Original Article

Impact of H-Type Hypertension on Intraplaque Neovascularization Assessed by Contrast-Enhanced Ultrasound

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Aim: H-type hypertension is connected with carotid atherosclerotic plaques and stroke, whereas neovascularization is a dominant contributor to plaque vulnerability. However, the correlation between H-type hypertension and plaque vulnerability remains unclear. This study aims to explore the influence of H-type hypertension on intraplaque neovascularization (IPN).

Methods: We enrolled 235 patients with carotid plaques into the investigation and classified them into four groups: H-type hypertension group, simple hypertension group, isolated hyperhomocysteinemia group, and control group. Contrast-enhanced ultrasound (CEUS) was performed on them and IPN was evaluated using semi-quantitative visual grading: grade 1 (no microbubbles or microbubbles limited to the adventitial side and/or shoulder of plaque) and, grade 2 (diffused microbubbles within plaque or microbubbles enter plaque core). To analyze the correlation between H-type hypertension and the degree of plaque enhancement, logistic regression was used.

Results: Compared with those with CEUS grade 1 plaques, those with CEUS grade 2 plaques had higher frequency of ischemic stroke (29.0% vs. 45.1%, $P<0.05$), hypertension (41.0% vs. 56.3%, $P<0.05$), and H-type hypertension (18.0% vs. 29.6%, $P<0.05$). No significant differences existed in plaque morphology, plaque echogenicity, and the severity of carotid artery stenosis between the degree of plaque enhancement (all $P>0.05$). H-type hypertension (multivariate-adjusted OR: 3.036, 95% CI: 1.258–7.329) was independently connected with the degree of plaque enhancement even after adjusting for other covariates.

Conclusion: H-type hypertension is expressly connected with the degree of plaque enhancement and may facilitate plaque vulnerability. Our findings may offer a new insight for treating vulnerable plaque, lowering blood pressure, and lowering homocysteine equally crucial.

Key words: Carotid atherosclerotic plaque, H-type hypertension, Contrast-enhanced ultrasound, Neovascularization, Ischemic stroke

Introduction

Stroke has become one of the most common fatal diseases in our country[1], and atherosclerotic plaque is an important pathological basis for stroke; particularly, the rupture of vulnerable plaque improves the risk of thromboembolic stroke[2]. Earlier investigations have proved[3, 4] that intraplaque neovascularization (IPN) plays a significant role in plaque vulnerability. The diameter of contrast-enhanced ultrasound (CEUS) microbubbles was equivalent to that of the red blood cells; thus, it may serve as a good vascular tracer and visualize the distribution of neovessels within each plaque dynamically. Research has confirmed that the histological microvessel density of exfoliated carotid plaques is strongly correlated with the degree of plaque enhancement[5], which may suggest that CEUS is a reliable tool to assess plaque vulnerability.

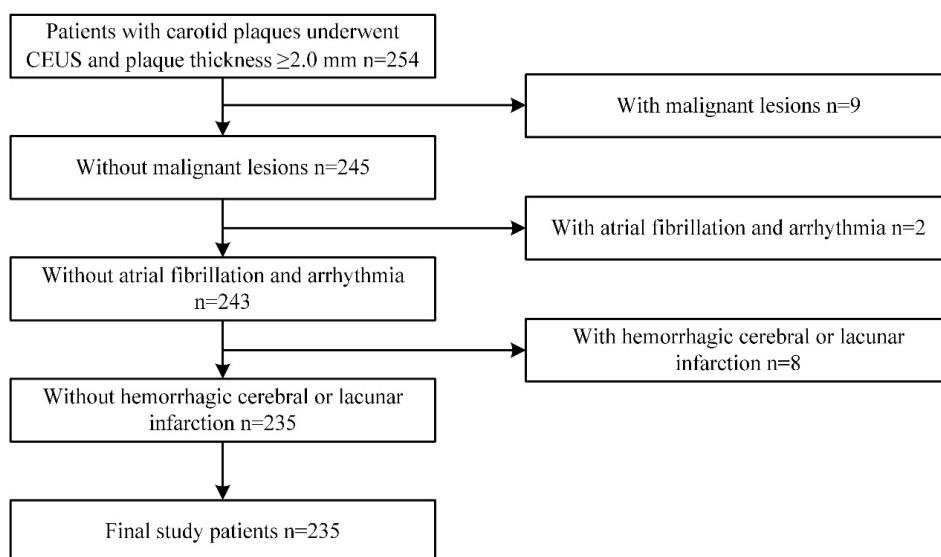H-type hypertension is a special type of

Fig. 1. The selection flowchart of patients

hypertension, associated with high homocysteine. There is a notice that approximately 75% of Chinese hypertensive patients are H-type hypertension[6]. H-type hypertension has a certain correlation with the presence of atherosclerotic plaques, affecting the occurrence and recurrence of stroke[7, 8]. Thus, the study on H-type hypertension has gradually acquired wide attention. However, few investigations regard the correlation between H-type hypertension and plaque vulnerability. Our investigation aims to elucidate the correlation between H-type hypertension and the degree of plaque enhancement, further understanding the influence of H-type hypertension on plaque vulnerability.

Materials and Methods

Patients

The entire sample comprised 235 patients with carotid atherosclerotic plaques who performed CEUS in the Ultrasound Medical Center of the Lanzhou University Second Hospital from September 2018 to July 2020. Indication criteria were as follows: 1) the patient was ≥ 18 years old; 2) at least one or more atherosclerotic plaques were identified on traditional gray-scale ultrasound with a plaque thickness of ≥ 2.0 mm. If more than one plaque were discovered, only the relatively largest plaque was enrolled in the study; 3) the patient was not allergic to the contrast agent used in the CEUS examination. Exclusion criteria of the investigation were the following: 1) patients with severe liver, kidney, or lung dysfunction or secondary hypertension; 2) those who took folic acid, vitamin B12, or other drugs that potentially influenced the

homocysteine (Hcy) metabolism; 3) those with atrial fibrillation and other arrhythmias that could cause a cardiogenic stroke; and 4) those with hemorrhagic cerebral or lacunar infarction confirmed via computed tomography (CT) or brain magnetic imaging (MRI). Additionally, the baseline parameters of patients were recorded, which covered sex, age, lipid profile, and smoking status. The history of patients' diseases, such as hypertension, diabetes mellitus, and stroke was analyzed through a standard interview. Patients who smoked at least one cigarette per day for over 1 year were identified as smokers. The World Health Organization (WHO) criterion[9] is referenced to diagnose ischemic stroke. According to the side of target plaque selected for CEUS and the analysis of CT or MRI results, ischemic stroke was further classified as ipsilateral ischemic stroke, contralateral ischemic stroke or bilateral ischemic stroke. The diagnostic criteria for hypertension are blood pressure of ≥ 140/90 mmHg or taking antihypertensive drugs[10]. The diagnosis of diabetes meets the WHO diagnostic criteria, namely, fasting blood glucose of ≥ 126 mg/dL or 2 h postprandial blood glucose of ≥ 200 mg/dL or treatment with hypoglycemic agents[11]. H-type hypertension is a special type of hypertension, which is associated with a Hcy concentration of ≥ 10umol/L[12]. The patients in the investigation were classified into four groups: the H-type hypertension group, simple hypertension group, isolated hyperhomocysteinemia (HHcy) group, and control group, according to hypertension or Hcy levels. All investigation patients who participated in this study provided informed consent. **Fig. 1** shows the selection flowchart of patients.

Instruments and Methods

Philips iU22 (Philips, Amsterdam, Netherlands) color Doppler ultrasound diagnostic instrument with L9-3 probe (5–9 MHz) was selected for routine and CEUS examinations. First, the patient lay on the examination bed with the head oriented toward the contralateral direction and fully exposed the neck. The probe was applied to scan the bilateral common carotid arteries, carotid bifurcations, and internal and external carotid arteries in transverse and longitudinal directions. The size, location, and the number of plaques were recorded, and the severity of carotid stenosis was categorized as mild, moderate, or severe. According to the surface of atherosclerotic plaque, the surface of the plaque could be divided into three types: smooth, irregular, and ulcerated. Meanwhile, the definition of ulcer plaque is that the luminal boundary of carotid plaque has a rupture of at least 1 × 1 mm, and the rupture is filled with colored blood flow signals or CEUS microbubbles [13]. On conventional gray-scale ultrasound, the echogenicity of adjacent sternocleidomastoid muscles was used as a reference, and plaques were segmented into hypoechoic, isoechoic, hyperechoic, or mixed echoic. After selecting the target plaque, the instrument was adjusted to the CEUS mode, and the contrast ultrasound system setting was as follows: the mechanical index was 0.05–0.07, the gain was 85%–95%, and the depth was 2.5–3.5 cm. Patients received 2.4 mL contrast microbubbles (SonoVue; Bracco, Milan, Italy) through the antecubital vein and were immediately rinsed with 5 mL of 0.9% sodium chloride saline. Simultaneously, patients were instructed to breathe quietly and try to avoid swallowing. Real-time observation of the selected plaque in long-axis imaging was stored 90 s for subsequent analysis. The spot hyperechoic lesions that moved rapidly and dynamically within the plaque or adventitia were considered as neovessels; otherwise, the fixed light spot may be caused by small calcification. The carotid plaque neovessels were assessed via a semi-quantification visual grading based on the presence and location of microbubbles within every plaque [14]: grade 1 (no microbubbles or microbubbles limited to the adventitial side or shoulder of the plaque) and grade 2 (diffused microbubbles within the plaque or microbubbles enter the plaque core), as shown in **Fig. 2**. The IPN grading of CEUS was determined by two senior ultrasound doctors with no prior knowledge of the patients' baseline parameters. If there was disagreement between the two doctors, they discussed it together to reach a final consequence.

Laboratory Biochemical Indexes

The fasting 5 mL blood samples were drawn through the vein within 24 h after hospitalization. Meanwhile, the Roche Cobas 8000 (Roche, Basel, Switzerland) biochemical analyzer was selected to determine Hcy, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c). Hcy concentration of ≥ 10 µmol/L was regarded as HHcy [12].

Statistical Analysis

The research data were statistically analyzed by using SPSS 22.0 (SPSS, Chicago, USA). The continuous variables involved in the study were described as mean ± SD, and the categorical variables were reported as frequencies or percentages (%). Then, a one-way Analysis of Variance test or the Kruskal–Wallis test was applied to analyze continuous variables, and the difference between the two groups was compared using the Mann–Whitney U test. The Chi-square (χ^2) test or Fisher's exact test was used to analyze categorical variables. Ordinal univariate and multivariate logistic regression analyses were used to analyze the independent determinant that may impact the degree of plaque enhancement. $P < 0.05$ was regarded as statistically significant.

Results

Baseline Parameters between the Degree of Enhancement

Among the enrolled patients, 100 (42.6%) were regarded as CEUS grade 1 and 135 (57.4 %) as CEUS grade 2. The frequency of ischemic stroke and hypertension in CEUS grade 2 was 76 (56.3%) and 61 (45.1%), respectively, which were significantly higher than those in CEUS grade 1 (all $P < 0.05$). Moreover, in the target plaques of either CEUS grade 2 or CEUS grade 1, the frequency of ipsilateral ischemic stroke was higher than that of contralateral ischemic stroke (34.8% vs. 8.1%) and (25.0% vs. 4.0%), and bilateral ischemic stroke was the lowest (2.2% and 0%). A statistical difference of LDL-c in CEUS grade 1 compared with that of CEUS grade 2 was significant ($P < 0.05$). Other baseline parameters such as sex, age, diabetes mellitus, blood pressure, smoking, and other blood lipids were not statistically significant between the degree of plaque enhancement ($P > 0.05$) (**Table 1**).
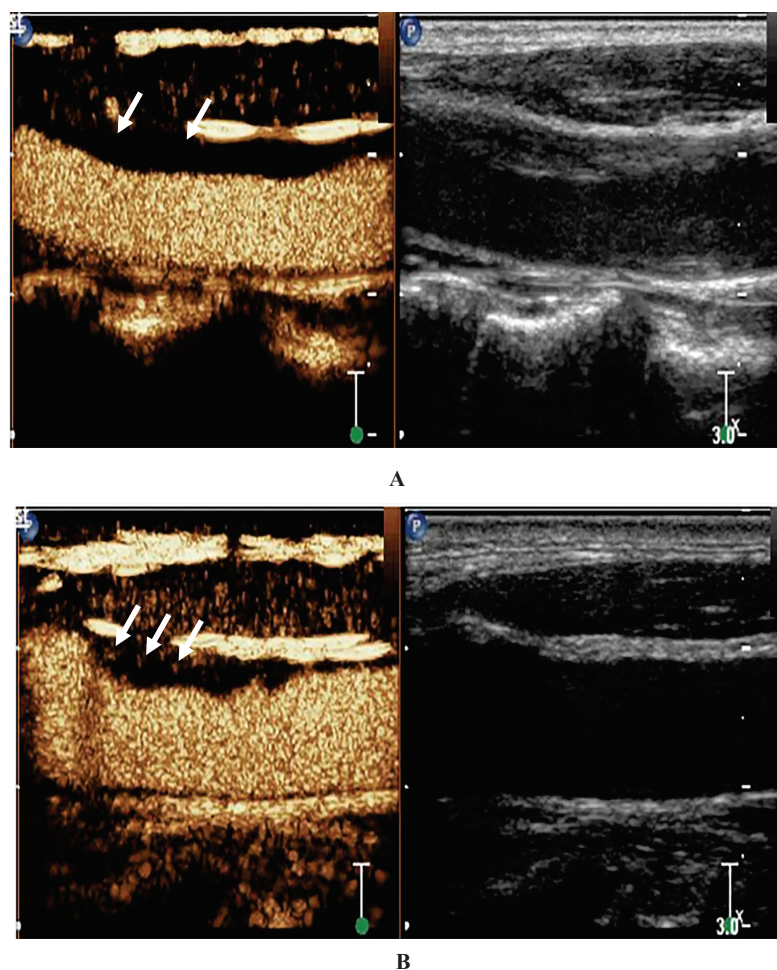
Fig. 2. IPN grading of CEUS

A, Grade 1: no microbubbles within the plaque (white arrows). B, Grade 2: extensive microbubbles within the ulcerative plaque (white arrows).

Table 1. Baseline parameters between the degree of enhancement

Variable	Grade 1	Grade 2	P value
Age (years)	63.44 ± 8.85	64.00 ± 9.53	0.647
Male (n, %)	79 (79.0)	109 (80.7)	0.742
Hypertension (n, %)	41 (41.0)	76 (56.3)	0.020
Diabetes mellitus (n, %)	36 (36.0)	52 (38.5)	0.693
Ipsilateral ischemic stroke (n, %)	25 (25.0)	47 (34.8)	
Contralateral ischemic stroke (n, %)	4 (4.0)	11 (8.1)	0.046
Bilateral ischemic stroke (n, %)	0 (0)	3 (2.2)	
Systolic pressure (mmHg)	140.96 ± 22.68	142.31 ± 20.59	0.634
Diastolic pressure (mmHg)	81.15 ± 14.21	80.22 ± 11.93	0.597
TC (mmol/L)	4.05 ± 1.14	3.78 ± 1.05	0.062
TG (mmol/L)	1.77 ± 1.32	1.76 ± 1.48	0.931
HDL-c (mmol/L)	1.41 ± 2.80	1.08 ± 0.35	0.183
LDL-c (mmol/L)	2.55 ± 0.94	2.31 ± 0.89	0.048
Smoking (n, %)	35 (35.0)	49 (36.3)	0.838

Table 2. Correlation between plaque characteristics and the degree of enhancement

Variable	Grade 1	Grade 2	*P* value
Plaque echogenicity (*n*, %)			
Hypoechoic	54 (54.0)	90 (66.7)*	
Isoechoic	13 (13.0)	18 (13.3)	0.146
Hyperechoic	7 (7.0)	5 (3.7)	
Mixedechoic	26 (26.0)	22 (16.3)	
Plaque morphology (*n*, %)			
Smooth	46 (46.0)	62 (45.9)	
Irregular	49 (49.0)	55 (40.7)	0.084
Ulcerated	5 (5.0)	18 (13.3)*	
Carotid stenosis (*n*, %)			
Mild	57 (57.0)	91 (67.4)	
Moderate	37 (37.0)	36 (26.7)	0.227
Severe	6 (6.0)	8 (5.9)	

Note: Compared with grade 1 *P<0.05.

Table 3. Baseline parameters of H-type hypertension patients

Variable	H-type hypertension	Isolated HHcy	Simple hypertension	Control	*P* value
Age (years)	65.38 ± 9.21	63.50 ± 9.66	62.41 ± 9.06	63.89 ± 8.70	0.375
Male (*n*, %)	50 (86.2)	58 (78.4)	43 (79.2)	37 (84.1)	0.278
Diabetes mellitus (*n*, %)	31 (53.4)	13 (17.6)★	27 (45.8)▲	17 (38.6)★▲!	0.000
Ischemic stroke (*n*, %)	34 (58.6)	29 (39.2)★	19 (32.2)★▲	8 (18.2)★▲	0.000
Smoking (*n*, %)	18 (31.0)	27 (36.5)	24 (40.7)	15 (34.1)	0.740
Systolic pressure (mmHg)	146.79 ± 19.56	137.20 ± 18.79☆	151.22 ± 24.69△	129.98 ± 15.64☆‡	0.000
Diastolic pressure (mmHg)	83.16 ± 12.89	77.66 ± 12.51☆	85.17 ± 13.52△	76.14 ± 10.23☆‡	0.000
TC (mmol/L)	3.68 ± 1.05	3.82 ± 1.06	3.97 ± 1.09	4.18 ± 1.18★	0.114
TG (mmol/L)	1.70 ± 1.14	1.45 ± 0.63	2.19 ± 2.01	1.81 ± 1.58	0.179
HDL-c (mmol/L)	1.02 ± 0.27	1.12 ± 0.31	1.64 ± 3.65	1.10 ± 0.23	0.073
LDL-c (mmol/L)	2.16 ± 0.85	2.42 ± 0.86	2.41 ± 0.83	2.71 ± 1.11☆	0.031

Note: Compared with H-type hypertension ★*P<0.05*, ☆*P<0.01*. Compared with Isolated HHcy ▲*P<0.05*, △*P<0.01*. Compared with Simple hypertension !*P<0.05*, ‡*P<0.01*. 1 mm Hg=0.133 kPa.

Correlation between Plaque Characteristics and the Degree of Enhancement

In terms of plaque characteristics, we observed that ulcerative plaques in CEUS grade 2 have a higher proportion than those in CEUS grade 1 (5.0% vs. 13.3%) (*P<0.05*). Although no correlation was found between the degree of plaque enhancement and plaque echogenicity in our study, more neovascularization was seen frequently in hypoechoic plaques, the proportions of which in CEUS grade 1 and CEUS grade 2 were 54.0% and 66.7%, respectively (*P<0.05*). When comparing the degree of carotid artery stenosis between the degree of plaque enhancement, no significant difference was discovered (*P>0.05*) **(Table 2)**.

Baseline Parameters of H-Type Hypertension Patients

Compared with the other three groups, the patients with H-type hypertension tended to have a history of diabetes mellitus and ischemic stroke (all *P<0.05*). Additionally, when comparing the systolic pressure, diastolic pressure, and LDL-c between the four groups, statistical differences were noted in all parameters (all *P<0.05*). Other baseline parameters between the four groups did not reach significant differences **(Table 3)**.

Correlation between H-Type Hypertension and the Degree of Enhancement

Then, we analyzed the correlation between H-type hypertension and the degree of plaque enhancement. **Table 4** presents the consequences. Diffuse neovessels (CEUS grade 2) were seen

Table 4. Correlation between H-Type Hypertension and degree of enhancement

Variable	Grade 1	Grade 2	P value
Control (n, %)	27 (27.0)	17 (12.6)*	
H-type hypertension (n, %)	18 (18.0)	40 (29.6)*	0.022
Isolated HHcy (n, %)	31 (31.0)	43 (31.9)	
Simple hypertension (n, %)	24 (24.0)	35 (25.9)	

Note: Compared with grade 1 *P<0.05.

Table 5. Ordinal logistic regression analyses of plaque degree of enhancement

Factor	OR	95% CI	P value
Univariate			
Control		Reference	
H-type hypertension	3.529	1.549–8.039	0.003
Isolated HHcy	2.203	1.028–4.723	0.042
Simple hypertension	2.316	1.042–5.148	0.039
Multivariate			
Model 1			
Control		Reference	
H-type hypertension	3.495	1.533–7.971	0.003
Isolated HHcy	2.226	1.036–4.780	0.040
Simple hypertension	2.370	1.060–5.301	0.036
Model 2			
Control		Reference	
H-type hypertension	3.036	1.258–7.329	0.014
Isolated HHcy	2.042	0.910–4.582	0.083
Simple hypertension	2.269	0.972–5.300	0.058

Model 1: Modulated sex and age.
Model 2: Modulated sex, age, ischemic stroke, plaque morphology, and plaque echogenicity.

frequently in H-type hypertension 40 (29.6%) than in the control group, which was rated as CEUS grade 2 plaques only 17 (12.6%) (P=0.022).

In a univariate logistic analysis, H-type hypertension (OR: 3.529, 95% CI: 1.549–8.039), isolated HHcy (OR: 2.203, 95% CI: 1.028–4.723), and simple hypertension (OR: 2.316, 95% CI: 1.042–5.148) were all correlated with the degree of plaque enhancement (P=0.003, 0.042, 0.039). The multivariate logistic regression analyses presented in model 1, after modulating sex, age, H-type hypertension (OR: 3.495, 95% CI: 1.533–7.971), simple hypertension (OR: 2.370, 95% CI: 1.060–5.301), and isolated HHcy (OR: 2.226, 95% CI: 1.036–4.780), still had significant correlations with the degree of plaque enhancement (P=0.003, 0.036, 0.040). However, in model 2, after modulating sex, age, ischemic stroke, plaque morphology, and plaque echogenicity, the consequence demonstrated that only H-type hypertension was the potent independent predictor for the degree of plaque enhancement. To be specific, compared with patients without hypertension and HHcy, those with H-type hypertension were 3.036 times (95% CI: 1.258–7.329, P=0.014) at risk of having elevated plaques CEUS grades **(Table 5)**.

Discussion

Traditionally, carotid artery stenosis is the primary dangerous element for stroke and the major parameter for revascularization[15, 16]. Presently, there seem to be some changes that most ischemic strokes occur in patients only with mild or moderate arterial stenosis but vulnerable plaques[17]. Thus, studying the factors that may influence the vulnerability of carotid plaque is beneficial to stratify the risk of atherosclerosis-related events, which are the major measures to prevent ischemic stroke. For the past few years, some studies have indicated that carotid IPN is an essential factor for vulnerable plaques[3, 4]. Additionally, as a widely accepted method in clinical work, CEUS is a simple and safe method to visualize

the situation of IPN and can assess the vulnerability of plaques. What is clear is that, as a vital factor in the progression of carotid atherosclerotic plaque, hypertension could also participate in the development of stroke[18]. Meanwhile, HHcy is a perilous parameter for hypertension and positively related to stroke[19]. H-type hypertension is identified as hypertension with elevated Hcy (≥ 10 μmol/L). The correlation between H-type hypertension and the occurrence of atherosclerotic plaques has been observed in some former studies. Guo *et al.*[20] found that H-type hypertension was a crucial perilous parameter for the occurrence of carotid atherosclerotic plaques. Another literature[7] reported that patients with H-type hypertension were 1.63 times at risk of having atherosclerotic plaques compared with those with simple hypertension. The research results of Hu *et al.*[21] showed that patients with H-type hypertension were more likely to have carotid artery structure and function damage, which may be related to the synergistic effect of hypertension, high Hcy, and inflammatory factors. Their findings provided strong evidence for the positive correlation between H-type hypertension and atherosclerotic plaques. However, would H-type hypertension affect the vulnerability of atherosclerotic plaques? What H-type hypertension had to do with plaque neovascularization? The investigation was undertaken to determine the correlation between H-type hypertension and the degree of plaque enhancement, as well as the effect of H-type hypertension on plaque vulnerability.

In this investigation task, the frequency of ischemic stroke in CEUS grade 2 plaques was higher than that in CEUS grade 1 plaques. Additionally, it was found in this retrospective study that the higher degree of the target plaque enhancement selected for CEUS, the more prone to ipsilateral ischemic stroke. The results may reveal that the higher degree of plaque enhancement made plaques more vulnerable and relatively easy to rupture, fall off, and bleed, leading to cerebral embolism. Our consequences were similar to those of the previously published studies[22, 23], which showed that symptomatic patients had a higher density of IPN than did asymptomatic patients. Additionally, our research presented that hypoechoic plaques often had more IPN, which may be because the hypoechoic plaque was mainly composed of lipid and hemorrhage[24] and relatively vulnerable. Conversely, highly fibrous tissue content was associated with hypoechoic plaques[25] and relatively stable. Although no significant difference between the surface of plaque morphology and the degree of plaque enhancement was discovered, the proportion of ulcerative plaques in CEUS grade 2 was

significantly higher. The consequence may explain why ulcerative plaques were more vulnerable and had a higher peril of stroke than did smooth and irregular plaques[26]. This is probably because a host of neovessels are immature and fragile, as well as their structure and function are abnormal and prone to rupture, causing a thromboembolic stroke[27, 28]. Notably, the conventional parameter such as the degree of carotid stenosis failed to correlate with the degree of plaque enhancement, which is different from Margreet *et al.* study[28]. The main reason for the consequence may be partly related to the selected sample that most of the patients were mildly carotid artery stenosis in this investigation.

Moreover, in terms of the independent determinants that may affect the degree of plaque enhancement, univariate and multivariate logistic regression analysis showed that H-type hypertension, isolated HHcy, and simple hypertension were all significantly correlated with the degree of plaque enhancement. However, after adjusting for confounding factors, only H-type hypertension (multivariate-adjusted OR: 3.036, 95% CI: 1.258–7.329, $P=0.014$) was an independent factor influencing the degree of plaque enhancement. The synergistic effect between hypertension and HHcy has been found in some past researches[29, 30]. On the one hand, the mechanisms may be that Hcy could aggrandize the recruitment of macrophages by the inner walls of the blood vessels, promote their mature differentiation to form inflammatory monocytes, and increase the secretion of chemokine 1 and IL-8, leading to the formation of atherosclerosis[31]. At the same time, Hcy could prevent the cholesterol efflux from THP-1 macrophages and participate in lipid metabolism and accumulation, further aggravating atherosclerotic plaque[32]. On the other hand, as a perilous parameter for hypertension, Hcy may stimulate the oxidative stress of vascular endothelial cells, cut down the release of nitric oxide, elicit vascular smooth muscle cells migration, and impair endothelial function, exacerbating the damage of blood vessels and the growth of atherosclerotic plaque[33]. Moreover, high Hcy may activate the inflammatory body NLRP3 through the ROS pathway, aggravate the inflammatory reaction within plaques, and expedite the vulnerability of the plaque[34, 35]. Apart from inhibiting the relaxation function of blood vessels by injuring the integrity of vascular endothelium, Hcy could lower the production of endogenous hydrogen sulfide[36]. It also can activate the angiotensin-converting enzyme and make the arterial wall stiffness and vascular tone boost, which may exacerbate hypertension disease[37]. Subsequently,

it was worth noting that in the H-type hypertension group, the proportion of ischemic stroke and CEUS grade 2 plaques were both higher than those in the other three groups. This may forecast that H-type hypertension may facilitate the growth of new blood vessels and make the plaque vulnerable, ultimately bringing about the occurrence of ischemic stroke. Thus, once hypertension is accompanied by hyperhomocysteinemia, the patients with atherosclerosis plaques are at greater peril of developing vulnerable plaques.

The limitations of this investigation should be acknowledged. 1) The sample size selected in this study was from the same hospital; consequently, there was a certain selection bias. If a large-scale and multi-center joint study can be conducted in the future, more accurate results may be reached. 2) The largest atherosclerotic plaque was selected for analysis, which may not be the vulnerable plaque causing the stroke, which is why, in our study, some patients had stroke opposite to the target plaque. In the future, our research may focus on the study of ipsilateral ischemic stroke with vulnerable plaques. 3) The influence of Hcy lowering in combination with anti-hypertension on the treatment of plaque vulnerability may be worth exploring in the future.

In a nutshell, H-type hypertension is expressly connected with the degree of plaque enhancement and may promote plaque vulnerability. Our findings can offer a new insight for the treatment of vulnerable plaque by lowering blood pressure and Hcy levels.

Acknowledgements

Conflict of Interest

The authors declare that they have no conflict of interest.

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