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Increased heterogeneity of brain perfusion predicts the development of cerebrovascular accidents

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Abstract

The heterogeneity of brain perfusion is related to the risk factors of thromboembolic events such as antiphospholipid syndrome. However, the effectiveness of brain perfusion heterogeneity as a marker to predict thromboembolic events has not been confirmed. Our objective was to evaluate the effectiveness of brain perfusion heterogeneity as a marker to predict the development of cerebrovascular accidents. In this retrospective cohort study, patients who underwent Tc-99m ECD brain SPECT from January 1, 2006 through December 31, 2008 were included. Each study was reoriented with the Talairach space provided by the NeuroGam Software package. Heterogeneity of brain perfusion was measured as the coefficient of variation. The study outcome was the risk of cerebral vascular accidents in patients with increased heterogeneity of brain perfusion between January 1, 2006 and December 31, 2015. A multiple Cox proportional hazards model was applied to evaluate the risk of cerebrovascular accidents. A total of 70 patients were included in this study. The median age was 39 years (range, 28 – 59 years). There were 55 (78.6%) women. For increased heterogeneity of brain perfusion, the hazard ratio of cerebrovascular accidents was 2.68 (95% CI, 1.41 – 5.09; $P=.003$) after adjusting for age, sex, hypertension, diabetes mellitus, and dyslipidemia. Our study suggests that increased heterogeneity of brain perfusion is associated with an increased risk of cerebrovascular accidents.

Abbreviations: CI = confidence interval, ECD = ethyl cysteinate dimer, SPECT = single-photon emission computed tomography.

Keywords: brain perfusion, heterogeneity, cerebrovascular accidents

1. Introduction

Brain perfusion has been applied to evaluate the prognosis of carotid artery stenosis and neurodegenerative diseases. Several modalities have been used to evaluate brain perfusion, including transcranial Doppler (TCD), xenon-enhanced computed tomography (CT), phase-contrast magnetic resonance angiography (MRA), single-photon emission computed tomography (SPECT), and positron emission tomography (PET).[1–5] However, in the Rotterdam study, impaired global brain perfusion did not increase the risk of ischemic stroke.[6] A previous study showed that SPECT not only can evaluate global brain perfusion but also detect the heterogeneity of brain perfusion.[7] In the non-criteria antiphospholipid antibody carrier study, the heterogeneity of brain perfusion was related to the number of patients carrying antiphospholipid antibodies. The increased number of antiphospholipid antibodies was associated with the risk of thromboembolism events. Patients with increased heterogeneity of brain perfusion who developed ischemic stroke were also noted in the study.[8] Whether the SPECT-changes predict the clinical consequences of cerebrovascular accidents is an important question. Therefore, we conducted this study to evaluate the effectiveness of brain perfusion heterogeneity as a marker to predict the development of cerebrovascular accidents.

2. Materials and methods

2.1. Patients

In this cohort study, adults (age ≥18 years) who underwent Tc-99m ECD brain SPECT at the National Taiwan University

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Data sharing statement: Data are available on reasonable request. Please email the corresponding author to request the relevant data.

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

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Hospital and its branch hospitals from January 1, 2006 to December 31, 2008 were included retrospectively. Patients with cerebral vascular accidents before or one month within brain SPECT were excluded. The study outcome was the development of cerebral vascular accidents between January 1, 2006 and December 31, 2015. The collected parameters included age, sex, clinical presentations, status of hypertension, diabetes mellitus, dyslipidemia, and cerebral vascular accidents. The study was approved by the Research Ethics Committees and Institutional Review Board of National Taiwan University Hospital (NTUH REC Number: 201409053 RINA). Informed consent was waived due to the retrospective nature of the study and the analysis used anonymous clinical data.

2.2. Tc-99m ECD Brain SPECT

SPECT is a three-dimensional radionuclide imaging technique using a gamma camera, and Tc-99m ECD is the radiopharmaceutical injected into the patient's body that subsequently distributes in the brain to allow image acquisition. A total of 740-1110 MBq 99mTc-ethyl cysteinate dimer (Neurolite, Institute of Nuclear Energy Research, Taiwan) was administered intravenously to each participant. After injection, participants laid down for 20 min in a dark and soundless room in order to decrease any stimulation from the environment. A Siemens Symbia T2 (Siemens Healthcare Systems, Erlangen, Germany) or GE Infinia Hawkeye (GE Healthcare, Waukesha, WI, USA) dual-head gamma camera was used to acquire radionuclide signals. Fan-beam collimators were used for the GE Infinia Hawkeye, with an energy window of 140 keV (± 7%). Imaging data were obtained with 360° acquisition for 60 projections at 20 s/projection in a 128 × 128 matrix and processed in an XELERIS Workstation (Version 1.1362) using filtered back projection (FBP) reconstruction with a Butterworth filter (order, 10; cutoff, 0.45). Low-energy and high-resolution parallel hole collimators were used for the Siemens Symbia T2, with an energy window setting of 140 keV (± 10%). After 360° image acquisition with 64 projections at 30 s/projection in a 128 × 128 matrix, the data were processed in a Syngo Workstation (Version 7.0.7.14), using FBP reconstruction with a Metz filter. Each study was reoriented with the Talairach space provided by the NeuroGam Software package (GE Medical Systems, Segami Corporation, Columbia, MD, USA). Regions of interest (ROI) were classified according to the territory of the major brain supplying blood vessels, including the anterior cerebral, middle cerebral, and vertebral arteries. The activity of each signal was compared to the maximal signal uptake of the cerebellum. Heterogeneity of brain perfusion was measured as the coefficient of variation, which was defined as the ratio of the standard deviation to the mean. The image of the brain perfusion scan with reprehensive case data acquisition is presented in Figure 1.

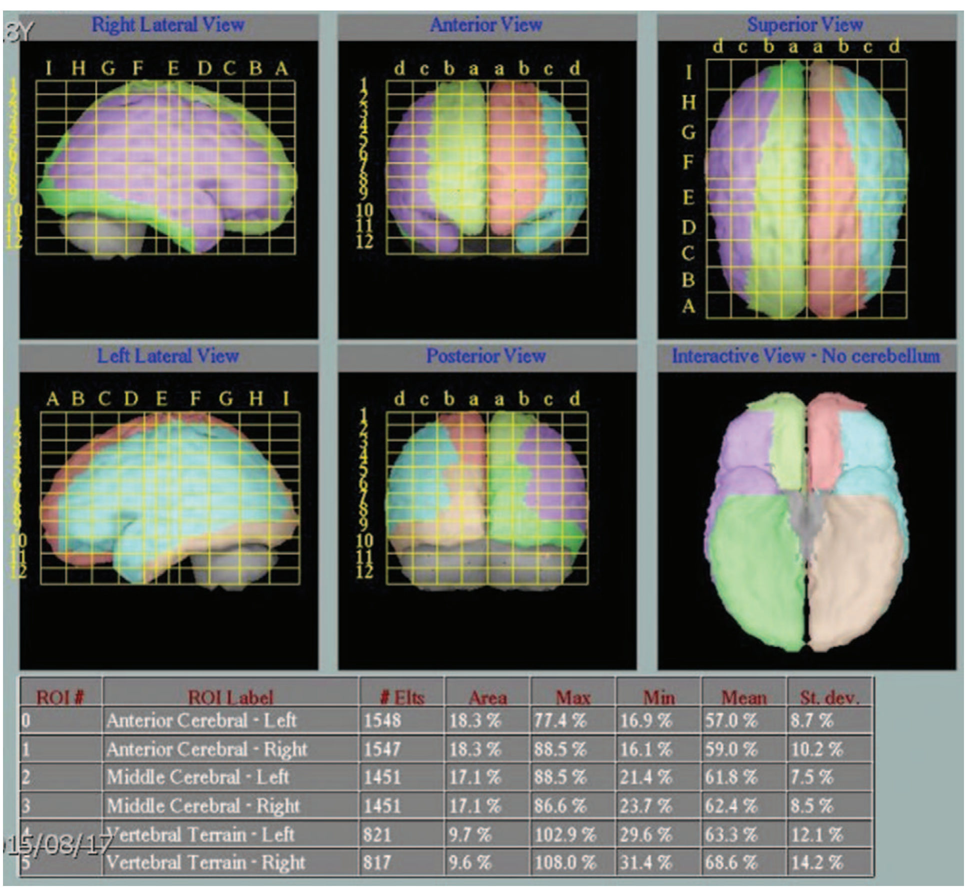

Figure 1. Images of Tc-99m ECD brain SPECT with reprehensive case data acquisition. The images demonstrate brain regions of interest (ROIs) classified by the territories of blood vessel supply. The activity of each signal was compared to the maximal uptake of the cerebellum, and the maximal, minimal, and mean activities, and standard deviation were calculated.

Table 1

Baseline characteristics of patients.

	Non-CVA (n=65)	CVA (n=5)	Total (n=70)
Age (years)	39 (28-57)	43 (27-62)	39 (28-59)
Female	51 (78.5)	4 (80.0)	55 (78.6)
Hypertension	4 (6.2)	1 (20.0)	5 (7.1)
Diabetes mellitus	2 (3.1)	1 (20.0)	3 (4.3)
Hyperlipidemia	4 (6.2)	2 (40.0)	6 (8.6)

Values are median (interquartile range) or n (%).
CVA = cerebrovascular accident.

2.3. Statistical analysis

Continuous variables are presented as the mean, standard deviation, median, and interquartile range (IQR). Categorical variables are presented as percentages. A Mann–Whitney *U* test and Fisher's exact test were applied to evaluate the differences between groups. The study outcome was the incidence of cerebral vascular accidents. A multiple Cox proportional hazards model was applied to evaluate the risk of cerebral vascular accidents. A Kaplan–Meier survival curve was used to demonstrate the event-free survival in patients, which were grouped according to the heterogeneity of brain perfusion. *P*-values < .05 were considered statistically significant. Liu's method was used to determine the optimal cutoff value of the receiver operating characteristic (ROC) curve. All statistical analyses were performed using Stata 15.1 (Stata Crop, College Station, TX, USA).

3. Results

A total of 70 patients were included in this study. The median age was 39 years (range, 28 – 59 years). There were 55 (78.6%) women. The median duration of follow-up was 7.49 (IQR, 1.60-8.24) years. The baseline characteristics of patients are shown in Table 1. The mean brain perfusion was not significantly associated with the development of cerebral vascular accidents (95% confidence interval [CI], 0.82–1.44; *P*=.565). For increasing heterogeneity of brain perfusion, the hazard ratio (HR) of cerebral vascular accidents was 2.68 (95% CI, 1.41–5.09; *P*=.003) after adjusting for age, sex, HTN, DM, and dyslipidemia. The results of the multiple Cox proportional hazards model for CVA risk factors are shown in Table 2. The area under the ROC curve for the prediction of cerebral vascular accidents due to the heterogeneity of brain perfusion was 0.77, and the optimal cutoff value was 15.74%. The Kaplan–Meier survival curve for CVA-free survival of different brain perfusion heterogeneity groups is presented in Figure 2.

Table 2

Multiple Cox proportional hazard model for cerebrovascular accident risk factors.

	Unadjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
Heterogeneity of brain perfusion	1.88 (1.28-2.76)	.001	2.68 (1.41-5.09)	.003
Age	1.01 (0.96-1.07)	.594	0.98 (0.90-1.07)	.690
Male	1.01 (0.11-9.03)	.994	0.02 (0.00-3.33)	.138
Hypertension	4.02 (0.44-36.57)	.216	3.95 (0.12-132.58)	.443
Hyperlipidemia	8.84 (1.45-53.97)	.018	10.99 (0.48-250.32)	.133

HR = hazard ratio; CI = confidence interval.

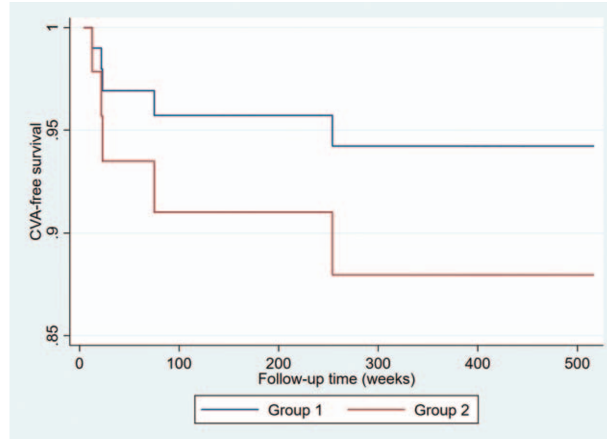

Figure 2. CVA-free survival. Patients were categorized according to the heterogeneity of brain perfusion. Group 1 had a less than average brain perfusion heterogeneity. Group 2 had an equal or greater than average brain perfusion heterogeneity. Patients with increased heterogeneity of brain perfusion had poor CVA outcomes.

4. Discussion

The risk factors for cerebral vascular accidents include carotid plaque, male sex, hypertension, and chronic kidney disease.[9,10] Furthermore, impaired collateral circulation and hemodynamics influence cerebral vascular autoregulation and are considered important factors for the development of ischemic stroke.[11] Cerebral autoregulation is a phenomenon that maintains stable cerebral blood flow despite variations in cerebral perfusion pressure. It is an important protective mechanism to avoid neurons being damaged in a low-oxygen environment related to low brain perfusion.[12–14] However, there is still no gold standard method to measure cerebral vascular autoregulation. Heterogeneity of brain perfusion was used to evaluate the prognosis of neurodegenerative diseases and cerebral vascular accidents.[15,16] We propose that the increasing heterogeneity of brain perfusion may infer the dysregulation of cerebral autoregulation and may be related to the development of cerebral vascular accidents. Our study showed that increased heterogeneity of brain perfusion is significantly associated with an increased risk of cerebrovascular accidents.

In terms of selecting a radiopharmaceutical, there are two radiopharmaceuticals commonly used in Taiwan for brain perfusion imaging: Tc-99m hexamethylpropyleneamine oxime (HMPAO) and Tc-99m ECD. Compared to Tc-99m HMPAO, Tc-99m ECD has the advantage of an optimal target-to-background ratio.[17] Therefore, the Tc-99m ECD was used in our study. Traditionally, the visual interpretation of brain SPECT images relies on the experience of the investigator. With the help of the NeuroGam software package, the analysis of SPECT brain perfusion images becomes semiquantitative.[18,19] The examination results of brain SPECT are presented as numbers and tables which may minimize the interobserver and intraobserver variability.

Previous studies showed that the heterogeneity of perfusion was more sensitive than the mean of perfusion in detecting early abnormalities in the microcirculation of the brain.[8,20] A clear cutoff value of the heterogeneity of brain perfusion will help physicians evaluate the risk of CVA in clinical practice.

Therefore, ROC curve analysis was performed in our study, and the optimal cutoff value for the heterogeneity of brain perfusion was 15.74%, according to Liu's method. However, since this is a single center study in Taiwan, more research with different ethnic groups is needed to validate this methodology.

This retrospective cohort study has several limitations. First, with the exception of SPECT, several modalities have been applied to evaluate brain perfusion, including transcranial Doppler, xenon-enhanced computed tomography, phase-contrast magnetic resonance angiography, and positron emission tomography. However, in this study, only SPECT was used to evaluate brain perfusion. Studies using different modalities are needed to validate the results of this study. Second, selection bias should be considered in this retrospective study. Patients received brain SPECT due to diverse neuropsychiatric presentations such as headache, dizziness, vertigo, and psychosis. The patients in this study could not well represent a homogeneous group. Third, the sample size of this study was relatively small. A study with a larger sample size would be beneficial for testing statistical validity.

5. Conclusion

Our study suggests that increased heterogeneity of brain perfusion is associated with an increased risk of cerebrovascular accidents. Tc-99m ECD brain SPECT can be used to evaluate the heterogeneity of brain perfusion.

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References

[1] Markus HS. Cerebral perfusion and stroke. J Neurol Neurosurg Psychiatry 2004;75:353–61.
[2] Prabhakaran S. Imaging markers of stroke risk in asymptomatic carotid artery stenosis. Brain Circ 2015;1:38.
[3] Sweeney MD, Kisler K, Montagne A, et al. The role of brain vasculature in neurodegenerative disorders. Nat Neurosci 2018;21:1318–31.
[4] Suri S, Topiwala A, Chappell MA, et al. Association of midlife cardiovascular risk profiles with cerebral perfusion at older ages. JAMA Netw Open 2019;2: e195776-.
[5] Hashimoto H, Nakanishi R, Mizumura S, et al. Prognostic value of 99m Tc-ECD brain perfusion SPECT in patients with atrial fibrillation and dementia. EJNMMI Res 2020;10:1–9.
[6] Fani L, Bos D, Mutlu U, et al. Global brain perfusion and the risk of transient ischemic attack and ischemic stroke: the Rotterdam study. J Am Heart Assoc 2019;8:e011565.
[7] Modzelewski R, Janvresse E, de la Rue T, et al. Comparison of heterogeneity quantification algorithms for brain SPECT perfusion images. EJNMMI Res 2012;2:40.
[8] Lin TS, Hsu PY, Chang CH, et al. Increased heterogeneity of brain perfusion is an early marker of central nervous system involvement in antiphospholipid antibody carriers. PloS one 2017;12:e0182344.
[9] Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:3754–832.
[10] Boehme AK, Esenwa C, Elkind MS. Stroke risk factors, genetics, and prevention. Circ Res 2017;120:472–95.
[11] Grubb RLJr, Derdeyn CP, Fritsch SM, et al. Importance of hemodynamic factors in the prognosis of symptomatic carotid occlusion. JAMA 1998;280:1055–60.
[12] Armstead WM. Cerebral blood flow autoregulation and dysautoregulation. Anesthesiol Clin 2016;34:465–77.
[13] Yang SH, Liu R. Caplan LR, Biller J, Leary MC, et al. Cerebral autoregulation. Primer on Cerebrovascular Diseases 2nd ed.2017; Academic Press, 57–60.
[14] Panerai RB. Cerebral autoregulation: from models to clinical applications. Cardiovasc Eng 2008;8:42–59.
[15] Volkow ND, Zhu W, Felder CA, et al. Changes in brain functional homogeneity in subjects with Alzheimer's disease. Psychiatry Res 2002;114:39–50.
[16] Mustonen T, Koivisto T, Vanninen R, et al. Heterogeneity of cerebral perfusion 1 week after haemorrhage is an independent predictor of clinical outcome in patients with aneurysmal subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry 2008;79:1128–33.
[17] Ziessman HA, O'Malley JP, Thrall JH. Nuclear Medicine: The Requisites. 4th ed.2013;Elsevier Health Sciences, 350-377.
[18] Fu P, Zhang F, Gao J, et al. NeuroGam software analysis in epilepsy diagnosis using 99mTc-ECD brain perfusion SPECT imaging. Med Sci Monit 2015;21:2801.
[19] Fu P, Wei L, Zhang F, et al. Added value of NeuroGam software analysis in single photon emission computed tomography localization diagnosis of epilepsy in interictal stage. Med Sci Monit 2018;24:1494.
[20] Barberini L, Serra A, Piras B, et al. Heterogeneity of antiphospholipid syndrome (APS) as characterized by brain perfusion techniques. Towards new ways of syndrome characterization. Int J Ment Health Syst 2019;1:1–7.