The application of ultrasound B-flow imaging in detection of carotid atherosclerotic micro-vessel with ischemic cerebrovascular disease

Ying H. Wang, MM, Qi C. Zheng, BM, Gong X. Yuan, MM, Jiang H. Ren, MM.

ABSTRACT

الأهداف: التحقق من ظهور وخصائص الأوعية الدموية الدقيقة داخل لوحية الشريان السباتي المتصلبة باستخدام تصوير تدفق الدم بي وتصوير التباين الإيكوغرافي.

الطريقة: شملت الدراسة 78 مريض مصاب بتصلب الشريان السباتي والذين دخلوا إلى قسم تخطيط الصدى في مستشفى زونج نان، جامعة ووهان، ووهان، الصين وذلك خلال الفترة من أغسطس 2008م إلى يوليو 2011م، ولقد خضع كافة المرضى للفحص المعتاد وتصوير تدفق الدم بي. وخضع 51 مريض لتصوير تدفق الدم بي وتصوير التباين الإيكوغرافي. لقد قمنا بتقييم العلاقة بين نتائج تصوير تدفق الدم بي والأعراض السريرية الظاهرة في السكتة الدماغية الإقفارية والنوبة الإقفارية العابرة. وقمنا أيضاً بدراسة العلاقة بين الأعراض الوعائية الدماغية، والتضيق، ونوع اللويحة من جهة واكتشاف ظهور الأوعية الجديدة باستخدام تصوير تدفق الدم بي بواسطة اختبار χ^2، كما أننا قمنا بتقييم التوافق بين طريقتي التصوير باستخدام معامل كي، بالإضافة إلى حساب فعالية تصوير تدفق الدم بي أثناء تشخيص ظهور تصلب الأوعية الدقيقة.

النتائج: لقد كان هناك علاقة بين نتائج تصوير تدفق الدم بي وأعراض المريض، كما كان هناك توافق بين تصوير تدفق الدم بي وتصوير التباين الإيكوغرافي وذلك في تشخيص تكون الأوعية الدموية الدقيقة (k=0.406). كما تم حساب التالي لتقييم تصوير تدفق الدم بي: درجة الحساسية (0.483)، والدقة (0.599)، والقيمة التوقعية الإيجابية (0.933)، والقيمة التوقعية السالبة (0.583)، والمضبوطية (0.686). ولقد كان هناك علاقة واضحة من الناحية الإحصائية بين ظهور الأعراض الوعائية الدماغية وظهور إشارات في تصوير تدفق الدم بي داخل لويحة الشريان السباتي (B= 2.422, CI: 1.728–73.407).

خاتمة: أظهرت هذه الدراسة بأن تصوير تدفق الدم بي يعد أقل حساسية من تصوير التباين الإيكوغرافي، غير أن هذه الطريقة يمكن الاعتماد عليها للكشف عن تصلب الأوعية الدقيقة للشريان السباتي.

Objective: To investigate the detection and characterization of micro-vessels within the carotid atherosclerotic plaque using B-flow imaging (BFI) ultrasound with contrast-enhanced ultrasound (CEU) as the reference standard.

Methods: Between August 2008 and July 2011, 78 patients with carotid atherosclerosis that were admitted at the Department of Ultrasonography in ZhongNan Hospital of Wuhan University, Wuhan, China underwent standard and BFI examination. Fifty-one patients received both BFI and CEU. We evaluated the relationship between BFI findings, and clinical symptoms in ischemic stroke, or transient ischemic attack patients. The correlation of cerebrovascular symptoms, stenosis, and plaque type on the detection of neovessels by BFI were statistically evaluated using χ^2 test (McNemar test). The agreement of the 2 sonographic methods was assessed by κ coefficient. The diagnostic efficacy of BFI for carotid atherosclerotic micro-vessel detection was also calculated.

Results: The BFI findings of micro-vessel were correlated to patient's symptom. The agreement between BFI and CEU for diagnosis of microvascularization was good (κ=0.406). The following was calculated: sensitivity (0.483); specificity (0.955); positive predictive value (0.933); negative predictive value (0.583); and accuracy of BFI (0.686). Logistic regression demonstrated a significant association between cerebrovascular events and the presence of BFI signals within carotid plaques (B: 2.422; 95% confidence interval: 1.728-73.407).

Conclusion: Compared with CEU, the BFI is less sensitive, however, it is a valid and practical method for detection of carotid atherosclerotic micro-vessels.

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From the Departments of Ultrasonography (Wang, Zheng), Geriatric Medicine (Yuan), and Internal Medicine (Ren), Zhongnan Hospital of Wuhan University, Wuhan, China.

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Address correspondence and reprint request to: Dr. Jiang H. Ren, Department of Internal Medicine, Zhongnan Hospital of Wuhan University, 169 Donghu Road, Wuhan 430071, Hubei, China. Tel. +86 (138) 86089196. Fax. +86 (27) 88517505. E-mail: 1311271032@qq.com

It is known that atherosclerotic cerebrovascular disease remains as one of the leading causes of morbidity and mortality in Chinese population. In view of the effectiveness of early intervention, the importance of identifying "high-risk" plaque or individual becomes more urgent. The vasa vasorum (VV) is located in the adventitia of the large arteries, and provides the nutritional needs of the artery.[1] However, pathological neovascularization from the adventitia into a plaque may contribute to progression of a stable atherosclerotic lesion, to a lesion with a high-risk of rupture by instigating leucocyte recruitment, and intraplaque hemorrhages.[2] Current studies confirm a pronounced relationship between neoangiogenesis from adventitial VV into the plaque, plaque vulnerability, and cerebro- and cardiovascular events.[3,4] The B-flow imaging (BFI) is a promising imaging technique, which provides direct visualization of blood flow during gray-scale sonography. The BFI offers simultaneous display of high resolution, spatial, and temporal depiction of blood flow. Wachsberg[5] believed that the BFI's ability to show slow flow, its high spatial resolution, and its avoidance of factitious flow made it a good complementary technique to Doppler sonography. As the moving blood is depicted as a gray-scale signal, discrimination of both high- and low blood flow is much more accurate and sensitive in BFI, compared with color Doppler flow imaging (CDFI). This unique characteristic along with the relative ease of obtaining BFI, makes it an appealing alternative in the detection of peri- and intraplaque micro-vessels in atherosclerotic plaques. Contrast-enhanced ultrasound (CEU) has been applied in previous studies to investigate intraplaque neovascularization. Our study was designed to evaluate the ability of BFI to visualize micro-vessel of atherosclerotic carotid arteries in comparison with CEU. Therefore, we aim to evaluate the presence of micro-vessel in symptomatic and asymptomatic patients with carotid atherosclerosis with both BFI and CEU.

Methods. Between August 2008 and July 2011, we enrolled 78 patients (54 male, 24 female) in the study. The mean age of these patients was 62.7 years (range 39-91 years). The patients were selected from those referred for carotid ultrasound based on clinical indications (symptomatic cerebrovascular disease and screening for cardiovascular risk factors) at the Department of Ultrasonography in ZhongNan Hospital of Wuhan University, Wuhan, China. One carotid atherosclerotic plaque thicker than 2 mm at least was the inclusion criterion. Among them, 43 cases were in the "no symptom" group, and 35 cases belonged to transient ischemic attack/acute ischemic stroke group (TIA/stroke group). Patients in the "no symptom" group were with plaque in the carotid artery, but without any symptoms of ischemic cerebrovascular disease. The patients in the TIA/stroke group were diagnosed with TIA, or acute ischemic stroke by trained neurologists. Patients with coronary heart disease, posterior circulation ischemia, or brain hemorrhage were excluded from the study. The presence of traditional cardiovascular risk factors, including age, gender, hypertension (casual blood pressure ≥160/95 mm Hg, or receiving antihypertensive medication), hyperlipidemia (serum total cholesterol ≥5.7mmol/L, or receiving medication), diabetes mellitus (fasting plasma glucose ≥7.77mmol/L, or receiving medication), and smoking were recorded. The protocol was approved by the hospital ethical committee, and informed consents were obtained from all patients before their examinations. The study was conducted according to the principles of Helsinki Declaration.

Utilizing a 9-L probe with transmission frequency of 6-8 megaHertz (MHz) (Logiq 9, GE Healthcare, Milwaukee, Wisconsin, USA) standard carotid ultrasound was performed. The BFI ultrasound and CEU were performed with the same probe. In each patient, both longitudinal and transverse scans were carried out. Each plaque detected was observed carefully with standard and BFI ultrasound. The plaque with the highest grade of peri- and intraplaque micro-vessel detected by BFI, along with its thickness and stenosis degree were analyzed. Among the 78 patients, 51 patients were submitted for CEU. If one soft plaque and one mixed plaque of similar thickness were both present in one case, only the soft plaque was observed and analyzed. The examination was digitally stored for later review. The CEU examination was performed after a bolus injection in an antecubital vein of SonoVue 2.5 ml (Bracco, Geneva, Switzerland) followed by 5 ml saline flush. The diagnosis of atherosclerotic plaques was made according to the Mannheim consensus as focal structures encroaching into the arterial lumen.[6] Stenosis degree was graded according to the guidelines.[7] The BFI signal was defined as follows: negative - no flow signals were noted within the plaque, or the adventitial tissue; and positive - clear visible flow signals appeared within the plaque, or the adventitial tissue. Intraplaque

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neovascularization by CEU was graded on a grading scale published previously:[8] Grade I - showed on appearance of microbubbles within the plaque; Grade II - showed a clear visible enhancement in basilar part or shoulder of the plaque; Grade III - showed a clear visible enhancement in both basilar part and shoulder of the plaque; Grade IV - showed a clear visible enhancement in basilar part, shoulder, and center of the plaque. The correlation of ischemic cerebrovascular symptom, stenosis, and plaque type on the detection of microvessels by BFI was statistically evaluated using an χ^2 test (McNemar test). Each plaque detected for each patient was analyzed. The κ coefficient was used to evaluate the consistency of BFI and CEU. The CEU was used as the reference standard. Sensitivity, specificity, positive and negative predictive values, and accuracy of BFI for neovessel detection were calculated. Differences in background factors between patients with, and without an ischemic cerebrovascular event were statistically compared using the Student independent t-test for age, and χ^2 test for gender and traditional cardiovascular risk factors, including hypertension, diabetes, hyperlipidemia, and smoking. Differences in the ultrasonic characteristics were also compared using χ^2 test for stenosis >50%, and BFI signal detection. An association between these variables and ischemic cerebrovascular events was further analyzed using a logistic regression model, to determine independent variables. Statistical significance was taken as $p<0.05$ using the Statistical Package for Social Sciences version 16.0 (SPSS Inc, Chicago, IL, USA).

Results. During the study period, 78 patients with carotid atherosclerosis received standard carotid ultrasound and BFI examinations. Among them, 51 patients underwent carotid CEU. In total, 132 plaques were detected in those patients. The most common location of the atherosclerotic plaques was at the common carotid artery bifurcation, and the initial segment of internal carotid artery. A total of 69.7% were <50% in area stenosis, and 30.3% were >50% in area stenosis. It was found that 39.4% of these lesions were hypo-isoechoic, 23.5% were hyperechoic, and 37.1% were mixed. With BFI modality, in addition to the moving gray signals in the artery lumen, minute linear, or cluster pattern signals were regarded as a sign of flow within the atherosclerotic lesion, or arterial wall. The periplaque signal is defined as BFI signal in the adventitial area of the carotid artery, while the intraplaque signal is defined as BFI signal within the carotid artery plaque.

Utilizing BFI, our study revealed peri- and intraplaques vascular signals in several patients. We observed a certain gross linear flow signal penetrating the basilar part of a hypoechoic plaque (**Figures 1A & 1C**), while there was no signals detected by CDFI (**Figure 1B**). Meanwhile, the BFI showed an adjacent rim-like flow signal in the adventitial area of a hypoechoic thick plaque (**Figures 2A & 2C**), however CDFI could not detect such flow signal (**Figure 2B**). We also detected a tiny cluster flow signal into the shoulder of a hypoechoic plaque with the irregular surface (**Figures 3A & 3B**), which was extensively enhanced in the basilar part after injection of contrast agent (**Figures 3C & 3D**). There was a significant relationship between severe stenosis and BFI signal detection ($p=0.002$). Furthermore, the peri- or intraplaque vessels signal detected by BFI more frequently occurred in the hypo-isoechoic plaques than in other types, which was noted in 25% of hypo-isoechoic plaques as opposed to 3.2% in hyperechoic

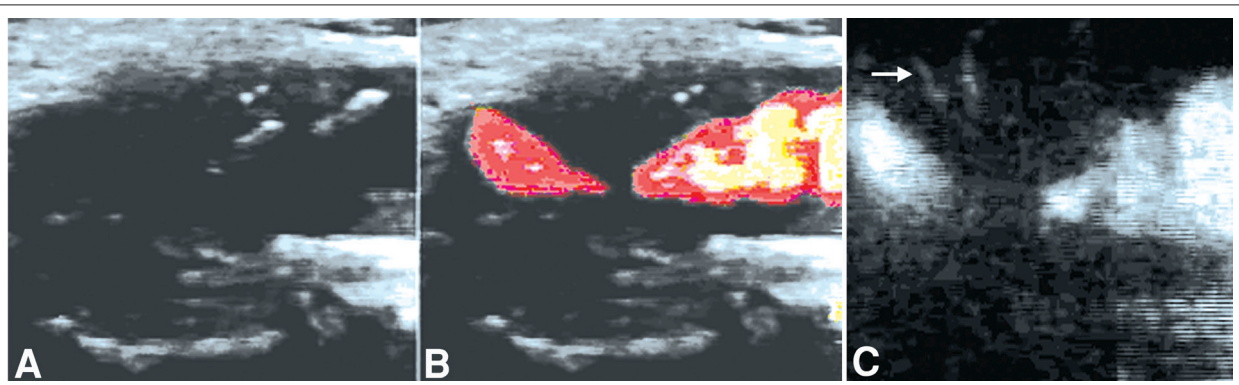

Figure 1 - Ultrasound longitudinal images of a carotid plaque showing: **A**) a B-mode ultrasound longitudinal image of a large hypoechoic plaque; **B**)color Doppler flow imaging of the same plaque without flow signal within the plaque; **C**) a B-flow imaging of the plaque containing multiple linear signals within the plaque (arrow), highly suggestive of intraplaque microvessels.

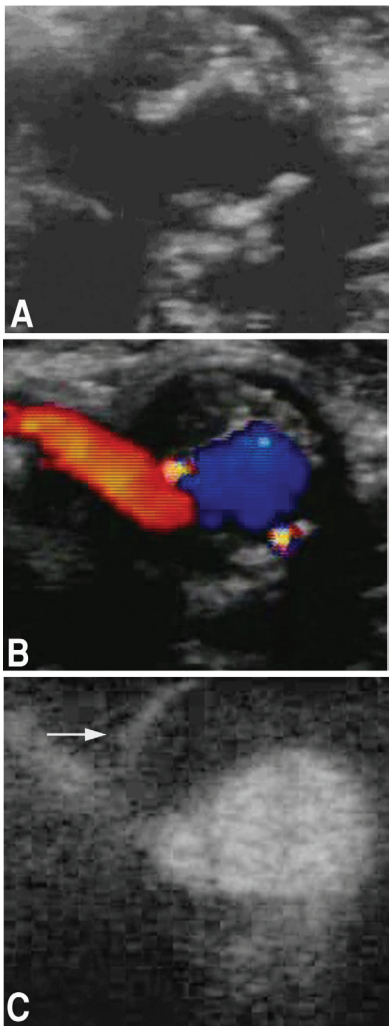

Figure 2 - Ultrasound transverse images of a carotid plaque showing: **A**) B-mode ultrasound transverse image of a large hypoechoic plaque; **B**) a color Doppler flow imaging of the same plaque without flow signal within the plaque; **C**) B-flow imaging of the plaque containing a rimlike signal in periadventitial area (arrow) highly suggestive of microvessels with the adventitial layer.

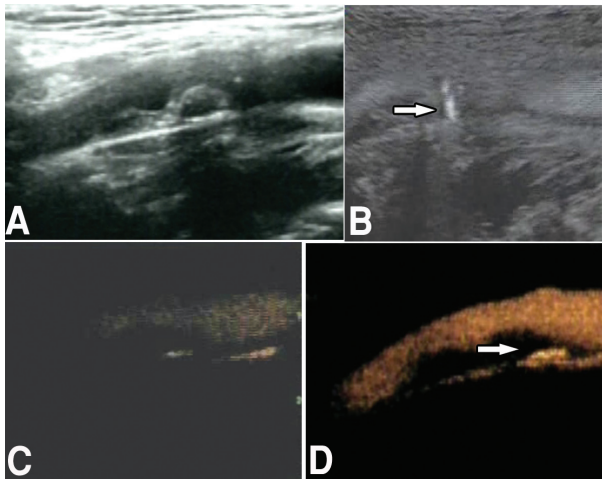

Figure 3 - Ultrasound longitudinal images of a carotid plaque showing: **A**) a B-mode ultrasound longitudinal image of a large hypoechoic plaque; **B**) B-flow imaging of the plaque containing multiple cluster signals into the shoulder of plaque (arrow), highly suggestive of micro-vessels; **C**) Longitudinal view obtained 14 seconds after injection of the contrast agent. There was slight enhancement in the basilar part of the plaque; **D**) Longitudinal view obtained 21 seconds after injection of a contrast agent. The plaque (arrow) was extensively enhanced in the basilar part, 21 seconds after injection of the contrast agent.

Table 1 - Atherosclerotic neovascularization on BFI and its association with the clinical characteristics.

Variables	BFI signals		*P*-value
	Negative	Positive	
Clinical characteristics			0.014
TIA/stroke group	67	16	
No symptom group	47	2	
Ultrasound findings			0.002
Area stenosis			
Stenosis <50%	85	7	
Stenosis >50%	29	11	
Echo inside of plaque			0.006
Hypo-isoechoic	39	13	
Hyperchoic	30	1	
Mixed	45	4	

Data are expressed as number of plaques. Analysis of χ^2 test compared with B-flow imaging (BFI) signal. TIA - transient ischemic attack

plaque, and 8.2% in the mixed (p=0.006). Finally, the occurrence rate of carotid neovessels detected by BFI in TIC/stroke group was 19.3% as opposed to 4.1% in the "no symptom" group (p=0.014) (**Table 1**). Fifty-one patients that underwent CEU and plaques were categorized by enhanced characteristics. The percentage of detection of micro flow in grade III was significantly higher than that in grades I (p=0.000) and II with CEU

Table 2 - Comparison between the B-flow imaging (BFI) findings and category results of contrast-enhanced ultrasound (CEU).

BFI signal	CEU category			
	I	II	III	IV
-	21	9	5	1
+	1	2	8	4

Data are expressed as number of subjects. Comparison of the 2 groups by Fisher exact tests. CEU III versus CEU I: p=0.000; CEU III versus CEU II: p=0.047; CEU IV versus CEU III: p=0.615

(p=0.047). There was no significant difference between grade III and IV (p=0.615) (**Table 2**). The agreement for diagnosis of carotid atherosclerotic neovessels between BFI and CEU was fairly good (κ=0.406, p=0.001). Using CEU as the reference standard, the results are shown in **Table 3**. Above all, more BFI signals were detected significantly in patients with ischemic cerebrovascular event than in those without ischemic cerebrovascular event (37.1% versus 4.7%; p=0.000). Although all atherosclerotic disease risk factors were more frequent in TIC/stroke group, however, it did not differ between the 2 groups (**Table 4**). We also used a logistic regression model for comparing these variables and found a significant association between ischemic cerebrovascular events and BFI signals detection (B - 2.422; 95%CI: 1.728-73.407)(**Table 5**).

Table 3 - The agreement for carotid atherosclerotic neovascularization diagnosis between B-flow imaging (BFI) and contrast-enhanced ultrasound (CEU).

BFI signal	Carotid CEU	
	+	-
+	14	1
-	15	21
Validity values (%)		
Sensitivity	48.3	(29.9-67.1)
Specificity	95.5	(75.1-99.8)
Predictive value positive	93.3	(66.0-99.7)
Predictive value negative	58.3	(40.9-74.0
Accuracy	68.6	(53.9-80.4)

negative - no flow signals were noted within the plaque, or the adventitial tissue; positive - clear visible flow signals appeared within the plaque, or the adventitial tissue

Table 4 - Background characteristics in patients with carotid plaque findings included in the study.

Variables	No symptom group (n=43) n (%)		TIA/Stroke group (n=471) n (%)		*P*-value
Age, years, mean±SD	58±9		69±10		<0.001
Male	29	(67.4)	25	(71.4)	0.704
Risk factors					
Hypertension	18	(41.9)	21	(60.0)	0.111
Hyperlipidemia	17	(39.5)	16	(45.7)	0.583
Diabetes	13	(30.2)	16	(45.7)	0.159
Smoking	9	(20.9)	14	(40.0)	0.066
Carotid ultrasonography Findings					
Area stenosis >50%	15	(34.9)	22	(62.9)	0.014
Presence of BFI signals	2	(4.7)	13	(37.1)	0.000

χ^2 test was used to compare categorical variables, and t-test was used to compare continuous variables

Discussion. Previous clinical trials investigating intraplaque angiogenesis mainly applied CEU with a contrast agents. Our study aimed to identify arterial atherosclerotic neovessel network in human carotid arteries with BFI carotid ultrasound. The BFI sonography can provide real-time visualization of vascular hemodynamics, which is accomplished by directly visualizing blood cells in a gray-scale display, and preferentially suppresses non-moving vessel walls and adjacent tissues. Doppler sonography, using a high-pass filter to suppress low-amplitude frequency shifts caused by physiologic movement of the soft-tissue structure can obliterate Doppler shifts by slow flow, while BFI technique can excellently depict mobile blood cells of both high- and low velocity flow.[9] Other advantages include the independence of the transmit angle, and the lack of color blooming, or aliasing artifacts associated with Doppler techniques. Therefore, it becomes easier to sensitively, and precisely detect slow flow with BFI than other sonographic flow imaging techniques. All these features make BFI a suitable modality for the detection of little intraplaque, or adventitial microvessels.

The theory of atherosclerosis demonstrates that the plaque originates from the hyperplasia of arterial intima and media. However, the adventitia also plays

Table 5 - Logistic regression model for predictors of occurrence of a cardiovascular event including B-flow imaging (BFI) signal.

Variables	B	SE	Wald	df	*P*-value	Exp (B)	95% CI for Exp (B)	
							Lower	Upper
Age	0.152	0.048	9.882	1	0.002	1.164	1.059	1.280
Male	-0.460	0.858	0.287	1	0.592	0.631	0.118	3.391
Hypertension	0.252	0.749	0.114	1	0.736	1.287	0.296	5.591
Hyperlipidemia	0.990	0.775	1.634	1	0.201	2.692	0.590	12.285
Diabetes	0.769	0.751	1.048	1	0.306	2.158	0.495	9.413
Smoking	1.446	0.862	2.811	1	0.094	4.245	0.783	23.013
Area stenosis >50%	0.263	0.823	0.102	1	0.750	1.300	0.259	6.528
BFI signal	2.422	0.956	6.412	1	0.011	11.264	1.728	73.407
Constant	-12.130	3.332	13.252	1	0.000	0.000		

B - regression coefficient; SE - standard error; df - degrees of freedom; Exp - estimate of odds ratio; CI - confidence interval

an important role in the plaque's progression. An abnormal hyperplasia of VV could extend into the plaque internal structure, providing nutrients, and promoting a vulnerable lesion to form. Thus, the VV of arterial adventitia and intraplaque angiogenesis constitute an integrated network of atherosclerotic neovascularization. Based on the principle of BFI modality, we considered that the presence of BFI signals detected in the atherosclerotic carotid artery was the manifestation of a major vessel from the adventitia layer, and minor vessel from the artery lumen both into the atherosclerotic plaques, being potential features of a vulnerable lesion.

With BFI, 2 distinct microvessel manners were identified within the carotid arterial atherosclerotic plaques. Several gross linear or cluster signals were detected, usually originating from the basilar part to the plaques' shoulder. Another type of neovessel originated from the external layers of the vascular wall was present as the rimlike flow signal around the wall or the stick signal in the wall. Intraplaque microvessel was more often visualized in the eccentric and large atherosclerotic lesions. All these types of signals were present mainly in the hypo-isoechoic area of the plaques. Since plaque echolucency is a hallmark of high-risk lesions, our finding was in accordance with the assumption that more unstable plaques have a higher degree of neovascularization.[10] One or both types of BFI signals were found in some patients, which constituted the microvessel network of the atherosclerotic artery as a whole. In a post-mortem study, Fleiner et al[11] also identified 2 angiogenic events in symptomatic atherosclerosis, ectopic neovascularization, and a hyperplasia of VV, which provides pathological evidence for our sonographic findings.

In this study, we found that BFI findings of atherosclerotic microvessels correlated well with the subjects' clinical history of TIA or ischemic stroke. This observation was in agreement with the previous findings.[12,13] Because symptoms reflect actual plaque rupture or thromboembolic activity, our findings suggested that plaque's micro-vessel detected by BFI was related to the events within the plaque, which lead to ischemic cerebrovascular events. Virmani et al[14] reported that immature blood vessels of arterial neoangiogenesis was a viable source of intraplaque hemorrhage providing erythrocyte-derived phospholipids and free cholesterol, which might promote the transition from a stable to an unstable lesion.

We consider BFI a sort of contrast-enhanced technique, which utilizes circulating blood cells as an endogenous contrast agent. The CEU, on the other hand is a technique, which requires exogenous contrast agent to enhance the visualization of microvessels. The differing mechanisms between BFI and CEU resulted in different sonographic patterns. The BFI could not obtain the lesion's entire information of microcirculation, but can discern minute vessels. By taking CEU as the reference standard, with relatively high specificity and low sensitivity, we found that BFI is a unique modality of ultrasound, which can detect tiny peri- and intraplaque vascular signals in carotid plaque as a supplement to CEU.

There are 3 most promising non-invasive imaging techniques for the diagnosis of atherosclerotic microvascular network: microscopic 3-dimensional CT, contrast magnetic resonance imaging (MRI), and CEU.[15,16] Microscopic CT is limited to the application of animal studies. Contrast MRI is expensive, and impractical in daily practice, especially in primary health care sector. Recently, researchers have utilized CEU as an imaging tool to study plaque microvessel. Ultrasound contrast agent is a medium, which can be visualized in transit through the VV.[17] Feinstein[18] firstly described their experience with CEU for identifying carotid plaque. Shah et al[8] reported good correlation between carotid CEU imaging of intraplaque neovascularization and a semiquantitative histological score on surgical specimens. However, carotid CEU is usually a secondary medical procedure based on ultrasonographic findings in an initial examination, and requires injection of contrast medium. Due to the expense of ultrasonic contrast agents and the inconvenience of an additional medical procedure, CEU presents difficulties if it is to be carried out comprehensively throughout China. Comparatively, BFI is a less expensive, and more convenient ultrasound imaging strategy for the assessment of plaque's microvessel. Furthermore, in light of its relatively simple application, BFI generates fewer distractions and better repeatability. Thus, the imaging results should be easily standardized into certain criteria.

Due to BFI's clinical validity and its ability to investigate atherosclerotic microvessels, our results represented a more valid and practical imaging tool for identification of vulnerable plaque in carotid atherosclerotic patients. The detection of arterial microvessels by BFI may be a new harbinger for early clinical intervention in the development of atherosclerosis. Meanwhile, BFI can provide non-invasive monitoring of anti-atherosclerotic therapy.

Our investigation had several limitations. Further studies are required to confirm our findings in a larger patient population. This will be the goal of our future

research. Another limitation of the present study was the subjectivity in grading of both the BFI and CEU images. Computer aided programs to analyze and quantify plaque neovascularization with BFI and CEU should be validated for consistency of grading. Moreover, when comparing the diagnostic performance of BFI and carotid CEU, only the thickest plaque was chosen for analysis. The thickest might not be the one with the most contrast enhancement.

In conclusion, our preliminary results show that BFI allows the presentation of carotid plaque's peri- and intraplaque micro-vessels in fairly good agreement with CEU. Patients with ischemic cerebrovascular symptoms have more BFI signals than asymptomatic patients.

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