVIM in 46 patients with IS, and conducted correlation analysis between IVIM parameters and ASL parameters, and found that the two parameters had good consistency in evaluating the changes of cerebral blood flow perfusion. By comparing the IVIM parameter values of bilateral cerebellar hemispheres in patients with CCD-positive subacute ischemic stroke, Pan Lijun[46] found that D* decreased and F increased in the contralateral cerebellar hemispheres of infarct, while there was no significant difference in D and ADC values, which further verified that CCD signs were related to perfusion changes.

4. Summary and prospect

As a new MR technology, IVIM has attracted extensive attention because of its short imaging time, no contrast agent, and almost all the signals come from capillaries. A large number of studies have shown that IVIM has a good correlation with DSC and ASL, which IS widely used in tumors and IS. When applied to IS, it can not only well separate the ischemic core and penumbra, but also can be applied to CCD and HT, and can complement the separation of the ischemic core and penumbra. However, there are still many challenges in the clinical promotion of IVIM. First of all, the selection criteria for b value at home and abroad have not been unified, which leads to a lack of good consistency in the IVIM parameter information obtained by many scholars. The poor repeatability of parameter D* is also a problem. Secondly, the selection of IVIM model, parameter fitting and parameter analysis software are also controversial. Although many scholars have made great efforts in image optimization, for example, Min Jung Jang proposed to use cNMF for automatic segmentation of IVIM images, Ivan I

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Maximov can improve the signal-to-noise ratio of IVIM images by applying 7T ultra-high field strength NMR equipment to improve the image quality of IVIM. And some other methods such as Bayesian estimation and fusion bootstrap motion can also improve the image quality of IVIM. However, these image improvement methods are still in the exploration stage, and no unified standard has been formed. Secondly, the parameter map of IVIM has high requirements for SNR, so it has high requirements for MR hardware equipment and its acquisition sequence. This problem also makes it difficult for IVIM to be widely used in clinical practice at present. Finally, most of the studies on IVIM in IS focused on proving the consistency between IVIM parameters and DSC and ASL parameters, and a few were used to separate the ischemic penumbra and infarct core. However, there are few studies on early prevention, evaluation of treatment effect, and detection of functional recovery in IS patients. However, the value of IVIM in the diagnosis and treatment of IS patients IS beyond reproach. At present, the research of IVIM IS still in the basic stage, and it has not been really applied in clinical practice. Through the combined application with other imaging methods, precise diagnosis and treatment can be provided for early IS patients, and the lives of patients can be saved as much as possible, and the recovery of patients can be improved, so as to create the maximum benefits for IS patients.

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