Evaluating the Efficacy of Atorvastatin on Patients with Carotid Plaque by an Innovative Ultrasonography

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Background: The present study aimed to explore the efficacy of atorvastatin on patients with carotid plaque, applying superb microvascular imaging (SMI), and contrast-enhanced ultrasound (CEUS) for evaluating carotid intraplaque neovascularization. *Methods:* A total of 82 patients (82 carotid plaques) who were randomized into treatment group and control group underwent conventional ultrasound, CEUS, and SMI examinations. Patients in treatment group received a dose of 20 mg atorvastatin per day for 6 months while those in control group received placebo instead. Lipid parameters were assessed and intraplaque neovascularization were evaluated by CEUS and SMI before and 6 months after atorvastatin treatment. *Results:* No significant differences were found between the 2 groups at the study entry. Patients with atorvastatin treatment received marked improvement in total cholesterol, triglyceride, and LDL-cholesterol compared with those in control group ($P < .001$). In treatment group, SMI-detected intraplaque neovascularization reduced from 69.23% to 48.72% while CEUS-detected ones reduced from 76.92% to 69.23%. By contrast, the percentage of intraplaque neovascularization in control group did not change too much either by SMI (65.12%, 67.44%) or CEUS (74.41%, 74.41%). The consistency between CEUS and SMI was above .75 at all assessments ($P < .001$). *Conclusions:* Atorvastatin treatment works for patients with carotid plaque by reducing LDL-cholesterol and improving plaque regression. Second, the consistency between SMI and CEUS in visualizing intraplaque neovascularization is good. That indicates a high possibility to identify carotid plaque instability by a safer and cheaper ultrasonography without contrast agent.
Key Words: Carotid plaque—atorvastatin—contrast-enhanced ultrasonography—superb microvascular imaging—intraplaque neovascularization

Introduction

The stroke prevalence in China has increased over the past 3 decades, leading to a high mortality and severe disability among survivors.[1] Among all types of stroke, ischemic stroke accounts for approximately 87%.[2] Research identified the close relationship between ischemic stroke and carotid plaque, figuring out that the rupture of carotid plaque might be the main cause.[3]

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Therefore, identifying a high-risk plaque is pivotal. That could be achieved by early detection of intraplaque neovascularization.[4] Contrast-enhanced ultrasound (CEUS) is largely applied in visualizing intraplaque neovascularization.[5-7] CEUS generates contrast medium microbubble as an intravascular tracer. As a result, the usage of contrast agent makes CEUS not 100% applicable since allergic reactions may occur in some patients.[8] Recently, superb microvascular imaging (SMI) has emerged as an advanced color Doppler ultrasonography, showing the ability to visualize very low-velocity blood flows.[9-11] Previous studies supported the performance of SMI in depicting the minute vessels and slow-speed blood flows with high resolution and low artifacts. However, by far, to the best of our knowledge, few researches have applied SMI in evaluating carotid plaque neovascularization compared to CEUS.

Treatment with statins has been widely known as a first line therapy for patients with atherosclerosis.[12] Statins are capable of reducing vascular events in the prevention of ischemic stroke.[13] Atorvastatin is considered a well-established member of statin class. The effect on cholesterol lowering has been proved by different trials.[14,15] Furthermore, previous study explored the treatment with statins on pleiotropic effects such as the effect on angiogenesis. Angiogenesis, the formation of new blood flows, plays a contradictory role in atherosclerotic disease. Its linkage with plaque growth, rupture, and intraplaque hemorrhaging has been confirmed by various researches.[16,17] Therefore, the present study was designed to evaluate the efficacy of atorvastatin on patients with carotid plaque, applying SMI and CEUS for visualizing intraplaque neovascularization. The secondary purpose was to explore the consistency between SMI and CEUS in carotid imaging.

Materials and Methods

This prospective clinical study was approved by our Ethics Committee. All participants in the study were provided with information about all examinations and procedures and provided informed consent to participate in the study.

Patient Selection

From June 2017 to February 2018, 117 patients with ischemic stroke were referred for carotid imaging with the detection of carotid atherosclerosis. The identification of ischemic stroke was confirmed by a computerized tomographic scan positive for ischemic lesions. In total, 60 male patients and 26 female patients (age range, 51-81 years; mean age, 65.78 ± 6.77 years) were enrolled for the present study by conforming to the following inclusion criteria: (1) the stroke occurred within 30 days, (2) at least 1 carotid atherosclerotic plaque was detected. (3) No statin treatment history or stop having any statin therapy for more than 2 months. Figure 1 shows the participants selection criteria. The patient's demographic characteristics, including gender, age, and comorbidity were recorded.

Study Design

All the patients were randomized into 2 groups, treatment group (G1) and control group (G2). Each group

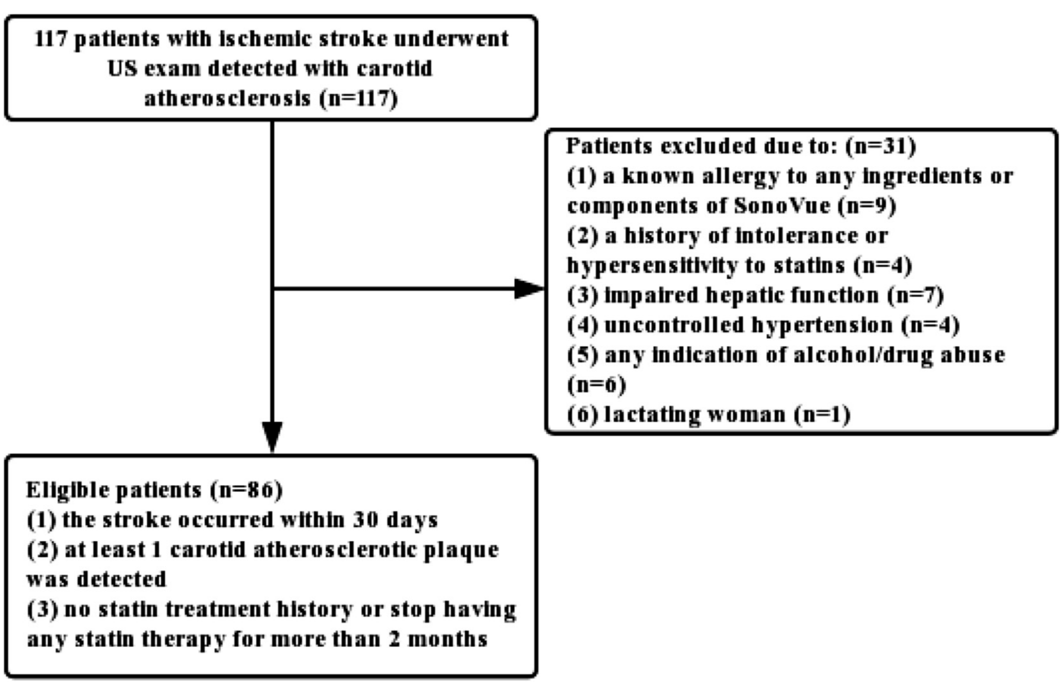

Figure 1. *Participants selection process.*

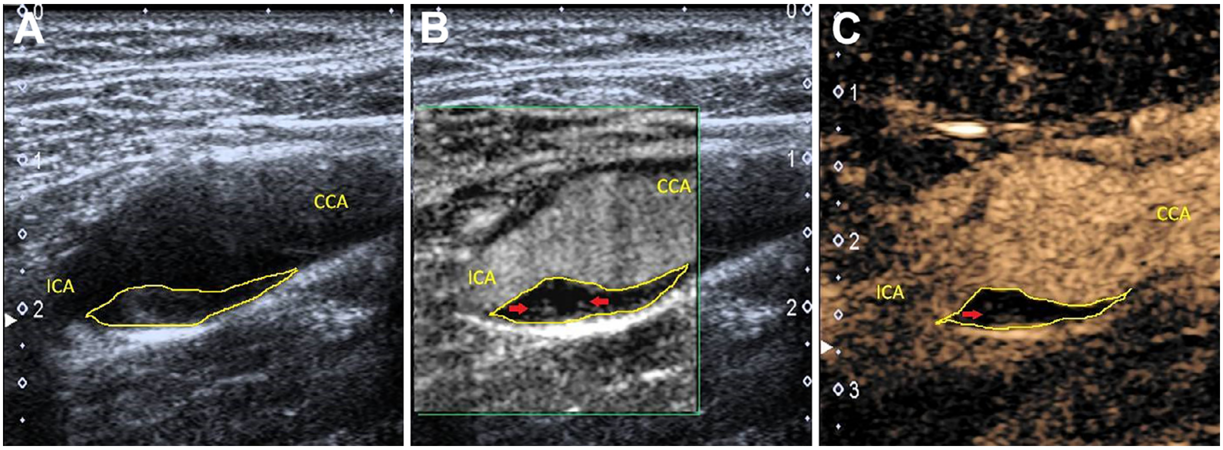

Figure 2. *Grayscale ultrasound, SMI, and CEUS images in one 67-year-old male patient at T0. (A) Grayscale ultrasound sagittal image. (B) SMI sagittal image. (C) CEUS sagittal image. Abbreviations: ICA, internal carotid artery; CCA, common carotid artery; CEUS, contrast-enhanced ultrasonography; SMI, superb microvascular imaging; T0, baseline. (Color version of figure is available online.)*

consisted of 43 participants. Patients in G1 received a dose of atorvastatin (trade name: Lipitor, Pfizer) 20 mg daily for 6 months while G2 patients received a placebo instead. Study assessments at each of 2 visits (baseline [T0], and 6-month after atorvastatin treatment [T1]) consisted of carotid screening (B-mode ultrasound [US], SMI, and CEUS), and fasting laboratory assays for lipids, namely, low density lipoprotein cholesterol (LDL-C), total cholesterol, and triglyceride.

Image Acquisition

All patients in the study initially underwent a grayscale ultrasound exam (Fig. 2, A and 3, A). Patients were requested to lie in the supine position with the visualization of the extracranial carotid arteries in both longitudinal and transverse planes. Once a plaque was detected, the maximal carotid plaque thickness was measured by the view showing the thickest cross-section of the plaque. In case of more than 1 separate plaque, only the thickest was included in our analysis. Grayscale ultrasound was followed by monochrome SMI examination, remaining the same probe position. The frame rate of monochrome SMI was 50-60 fps while the velocity was modified to less than 2.0 cm/s. The plaque was observed for 60 seconds with the storage of video images in our internal online database (Fig. 2, B and 3, B).

The CEUS imaging protocol was performed using an ultrasound contrast agent, SonoVue (Bracco, Milan, Italy). A volume of 4 mL contrast agent dissolved in .9% saline solution was injected in an antecubital vein in a bolus fashion through a 20-gauge cannula, followed by flushing with 5 mL saline. Complete bubble destruction was performed by scanning the carotid area at a high mechanical index. Digital cine clips were acquired and digitally stored for subsequent analysis (Fig. 2, C and 3, C).

Carotid imaging was performed by the same radiologist, who had over 3 years of experience in carotid

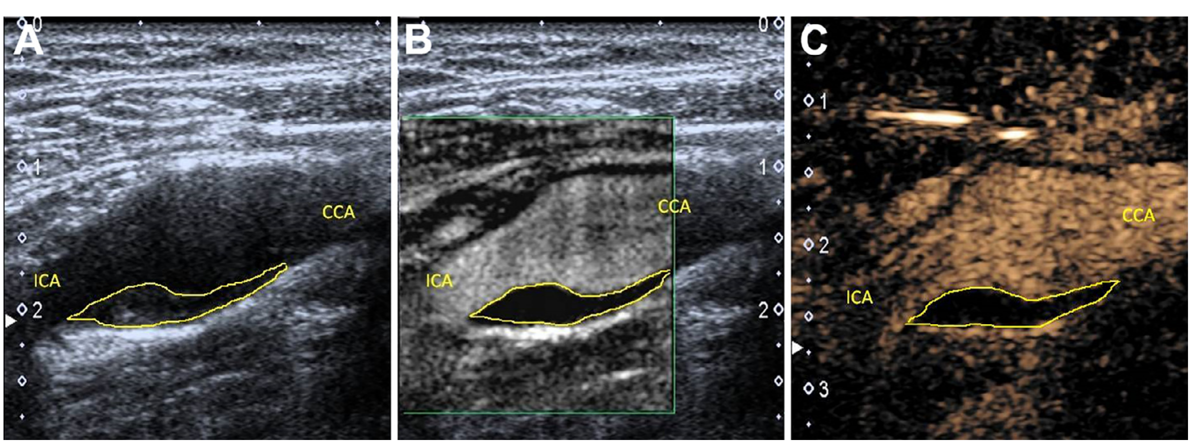

Figure 3. *Grayscale ultrasound, SMI, and CEUS images in the same 67-year old male patient at T1. (A) Grayscale ultrasound sagittal image. (B) SMI sagittal image. (C) CEUS sagittal image. Abbreviations: CEUS, contrast-enhanced ultrasonography; SMI, superb microvascular imaging; T1, 6-month after atorvastatin treatment. (Color version of figure is available online.)*

imaging. The Toshiba Aplio 500 ultrasound machine (Toshiba Medical System Corporation, Tokyo, Japan) with a 7.5 MHz linear-array transducer was used in all imaging procedures.

Reading Protocol

SMI-assessed vascular quantity was graded as absent (grade 0), moderate (grade 1), or marked (grade 2).[5] For grade 0, no blood flow was detected; marked (grade 2) vascularity included the visualization of a pulsating, arterial vessel within the plaque. Grade 1 was considered less neovascularization than noted in grade 2.[5]

The grading stratification for the observed neovascularization by CEUS was categorized into as follows, which was applied in previous studies.[18,19] For grade 0, no visible microbubbles in the plaque, or microspheres confined only to the adjacent adventitial layer (no enhancement). Moderate (grade 1) visible appearance of moving bubbles in the plaque either at the adventitial side or plaque shoulder, whereas grade 2 visualized extensive microbubbles moving into the plaque core, indicating rich intraplaque neovascularization.

The images were evaluated by 2 radiologists who had 8 years and 5 years of experience in carotid imaging. If any disagreement occurred, a third senior radiologist was consulted who had more than 10 years of experience in carotid ultrasonography, until a consensus was reached. All 3 radiologists were blinded to participant history.

Statistical Analysis

The chi-squared test or Fisher's exact test was applied to categorical variables, while an independent *t* test was used to compare continuous variables. Efficacy of atorvastatin evaluated by lipid parameters and neovascularization assessed by CEUS and SMI were compared between G1 and G2 using the Wilcoxon rank-sum test. The κ coefficient test was applied to evaluate the consistency of grading results of CEUS and SMI. The larger κ value indicated better consistency. Good consistency could be interpreted when κ value was above .75. P values <.05 were considered to be statistically significant. Data analysis was performed using the SPSS version 25.0 software package SPSS Inc., Chicago, IL, USA.

Results

Baseline Characteristics

Of the original study population, 4 patients in G1 were discontinued during the study period. Reasons for withdrawal were adverse events (n = 2), lost to follow-up (n = 1), and death (n = 1). None of the patients in G2 dropped off. In total, 39 plaques of 39 patients in G1 and 43 plaques of 43 patients in G2 were analyzed in the study. The baseline characteristics of patients at study

Table 1. *Baseline and conventional ultrasound characteristics of total patient population*

Characteristic	G2 (n = 43)	G1 (n = 39)	*P*
Gender			.062
Male	26 (60.5%)	8 (20.5%)	
Female	17 (39.5%)	31 (79.5%)	
Age years (mean ± SD)	66.65 ± 7.26	65.28 ± 6.23	.560
Body mass index kg/m^2 (mean ± SD)	25.83 ± 3.89	25.77 ± 4.68	.416
Hypertension			.974
Yes	23 (53.5%)	21 (53.8%)	
No	20 (46.5%)	18 (46.2%)	
Diabetes mellitus			.259
Yes	23 (53.5%)	16 (41.0%)	
No	20 (46.5%)	23 (59.0%)	
Dyslipidemia			.692
Yes	28 (65.1%)	27 (69.2%)	
No	15 (34.9%)	12 (30.8%)	
Smoking			.666
Yes	20 (46.5%)	20 (51.3%)	
No	23 (53.5%)	19 (48.7%)	
History of stroke			.611
Yes	4 (9.3%)	5 (12.8%)	
No	39 (90.7%)	34 (87.2%)	
Plaque echogenicity			.319
Hypoechoic	16 (37.2%)	21 (53.8%)	
Isoechoic	15 (34.9%)	10 (25.6%)	
Mixed hyperechoic	12 (27.9%)	8 (20.5%)	

G1, Treatment group; G2, Control group.

Table 2. *Lipid parameters assessed before and 6-month after atorvastatin treatment*

	G2	G1	z	*P*
T0				
TC	5.58 ± 1.55	5.74 ± 1.23	.014	.989
TG	3.06 ± .73	3.01 ± .62	.172	.864
LDL-C	4.09 ± .61	4.17 ± .31	.088	.930
T1				
TC	5.32 ± 1.06	3.30 ± .65	6.848	<.001*
TG	3.06 ± .51	1.88 ± .37	7.479	<.001*
LDL-C	4.05 ± .72	2.37 ± .60	7.015	<.001*

G1 treatment group, G2 control group, T0 baseline, LDL-C low density lipoprotein cholesterol, T1 6-month after atorvastatin treatment, TC total cholesterol, TG triglyceride.

*Indicates statistically significant difference.

entry are shown in Table 1. There were no significant differences between the 2 groups in any of the baseline characteristics.

Efficacy of Atorvastatin Assessed by Lipid Parameters

A marked great proportion of patients in G1 had achieved significant decrease in total cholesterol, triglyceride, and LDL-C to a normal level compared with those in G2 (Table 2). To highlight, 89.74% of patients receiving atorvastatin 20 mg had achieved the LDL-C goal less than equal to 3.2 mmol/L after a 180-day treatment.

Efficacy of Atorvastatin on Ultrasonography-assessed Intraplaque Neovascularization

Neovascularization was detected in 75.61% of total plaques (62 of 82) by CEUS and 67.07% of all plaques (55 of 82) by SMI at T0. Take patients in G1 for example, CEUS showed no vascularity (grade 0) neovascularization in 9 plaques (23.08%), grade 1 in 14 plaques (35.90%), and grade 2 in 16 plaques (41.03%) at baseline (Table 3). After a 6-month interval, the number of plaque scored as grade 0 increased from 9 to 18 whereas the number of grade 2 plaques decreased from 41.03% to 20.51% under CEUS examination. However, plaque neovascularization regression was not observed in G2. Instead, CEUS showed 2 more plaques in G2 upgraded from grade 1 to grade 2 at T1.

To compare the consistency between CEUS and SMI in evaluating plaque neovascularization, we then evaluated the same carotid plaques with SMI (Table 3). The evaluation by SMI came up with a similar finding. The efficacy of atorvastatin could be explained by a downward trend of grade 2 plaques and an upward trend of grade 0 plaques (P = .026). In baseline study, 13 plaques (33.33%) were noted as grade 2 and 12 plaques (30.77%) as grade 0. The number of grade 2 plaques was decreased to 6 (15.38%) whereas the number of grade 0 plaques was increased to 20 (51.28%) after a 6-month atorvastatin treatment.

Consistency between SMI and CEUS

Regarding grading results, the κ test results of all 4 comparisons were above .75, indicating that SMI and CEUS have good consistency for the detection of intraplaque neovascularization (Table 4). All plaques rated as grade 0 by CEUS were also interpreted as grade 0 by SMI. In G1, the sensitivity of grade 2 plaques by CEUS was 18.75% and 18.18% higher than that by SMI at T0 and T1 (P < .001). The same finding was also discovered in control group. The sensitivity of grade 2 plaques by CEUS was 25% and 23.08% higher than that by SMI at T0 and T1, respectively (P < .001).

At 4 assessments, all the specificity of SMI was 100% (all patients with no CEUS enhancement were not detected blood flow signals by SMI). However, SMI sensitivity was lower, 90.0% (27 of 30), 90.48% (19 of 21), 87.50% (28 of 32), and 90.63% (29 of 32), respectively. For instance, 3 of 30 patients in treatment group presented contrast-enhanced plaques on CEUS but without intraplaque blood flow signals detected by SMI. The comparison of the consistency of SMI and CEUS for the diagnosis of neovascularization showed κ greater than .75 and P less than .001 at all 4 evaluations (Table 5).

Discussion

Cerebrovascular disease is a form of vascular disease, as is atherosclerotic disease of the aorta, carotid arteries, and

Table 3. *Neovascularization graded by CEUS and SMI examinations*

	CEUS					SMI				
	Grade 0	Grade 1	Grade 2	z	*P*	Grade 0	Grade 1	Grade 2	z	*P*
G1 (n = 39)										
T0	9	14	16	2.370	.018*	12	14	13	2.120	.034*
T1	18	13	8			20	13	6		
G2 (n = 43)										
T0	11	21	11	.298	.766	15	19	9	.288	.773
T1	11	19	13			14	19	10		

G1, Treatment group; G2, Control group; T0, Baseline; T1, 6-month after atorvastatin treatment.

*Indicates statistically significant difference.

Table 4. *Grading results of CEUS and SMI*

T0					
G1	SMI grading			κ coefficient	*P*
CEUS grading	Grade 0	Grade 1	Grade 2	.768	<.001*
Grade 0	9	0	0		
Grade 1	3	11	0		
Grade 2	0	3	13		
G2	SMI grading				
CEUS grading	Grade 0	Grade 1	Grade 2	.782	<.001*
Grade 0	11	0	0		
Grade 1	4	17	0		
Grade 2	0	2	9		
T1					
G1	SMI grading			κ coefficient	*P*
CEUS grading	Grade 0	Grade 1	Grade 2	.835	<.001*
Grade 0	18	0	0		
Grade 1	2	11	0		
Grade 2	0	2	6		
G2	SMI grading				
CEUS grading	Grade 0	Grade 1	Grade 2	.786	<.001*
Grade 0	11	0	0		
Grade 1	3	16	0		
Grade 2	0	3	10		

G1, Treatment group; G2, Control group; T0, Baseline; T1, 6-month after atorvastatin treatment.
*Indicates statistically significant difference.

lower extremity arteries. Carotid arteries are accessible to assess characteristics of atherosclerotic plaque. On the basis of published reports, neovascularization was immature and fragile, especially the ones in plaque shoulders, and therefore caused intraplaque hemorrhage and plaque rupture.[20] Therefore, the need for accurate diagnosis and prevention therapy is indeed. Statins are considered as indispensable in the treatment of carotid artery stenosis[21] which attributed to 15%-25% of ischemic stroke.[22] Several studies have confirmed its improvement in reducing plaque neovascularization.[12,13] That has been achieved via multiple mechanisms such as reduction in LDL-C levels. Indeed, multiple studies demonstrated the strong correlation between reducing LDL-C and lowering the risk of acute and chronic cardiovascular events.[23,24] Similar results were seen in the present study. Thirty-five out of 39 patients on atorvastatin therapy for 6 months achieved the LDL-C goal of less than equal to 3.2mmol/L. This finding was similar to that reported using similar doses of atorvastatin.[25,26] By contrast, none of the patients in control group met the same goal.

Table 5. *Detection of intraplaque neovascularization by CEUS and SMI*

T0-G1	CEUS		κ coefficient	*P*
SMI	Negative	Positive		
Negative	9	3	.806	<.001
Positive	0	27		
T1-G1				
Negative	18	2	.898	<.001
Positive	0	19		
T0-G2				
Negative	11	4	.782	<.001
Positive	0	28		
T1-G2				
Negative	11	3	.832	<.001
Positive	0	29		

G1, Treatment group; G2, Control group; T0, Baseline; T1, 6-month after atorvastatin treatment.
*Indicates statistically significant difference.

On the other hand, identifying changes in plaque neovascularization is another method to monitor the therapeutic effects on carotid intraplaque neovascularization. Back in 2007, Koutouzis et al[12] first demonstrated the correlation between statin treatment and reduced intraplaque angiogenesis in humans by evaluating the intensity of intraplaque angiogenesis using the antibody CD34. Therefore, the detection on intraplaque neovascularization by a quick and noninvasive imaging technique is of major clinical interest. CEUS is applied to visualize plaque neovascularization as a promising tool for some years.[27] Real-time images of microbubbles are generated by CEUS to present vascularized tissues and demonstrate microcirculatory perfusion. Therefore, observation microbubbles within carotid plaque were applied as a measure of revealing neovascularization, first reported by Feinstein et al.[28] Vicenzini et al[29] randomly selected 23 patients with carotid plaques of distinct degrees of stenosis and found plaque vascularization in the fibrous and fibro-fatty tissue by observing microbubbles within the plaque. Saito et al[30] conducted a quantitative evaluation using CEUS to detect intraplaque neovascularization and confirmed the capability of CEUS in predicting and stratifying plaque vulnerability. In our study, we observed 76.92% patients in G1 and 74.42% patients in G2 with intraplaque neovascularization at T0 by CEUS. Thereafter, less neovascularization (21 of 39) was detected after a 6-month atorvastatin treatment in treatment patients whereas no plaque regression was found in patients who did not receive atorvastatin therapy.

The use of CEUS provides the first option to identify changes in plaque neovascularization but with some limitations. First of all, the use of intravenous contrast agents which might result in allergy or even adverse reaction in certain patients. Second, the additional cost due to CEUS examination may not be affordable for all patients. With the advent of an innovative Doppler ultrasonography method, SMI delineates a broader range of blood flow signals with higher resolution. Compared with CEUS, SMI is quicker and cheaper as well as more risk-free. In this study, all plaques with bloodstream signals detected by SMI revealed corresponding enhancement on CEUS at 2-study visits. In other words, CEUS obtained an enhancement in more participants, which indicated a superior detection capability but with possibility of overestimating unstable plaques. This, in accordance with our results showing all higher-grade plaques assessed by CEUS had either same-grade or lower-grade plaques interpreted by SMI. Similarly, Oura et al[31] demonstrated all 12 patients with SMI-detected intraplaque neovascularization presented enhancement on CEUS. That reconfirmed our results that SMI obtained a 100% specificity compared with CEUS. The consistency between CEUS and SMI in visualizing intraplaque blood flow signals was therefore good ($\kappa > .75$, $P < .001$). That provided a new inspiration in the clinical evaluation of carotid artery plaque instability. Only perform confirmatory CEUS exam in the circumstances when no intraplaque neovascularization were detected by SMI.

Our study has certain limits. First, the study was a single-center with limited study population. Therefore, a multi-center and larger sample was needed for future study. Second, the study applied the use of semiquantitative image analysis, which might be relatively subjective. A more objective quantitative analysis would be applied for further research.

Conclusions

In conclusion, our results confirm that atorvastatin treatment works for patients with carotid plaque by reducing LDL-C and improving plaque regression. Second, the consistency between SMI and CEUS in visualizing intraplaque neovascularization is good. That indicates SMI may facilitate the identification and characterization of carotid intraplaque neovascularization as a safer and cheaper ultrasound technology but without contrast agent compared with CEUS. SMI represents a potentially vital and efficacious diagnostic method for the accurate diagnosis of patients with carotid plaque.

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