Admission Heart Rate Variability is Associated with Depression and Cognition in Patients with Acute Mild-Moderate Ischemic Stroke

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Abstract

Background Stroke has been shown to cause cardiac autonomic dysfunction. Depression and cognitive impairment are common complications after acute ischemic stroke (AIS). The relationship between poststroke depression (PSD) and cognitive impairment (PCI) and heart rate variability (HRV) was unclear. The purpose of this study was to investigate whether the decreased HRV was related to PSD and PCI in patients with mild-moderate AIS. Methods Changes in HRV after AIS were assessed using the nonlinear fractal dimension (FD) method, and patients within 72 hours of AIS were included in the study. 476 patients were included in this study. All patients underwent mood tests, cognitive test at 3 months. Cognitive and mood state were assessed using the Montreal Cognitive Assessment (MoCA) and the 15-item Stroke Specific Geriatric Depression Scale (GDS), respectively. PSD was defined if $GDS \geq 5$ and PSCI was defined if $MoCA < 26$. We assessed the relationship between FD and PSD and PSCI at 3 months. Results 50.84% (242/476) of patients had PSD, and 33.19% (158/476) of patients had PSCI. Compared with no PSD group, the lower NIHSS and FD value, and higher prevalence of $FD \leq 1.05$ were more likely in patients with PSD ($P < 0.05$). Compared with no PSCI group, the higher prevalence of $FD \leq 1.05$ were more likely in patients with PSCI ($P < 0.05$). In fully adjusted models, the $FD \leq 1.05$ was significantly associated with PSD (adjusted OR, 3.31; 95%CI, 1.81–5.43; $P = 0.000$), and PSCI (adjusted OR, 1.88; 95%CI, 1.11–3.16; $P = 0.018$). Conclusions These results suggested that $FD \leq 1.05$ after AIS could be used as an objective tool for early prediction of PSD and PSCI, providing guidance for the treatment of PSD and PCI, and improving the prognosis of patients.

Background

Stroke was the most important disabling and fatal disease in China [1]. Stroke could lead to physical disability, cognitive and emotional impairments. Post-stroke depression (PSD) was very common after stroke. Previous studies had shown that the prevalence in the first year after stroke was about 41.8% [2]. PSD might be caused by physical disability [3]. PSD had negative effects on the recovery, mortality, quality of life, physical and cognitive functions of stroke patients [4–6].

There were many reports about cognitive impairment after stroke [7,8]. Post-stroke cognitive impairment (PSCI) could lead to increased risk of death, decreased functional recovery, and evolve to dementia [9–11]. Over time, there appeared to be a complex interaction between depressive symptoms and cognitive function in stroke patients. Cognitive impairment and depressive symptoms might overlap each other [13,14], and both might coexist in stroke patients [15,16], cognitive impairment might also be caused by depression [17].

It had been reported that stroke could cause cardiac autonomic dysfunction and heart rate variability (HRV) decreased, which reflecting poor parasympathetic regulation. Decreased HRV was also related to depression [19] and poor cognitive function [20]. Because healthy heart rates were slightly irregular and chaotic, chaos theory could better explain the dynamics of heart rate. In physiological and pathological conditions, nonlinear methods could provide new ideas for HRV research [21–23]. FD was a characteristic

parameter in chaos theory, which could quantify the complexity of HRV and was one of the most commonly used nonlinear methods. FD method had the advantages of high precision and simple calculation. FD was related to dimensional complexity, and it estimates the self-similarity of a time interval in time series [24].

The purpose of this study was to discuss whether the reduction of FD was related to depression and cognitive function after mild-moderate AIS.

Methods

Study Population

Patients with mild-moderate acute ischemic stroke(AIS) within 72 hours of onset were selected. All patients met the WHO diagnostic criteria, were confirmed by brain CT or diffusion weighted imaging (DWI) magnetic resonance imaging (MRI). Eligible patients were admitted to our stroke ward. The severity of stroke was assessed by the the National Institutes of Health Stroke (NIHSS) score. All study participants or their legal representatives agreed to participate in the trial and they also signed informed consent. This study was approved by the local ethics committee.

Inclusion criteria

Only patients who met all of the following criteria were included in the study: (1). Aged from 18-80 years old; (2) Acute ischemic stroke occurred for the first time within 72hours after onset; (3) The lesion was single and related to clinical manifestations; (4). Finnish-speaking; (5). Able to co-operate; (6). NIHSS score $\leq$ 8; (7). All patients were not treated with intravenous thrombolysis or mechanical thrombolysis. All patients received standard medical treatment, including aspirin and lipid-lowering drugs.

Exclusion criteria

(1) cerebral hemorrhage, cardiogenic stroke, Brainstem or cerebellar stroke; (2) pre-existing neurological or psychiatric diseases that affect cognitive function; (3). Patients with severe heart disease and various severe arrhythmias (such as acute myocardial infarction, history of tachycardia/tachycardia or atrial fibrillation), diabetes with disease duration longer than 5 years and evidence of neuropathy; (4). Severe lung disease, renal failure (estimated glomerular filtration rate $\leq$ 30ml/min.1.73m²), and active malignancies; (5) aphasia or severe hearing impairment; (6), fever (38°C or higher), hypoxemia (arterial oxygenation hemoglobin saturation < 90%); (7) drug or alcohol abuse. All patients were followed up for 3 months.

Data Collection and Scale Assessment

Detection of 12-lead ECG and HRV in the next morning 9:00 to 10:00 AM, patients with relaxation supine state, in the quiet environment, the room temperature was about 22°C.

The ECG sampling frequency was 1000hz and required 15 minutes to obtain continuous R-R interval sequences, about 2,000 beats. The R-R interval sequences were passes through a filter to eliminate interfering factors, such as noise, artifacts, and premature beats. All R-R interval sequences were automatically edited at first, and then carefully edited manually. Excluding the interfering part, only the part of > 90% pure sinus beats were included in the analysis. Finally, 512 continuous R-R interval sequences were selected for HRV analysis.

The chaotic characteristics of R-R sequences were represented by FD, which was used to quantify the complexity of the R-R dynamic changes, FD equation was $FD = \log N(\epsilon) / \log(1/\epsilon)$, ϵ was the range, which was used to monitor the R-R interval, and $N(\epsilon)$ was the number of the R-R intervals [29]. FD parameters of each subject were calculated automatically by off-line computer software. Decreased FD was defined as $FD \leq 1.05$ according to our previous studies [30,31].

Depression was assessed 3 months later. The patients were assessed by an experienced neurologist who blinded to the clinical study and the patient's clinical information. Depression was assessed using the 15-item Stroke Specific Geriatric Depression Scale (GDS), it consists of 15 questions with a total of 15 points. Diagnostic criteria: 0-4, no depression; 5-8, mild depression; 9-11, moderate depression; 12-15, severe depression.

The Montreal Cognitive Assessment (MoCA) was used for the assessment of cognitive impairment, with a range of 0 to 30 points. A lower MoCA score indicates more severe cognitive impairment, and a score <26 was considered to be cognitive impairment.

Statistical Analysis

Patients were divided into PSD and PSD groups, PSCI and PSCI groups. Demographic characteristics, vascular risk factors, current smoking, and so on were compared between two groups in univariate analysis, distributions of continuous variables were determined by the Kolmogorov–Smirnov test, while Mann–Whitney two sample test was applied in case of non-normal distributions. We used Pearson χ^2 test, Fisher exact 2-sided test, or Student t test for data analyze. Adjusting for all confounders (such as age, baseline NIHSS score, gender, BMI, hypertension, current smoking, diabetes, hyperlipidemia, insular stroke, family history of stroke, etiology, and drug use), multivariate logistic regression was used to analyze the relationship between FD and outcomes (PSD, PSCI). The adjusted odds ratio (OR) and 95% confidence interval (CI) represent the analysis results. SPASS 22.0 software was used for all data analyze. $P < 0.05$ was considered as statistically significant.

Results

Characteristics of the study subjects

A total of 476 patients were included in the study, including 48.95%(233) males and 51.05%(243) females, with an average age of 65.88 ± 10.14 years (39-80 years), there were 313 patients with hypertension, 144 with diabetes, 235 with hyperlipidemia, and 127 with smoking. The mean NIHSS score was $6.55(\pm 1.93)$. During the 3-month follow-up, no patients died and no patients No patients were lost to follow-up.

Univariable Models for Predictors of PSD

242 (50.84%) patients had PSD. The comparison of basic characteristics between PSD group and PSD group was shown in table 1. Age distribution, gender distribution, BMI, hypertension and diabetic prevalence, lipid profiles, and so on were similar between these 2 groups. Patients with PSD showed significantly lower NIHSS (6.12 ± 2.16 vs 6.69 ± 1.85 ; $P=0.007$) than patients with no PSD. Compared with the PSD group, the FD value in the PSD group was lower (1.33 ± 0.36 vs 1.41 ± 0.32 , $P=0.001$), and the prevalence of $FD \leq 1.05$ was higher (26.03% vs 10.68%, $P=0.000$).

Univariable Models for Predictors of PSCI

PSCI occurred in 158 patients (33.19%) at 3 months. At baseline, age and gender distribution, BMI, the prevalence of hypertension, diabetes mellitus, and blood lipid profile, and soon were similar between the two groups (table 2). Compared with no PSCI group, the prevalence of $FD \leq 1.0$ in PSCI was higher 1.05(25.68%vs 15.41%, $P<0.014$). However, there was no significant difference in FD value between the two groups.

Multivariable Models on the Association between $FD \leq 1.05$ and PSD, PSCI

There was an association between $FD \leq 1.05$ and PSD (OR,2.94, 95%CI,1.78-4.87, $P=0.000$), and with PSCI (OR,1.90, 95%CI,1.12-2.89, $P=0.014$) in unadjusted models. In the multivariable logistic regression model after adjustment for confounding factors, $FD \leq 1.05$ was significant predictor for PSD (adjusted OR, 3.31; 95%CI, 1.81–5.43; $P=0.000$), and PSCI (adjusted OR,1.88; 95%CI, 1.11–3.16; $P=0.018$) (Table 3), after controlling for confounding factors, NIHSS was associated with PSD (adjusted OR,1.20; 95%CI, 1.09–1.32; $P=0.000$), but PSCI was not significantly associated with NIHSS.

Discussion

Cardiac dysautonomia was a common complication of stroke, HRV analysis was a common tool for studying cardiac autonomic control. In previous studies, linear statistical methods (time-domain and frequency-domain methods) were usually used to analyze HRV, which detected the overall amplitude of RR interval fluctuation around its mean value [32]. However, it provided very limited HRV information because the nonlinear mechanism seems to be involved in the origin of heart rate dynamics [33].

FD was one of the most common nonlinear parameters in chaotic characteristics, and could quantify the complexity of HRV [24]. FD algorithm estimated the self-similarity of a time interval in time series, which was related to the complexity of time series. In this study, FD was used to evaluate the status of autonomic function of AIS.

HRV had been the focus of research on biomarkers for depression and cognition after AIS in the last couple of decades [34], only the traditional time linear method was considered [35,36]. In this study, we investigated the relationship between FD, depression and cognition after AIS.

Our results showed significant differences between groups of patients with PSD and no PSD. Lower FD values and the higher prevalence of $FD \leq 1.05$ in PSD group compared to no PSD group. This result might be due to the reduced ability of the parasympathetic nervous system to regulate heart rate through vagal activity [37,38], and the reduced short-term flexibility of ANS to adapt to environmental and task changes [39-41].

Interestingly, we also founded that the incidence of decreased $FD \leq 1.05$ was higher in the PSCI groups, but FD value in early poststroke phase did not differ in the two groups. It was possible that because of the subject we studied, stroke patients are mild-moderate acute ischemic stroke, and the low incidence of PSCI in the mild-moderate stroke. This study showed that cognitive impairment was more likely in patients with $FD \leq 1.05$. The results of this study support the relationship between low vagal tone and poor cognitive function. The prediction of cognitive function by the HR parameters measured could be explained by the well-known effect of post-stroke depression on cognitive function in early phase. However, it had recently been reported that reduced HRV at rest was associated with reduced whole-brain perfusion, which itself was associated with an increased risk of post-stroke dementia. Therefore, the effect of decreased HRV on chronic cognitive function may be mediated by cerebral perfusion insufficiency [42,43].

After adjusting for fully confounders, the results showed that there were significant association of $FD \leq 1.05$ with risks of 3-month PSD and PSCI after AIS. To conclude, This study found that FD measurement was helpful in predicting PSD and PSCI in the early stage of stroke, especially in the case of severe aphasia or cognitive impairment, in which questionnaire could not be used.

However, due to some limitations, these results must be carefully interpreted and could not be generalized to all stroke patients. First, the patients were mild-moderate stroke, and severe stroke was excluded.

Second, the absence of FD measurements at the 3-month, which did not clarify the causal relationship between cardiac autonomic function, depression, and cognitive impairment after stroke. Third, although we adjusted the NIHSS score, the NIHSS score was related to the infarct volume, we did not measure the infarct volume in this study. Fourth, previous studies had shown that bilateral insular lesions might have different effects on cardiac autonomic function. We did not analyze the possible effects of bilateral insular stroke on FD, PSD and PSCI. In addition, larger multicenter clinical studies should be needed to confirm our results, which may provide a better understanding of the pathophysiological mechanisms between poststroke autonomic function, cognitive impairment, and mood disorders. However, despite these limitations, the advantage of our study lies in its large sample size, the adjustment of various confounders in its analysis, and the use of standardized methods to measure FD.

Conclusions

In summary, our findings suggested that decreased FD in AIS was associated with an increased risk of PSD and PSCI at 3 months. Low HRV may be a sign of higher susceptibility to PSD and PSCI. FD has potential predictive value for PSD and PSCI after ischemic stroke.

Abbreviations

CI: Confidence Interval; M: Mean; OR: Odds Ratio; SD: Standard Deviation; FD: fractal dimension; PSD: Poststroke depression; AIS: acute ischemic stroke; HRV: heart rate variability; PSCI: Post-stroke cognitive impairment;

Declarations

Ethics approval and consent to participate

This study was approved by the the Medical and Health Research Ethics Committee of the Second people's Hospital of Chengdu. The present study was carried out on the Helsinki declaration. This study followed the regulations of local laws and regulatory agencies to keep patients' medical information confidential. Prior to registration, the physician provided each patient or their legal representative with detailed information about the purpose, scope, and possible consequences of the trial. Clinical trials do not require intervention. All patients or their close relatives signed the consent form.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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This work was funded by the Health and Family Planning Commission of Chengdu (2015009), which is not involved in the database management (collection, analysis, interpretation of data) and has no access to patient information. The funding body did not participate in designing the study or writing the manuscript. The study protocol has undergone peer-review process by the funding body.

Authors' contributions

LYH was responsible for data collection and analysis, as well as the writing of the first draft and subsequent drafts of the paper. RX and JW were responsible for the design and interpretation of the study. LLZ was responsible for data analysis. WD was responsible for the conceptual interpretation of the study, and HY was responsible for the design of FD off-line calculation software. All authors read and approved the final manuscript for publication

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Tables

Table 1. Comparison of baseline characteristics between patients with no PSD and PSD groups.

	no PSD group (234)	PSD group (242)	OR(95%CI)	P*
Age, y(Mean SD)	66.01±10.34	65.74±9.96		0.767
NIHSS score(Mean SD)	6.69±1.85	6.12±2.16		0.007
FD (Mean SD)	1.41±0.32	1.33±0.36		0.001
FD≤1.05,n(%)	25(10.68)	63(26.03)	2.94(1.78-4.87)	0.000
Females,n(%)	118(50.43)	125(51.65)	1.05(0.73-1.51)	0.789
Men,n(%)	116(49.57)	117(48.35)	1.05(0.73-1.51)	0.789
BMI≥24 kg/m, n(%)	64(27.35)	76(31.40)	1.22(0.82-1.81)	0.332
Hypertension,n(%)	163(69.66)	150(61.98)	0.71(0.49-1.04)	0.078
Current smoking,n(%)	62(26.50)	65(26.86)	1.02(0.68-1.53)	0.929
Diabetes, n(%)	77(32.91)	67(27.69)	0.78(0.53-1.16)	0.215
Hyperlipidemia,n(%)	109(46.58)	126(52.07)	1.25(0.87-1.79)	0.231
Insular stroke,n(%)	47(20.09)	55(22.73)	1.17(0.75-1.82)	0.483
Family history of stroke,n(%)	44(18.80)	47(19.42)	1.04(0.66-1.64)	0.864
Etiological classification				
Large artery atherosclerosis,n(%)	96(41.03)	118(48.76)	1.36(0.95-1.97)	0.090
Lacunar, n(%)	91(38.89)	75(30.99)	0.71(0.48-1.03)	0.071
Other known causes, n(%)	2(0.85)	5(2.07)	2.45(0.47-12.74)	0.272
Undetermined, n(%)	48(20.51)	42(17.36)	0.81(0.51-1.29)	0.379
Medications use				
Antiplatelet, n(%)	59(25.21)	57(23.55)	0.91(0.60-1.39)	0.673
Antihypertensive, n(%)	139(59.40)	124(51.24)	0.72(0.50-1.03)	0.073
Lipid-lowering medications, n(%)	83(35.47)	97(40.08)	1.22(0.84-1.76)	0.300

*Comparison between no PSD and PSD groups. Continuous variables are expressed as mean ± standard deviation(SD). Categorical variables are expressed as frequency(percent) for P values, Pearson χ^2 test, Fisher exact 2-sided test, and Student t test were used when appropriate. Distributions of continuous variables were determined by the Kolmogorov–Smirnov test, Mann–Whitney two sample test was applied in case of non-normal distributions.

Table 2. Comparison of baseline characteristics between patients with no PSCI and PSCI groups.

	no PSCI group (318)	PSCI group (158)	OR(95%CI)	P*
Age, y (Mean SD)	65.69±10.12	66.26±10.20		0.561
NIHSS score (Mean SD)	6.51±1.97	6.63±1.85		0.724
FD (Mean SD)	1.39±0.34	1.36±0.36		0.531
FD≤1.15, n(%)	49(15.41)	39(24.68)	1.80(1.12-2.89)	0.014
Females, n(%)	169(53.14)	74(46.84)	0.78(0.53-1.14)	0.195
Men, n(%)	149(46.86)	84(53.16)	0.78(0.53-1.14)	0.195
BMI≥24 kg/m, n(%)	101(31.76)	39(24.68)	0.70(0.46-1.08)	0.111
Hypertension, n(%)	206(64.78)	107(67.72)	1.14(0.76-1.71)	0.524
Current Smoking, n(%)	79(24.84)	48(30.38)	1.32(0.86-2.02)	0.198
Diabetes, n(%)	93(29.25)	51(32.28)	1.15(0.76-1.74)	0.498
Hyperlipidemia, n(%)	159(50.00)	76(48.10)	0.93(0.63-1.34)	0.696
Insular stroke, n(%)	73(22.96)	29(18.35)	0.75(0.47-1.22)	0.249
Family history of stroke, n(%)	57(17.92)	34(21.52)	1.26(0.78-2.02)	0.348
Etiological classification				
Large artery atherosclerosis, n(%)	139(43.71)	75(47.47)	1.16(0.79-1.71)	0.438
Lacunar, n(%)	115(36.16)	51(32.28)	0.84(0.56-1.26)	0.402
Other known causes, n(%)	4(1.26)	3(1.90)	1.52(0.34-6.87)	0.584
Undetermined, n(%)	61(19.18)	29(18.35)	0.95(0.58-1.55)	0.828
Medications use				
Antiplatelet, n(%)	70(22.01)	46(29.11)	1.46(0.94-2.25)	0.089
Antihypertensive, n(%)	171(53.77)	92(58.23)	1.20(0.82-1.76)	0.357
Lipid-lowering medications, n(%)	122(38.36)	58(36.71)	0.93(0.63-1.38)	0.726

*Comparison between no PSCI and PSCI groups. Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as frequency(percent) for P values, Pearson χ^2 test, Fisher exact 2-sided test, and Student t test were used when appropriate. Distributions of continuous variables were determined by the Kolmogorov–Smirnov test, Mann–Whitney two sample test was applied in case of non-normal distribution.

Table 3 Multivariable Models Showing Association Between FD≤1.05 and Prognosis

	OR (95% CI)	P*
PSCI	1.88 (1.11–3.16)	0.018
PSD	3.31(1.81–5.43)	0.000

*Multivariable adjusted for age, baseline NIHSS score, sex, BMI, hypertension, current smoking, current alcohol drinking, diabetes, hyperlipidemia, insular stroke, family history of stroke, etiological classification, medications use.