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Cognitive Functional Impairment and Hemodynamic Changes in Patients with Symptomatic Leukoaraiosis

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Abstract

Objective: The pathogenesis of leukoaraiosis is still unclear. Many studies have determined that changes in the hemodynamics associated with leukoaraiosis, impaired cerebrovascular reserve, and intracranial hypoperfusion can lead to various clinical manifestations such as motor or cognitive impairment. The purpose of this study was to investigate the relationship between cognitive functional changes and imaging characteristics in patients with symptomatic leukoaraiosis, and to observe the corresponding changes in hemodynamics. *Methods*: A total of 203 Han patients (aged 43 - 93 years) with symptomatic leukoaraiosis were included in this study. Head magnetic resonance imaging was semi-quantified according to the Fazekas grading standard. Then, each patient was evaluated in terms of cognitive (Montreal scale) and executive function (trail-making test A [TMTA] and TMTB). Specifically, the TMTA asks patients to connect points on a piece of paper numbered from 1 to 25 in order and the TMTB asks patients to arrange numbers and letters in alternating order. In the current work, revised versions of these tests used are to include numbers in square and circular shapes where the shapes needed to be arranged in alternating order. The time required to complete the TMTA and TMTB was recorded. The changes in the blood flow velocity of the middle cerebral artery were also observed using routine Transcranial Doppler ultrasound and the breath-holding test. The dynamic curves of blood flow velocity during the breath-holding test were examined. *Results*: The cognitive and executive functions of patients with leukoaraiosis are related to the classification of image-based disease characteristics. In this sense, the more serious the leukoaraiosis is, the larger the impairment of cognitive and executive function is. According to the breath-holding test, the peak pattern of the blood flow velocity in the middle cerebral artery was significantly dif-

ferent between the various grades of leukoaraiosis. The peak type of Fazekas grade 0 and I was in the same direction, while the peak type of Fazekas grade II and III was significantly opposed (both $p < 0.05$). *Conclusions*: The impairment of cognitive and executive functions in patients with leukoaraiosis correlates with the severity of image-based disease manifestations, which are generally depicted as intracranial hypoperfusion.

Keywords

Leukoaraiosis, Cerebral Hemodynamics, Transcranial Doppler Ultrasound, Breath-Holding Test, Peak Type, Middle Cerebral Artery, Cognitive Function, Executive Function

1. Introduction

With the current aging rate of the general population, the small cerebral vascular disease has become an important research topic in the field of neurology. In particular, leukoaraiosis has become characterized by a group of clinical syndromes with imaging characteristics associated with small cerebral vascular diseases [1] (Hainsworth *et al.*, 2017). As many as 30 years ago, Hachinski *et al.* [2] (Hachinski *et al.*, 1987) proposed imaging-based diagnostic criteria for leukoaraiosis, which has since inspired a large number of studies surrounding leukoaraiosis. When using both T2-weighted and fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) sequence, leukoaraiosis can be characterized by white matter hyper-intensity [3] (Wardlaw *et al.*, 2013). According to imaging features, leukoaraiosis can be classified into either periventricular or subcortical subtypes. Since the artery supplying blood to the white matter region is the terminal or perforating artery, it is located in the watershed area and the blood vessels are often long and curved. Therefore, during cerebral ischemia or hypoperfusion, these areas are prone to ischemic changes and can result in changes to the imaging characteristics [4] (Markus *et al.*, 2000). If the case is complicated by risk factors for cerebrovascular disease such as age [5] (Lin *et al.*, 2017b), hypertension[6] (Kokubo *et al.*, 2015; [7] Leung *et al.*, 2017), diabetes [8] (Maccarrone *et al.*, 2017), or dyslipidemia [9] (Shi *et al.*, 2017), cerebral arteriosclerosis can gradually develop and results in clinical manifestations [10] (Lin *et al.*, 2017a) such as dyskinesia, abnormal gait, urinary incontinence [11] (Chiu *et al.*, 2015), cognitive decline [12] (Cheng *et al.*, 2017; [13] Li *et al.*, 2017; [14] Sivakumar *et al.*, 2017), and depression. Importantly, many of these co-morbidities can lead to impaired memory function. Recently, a 10-year clinical study examined 2000 patients with acute stroke or transient cerebral ischemia, including 222 patients with pure motor stroke. It was found that compared with non-lacunar stroke patients, pure motor stroke patients exhibited a better prognosis, significantly reduced complications and in-hospital mortality, shorter hospital stay and better recovery of clinical symptoms. Nevertheless, it should be mentioned that 85% of

pure motor strokes are caused by lacunar infarction and 15% by other stroke subtypes [15] (Arboix A *et al.*, 2001).

While various imaging and clinical manifestations of leukoaraiosis have been documented, the pathogenesis of this disease is not yet clear. Many studies have examined the hemodynamics associated with leukoaraiosis and suggest that, compared to healthy individuals, the cerebrovascular function is impaired and intracranial hypoperfusion is present. Some work has utilized transcranial Doppler ultrasound (TCD) observations such as blood flow velocity (BFV) and the pulsatility index (PI) to investigate their dynamic evolution. Fisse *et al.* [16] (Fisse *et al.*, 2016) have suggested that the intracranial large arterial blood flow spectrum of TCD can provide information regarding the functional status of related downstream micro-vessels. Similarly, Malojcic *et al.* [17] (Malojcic *et al.*, 2017) reported that non-invasive ultrasonography can assess intracranial hypoperfusion caused by vascular disease. By evaluating the autoregulation of cerebral blood flow, Guo *et al.* [18] (Guo *et al.*, 2015) found that the dynamic brain-regulatory function of the middle cerebral artery (MCA) and the posterior cerebral artery (PCA) regulate the function of the entire brain. In particular, this work concluded that the impairment of dynamic brain function in small cerebral vascular disease is not only unilateral or bilateral, and by contrast, affects the entire brain.

In this study, we acquired MRI data from patients with symptomatic leukoaraiosis and evaluated their cognitive and executive function to identify the relationship between the clinical disease manifestations and the imaging characteristics. The TCD was then used for routine examination and to evaluate the breath-holding test to observe the dynamic evolution of the BFV in the MCA. TCD was also used to obtain two different types of peak blood flow patterns and to analyze the imaging features of leukoaraiosis to further investigate the mechanism of vascular regulation. This is the first study that examines the hemodynamic changes of patients with symptomatic leukoaraiosis using the dynamic BFV curve of the breath-holding test and provides a theoretical basis for the pathogenesis of leukoaraiosis.

2. Materials and Methods

Patients

A total of 203 patients (of Han nationality) were enrolled in this study from the Department of Neurology at the Fifth People's Hospital of Shenyang between November 2016 and October 2017. Patients were either diagnosed with ischemic stroke or showed clinical chronic progressive ischemic symptoms that included dizziness, headache, memory loss, depression, aphasia, numbness, and gait instability. Leukoaraiosis was diagnosed based on a brain MRI. There were 167 patients (82.3%) with acute cerebral infarction, 15 patients (7.4%) with transient cerebral ischemia, and 21 patients (10.3%) with chronic ischemic cerebrovascular disease. Among them, 150 patients exhibited pure motor hemiparesis (73.9%), 10 pure sensory stroke (4.9%), 24 sensorimotor syndrome (10.3%), 6 atax-

ia-hemiplegia (3.0%), 12 (5.9%) dysarthria-clumsy hand and 5 (2.5%) atypical lacunar syndromes.

The individual medical profiles were documented and included age, gender, smoking and drinking history, hypertension, diabetes, coronary heart disease and previous stroke history. Additionally, various laboratory examinations, including routine blood and urine tests, as well as tests for liver and renal function, thyroid function and immunity were performed on every individual. Electrocardiography, carotid artery ultrasound, head computed tomography (CT), and head MRI were also performed.

The exclusion criteria included the following: 1) contraindications to brain MRI; 2) severe cerebrovascular disease sequelae, such as disturbance of consciousness and visual impairment, which do not cooperate with the behavioral assessments; 3) severe respiratory, cardiovascular, or hepatorenal diseases; 4) white matter damage, such as subcortical arteriosclerotic encephalopathy, autoimmune white matter demyelination, hypoxic encephalopathy, normal intracranial pressure hydrocephalus, hypoglycemia- or toxication-induced encephalopathy, multiple sclerosis, or hereditary white matter disease; 5) disability that prevents Valsalva action; 6) diameter of intracranial infarction lesion > 1.5 cm; or 7) moderate or severe stenosis (>50%) of intracranial or extracranial carotid artery, MCA, or vertebro-basilar artery.

This study was approved by the local Ethics Committee with a clinical registration number of ChiCTR1800014421. Written informed consent was obtained from each participant.

Radiological Evaluation

Brain MRI sequences, including T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR) and magnetic resonance angiography (MRA), were acquired from all patients using a General Electric 1.5T MRI scanner (GE Healthcare, Waukesha, WI). The MRI data was reviewed by two radiologists and one neurologist independently. The clinical severity of leukoaraiosis was evaluated according to the Fazekas scale: no leukoaraiosis (grade 0), mild leukoaraiosis (grade I), moderate leukoaraiosis (grade II), and severe leukoaraiosis (grade III) [19] (Fazekas *et al.*, 1987).

Cognitive Assessment

Individual cognitive function was assessed according to the Montreal cognitive assessment system (MoCA). Executive function was assessed using the trail making test Part A (TMTA) and Part B (TMTB). Double-blind testing was performed by two neurologists, independently. The TMTA asks patients to connect points numbered from 1 to 25 on a piece of paper in order and the TMTB asks patients to arrange numbers and letters in alternating order. In the current work, revised versions of these tests were use is to include numbers in square and circular shapes where the shapes needed to be arrange in alternating order. The time required to complete the TMTA and TMTB was ultimately recorded.

TCD Examination

Conventional TCD tests were performed to exclude patients with intracranial

vasculature exhibiting moderate or severe stenosis (>50%). Additionally, the TCD examination was performed after the breath-holding test. Blood flow signals were detected via the left temporal window using a 2.0 MHz pulse probe at a depth of 50 - 65 mm. When the unilateral common carotid artery was compressed along the anterior border of the sternocleidomastoid muscle, the BFV of the ipsilateral MCA was significantly reduced. The baseline BFV was measured in the resting state, and the mean BFV of the bilateral MCA was calculated. Following this, the patient was told to take a deep breath and subsequently hold his/her breath for 30 seconds. The mean BFV of the bilateral MCA after the breath-holding test as well as the breath holding time were documented. Finally, the average value of the bilateral BFV was used to draw the dynamic curve of the whole breath-holding process.

Statistical Analysis

The SPSS 24.0 software (SPSS Inc., Chicago, IL, USA) was used to perform all statistical analyses. Enumeration data are presented as percentages and were analyzed using a Chi-square test. Quantitative data with a non-normal distribution and heterogeneity of variance were compared using a Kruskal-Wallis test (Bonferroni corrected for multiple comparisons). *P-values* ≤ 0.05 were considered significant.

3. Results

Clinical Characteristics and Laboratory Parameters

The patients' age ranged from 43 to 93 years. Among the four groups designated by the Fazekas grading system, there was no significant difference in gender (p = 0.056), smoking history (p = 0.314), hypertension (p = 0.448), or diabetes (p = 0.918). By contrast, older age (p = 0.006), coronary heart disease (p = 0.000) and stroke history (p = 0.004) were identified as independent risk factors for leukoaraiosis.

Among the four groups, there was no difference in the level of serum total cholesterol (p = 0.090), triglyceride (p = 0.551), low-density lipoprotein (p = 0.522), high-density lipoprotein (p = 0.317), apolipoprotein A/B (p = 0.307), apolipoprotein A1 (p = 0.670), glycosylated hemoglobin (p = 0.825), or homocysteine (p = 0.708). The statistical results are summarized in Table 1.

Cognitive Functions

The individual MoCA scores ranged from 9 to 29 (mean ± SD: 21.63 ± 4.964). Pairwise comparisons showed no difference in MoCA scores between the leukoaraiosis grade II and grade III groups (p = 0.473) or between the grade 0 and grade I groups (p = 1.000). The MoCA scores in the grade 0 group were significantly higher than those in the grade II (p = 0.000) and grade III (p = 0.000) groups. The MoCA scores in the grade I group were significantly higher than those inthe grade II (p = 0.000) and grade III (p = 0.000) groups.

The individual TMTA scores ranged from 30 to 170 (mean ± SD: 69.62 ± 35.127) and the individual TMTB scores ranged from 40 to 390 (mean ± SD: 150.67 ± 76.339). Pairwise comparisons showed no difference in the TMTA or

Table 1. Clinical characteristics and laboratory examination results of the included patients with leukoaraiosis.

Characteristics	Fazekas scale				Statistical value	*p* value
	Grade 0	Grade I	Grade II	Grade III		
Total number (n)	44	79	44	36	-	-
Age (years; mean ± SD)	61.02 ± 7.9	66.97 ± 11.1	71.75 ± 10.82	76.14 ± 8.1	22.886	0.006
Male/female	25/19	40/39	22/22	10/26	7.558	0.056
Smoking history	43.2%	36.7%	29.5%	25.0%	3.5555	0.314
Hypertension	70.5%	72.2%	79.5%	83.3%	2.656	0.448
Diabetes	31.8%	35.4%	38.6%	33.3%	0.502	0.918
Coronary heart disease	15.9%	4.2%	34.1%	61.1%	17.883	0.000
Stroke history	27.3%	31.6%	52.3%	58.3%	13.080	0.004
Total cholesterol (mmol/L)	4.84 ± 1.35	4.56 ± 1.37	4.08 ± 1.07	4.55 ± 1.21	6.502	0.090
Triglyceride (mmol/L)	2.44 ± 1.99	2.06 ± 0.93	2.00 ± 0.73	1.95 ± 0.85	2.106	0.551
Low-density lipoprotein (mmol/L)	3.50 ± 1.02	3.56 ± 1.12	3.30 ± 0.79	3.60 ± 0.92	2.251	0.522
High-density lipoprotein (mmol/L)	1.33 ± 0.43	1.21 ± 0.42	1.35 ± 0.46	1.28 ± 0.42	3.527	0.317
Apolipoprotein A/B	1.09 ± 0.57	0.93 ± 1.84	0.97 ± 0.13	0.98 ± 0.34	3.606	0.307
Apolipoprotein A1 (mg/L)	0.87 ± 0.44	0.86 ± 0.07	0.87 ± 0.52	0.87 ± 0.59	1.553	0.670
Glycosylated hemoglobin (%)	6.33 ± 1.30	6.42 ± 1.43	6.22 ± 1.15	6.46 ± 1.53	0.902	0.825
Homocysteine (mmol/L)	17.9 ± 8.63	19.5 ± 9.58	23.4 ± 22.8	22.5 ± 16.2	1.389	0.708

Quantitative data with a non-normal distribution and heterogeneity of variance were compared using a Kruskal-Wallis test.

TMTB scores between the grade II and grade III groups (TMTA: $p = 0.685$; TMTB: $p = 0.364$) or between the grade 0 and the grade I groups (TMTA: $p = 1.000$; TMTB: $p = 1.000$). The TMTA and TMTB scores in the grade 0 group were significantly lower than those in the grade II ($p = 0.000$) and grade III ($p = 0.000$) groups. The TMTA and TMTB scores in the grade I group were significantly lower than those in the grade II ($p = 0.000$) and the grade III ($p = 0.000$) groups. The cognitive evaluation results are summarized in Table 2.

TCD Examination

TCD was used to record the breath-holding test for patients with leukoaraiosis and to draw the average BFV curves of the bilateral MCA. The time points for which data was plotted were 0, 3, 5, 10, 15 seconds after the start of deep inspiration, 30 seconds until the deep inspiration stopped, and 6 and 15 seconds after deep exhalation. In general, we observed two different spatial-temporal profiles of the BFV curves that we refer to as a same-direction peak type (Figure 1) and an opposite direction peak type (Figure 2).

The peaks of each group were compared using a chi-square test and resulted in significant differences among the groups ($p = 0.000$). There was no significant difference between grade 0 and I and there was no significant difference between

leukoaraiosis II and III grade. However, there was a significant difference between grade II and grade 0, between grade II and grade I, between grade III and grade 0, and between grade III and grade I. The results are summarized in Table 3, Table 4 and Figure 3.

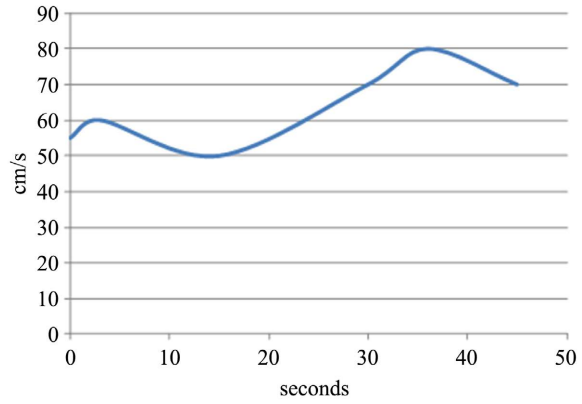

Figure 1. Representative cerebral blood flow (CBF) curve of the same direction peak type.

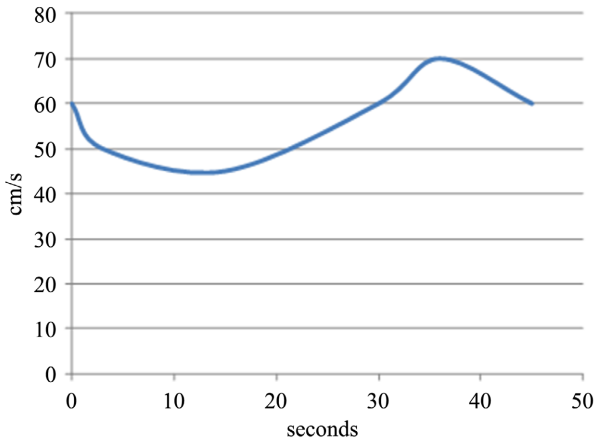

Figure 2. Representative cerebral blood flow (CBF) curve of the opposite direction peak type.

Table 2. Cognitive evaluation results of the included patients with leukoaraiosis.

Fazekas scale	Number (n)	MoCA (mean ± SD)	TMTA (mean ± SD)	TMTB (mean ± SD)
Grade 0	44	25.09 ± 2.270	47.84 ± 12.232	100.80 ± 50.807
Grade I	79	24.81 ± 1.955	48.43 ± 13.522	110.57 ± 50.991
Grade II	44	17.66 ± 4.281	94.27 ± 31.815	198.77 ± 60.132
Grade III	36	15.25 ± 2.298	112.58 ± 31.845	240.83 ± 46.888

Data are expressed as the median/interquartile range. Quantitative data with a non-normal distribution and heterogeneity of variance were compared using a Kruskal-Wallis test. Fazekas scale: No leukoaraiosis (grade 0), mild leukoaraiosis (grade I), moderate leukoaraiosis (grade II), and severe leukoaraiosis (grade III). MoCA: Montreal Cognitive Assessment; TMTA: Trail-making test Part A; TMTB: Trail-making test Part B.

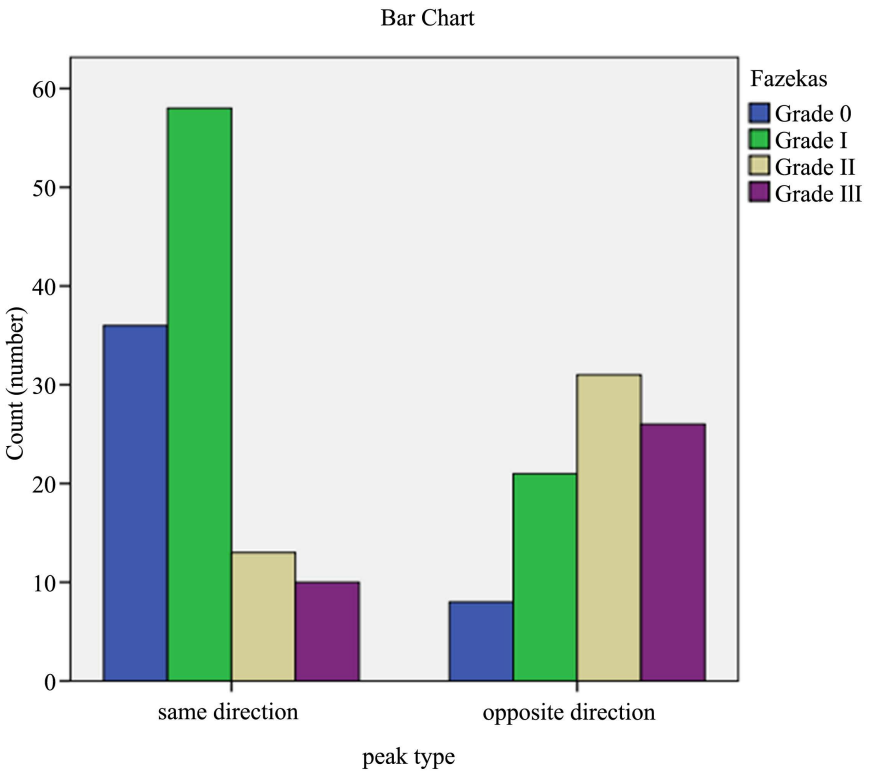

Figure 3. Bar chart comparing the distribution of peak types among the Fazekas scale patient subgroups.

Table 3. Peak type Chi-square test comparison between the different Fazekas scale patient subgroups.

	Statistical value	Degree of freedom	*p* value
Pearson chi square	45.960a	3	0.000
Likelihood ratio (L)	47.496	3	0.000
Linear correlation	39.083	1	0.000

The peaks of each group were compared using a Chi-square test. The results showed significant differences among the groups (p = 0.000). There was no significant difference between grade 0 and I and there was no significant difference between leukoaraiosis II and III grade. There was a significant difference between grade II and grade 0, between grade II and grade I, between grade III and grade 0, between grade III and grade I.

Table 4. Comparison of peak distributions between the different Fazekas scale patient subgroups.

peak type	Fazekas 0	Fazekas I	Fazekas II	Fazekas III
number	44	79	44	36
same direction	36a (30.8%)	58a (49.6%)	13b (11.1%)	10b (8.5%)
opposite direction	8a (9.3%)	21a (24.4%)	31b (36.0%)	26b (30.2%)

Each subscript letter indicates that there is no significant difference in column proportions between these categories.

4. Discussion

At present, it is believed that the pathogenesis of leukoaraiosis is associated with intracranial atherosclerosis [20] (Nam *et al.*, 2017), endothelial injury and oxidative stress [8] (Maccarrone *et al.*, 2017), the destruction of the blood-brain barrier [21] (Valdes Hernandez *et al.*, 2017), and progressive cerebral arteriosclerosis and intracranial hypoperfusion. When patients with leukoaraiosis suffer from long-term hypertension, diabetes, or other susceptibility factors of cerebrovascular disease, arterial stiffness increases [1] (Hainsworth *et al.*, 2017) and cerebrovascular arterial and lumen stenosis results in impaired autoregulation of whole cerebral blood vessels. However, this is a controversial theory regarding the pathogenesis of the disease [10] (Lin *et al.*, 2017a). Other studies have suggested that the hemodynamics of white matter lesions has since changed [22] (Turk *et al.*, 2016a) [23] (Turk *et al.*, 2016b). As we all know, the regulation of cerebral blood flow includes three aspects, namely blood pressure, neurogenic and metabolic regulation [24] (Hamel, 2006). Metabolic regulation is defined as the change of carbon dioxide metabolism, which further changes the diameter of small vessels (cerebrovascular reactivity) and leads to cerebral blood flow regulation that is consistent with the metabolic state. It is generally believed that when blood vessels are stimulated by vasodilatation and relaxation, the velocity of cerebral blood flow changes. It is in fact the responsiveness of cerebrovascular flow that is determined by these changes [25] (Smolinski and Czlonkowska, 2016).

A large number of studies [26] (van der Veen *et al.*, 2015; [12] Cheng *et al.*, 2017) have evaluated the cerebrovascular reactivity of leukoaraiosis using various neuroimaging methods, including TCD. Etherton *et al.* [27] (Etherton *et al.*, 2017) suggested that the FLAIR MRI sequence can macroscopically represent white matter, but cannot show the microstructure thereof. This group utilized diffusion tensor imaging (DTI) to observe a decrease in the anisotropic diffusion coefficient of normal white matter in the contralateral brain of the patients with acute ischemic stroke. It was further found that this reduction was associated with the impairment of nerve function at three months post-stroke. It is speculated that the integrity of the white matter after acute cerebral infarction can predict the prognosis of neurological function after stroke. However, due to the limitations of the application of DTI, more convenient, fast and accurate diagnostic tools are currently highly sought after by the medical community. Mok *et al.* [28] (Mok *et al.*, 2012) recently investigated the utility of TCD for screening small cerebral vascular disease and found that the increased PI of the MCA was related to the severity of white matter lesions. Interestingly, however, the PI was not related to the lacunar infarction or cerebral microhemorrhage. In general, an increased PI can be used as a screening marker for white matter lesions to indicate that a brain MRI is warranted. Altmann *et al.* [29] (Altmann *et al.*, 2016) also observed a decrease in the BFV and an increase in the PI of the middle cerebral arteries during acute stroke attacks in patients with small cerebral vascular disease using TCD. This work complements that of Arba *et al.* [30] (Arba *et al.*,

2017), that pointed out that blood flow changes in response to acute attacks of cerebral perfusion in patients with leukoaraiosis was related to the severity of the image. Turk *et al.* [22] (Turk *et al.*, 2016a) further found that the PI and resistance index of the patients with leukoaraiosis were slightly increased compared to the control group. In addition, the lower cerebral artery BFV and the increased stiffness of the carotid artery were found in the patients with leukoaraiosis as compared with the control group. This work suggests that the combination of these two features suggests a diagnosis of leukoaraiosis. These previous studies indicate that local stroke impairs the overall function of the brain, which is supported by the results of the current study using TCD that showed global brain dysfunction rather than local brain dysfunction. Despite this accumulating evidence, there is no uniform standard marker for the hemodynamic impairments associated with leukoaraiosis.

5. Conclusions

The current study shows for the first time the dynamic BFV of the MCA in the patients with symptomatic leukoaraiosis during the breath-holding test. The time-resolved behavior of the BFV showed the same peak shape for cases with Fzekas grades 0 and I, whereas cases with grades II and III exhibited an opposing direction peak pattern. More specifically, for Fazekas grade 0 and 1, we found that within 6 seconds after the start of deep inhalation, the BFV rose to a small peak and then soon decreased. After about 15 seconds, the BFV reached the lowest value and then began to rise until 30 seconds of deep inspiration. After starting excessive exhalation, the BFV peaked at about 6 seconds and then decreased again, gradually returning to the resting state value. For Fazekas grade II and II, the opposing direction peak pattern gradually decreased after deep inspiration began and did not increase until it reached the minimum value about 15 seconds after the deep inhalation started. Then, the BFV gradually increased and reached a peak after about 6 seconds of continuous exhalation after the end of the deep inhalation. The BFV then gradually fell back to the resting state value. The main difference between these two BFV behaviors is that within 6 seconds after the start of deep inhalation the BFV increased in one case and decreased in the other. Furthermore, as the descriptive name indicates, the same direction peak behavior exhibited two peaks in the same upward direction, while the opposing direction peak behavior exhibited two peaks in the opposite direction. There was also a statistically significant difference between the two peak types and the severity of leukoaraiosis imaging.

The different BFV behaviors that we observed were surprising and led us to ask how breathing may affect blood flow within the brain. In fact, various studies have reported that the autonomic nervous system regulates systemic vascular activity in the body [31] (Intharakham *et al.*, 2017). Additionally, the breath-holding test can detect the functional state of the afferent, central and efferent nerves in the sympathetic and parasympathetic baroreflex pathways [32] (Chida *et al.*,

1994). When a patient inhales deeply, oxygen is consumed by the metabolism of the body, which causes the partial pressure of carbon dioxide in cerebral arterial blood increases, the blood vessels to expand and the BFV to increase [33] (Ju *et al.*, 2017). Therefore, we believe that the two different peak shapes observed in this study are due to the impairment of autonomic nerve function in patients with leukoaraiosis, and that changes in hemodynamics exhibit impaired cerebral vascular function. The aggravation of leukoaraiosis causes intracranial hypoperfusion as well as clinical symptoms, such as cognitive and executive dysfunction. Intharakham *et al.* [31] (Intharakham *et al.*, 2017) recorded breath-holding test results from patients with lacunar infarction to observe changes in BFV, heart rate, and blood pressure in the MCA. The results suggested that parasympathetic nerve function was decreased in patients with lacunar infarction, however, an opposite conclusion was found in a study by Bohr *et al.* [34] (Bohr *et al.*, 2015). In order to verify the ability of the elderly autonomic nervous system to maintain physiological homeostasis of the brain, 45 elderly individuals (75 - 89 years old) were instructed to perform the Valsalva maneuver. The results showed that short-term repetitive hypoxia did not produce white matter hyperintensity, and did not support the cumulative effect of autonomic dysfunction on the formation of white matter lesions.

Since this study observed changes in hemodynamics in patients with leukoaraiosis, we further investigated the corresponding imaging markers of this phenomenon. Various studies [35] [36] (Blair *et al.*, 2016; Shi *et al.*, 2016) have used blood oxygen-dependent MRI and vascular stimulation to assess the vascular responsiveness of subcortical small vessel disease. Early studies showed that cerebrovascular reactivity decreased with increasing white matter lesions. After 4 years of follow-up observation, the occurrence of white matter lesions was found to be preceded by a gradual decrease in CBF. However, another study following patients suffering from a minor stroke and transient ischemic attack for three years found that CBF was reduced before the appearance of leukoaraiosis [37] (Bernbaum *et al.*, 2015). Another study investigated the progression of cognitive and cerebral changes in 30 patients with a first-ever lacunar infarct. The results indicated that frontal lobe dysfunction and regional cortical and subcortical grey matter atrophy best-differentiated lacunar infarct patients with and without cognitive impairment [38] (Grau-Olivares M *et al.*, 2010). Further investigations with larger sample sizes, possibly incorporating MRI-derived measures (*i.e.* DTI and cortical thickness evaluations), are needed to investigate the precise interactions between grey and white matter integrity. This will be particularly meaningful to identify cerebral mechanisms associated with progressive cognitive deterioration among such patients. In a separate study, more than half of the patients with a first-ever lacunar stroke and without cognitive impairment presented minor neuropsychological alterations. These minor alterations were mainly related not to leukoaraiosis but rather to the presence of clinically silent lacunar infarcts at the early stage of cerebral small vessel disease [39] (Blan-

co-Rojas L *et al.*, 2013). In the future, an indispensable line of research would be to precisely assess whether the presence of silent cerebral ischemia may affect the changes in brain structure and function. These patients can further be assessed as to whether neuropsychological alterations are a predictor of subcortical vascular dementia. In addition, it would also be interesting to determine if there exists a relationship between hemodynamic changes, silent lacunes (as measured via neuroimaging) and cognitive decline in symptomatic leukoaraiosis. Such an investigation would require a longer follow-up to observe the relationship between image changes and cerebral hemodynamics.

6. Limitations

The current study has some limitations that should be noted. One of the limitations is the quantification of white matter heterogeneity as we used a semi-quantitative method based on T2-weighted and FLAIR sequences. This approach may be less accurate than measuring white matter volumes, which should be performed in the future. Due to the poor cooperation of various patients, due to issues such as impaired cognitive function, hearing, and language skills, the breath-holding test could not be completed for all individuals. Therefore, the sample size in the current stud was small. Future large-sample and long-term clinical follow-up studies are needed to reveal the intrinsic link between the cognitive impairment of leukoaraiosis and imaging and cerebral hemodynamic changes.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

Authors' Contributions

Yuanhao Chen drafted the manuscript. Yujiao Lin collected and analyzed the data. Ying Bian reviewed the literatures and organized the data. Ying Bian conceived and designed the study. Yujiao Lin performed the TCD examinations. All authors read and approved the manuscript.

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