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Role of Contrast-Enhanced Ultrasound Sonography in the Medical Diagnostics of the Disease Activity in Patients With Takayasu Arteritis

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ABSTRACT The accurate diagnosis of Takayasu arteritis (TA) and the evaluation of its activity can bring significant challenges. In this paper, we sought to investigate a correlation between clinical activity and the enhancement of vessel wall acquired by contrast-enhanced ultrasound sonography (CEUS) in patients with TA, and to evaluate whether CEUS can be used to assess the disease activity of TA. Twenty TA patients with their carotid arteries affected were enrolled and divided into the active group and the inactive group according to the NIH scoring method. The white blood cell counts, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were obtained. Conventional ultrasound was performed to acquire the external diameter of the artery (D), intima-media thickness of the arterial wall (IMT), percent area stenosis, peak systolic velocity, end diastolic velocity, and resistance index. CEUS was performed to acquire the enhanced intensity (EI), derived peak intensity (DPI), and time to peak. The analysis showed that compared with the inactive group, D and IMT were significantly higher in the active group (6.50 ± 1.80 versus 9.20 ± 4.00 mm, 1.80 ± 0.40 versus 2.40 ± 0.70 mm, $p < 0.05$). EI and DPI were also significantly higher in the active group (38.20 ± 10.62 versus 80.80 ± 23.60 IU, 46.20 ± 10.20 versus 90.30 ± 24.60 IU, $p < 0.05$). Meanwhile, EI and DPI showed good correlation with CRP and ESR. Therefore, our study demonstrated that CEUS can increase the effectiveness of conventional ultrasound in differentiating active and inactive TA.

INDEX TERMS Carotid artery, contrast-enhanced ultrasound sonography, medical diagnostic, Takayasu arteritis, vasa vasorum.

I. INTRODUCTION

Takayasu arteritis (TA), was firstly described in 1908 by Japanese ophthalmologist Mikito Takayasu, is a chronic granulomatous arteritis of unknown etiology that involving the aorta and its major branches [1], [2]. TA involves the three layers of the arterial wall. Inflammatory process begins at the vasa vasorums in adventitia with infiltration of inflammatory cells and various substances which lead to neovascularization and reconstruction of the arterial wall. These neoformative vasa vasorums become parallels through which the inflammatory cells involve arterial walls. Later, the media and intima are involved due to destruction of smooth muscle cells, elastic fiber, and collagenous fiber. The arterial wall shows markedly thickening and fibrosis. Stenosis or occlusion may occur in the diseased artery and lead to a hypoxic environment. The hypoxic environment then lead to the generation of new blood vessels [3]–[6].

TA always extends over years with variable condition, and may cause varying degrees of neurologic symptoms secondary to hypertension or ischemia (postural dizziness, amaurosis, stroke and so on). Therefore, evaluation of the disease activity is necessary to guide therapy including symptom remission, glucocorticoid treatment, or surgical

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treatment [7], [8]. Acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are generally used indicators for detection of inflammation and disease activity. While mounting evidence has suggested that these markers can not distinguish active TA from inactive ones reliably [9]. Imaging techniques such as digital subtraction angiography (DSA), computed tomography angiography (CTA), magnetic resonance angiography (MRA), positron emission tomography (PET) are in common use to detect TA [10]–[13]. According to previous study, DSA is more sensitive, specific, and accurate than other imaging methods in estimating stenosis [14], but it fails to evaluate the disease activity of TA. The usefulness of CTA, MRA, and ^{18}F-fluorodeoxyglucose-positron emission tomography (^{18}F-FDG-PET) are limited due to the cost, radioactivity or the requirement of specialized equipment. Therefore, the optimal method to assess the disease activity, evaluate the efficacy, and monitor recrudescence has not been clarified precisely.

Ultrasound can effectively demonstrate thickening of the vessel wall, which may be an earlier symptom of the disease occurring before stenosis and dilatation [2]. Conventional ultrasound, color doppler flow imaging (CDFI), and pulse doppler imaging (PDI) can detect TA through thickening of the arterial wall, stenosis of the lumen, or occlusion [15], but they are failed to assess the disease activity as they can not demonstrate vasa vasorums or slight thickening of the arterial wall. Ultrasound contrast agent can act as red blood cell tracers to evaluate microcirculation and improve image quality significantly [16]. Contrast-enhanced ultrasound sonography (CEUS) is such a technique performed through injecting the contrast agent, microbubbles, into circulation to improve the quality of ultrasound imaging **(Fig. 1)**. It is now widely used in differential diagnosis of tumors, perfusion imaging of myocardium and other tissues [17], [18]. CEUS has been used to evaluate neovascularization and the stability of atherosclerotic plaques since enhancement was observed in carotid atherosclerotic plaques in 2004 [19]–[21]. The diameter of microbubbles is much smaller than that of erythrocytes thus the bubbles might be used as markers of neovascularization, which represent the initial inflammation of TA. Therefore, in addition to assessing the thickness of vessel wall and stenosis of lumen, CEUS can provide information of contrast enhancement of arterial wall, which represent inflammation of the artery and may be useful for disease screening, following up, and evaluation of efficacy. In 2011, Giordana *et al.* [22] and Magnoni *et al.* [23] have reported that it was feasible to assess the disease activity by CEUS. Further studies are needed to confirm these observations and the potential of this technique for monitoring the disease activity.

II. METHODS

A. PATIENTS

22 patients (21 female, 1 male) with a mean age of 32 (range from 17-56 years old), diagnosed with TA in the second affiliated hospital of Harbin Medical University during 2011 to 2014 were enrolled in this study. All patients met the 1990 criteria for classification of TA from American College of Rheumatology [24] and were divided into the active group and the inactive group according to the NIH scoring method [25]. Patients who had at least 2 of the following 4 features new onset or worsening were considered the active ones, the others were considered the inactive ones: (1) signs and symptoms of vascular ischemia or inflammation; (2) elevated ESR; (3) angiographic abnormalities; and (4) systemic symptoms not attributable to another disease. Carotid ultrasound was performed and 2 patients with no common carotid artery (CCA) involved were eliminate. 13 patients with bilateral CCA involved and 7 patients with unilateral CCA involved were remained. This study was approved by the institutional ethics committee of the second affiliated hospital of Harbin Medical University and all patients signed informed consent documents.

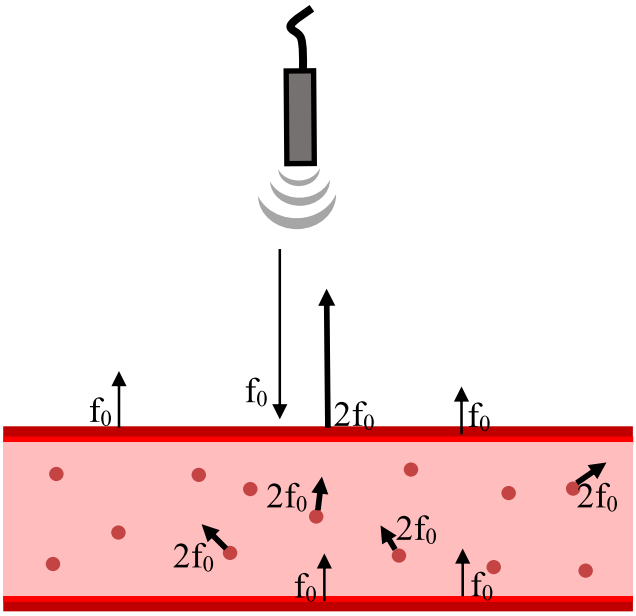

FIGURE 1. Transducers transmit an acoustic pulse with the frequency f_0. On receive, the vessel wall and the intima media generated the frequencies of f_0, while the second harmonic generation (SHG) with the frequencies $2f_0$ are generated by microbubbles. SHG improve the signal-noise ratio between the lumen and the tissue surrounding significantly, and show adequate delineation of the lumen from the intima-media.

B. LABORATORY EXAMINATION

The white blood cell (WBC) counts, CRP, and ESR were obtained from all patients within one week before ultrasound examination.

C. ULTRASOUND IMAGING

1) CONVENTIONAL ULTRASOUND

Ultrasound images were acquired from all patients using a CX50 CompactXtreme ultrasound machine (Philips Healthcare, Bothell, WA, USA) with a high-frequency linear probe (9-13MHz). During examinations, all patients took supine

position with their neck extended. Images were aquired in both longitudinal and transverse planes. For more accurate measurement, the depth was decreased to about 3cm with the optimal focal zone.

On Brightness-mode ultrasound, the external diameter (D), intima-media thickness (IMT), and percent area stenosis (PAS) of diseased CCA were measured. D, IMT, and PAS were measured in 3 continuous sections with 1mm interval and averaged for analysis.

Doppler ultrasound was used to evaluate blood flow characteristics in the diseased regions. Peak systolic velocity (PSV), end diastolic velocity (EDV), and resistance index (RI) were acquired and investigated.

2) CONTRAST-ENHANCED ULTRASOUND

Contrast mode was switched on to perform CEUS right after conventional ultrasound examination. Scanning depth (3cm), frequency (5MHz), dynamic range (20Hz), gain settings (52), and frame rate (35fps) were initially optimized and maintained constantly through examination. A low mechanical index (MI, 0.10) was used. MI was calculated using the following formula:

$$\mathrm{MI} = \mathrm{F}/\sqrt{f} \tag{1}$$

where F is the peak negative pressure during the relaxation period of ultrasonic propagation, f is the central frequency of probe.

CEUS was performed through intravenous injection of the contrast agent, SonoVue^{TM}(Bracco, Milan, Italy). A vial of SonoVue was diluted with 5mL saline to achieve a final concentration 1×10^8 microbubbles/mL. After locating the diseased region on longitudinal plane, 1.2mL diluted microbubbles were bolus injected intravenously and repeated if needed, following a 5mL saline flushing. Real-time movies were digitally recorded. Folllowing is the effective time of microbubbles:

$$T = (R \times \rho)/(2d \times Cs) \tag{2}$$

where R means the radius of microbubbles, ρ means the density of the gas in microbubbles, d is the dispersity of the gas, and Cs is the blood saturation constant of the gas. In our study, the effective time was about 3 minutes. Therefore, real-time dynamic images were observed and stored in 3 minutes. Every patient was injected 3-4 times with equal amounts of SonoVue with the interval of 10 minutes.

Data was analyzed offline using acoustic quantitative analysis software (QLAB). Enhancement features were observed and time-intensity curves (TICs) in the region of interest (ROI) were drawn. Derived peak intensity (DPI), enhanced intensity (EI), time to peak (TTP) were measured on TICs.

D. STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS20.0. Data were reported as median and range or mean standard deviation. *Student t* test, $\chi 2$ test and *Pearson* correlation analysis were used to compare D, IMT, EI and DPI between the two groups, and to reveal the correlation between contrast enhancement and the wall thickness or the disease activity. Correlations between EI, DPI and CRP or ESR were assessed by *Pearson two-tailed r* test. A p value of less than 0.05 was considered significant.

III. RESULTS

A. PATIENTS CHARACTERISTICS

Demographic, laboratory and clinical characteristics of patients were summarized in **Table 1**. According to the NIH criteria, 18 CCAs of 11 patients were contained in the active group and 15 CCAs of 9 patients were in the inactive group. In the active group, CRP and ESR were significantly higher compared with the inactive group (44.3±23.1 vs. 5.0±2.9mm/h, 74.2±28.7 vs. 21.3±6.0mg/L, $p < 0.05$). The WBC counts had no significant difference between the two groups. Among all the symptoms observed, headache (97.0%) was the most common symptom in all patients, followed by syncope (93.9%). Fever (30.3%) and arthralgia (18.4%) were less common symptoms.

B. ULTRASOUND IMAGES

1) CONVENTIONAL ULTRASOUND

As mentioned previously, CCAs in 65.0% (13/20) patients were bilaterally involved and 35.0% (7/20) were unilaterally involved. Internal carotid artery (ICA) and external carotid artery (ECA) were not easily affected in TA, accounting for 20.0% (4/20) and 15.0% (3/20), respectively. 7 patients (35.0%) were found subclavian arteries involved. Obstructive carotid disease (PAS > 50%) was present in 81.8% of all the CCAs involved. 2 CCAs in active patients were completely occluded. Post-stenotic dilatation was found in 3 CCAs.

Conventional ultrasound parameters of CCAs were shown in **Table 2**. In all patients who had carotid involvement, images on longitudinal planes showed hyperechogenic, homogeneous thickening of arterial walls (**Fig. 2a**). On transverse planes, the circumferentially thickening is termed the ''macaroni sign'' [26](**Fig. 2b**). CDFI was helpful to observe the boundary of vessels (**Fig. 2c**) and PDI was used to measure the velocity of blood flow (**Fig. 2d**). IMT in the active group was significantly higher than that in the inactive group (2.40±0.70 vs. 1.80±0.40mm, $p < 0.05$). D was 9.20±4.00mm in active lesions, which was significantly higher than that in inactive lesions (6.50±1.80mm, $p < 0.05$). There were no significant differences in PSV, EDV, and RI between the active group and the inactive group ($p > 0.05$).

2) CONTRAST-ENHANCED ULTRASOUND

In addition to displaying the diseased regions, CEUS improved imaging quality with greater enhancement and clearer boundary of arterial wall. Significant contrast enhancement was observed in all involved CCA walls in the active group. Vasa vasorum in diseased regions were shown through linear flow of microbubbles within the arterial

TABLE 1. Demographic, laboratory, and clinical characteristics of patients.

	Inactive Group n=9	Active Group n=11
Age(y)	39.3±12.0	23.6±8.6
Males/Females	0/9	1/11
Disease duration(m)	21.0±6.9	15.0±5.8
Laboratory findings		
WBC (10^9/L)	20.0±5.2	23.0±7.8
CRP (mg/L)	5.0±2.9	44.3±23.1*
ESR (mm/h)	21.3±6.0	74.2±28.7*
Systemic symptoms [n(%)]		
Weight loss	6(40.0%)	8(44.4%)
Fever	3(20.0%)	7(38.9%)
Dizziness	7(46.7%)	10(55.6%)
Syncope	14(93.3%)	17(94.4%)
Headache	14(93.3%)	18(100%)
Malaise	4(26.7%)	8(44.4%)
Arthralgia	2(13.3%)	4(22.2%)
Vascular manifestations [n(%)]		
Vascular accentuated	6(40.0%)	10(55.6%)
Carotodynia	6(40.0%)	9(50.0%)
Defective vision	0	1(5.6%)

*p <0.05 vs. the inactive group. ESR <15mm/h, CRP <10mg/L, WBC <10×10^9/L were considered normal.

TABLE 2. Conventional ultrasound parameters of common carotid arteries.

	Inactive group n=9	Active Group n=11
Numbers of involved CCA	15	18
D (mm)	6.50±1.80	9.20±4.00*
IMT (mm)	1.80±0.40	2.40±0.70*
PAS (%)	62.13±20.06	67.94±16.04
PSV (cm/s)	105.40±44.30	103.30±36.60
EDV (cm/s)	40.4±18.90	33.40±18.70
RI	0.68±0.04	0.70±0.07

*p <0.05 vs. the inactive group. CCA – common carotid artery; D – external diameter; IMT – intima-media thickness; PAS – percent area stenosis; PSV – peak systolic velocity; EDV – end diastolic velocity; RI – resistance index.

wall, especially along the adventitia (**Fig. 3a**). However, few bubbles were observed within the walls in the inactive group which meant there were no significant contrast enhancement (**Fig. 3b**). 2 CCAs in the active group were occluded with no contrast enhancement observed.

We traced the TICs of the 33 CCAs involved, results were shown in **Fig. 4**. In the active group, there were large amounts of contrast signal within the arterial walls (**Fig. 4a**), compared with the small amounts of contrast signal in the inactive group (**Fig. 4b**).

Table 3 showed the results of quantitative analysis of CEUS. EI and DPI were significantly higher in the active group compared with the inactive group (80.80±23.60 vs. 38.20±10.62IU, 90.30±24.60 vs. 46.20±10.20IU, $p < 0.05$). TTP between the two groups had no significant differences (10.35±0.62 vs. 10.98±0.67s, $p > 0.05$). **Fig. 5a-d** showed the correlation between EI and the parameters of IMT, D, CRP, and ESR. It was shown that EI had direct correlations with CRP ($r = 0.847$, $p < 0.05$) and ESR ($r = 0.887$, $p < 0.05$). The correlation between DPI and the parameters of IMT, D, CRP, and ESR were shown in **Fig. 5e-h**. Direct correlations between DPI and the parameters of CRP ($r = 0.840$, $p < 0.05$) and ESR ($r = 0.856$, $p < 0.05$) could also be observed.

C. REPRODUCIBILITY

EI and DPI were measured by three observers. The reliability among intra-observer agreement were assessed by intra-class correlation coefficient (ICC). Excellent agreement was demonstrated among the 3 observers for all measurements (ICC=0.998).

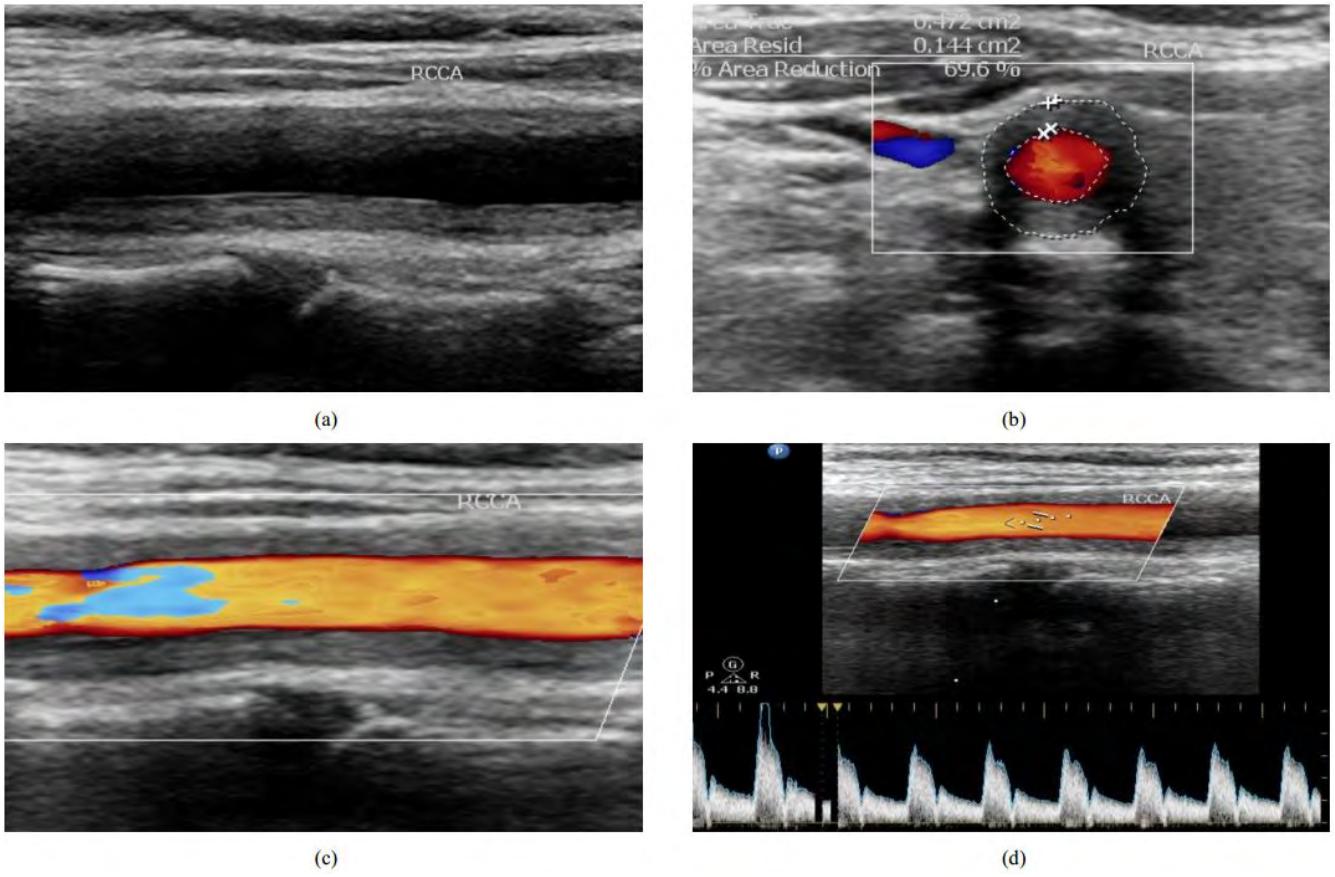

FIGURE 2. Conventional ultrasound images of a patient with Takayasu Arteritis whose right common carotid artery involved. (a) Longitudinal scan showed a hyperechogenic, homogenous thickening of the vessel wall. (b) On transverse scan, the homogenous, intermediate echoic circumferential thickening of the intima-media complex was termed the "macaroni sign". (c) Color Doppler flow imaging showed bright, narrow blood flow in the involved artery. (d) Pulse Doppler showed increased peak systolic velocity and high resistance index.

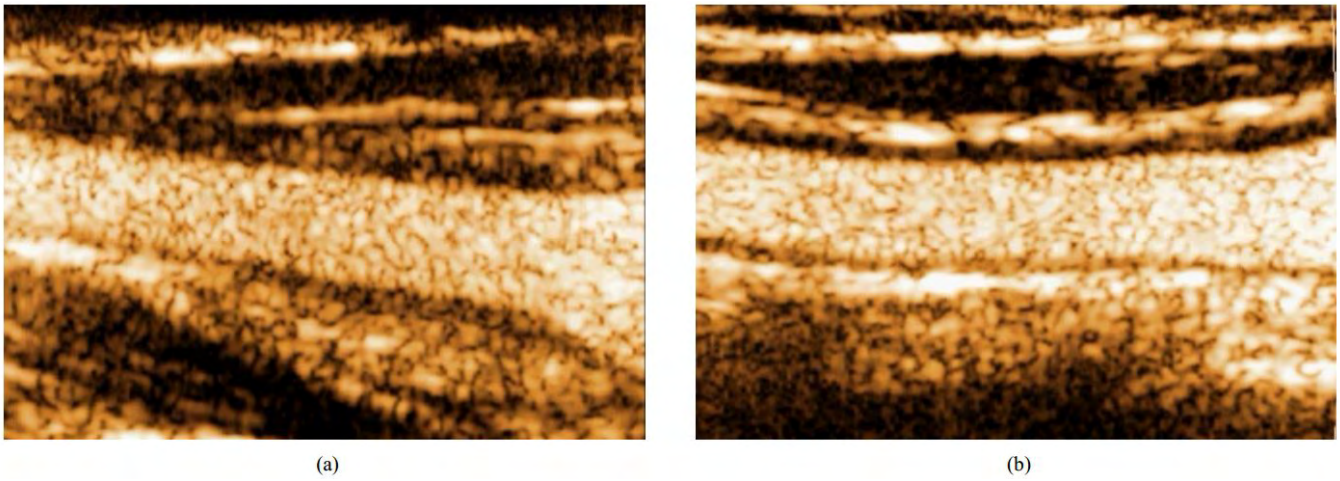

FIGURE 3. Contrast-enhanced ultrasound images of common carotid arteries. (a) In the active group, marked opacification could be observed in the vessel wall which represent vasa vasorum-derived neovascularization. (b) In the inactive group, bare contrast enhancement was observed indicated few vasa vasorum existed.

IV. DISCUSSION

TA is a chronic nonspecific inflammatory disease which involving all the three layers of arterial wall. Followed by intimal hyperplasia, which causes by myofibroblast proliferation, is fibrosis of the intima media, leading to stenosis and sometimes thrombosis [6]. Aneurysm can be detected in a few cases due to the destruction of elastin and collagen [27], [28]. Initial inflammatory changes are associated with

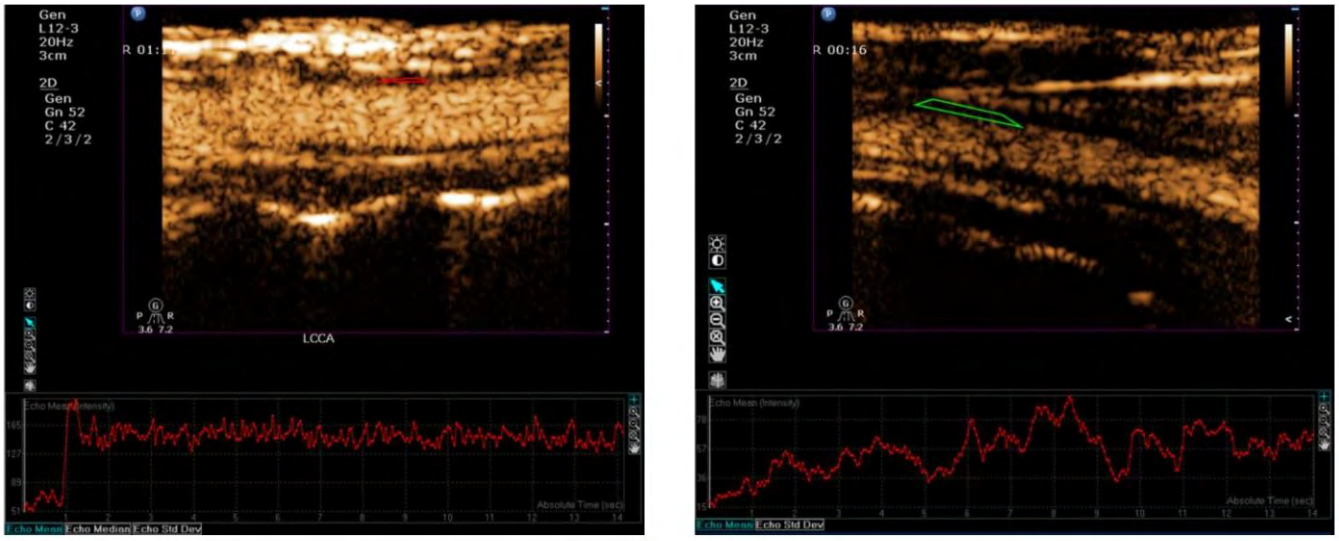

FIGURE 4. Time-intensity curves of the contrast-enhanced ultrasound images. (a) In the active group, high enhanced intensity (EI) was observed in the curve, with a derived peak intensity (DPI) around 180dB. (b) In the inactive group, EI stayed at a low level with a DPI around 80dB.

TABLE 3. Contrast-enhanced ultrasound parameters of common carotid arteries.

	Inactive Group n=9	Active Group n=11
EI (IU)	38.20±10.62	80.80±23.60*
DPI (IU)	46.20±10.20	90.30±24.60*
TTP (s)	10.98±0.67	10.35±0.62

*p <0.05 vs. the inactive group. EI – enhanced intensity; DPI – derived peak intensity; TTP – time to peak.

proliferation of vasa vasorum [29], which is the parallel for inflammatory cells to enter the arterial wall. Thus the density of neoformative vasa vasorum may be related to the disease activity of TA patients [6], [16]. It has been proved that the enhancement of neovascularization shown by CEUS had close correlation with the vasa vasorums seen in histology: the more contrast enhancement, the more vasa vasorums within the vessel wall [6]. As mentioned before, studies from Giordana *et al.* [22] and Magnoni *et al.* [23] have shown that CEUS can effectively assess the perfusion of neoformative vasa vasorums in involved arterial wall, which has provide a basis for application of CEUS in evaluation of the disease activity.

20 patients with TA underwent carotid CEUS in our study. Large or moderate amounts of contrast signal which was shown as movement of bright spots and linear flow of microbubbles was observed within the aterial walls in the 18 CCAs in the active group, while sparse bright spots was observed within the arterial walls in the 15 CCAs in the inactive group. This phenomenon indicated that CEUS can effectively evaluate neovascularization in TA and was consistent with cases reported by Giordana *et al.* [22] and Magnoni *et al.* [23]. TIC curve showed more perfusion in the active group than in the inactive group. QLAB analysis also showed higher EI and DPI in the active group than in the inactive group. These indicated that there were more neoformative vasa vasorums in the involved arterial walls in the active group, which was consistent with the pathology [4].

Studies have shown the correlation between the enhancement of arterial wall and the disease activity. Choe *et al.* [30] discovered in MRA examination that the delayed enhancement of the involved arterial wall was correlated with the elevation of ESR and CRP in patients with TA. Desai *et al.* [31] discovered delayed enhancement of arterial wall in 5 patients with elevated CRP compared with no obvious enhancement in the 2 patients with normal CRP. According to the *Pearson* correlation analysis in our study, linear positive correlation were ovserved between CRP and EI, ESR and EI, CRP and DPI, ESR and DPI in the 20 patients. It has suggested that patients with elevated CRP and ESR had contrast enhancement in their involved CCAs. This indicates that in patients with elevated CRP and ESR, enhamcement of involved arterial walls can be observed. With the elevation of CRP and ESR, enhancement of arterial wall becomes more obvious, the disease tends to be active, otherwise the disease tends to be stable. Therefore, we can come to the conclusion that EI can reflect the disease activity to some extent and CEUS is helpful to predict the progression of TA.

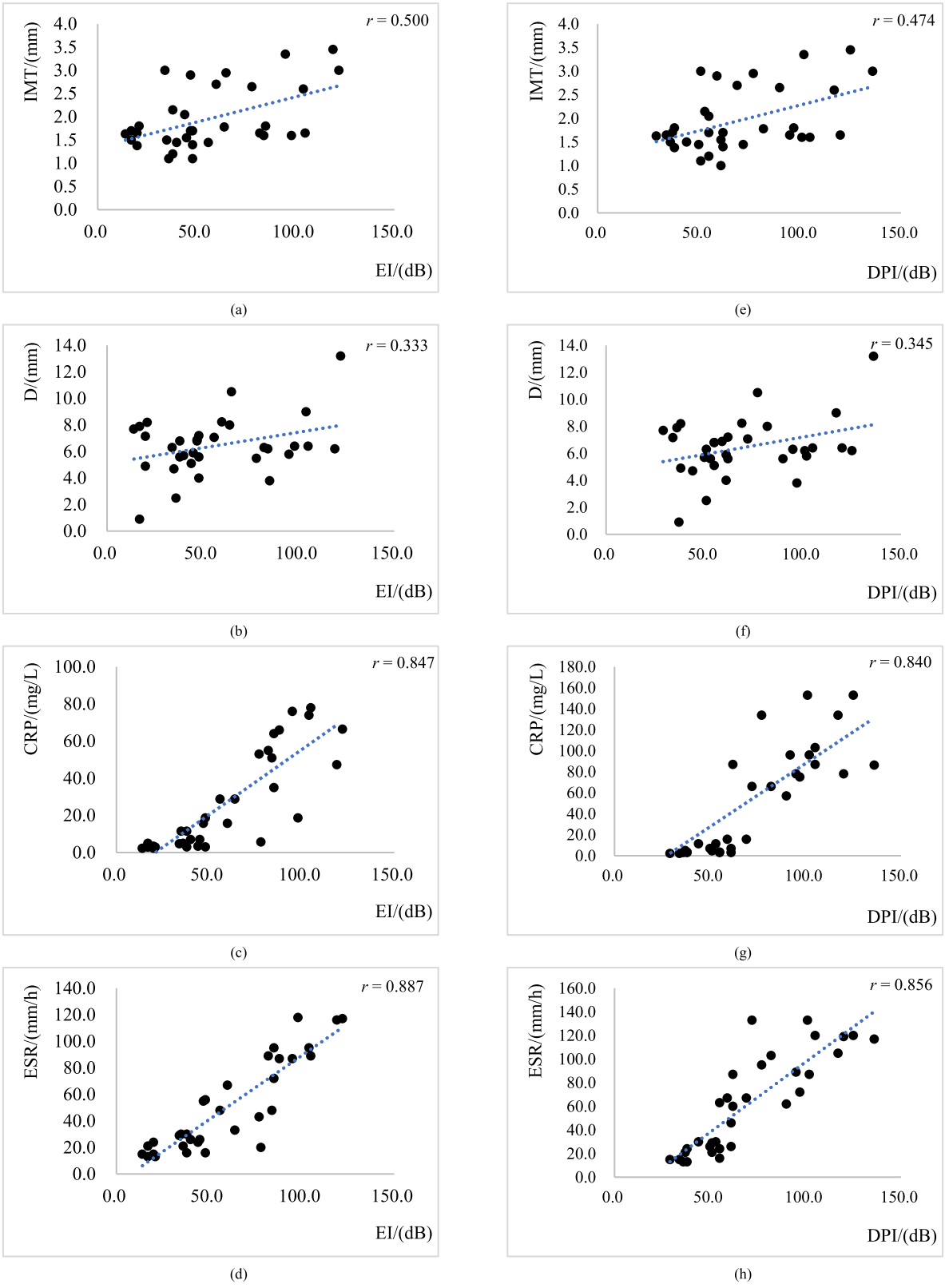

FIGURE 5. Correlations between enhanced intensity (EI) , derived peak intensity (DPI) and other parameters. (a) No correlation was observed between EI and the wall thickness. (b) No correlation was observed between EI and the external diameter. (c) CRP and EI showed a positive correlation ($r = 0.847$). (d) ESR and EI showed a positive correlation ($r = 0.887$). (e) No correlation was observed between DPI and the wall thickness. (f) No correlation was observed between DPI and the external diameter. (g) CRP and DPI showed a positive correlation ($r = 0.840$). (h) ESR andDPI showed a positive correlation ($r = 0.856$).

Studies have shown that thickening of the arterial wall and the external diameter of the artery did have some correlation with the activity of TA [3], [32]. In active stage, significant thickening of the arterial wall and stablity of the external diameter could be ovserved. While in inactive stage, the arterial wall thickened slightly and the external diameter narrowed. Our study has came to the same conclusion. But *Pearson* correlation analysis indicated there were no correlation between IMT and EI, D and EI. This is probably because that the pathological change of the arterial wall is mainly proliferation of fibrous tissue rather than inflammation. Thus, the intensity of contrast enhancement may not be high although the arterial wall is thickened significantly.

Our study has several limitations. We did not define all the factors, such as dynamic regulation of local microcirculation that influence the ability to visualize vasa vasorum according to its density. Besides, we did not assess the lesions in abdominal aorta and renal artery. Further studies are required to confirm our findings in more patients in different groups and in other diseased vascular districts.

V. CONCLUSIONS

Vasa vasorum-derived neovascularization is associated with TA's disease activity. Contrast enhancement can be observed within the involved arterial wall which indicates CEUS can be used to detect neovascularization in TA's vessel wall. EI and DPI show positive correlation with CRP and ESR which indicates CEUS can be used to assess the activity of TA. CEUS improve the image quality significantly and it appears to be a useful non-invasive, non-radioactive, and convenient imaging method to detect TA. Early use of CEUS is helpful for early detection of TA. They are helpful for the assessment of the disease activity and the evaluation of immunosuppressive therapy.

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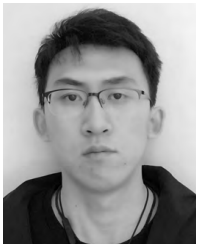

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