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Review Article

Research Status of Three-Dimensional Pseudo-Continuous Arterial Spin Labeling in Ischemic Cerebrovascular Diseases

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Abstract: Ischemic cerebrovascular disease (ICVD) is a kind of brain dysfunction caused by intracranial vascular disease, which has a serious threat to the patient's quality of life. With the development of ICVD in the direction of high incidence and young age, the early diagnosis of ICVD has become an urgent need in clinical practice. Three-dimensional pseudo-continuous arterial spin labeling (3D-pCASL) as a completely non-invasive perfusion imaging method can reflect changes of cerebral blood flow, and has been used in the study of ICVD. The aim of this paper is to review the research progress of 3D-pCASL in ICVD. By reviewing to the relevant domestic and foreign literatures on the value of ASL in ICVD in the past ten years, we found that 3D-pCASL technique has some advantages in the early evaluation of the abnormal perfusion of cerebral blood flow, the differential diagnosis, the reperfusion after cerebral infarction, the ischemic penumbra and the evaluation of prognosis, which has important guiding significance for the prevention of ICVD and the determination of the next treatment. Moreover, with the development of ASL technology and the appearance of new perfusion imaging method of ASL technology, it shows that it plays an inestimable role in the study of ischemic cerebrovascular diseases. In conclusion the role of 3D-pCASL in the cerebral perfusion of ICVD has been confirmed and has a very broad application prospect.

Keywords: Pseudo-Continuous Arterial Spinlabeling, Ischemic Cerebrovascular Disease, Brain, Magnetic Resonance Imaging

1. Introduction

Ischemic cerebrovascular disease (ICVD), mainly including transient ischemic attack (TIA) and cerebral infarction, refers to the disease of cerebral dysfunction due to decreased or disrupted cerebral blood flow caused by cerebral vascular stenosis, occlusion or carotid plaque rupture and thrombosis [1]. In general, the stopping of blood supply at the central zone for 6 min will cause the death of nerve cells, but as for the surrounding ischemic regions, their functions may be recovered if the blood flow passes through within 6 h [2-3]; therefore, it is critical for early diagnosis, early treatment and prognosis evaluation of cerebrovascular diseases.

Three-dimensional pseudo-continuous arterial spin labeling (3D-pCASL) is an imaging technique that may carry out non-invasive monitoring of blood flow changes. With the continuous progress of 3D-pCASL technology in recent years, its application value in ICVD has been increased year by year [4-5].

2. Basic Principles and Technical Progress of ASL

Through utilizing water molecules in autologous arterial blood as the endogenous tracer agent, ASL technique may quantitatively measure cerebral blood flow (CBF) based on

signal changes resulted from labeled and unlabeled blood flowing through tissues. As posted labeling delay (PLD) is an important parameter for ASL, the accurate selection of PLD is the basis for accurate quantification of CBF. In terms of labeling manners, ASL is divided into pulsed ASL (PASL) and continuous ASL (CASL), both of which were seldomly applied in clinical practice due to limitations of imaging technology and image quality at that time. However, with the continuous improvement of ASL, pseudo-CASL (pCASL), selective ASL (SASL), velocity-selective ASL (VSASL), acceleration-selective arterial spin labeling (AccASL) and vessel-encoded arterial spin labeling (VE-ASL) have been successively proposed, which have broadened the clinical application of ASL. At present, pCASL is the most widely used technique among all what mentioned above.

3. Research Progress of 3D-pCASL in Ischemic Cerebrovascular Disease

3.1. The Value of 3D-pCASL in Early Diagnosis of Ischemic Cerebrovascular Disease

In recent years, the incidence of ICVD has been increasing year by year, with high rate of disability and mortality, thus seriously affecting people's quality of life and health; therefore, it is quite important to carry out early diagnosis and early treatment against perfusion disorder of brain tissues. 3D-pCASL, as a brand new non-invasive imaging method for evaluating cerebral blood flow perfusion, can reflect the potential hemodynamic changes in the brain [6]. As studied, 3D-pCASL can monitor the changes of cerebral perfusion of patients with the risk of cerebral infarction prior to its onset; such as hypertension, which, as a risk factor for cerebral infarction, may change the structure of small blood vessels and damage the blood-brain barrier; and the changes in the structural integrity of blood vessels may lead to the decrease of the cerebral blood flow. 3D-pCASL reflect a decrease of cerebral perfusion level at the early stage of hypertension when the majority of normal images are normal [7]. Zaharchuk et al. [8] once studied 76 TIA patients and found that 47 of which were detected to be subject to abnormal brain perfusion with 3D-pCASL, while 18 of which were detected with diffusion weighted imaging (DWI), 10 of which were detected with magnetic resonance angiography (MRA), 24 of which were detected with the combination of DWI and MRA, and 23 of which were detected with dynamic susceptibility-weighted contrast-enhanced (DSC), indicating that 3D-pCASL is more sensitive than other imaging technologies.

3D-pCASL can also help to identify ICVD at an early stage, which is very important for developing proper therapeutic regimens. There are many patients with stroke mimic [9] that resembles ICVD in clinical manifestations. Thrombolytic therapy on the basis of CT examination alone may lead to unnecessary treatment for many non-stroke patients, and may lead to complications such as bleeding. ICVD shows a definite hypoperfusion on 3D-pCASL imaging, while some diseases characterized by a stroke attack such as mitochondrial encephalomyopathy, encephalitis, etc, usually show hyperperfusion. Therefore, stroke mimic can be eliminated by 3D-pCASL perfusion imaging to avoid incorrect treatment.

3.2. Diagnostic Value of 3D-pCASL for Macrovascular and Small Vascular Lesions of ICVD

The differentiation of macrovascular and small vessel lesions is of great clinical significance in clinical treatment. Pathologically, small vessel lesions are due to glassy degeneration or cellulose-like necrosis of the vascular wall, while macroangiopathy is caused by atherosclerosis [10]. Different pathological changes lead to different medications. In many cases, ICVD can not be really alleviated or improved because of its inability to distinguish the two kinds of pathological changes exactly.

Because small vessels in the brain are difficult to observe directly in human studies, they can only be judged by imaging methods to evaluate related brain parenchymal damage. For example, lacunar infarction, hyperintense of white matter, microhemorrhage, and perivascular space are common imaging features of small cerebral angiopathy [11]. However, the "lacunar infarction" shown by imaging is not all true small vessel disease. Though the stenosis or occlusion of arterioles due to atherosclerosis of the carrier artery, is morphologically characterized as "lacunar infarction", the responsible vessels are of macroangiopathy. Researches show that [12], some macrovascular lesions are only manifested as the lacunar infarction focuses with the size less than about 15mm due to sufficient collateral circulation compensation. In the 3D-pCASL perfusion images, the perfusion manifestations of macrovascular and small vessel lesions are different: macrovascular lesions show large-scale hypoperfusion changes in the corresponding vascular regions, while small vessel lesions manifest focal hypoperfusion changes in the relevant vascular regions. Therefore, we can detect the large vessel problem sensitively through 3D-pCASL perfusion imaging, for which the blind diagnosis as small vessel disease only based on the morphological "lacunar infarction" performance can be avoided. This is crucial for further treatment and the primary and secondary prevention of stroke. However, since there is still a lack of researches on the application of 3D-pCASL in the assessment of large and small vessel lesions of ICVD, more researches are needed to make verification.

3.3. Evaluation on Reperfusion After Infarction with 3D-pCASL

3D-pCASL does not require the injection of any contrast agent, so it has low cost and high repeatability of detection; more importantly, its imaging adopts water molecules in arterial blood as the endogenous tracer agent, rather than the blood-brain barrier, which is critical for evaluation on reperfusion after infarction of cerebral infarction patients. The reason is that reperfusion in the course of treatment of acute cerebral infarction means that the further thrombolytic therapy

should be stopped, otherwise it would cause bleeding, which, once combined with cerebral infarction, would result in a high rate of mortality. In general, the new vessels of reperfusion after infarction would be lack of complete blood-brain barrier, which would greatly reduce the accuracy of DSC relying on blood-brain-barrier imaging; however, 3D-pCASL does not rely on blood-brain barrier model, so it can reflect the presence of reperfusion more realistically [13]. Zhang S et al. [14] once studied 13 patients with acute cerebral infarction, 10 of whom had obvious hypoperfusion, and the other 3 had hypertransfusion due to the compensatory effect of collateral circulation around the hypoperfusion area; after thrombolytic treatment, the reexamination showed that several patients had blood flow reperfusion, which suggested partial restore of blood flow. It shows that 3D-pCASL can reflect the recovery of reperfusion after cerebral infarction, and has profound clinical significance in the accurate diagnosis and treatment of ICVD.

3.4. Evaluation of Ischemic Penumbra in Patients with Acute ICVD by 3D-pCASL

Ischemic penumbra (IP) is an unavoidable problem in the development of cerebral infarction. Its energy metabolism is preserved and its blood supply is inhibited. Defining and restoring IP has a positive therapeutic significance.

At present, perfusion-diffusion mismatch (PDM) is regarded as the "golden standard" for clinical evaluation of IP, which can be used to evaluate the extent, degree and type of ischemia. Viallon et al. [15] found that the hypoperfusion of cerebral infarction displayed by 3D-pCASL is consistent with that of dynamic sensitivity contrast enhanced magnetic resonance imaging (DSC-MRI). Zaharchuk et al. [16] compared acute IP with 3D-pCASL and DSC and found the over-evaluation of hypoperfusion by 3D-pCASL. That is because 3D-pCASL is sensitive to cerebral ischemia. The mismatched area of ASL-DWI not only includes IP, but also covers benign perfusion deficiency regions, namely that no infarct will occur even if no reperfusion is found. But the presence or absence of such benign perfusion deficiency regions are affected by PLD and the arterial transit time (ATT). The relationship between PLD and ATT is complicated. When PLD is significantly lower than ATT, CBF will be underestimated, because some of the labeled blood has not reached the vascular bed in this time frame. Conversely, when PLD is significantly higher than ATT, CBF is overestimated. Therefore, the use of mismatched regions by ASL-DWI to evaluate IP calls for further study.

3.5. Evaluation on Prognosis of Ischemic Cerebrovascular Disease with 3D-pCASL

In case of hypoperfusion due to stenosis or occlusion of brain tissue feeding artery, the brain tissue would maintain intracranial hemodynamic stability in a compensatory manner of generating a bypass artery or arterial anastomosis network; the formation of collateral circulation would be of great clinical significance. Studies [17] have shown that there is a significant correlation between the formation of collateral circulation and stroke outcome/prognosis. A nice collateral circulation can always improve the success rate of vascular recanalization treatment, thus promoting tissue reperfusion, reducing infarction volume, reducing the risk of hemorrhagic transformation after infarction, and effectively improving clinical outcome. But the clinical significance of collateral circulation must be combined with the time points and treatment process. The collateral circulation (within 6 hours) at an early stage often indicates a good prognosis, while late collateral circulation at the late stage or the existence of collateral circulation after thrombolysis should be paid high attention to. Collateral circulation at a late stage may happen with hemorrhagic transformation due to inappropriate treatment, and the collateral circulation that still exists after thrombolysis suggests that thrombolysis is ineffective. As the result, the accurate evaluation of collateral circulation is of high guiding value for the precise treatment of ICVD.

With the arterial transit artifact (ATA) on the image, 3D-pCASL can assess the formation of collateral circulation in the cerebral infarction area. ATA is a special phenomenon of ASL, and the creeping and linear high signal on brain surface caused by the retention of labeled blood in the blood vessel due to the slowing of the arterial blood flow under the pathological state. Zaharchuk et al. [18] conducted a systematic study of ATA, which confirmed that ATA was moderately consistent with digital subtraction angiography (DSA) in judging the collateral vessel formation, with high sensitivity and specificity. Therefore, 3D-pCASL can assess the prognosis based on the formation of collateral circulation. But it was reported that the increase of permeability of newly generated blood vessels would easily lead to hyperperfusion, bleeding and other complications after treatment [19]; therefore, the duration of thrombolytic therapy should be strictly controlled, and 3D-pCASL inspection should be timely conducted after thrombolytic therapy.

In addition, some patients would show crossed cerebellar diaschisis (CCD) after cerebral infarction, which refers to the phenomenon of metabolism and hypoperfusion in crossed cerebellum in case of unilateral supratentorial lesions. Studies have shown that the presence of CCD is also related to prognosis of cerebral infarction. Therefore, the accurate detection of CCD during clinical work could provide more information for clinical diagnosis and treatment of cerebral infarction and for therapeutic effect evaluation. 3D-pCASL could show the decrease of blood perfusion in crossed cerebellum of supratentorial lesions, which could provide an imaging basis for prognosis evaluation of cerebral infarction patients [20-21].

in the fine study of ICVD blood supply, the territorial ASL (tASL), also known as vessel-encoded arterial spin labeling, establishes a direct connection between the feeding artery and perfusion area; it can also selectively observe the blood perfusion of specific blood vessels, and show the opening of the communicating artery and secondary collateral circulation [22]. In some studies, tASL and DSA were conducted for 18 patients with intracranial or extracranial arterial stenosis or

occlusion to assess collateral circulation, which demonstrated that tASL can assess the formation of collateral circulation [23-24], and tASL MRA can realize quantitative assessment of CBF for specific cerebral blood flow [25]. Therefore, compared with other technologies, tASL has unparalleled advantages in assessment of fine diagnosis, treatment and prognosis.

4. Conclusion

With the above analysis, it could be found that 3D-pCASL technology has many outstanding clinical advantages in clinical application for ischemic cerebrovascular disease compared with other imaging techniques, but the realization of these clinical applications requires an appropriate PLD during imaging. However, in practice, the selection of PLD is currently empirical and cannot be accurately estimated [26]. Therefore, PLD requires a unified standard for applying ASL more deeply in diagnosis of the changes of cerebral blood flow due to cerebral small vessel disease and further identification of the location of cerebral arterial embolism in patients with cerebral infarction.

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