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Original Article

Effect of insomnia after acute ischemic stroke on cerebrovascular reactivity: a prospective clinical study in China

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ABSTRACT

Objective: To evaluate the effect of insomnia after acute ischemic stroke on cerebrovascular reactivity (CVR).

Methods: A total of 158 eligible patients with acute ischemic stroke were enrolled prospectively. Of these, six patients were lost to follow-up, and 152 were included in the final analysis. The patients were divided into the insomnia ($N = 24$) and non-insomnia ($N = 128$) groups based on the Athens Insomnia Scale. The insomnia group was further divided into benzodiazepine (BDZ) and non-BDZ treatment groups according to BDZ use status after ischemic stroke. The transcranial doppler ultrasound (TCD) breath-holding test was performed to calculate the breath-holding index (BHI) of the responsible cerebral middle artery, which was used to evaluate CVR. Then, univariate and multivariate linear regression analyses were carried out to determine the effect of insomnia after acute ischemic stroke on CVR.

Results: At one month after the onset of acute ischemic stroke, TCD-BHI was significantly higher in the non-insomnia group compared with the insomnia group ($p = 0.027$). In patients with insomnia, TCD-BHI was significantly higher in the BDZ treatment group compared with non-BDZ treatment group ($p = 0.039$). With age, hypertension, diabetes, hyperlipidemia, long-term smoking, blood homocysteine, and Athens Insomnia Scale score as independent variables, and TCD-BHI at one month after onset as a dependent variable, univariate and multivariate linear regression analyses indicated that the Athens Insomnia Scale score was an independent factor affecting TCD-BHI (regression coefficient, −0.013; 95% confidence interval (CI) −0.024 to −0.003).

Conclusion: Insomnia after acute ischemic stroke is an independent risk factor for CVR.

1. Introduction

Ischemic stroke represents the most common type of stroke, accounting for approximately 70% of all cases [1]; meanwhile, insomnia incidence after ischemic stroke is as high as 57% [2]. Insomnia refers to the inability to fall or stay asleep at night, affecting body functions during daytime, and at least three times per week for at least one month [3]. Insomnia after acute ischemic stroke could increase stroke recurrence [2,4–8] and impede functional recovery [9,10]. Cerebrovascular reactivity (CVR) reflects the diastolic function of cerebral arteries under stimulation by external vascular dilation factors. Reduced CVR is one of the manifestations of damaged cerebrovascular reserve function [11], and also affects recurrence and recovery in ischemic stroke [12–14]. Therefore, it is worth assessing whether insomnia after acute ischemic stroke impacts CVR, which is currently unknown. This study aimed to evaluate the effect of insomnia after acute ischemic stroke on CVR by a multivariate and prospective analysis.

2. Methods

2.1. Patients

Inclusion criteria were: (1) acute ischemic stroke, diagnosed by cranial magnetic resonance imaging; (2) age between 18 and 85

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years; (3) enrollment within three days of onset; (4) first stroke; (5) either middle cerebral artery considered to be responsible for the ischemic stroke; and (6) signed informed consent provided by the patients or their relatives.

Exclusion criteria were: (1) coma; (2) existing overt insomnia before ischemic stroke; (3) use of drugs for improving sleep within two weeks before the ischemic stroke; (4) existing overt respiratory dysfunction or obstructive sleep apnea syndrome; (5) no ability to cooperate in the transcranial doppler ultrasound (TCD) breath-holding test; (6) the offending middle cerebral artery showing complete occlusion; (7) unknown etiology; and (8) participation in another clinical study within three months.

2.2. Observation indicators and evaluation method

Age, gender, ischemic stroke etiology, history of hypertension and diabetes, history of long-term smoking (more than six months and 10 cigarettes per day), lung or urinary tract infection in the acute stage, and patient treatments were recorded. White blood cell (WBC) count, and blood lipid, homocysteine and hypersensitive c-reactive protein (hs-CRP) levels at baseline, Hamilton depression scale (HDS, 24 items) score at two weeks after onset, Athens Insomnia Scale score at one month after onset, and TCD breath-holding test at baseline were evaluated. Then, blood WBC count and hs-CRP, and TCD breath-holding test were reviewed at one month after onset.

The Athens Insomnia Scale, internationally recognized for the assessment of sleep quality, was used to evaluate sleep time and depth, as well as daytime sleepiness for the previous month. It has good validity and reliability, and insomnia is considered with a score above 6 [15].

The TCD breath-holding test is a major non-invasive method for evaluating CVR. Patients were placed in the supine position and calmly breathed for 5 min; after, they were instructed to hold their breath for 20–35 s after normal inspiration. The mean velocities of the offending middle cerebral artery at rest and breath-holding completion were evaluated and recorded, and the breath-holding index (BHI) was calculated according to the following formula: BHI = [(mean velocity at the end of breath holding − mean velocity at rest)/mean velocity at rest] × 100/time of breath holding (s) [11]. The higher the BHI in the TCD breath-holding test, the better the CVR, ie the better the cerebral blood flow reserve capacity [11].

2.3. Treatment

A treatment team from Neurology department of Shenzhen People's Hospital was in charge of the enrolled patients' therapy. All patients received treatments for stroke and associated risk factors according to the 2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke formulated by the American Heart Association and American Stroke Association [16]. All patients received aspirin (0.1 per day) and atorvastatin (20 mg per night) at the acute stage of ischemic stroke. Angiotensin II receptor antagonist or calcium channel blocker were used for antihypertensive therapy, and the goal blood pressure was 120–140 mmHg for systolic blood pressure and 70–90 mmHg for diastolic blood pressure in this study. When patients were enrolled, the treatment team would find out whether there was a tendency for insomnia according to consultation and experience, and use benzodiazepines (BDZs) for prophylactic treatment. Alprazolam (0.4 mg per night), a type of BDZ, was used to improve insomnia uniformly in this study. In case of post-stroke depression symptoms (eg, lack of interest, indifference and anxiety, with HDS scores $\geq$8) fluoxetine (20 mg per day), which is a kind of selective serotonin reuptake inhibitor (SSRI), was administered.

2.4. Grouping and endpoint event

The enrolled patients whose Athens Insomnia Scale scores exceeded six were assigned to the insomnia group, and the remaining individuals to the non-insomnia group. The insomnia group was further divided into the BDZ and non-BDZ treatment groups, according to BDZ use status after ischemic stroke.

The TCD-BHI at one month after acute ischemic stroke onset was set as the endpoint in this study.

2.5. Blinding method

Single blinding was adopted. Case data registration was performed by a special record keeper; the TCD breath-holding test was performed by a designated technician, and the Athens Insomnia Scale and HDS scores were assessed by a designated examiner. Neither of the above personnel was involved in any other study process other than their respective part.

2.6. Sample size estimation

We used the data of the first 20 enrolled patients for total sample size calculation. There were four cases in the insomnia group and 16 in the non-insomnia group. The mean TCD-BHI at one month after onset was 0.79 ± 0.41 in the insomnia group, and 1.02 ± 0.31 in the non-insomnia group. The underlying influential factors of TCD-BHI (eg, age, hypertension, diabetes, hyperlipidemia, long-term smoking, blood homocysteine, and Athens Insomnia Scale score) were set as independent variables, while TCD-BHI at one month after onset was considered a dependent variable. With a type I error α of 0.05, a type II error β of 0.20, a statistical power of 90%, and an expected loss ratio of about 10%, the total sample size was 158 cases as calculated by the *PASS 11.0* software (NCSS, USA).

2.7. Ethical standards

This study was approved by the Shenzhen People's Hospital Ethics Committee. Patients or their legal relatives provided signed informed consent before enrollment, and had the right to withdraw after enrollment.

2.8. Statistical analysis

SPSS 24.0 was used for all statistical analyses. Measurement data with normal distribution were mean ± standard deviation (SD), and were compared by *t*-test. Measurement data with skewed distribution were presented as median and quartile, and compared by the rank-sum test. Count data were compared by the chi-squared test. Univariate and multivariate linear regression analyses were used to evaluate whether insomnia after acute ischemic stroke was an independent risk factor for CVR. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline data of study

The study flowchart is shown in Fig. 1. A total of 158 patients who met the inclusion and exclusion criteria were enrolled from January 2016 to June 2018 in Shenzhen People's Hospital, including

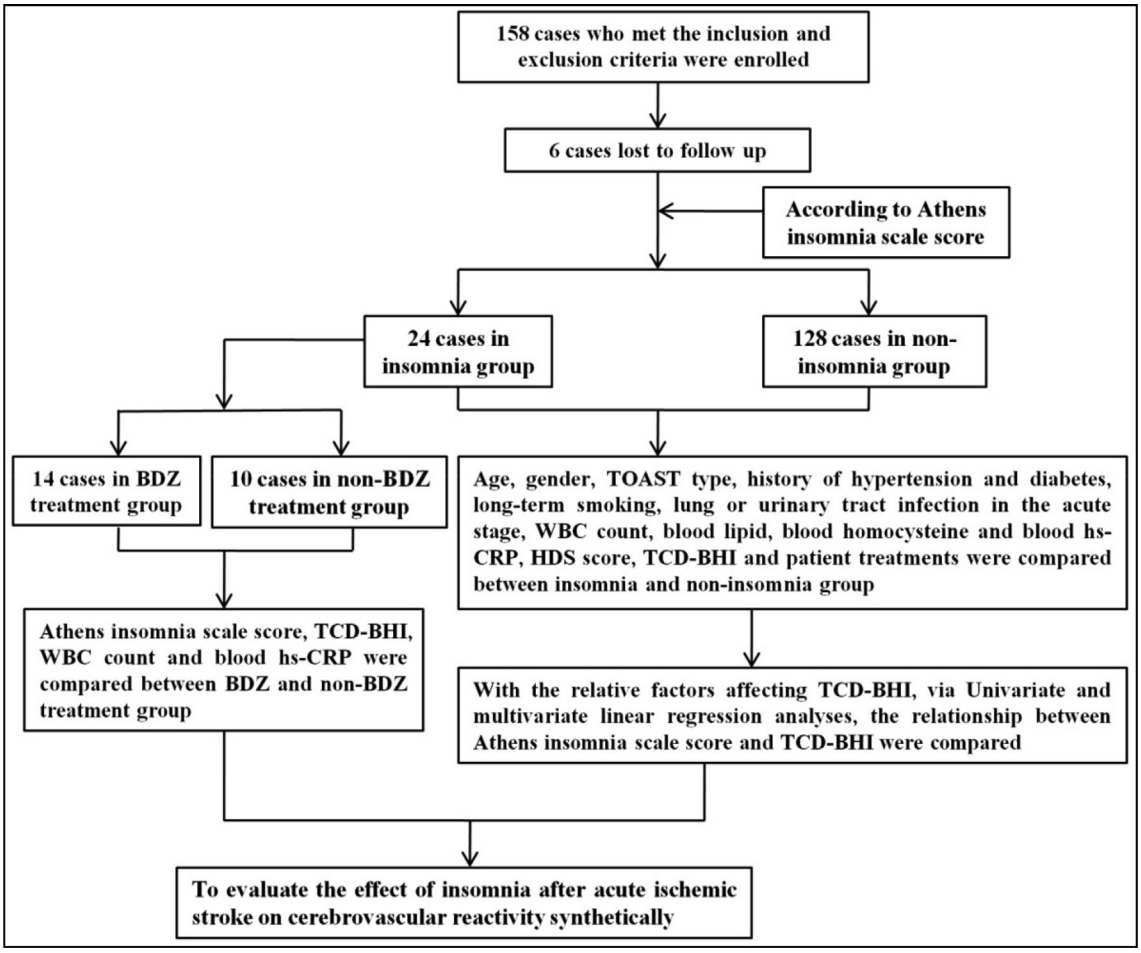

Fig. 1. Flowchart of study. BDZ, benzodiazepine; HDS, Hamilton depression scale; hs-CRP, hs-CRP, hypersensitive c-reactive protein; TCD-BHI, transcranial doppler ultrasound breath-holding index; TOAST, Trial of Org 10172 in acute stroke treatment; WBC, white blood cell.

six (3.8%) lost to follow up. Therefore, 152 patients were finally analyzed. According to the Athens Insomnia Scale scores, insomnia incidence after acute ischemic stroke was 15.8%; the enrolled patients were then divided into the insomnia ($N = 24$) and non-insomnia ($N = 128$) groups.

There were no significant differences in age, gender distribution, Trial of Org 10,172 in acute stroke treatment (TOAST) type, hypertension, diabetes, hyperlipidemia, long-term smoking, lung or urinary tract infection, TCD-BHI, WBC count, blood homocysteine and hs-CRP between insomnia and non-insomnia groups. HDS scores were significantly higher in the insomnia group compared with the non-insomnia group ($p < 0.001$) (Table 1).

3.2. Effect of insomnia on acute ischemic stroke at one month after onset

One month after onset, WBC count showed no significant difference between the two groups, while TCD-BHI was significantly higher and blood hs-CRP significantly lower in the non-insomnia group compared with the insomnia group ($p = 0.027$ and $p = 0.028$, respectively). The proportion of patients administered BZDs was significantly lower in the insomnia group compared with the non-insomnia group (58.3% vs 92.2%, $p < 0.001$). The proportion of patients administered SSRIs showed no significant difference between the two groups, although there was an increasing trend in the non-insomnia group (50.7% vs 37.5%, $p = 0.232$) (Table 2).

3.3. Comparison of Athens Insomnia Scale score and BHI in the insomnia group

Based on BDZ use status after ischemic stroke, the insomnia group was further divided into the BDZ ($N = 14$) and non-BDZ ($N = 10$) treatment groups. Athens Insomnia Scale scores were significantly higher in the non-BDZ treatment group compared with the BDZ treatment group ($p = 0.024$). TCD-BHI showed no significant difference between BDZ and non-BDZ treatment groups at baseline, but was significantly higher in the BDZ treatment group compared with the non-BDZ treatment group at one month after stroke onset ($p = 0.039$) (Table 3).

3.4. Univariate and multivariate analyses for factors affecting BHI

With age, hypertension, diabetes, hyperlipidemia, long-term smoking, blood homocysteine, and Athens Insomnia Scale score as independent variables, as well as TCD-BHI at one month after onset as a dependent variable, univariate linear regression analysis indicated that TCD-BHI was significantly correlated with age, long-term smoking, hypertension and Athens Insomnia Scale score ($p = 0.001$, $p = 0.030$, $p = 0.023$ and $p = 0.016$, respectively) (Table 4).

Table 1
Comparison of data at baseline between insomnia and non-insomnia groups.

	Insomnia group	Non-insomnia group	t, χ^2, Z-value	p
Number of cases, *N*	24	128		
Age (years)	65.25 ± 13.56	60.09 ± 13.50	1.719[a]	0.088
Female, *N* (%)	8 (33.3%)	41 (32.0%)	0.016[b]	0.900
TOAST type: LAA/SAO/CE/SOE, *N* (%)	10/9/3/2 (41.7%/37.5%/12.5%/8.3%)	47/58/16/7 (36.7%/45.3%/12.5%/5.5)	0.692[b]	0.875
Long-term smoking, *N* (%)	8 (33.3%)	48 (37.5%)	0.151[b]	0.698
Hypertension, *N* (%)	20 (83.3%)	82 (64.1%)	3.400[b]	0.065
Diabetes, *N* (%)	8 (33.3%)	48 (37.5%)	0.151[b]	0.698
Hyperlipidemia, *N* (%)	6 (25.0%)	33 (25.8%)	0.006[b]	0.936
Blood homocysteine (μmol/L)	16.37 ± 6.55	15.57 ± 10.08	1.099[a]	0.274
WBC count (10^9/L)	7.46 ± 3.40	6.80 ± 2.32	1.193[a]	0.235
Blood hs-CRP (mg/L)	4.80 (1.63, 7.68)	4.42 (2.31, 8.20)	−0.452[c]	0.651
Lung or urinary tract infection in the acute stage, *N* (%)	5 (20.8%)	22 (17.2%)	0.184[b]	0.668
BHI at baseline	0.77 ± 0.19	0.76 ± 0.18	0.140[a]	0.889
HDS score	13.29 ± 5.97	8.60 ± 5.71	3.672[a]	<**0.001**

BHI, breath-holding index; CE, cardiogenic embolism; HDS, Hamilton depression scale; hs-CRP, hypersensitive c-reactive protein; LAA, large artery atherosclerosis; SAO, small artery occlusion; SOE, stroke of other demonstrated etiology; TOAST, Trial of Org 10,172 in acute stroke treatment; WBC, white blood cell.
[a] Conducted *t*-test.
[b] Conducted chi-squared test.
[c] Conducted rank-sum test.

Table 2
Comparison of administered with benzodiazepine (BDZ) or selective serotonin reuptake inhibitors (SSRIs), breath-holding index (BHI), white blood cell (WBC) count and blood hypersensitive c-reactive protein (hs-CRP) at one month after onset between insomnia and non-insomnia groups.

	Insomnia group	Non-insomnia group	t, χ^2 value	p
Number of cases, *N*	24	128		
Administered with BDZ, *N* (%)	14 (58.3%)	118 (92.2%)	20.271[b]	<**0.001**
Administered with SSRIs, *N* (%)	9 (37.5%)	65 (50.7%)	1.427[b]	0.232
BHI at 1 month after onset	0.91 ± 0.27	1.03 ± 0.24	−2.236[a]	**0.027**
WBC count (10^9/L)	6.75 ± 2.13	6.30 ± 1.71	1.134[a]	0.258
Blood hs-CRP (mg/L)	3.80 (1.18, 17.98)	1.80 (0.70, 4.82)	−2.198[c]	**0.028**

[a] Conducted *t*-test.
[b] Conducted chi-squared test.
[c] Conducted rank-sum test.

Table 3
Comparison of Athens Insomnia Scale score and breath-holding index (BHI) between benzodiazepine (BDZ) and non-BDZ treatment groups for patients in the insomnia group.

	BDZ treatment group	Non-BDZ treatment group	t-value	p
Number of cases (*N*)	14	10		
Athens Insomnia Scale score	9.21 ± 2.91	12.20 ± 3.08	2.416[a]	**0.024**
BHI at baseline	0.77 ± 0.17	0.76 ± 0.23	−0.126	0.901
BHI at 1 month after onset	1.00 ± 0.23	0.77 ± 0.29	−2.199[a]	**0.039**

[a] Conducted *t*-test.

Table 4
Univariate linear regression analysis for factors affecting breath-holding index (BHI) after acute ischemic stroke.

	B-value	Standardized beta	t-value	p	95% CI
Constant	1.495				
Age	−0.005	−0.261	−3.380	**0.001**	−0.008 to −0.002
Long-term smoking	−0.088	−0.169	−2.189	**0.030**	−0.168 to −0.009
Hypertension	−0.092	−0.174	−2.290	**0.023**	−0.172 to −0.013
Diabetes	−0.017	−0.032	−0.429	0.669	−0.093 to 0.060
Hyperlipidemia	−0.040	−0.071	−0.948	0.345	−0.124 to 0.044
Blood homocysteine	−0.002	−0.092	−1.205	0.230	−0.006 to 0.002
Athens Insomnia Scale score	−0.013	−0.186	−2.447	**0.016**	−0.024 to −0.003

The four factors with significant correlations in univariate analysis were entered into a multivariate linear regression model as independent variables. The analysis showed that Athens Insomnia Scale score was an independent factor affecting TCD-BHI after acute ischemic stroke, with a negative correlation [regression coefficient of −0.013; 95% confidence interval (CI) −0.024 to −0.003] (Table 5).

4. Discussion

Stroke is closely associated with insomnia. A random population survey of 10 years showed that individuals with insomnia have a higher risk of stroke compared with the general population [4]. The incidence of insomnia after acute ischemic stroke is also very high [2], which could increase stroke recurrence and affect neurological

Table 5
Multivariate linear regression analysis for factors affecting breath-holding index after acute ischemic stroke.

	B-value	Standardized beta	*t*-value	*p*	95% CI
Constant	1.454				
Age	−0.005	−0.267	−3.486	**0.001**	−0.008 to −0.002
Long-term smoking	−0.096	−0.185	−2.445	**0.016**	−0.174 to −0.018
Athens Insomnia Scale score	−0.013	−0.190	−2.507	**0.013**	−0.024 to −0.003
Hypertension	−0.095	−0.180	−2.388	**0.018**	−0.174 to −0.016

CI, confidence interval.

function recovery. Impaired CVR influences recovery and recurrence in ischemic stroke [2,9,4–10]. Thus, taking into consideration other related factors [14,17–24] for CVR including age, hypertension, diabetes, hyperlipidemia, blood homocysteine, and long-term smoking, our study came to the conclusion via univariate and multivariate analyses that insomnia after ischemic stroke was an independent risk factor for CVR.

The incidence of insomnia after acute ischemic stroke in this study (ie, 15.8%) was far lower than previously reported. This might be mainly explained by different sleep-evaluation scales and proportions of patients using BDZ after ischemic stroke. To exclude the effect of long-term insomnia before ischemic stroke on CVR, patients with overt insomnia before stroke were excluded at enrollment. In addition, in the insomnia group, patients administered with BDZ not only had lower Athens Insomnia Scale scores, but also showed higher TCD-BHI compared with those not administered with BDZ. This further demonstrated that insomnia after ischemic stroke negatively affects CVR.

The effect of insomnia after ischemic stroke on CVR could involve several mechanisms. First, insomnia after ischemic stroke could inhibit nitric oxide (NO) secretion [5]. NO, a vasodilator secreted by vascular endothelial cells [25], is an important factor affecting CVR. Reduced NO secretion could damage the diastolic function of cerebral vessels and further reduce CVR [26,27]; indeed, there is evidence indicating that exogenous NO could reverse impaired CVR [28,29]. Cerebrovascular endothelial cells are damaged in patients with ischemic stroke; meanwhile, it was reported that insomnia inhibited the activity of NO synthase and reduces NO secretion in endothelial cells [5]. Therefore, insomnia after stroke might further damage CVR in patients with ischemic stroke. Second, insomnia can lead to low-grade inflammatory state [2,30]. In agreement, our study also demonstrated that blood hs-CRP, an inflammatory marker, was significantly higher in patients with insomnia. Although there was no difference between patients with and without insomnia in blood WBC count (which is another inflammatory marker) it showed an upward trend in patients with insomnia. Several studies have suggested that inflammation could damage CVR [31–33], which might be another reason why insomnia after ischemic stroke affects CVR. Third, insomnia can aggravate depression, and this study showed that HDS scores were significantly higher in patients with insomnia. In turn, depression damaged CVR [34]; thus, insomnia after acute ischemic stroke might also be a risk factor for CVR by aggravating post-stroke depression [35–38]. Finally, insomnia could lead to sympathetic hyperfunction [2], and sympathetic dysfunction involves cerebral arterioles and results in impaired CVR [39,40]. Several studies have confirmed that sympathetic hyperfunction promotes the secretion of the vasoconstrictors which included norepinephrine and neuropeptide Y, reducing the cerebral vasodilation function and subsequently impairing CVR [41].

Although long-term insomnia could aggravate arteriosclerosis [42], the evaluation period for CVR or insomnia was only one month after acute ischemic stroke in our study. Therefore, arteriosclerosis aggravation may not be involved in the effect of insomnia after ischemic stroke on CVR. In the present study, we not only excluded patients with overt insomnia before ischemic stroke, but also evaluated Athens Insomnia Scale scores and reviewed CVR at one month after ischemic stroke, which could increase the accuracy of the above findings, because the Athens Insomnia Scale assesses sleep status for the past month.

There were several limitations in this study. First, the sample size was relatively small, and further detailed stratification analyses could not be carried out. Second, our study focused on the effect of insomnia after ischemic stroke on CVR, regardless of how insomnia was caused. Considering the statistical multicollinearity, we could not put the HDS score and administration of BDZ in the multifactors regression analysis, thus a targeted designed study is needed next to demonstrate this. Third, we excluded patients who had obvious obstructive sleep apnea syndrome in the past by means of consultation or was observed to display obvious apnea during the TCD breath-holding test, but did not conduct the sleep monitoring, and that might miss diagnosis of mild obstructive sleep apnea syndrome, leading to bias in the result. Finally, the effect of insomnia after ischemic stroke on long-term CVR requires further investigation.

5. Conclusion

Insomnia after acute ischemic stroke is an independent risk factor for CVR, and might be associated with decreased NO secretion in cerebrovascular endothelial cells, low-grade inflammatory status, depression aggravation and sympathetic hyperfunction. Further investigation is required to evaluate the long-term effect of insomnia after ischemic stroke on CVR and unveil the underlying mechanisms.

Author contributions

Y.H. designed the study and drafted the manuscript. M.G. was responsible for the data collection. H.Z. made the evaluation of the Athens Insomnia Scale and HDS. J.D. conducted the TCD breath-holding test. Statistician X.W. conducted the statistical analysis. Y.G. was responsible for the coordination of the detailed research work, reviewed and revised the manuscript.

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Conflict of interest

All co-authors declare that they have no conflicts of interest relating to this work.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.07.005.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2019.07.005.

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