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Utility of contrast-enhanced ultrasound for the assessment of the carotid artery wall in patients with Takayasu or giant cell arteritis

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Aims Carotid contrast-enhanced ultrasound (CEUS) was recently proposed for the evaluation of large-vessel vasculitides (LVV), particularly to assess vascularization within the vessel wall. The aim of this pilot study was to evaluate the potential of carotid colour Doppler ultrasound (CDUS) and CEUS in patients with LVV.

Methods and results This prospective study included seven patients (mean age 48 ± 14 years, all females) with established LVV (Takayasu arteritis or giant cell arteritis). All patients underwent CDUS and CEUS (14 carotid arteries). Intima-media thickness, lumen diameter, Doppler velocities, vessel wall thickening, and lesion thickness were assessed. CEUS was used to improve visualization of the lumen-to-vessel wall border, and to visualize carotid wall vascularization. Four (57%) patients [7 (50%) carotid arteries] exhibited lesions, and the average lesion thickness was 2.0 ± 0.5 mm. According to the Doppler peak systolic velocity, 5 (35%) carotid arteries had a <50% stenosis, 1 (7%) had a 50–70% stenosis, and 1 (7%) had a ≥70% stenosis. The contrast agent improved the image quality and the definition of the lumen-to-vascular wall border. Carotid wall vascularization was observed in 5 (71%) patients [9 (64%) carotid arteries]. Five (36%) carotid arteries had mild-to-moderate vascularization, and 4 (29%) had severe wall vascularization.

Conclusion Carotid CDUS allows the assessment of anatomical features of LVV, including vessel wall thickening and degree of stenosis. Carotid CEUS improves the visualization of the lumen border, and allows dynamic assessment of carotid wall vascularization, which is a potential marker of disease activity in patients with LVV.

Keywords arteritis • contrast-enhanced ultrasound • Takayasu • giant cell arteritis

Introduction

Takayasu arteritis and giant cell arteritis are the most prevalent large-vessel vasculitides (LVV).[1] LVV is defined by a predominant but not exclusive involvement of large arteries. Takayasu arteritis and giant cell arteritis occur predominantly in women, and histopathological findings are similar.[2] Vascular imaging may play an important role in the diagnosis and follow-up of patients with LVV.[3] For the evaluation of disease activity and monitoring of treatment response, a reproducible, robust marker of disease activity is desired.[4]

Contrast-enhanced ultrasound (CEUS) is increasingly being used for vascular imaging indications.[5] Multiple studies have demonstrated that CEUS improves the visualization of the vessel lumen, leads to improved detection of atherosclerotic plaques, and allows visualization of intraplaque vascularization.[6,7] Carotid CEUS was recently proposed as a novel imaging modality for the evaluation of LVV, particularly to assess vascularization (vasa vasorum) within the vessel wall.[8,9] The aim of this pilot study was to evaluate the potential of carotid CEUS in patients with LVV. The hypothesis of this study was that carotid CEUS may be used in patients with LVV to improve visualization of the lumen and to assess vascularization within the carotid wall.

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Methods

Patient population and study protocol

The study protocol was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, The Netherlands. All patients provided informed consent. Consecutive patients with an established diagnosis of LVV (Takayasu arteritis or giant cell arteritis) were asked to participate in this prospective pilot study. Diagnoses were based on suggestive clinical features and radiological arterial imaging. All patients underwent a carotid colour Doppler ultrasound (CDUS) examination in conjunction with CEUS. Exclusion criteria were contraindications for the use of ultrasound contrast agent, such as unstable angina, acute cardiac failure, acute endocarditis, known right-to-left shunts, and known allergy for microbubble contrast agents.

Carotid ultrasound acquisition

The carotid CDUS and CEUS examination were performed using a Philips iU-22 ultrasound system (Philips Medical Systems, Bothell, USA), equipped with a L9-3 transducer. The patient was positioned in supine position with the head at a 45° angle turned to the contralateral side. For CDUS, a standardized image acquisition protocol based on the American Society of Echocardiography consensus statement was used.[10] In short, first the left common carotid artery (CCA), carotid bulb, internal carotid artery (ICA), and external carotid artery (ECA) were evaluated using B-mode ultrasound, colour Doppler imaging, and pulsed-wave Doppler imaging. The right carotid artery was evaluated in the same way.

For the CEUS examination, the ultrasound system was switched to its contrast mode. The contrast mode was using amplitude modulation techniques and a mechanical index of 0.06–0.08 to optimize the CEUS images. A side-by-side display mode with a simultaneous B-mode and CEUS image was used for optimal coordination of the ultrasound examination. Other presets were as follows: gain 30%, compression 60, and imaging depth 3.0 cm. These presets were adjusted per patient to obtain optimal quality of the ultrasound clips. CEUS was performed using intravenous administration of SonoVue™ ultrasound contrast agent (Bracco S.p.A., Milan, Italy). The ultrasound contrast agent was injected in boluses of 0.5 mL, and the bolus administration was repeated when necessary. First, the left CCA, carotid bulb, ICA, and ECA were evaluated, with special emphasis for the present carotid lesions and atherosclerotic lesions. The right carotid artery was evaluated in the same way. For both standard carotid ultrasound and CEUS of the carotid arteries, cineclips were digitally stored and reviewed offline.

Carotid ultrasound analysis

Carotid ultrasound studies were reviewed offline by two independent observers unaware of the clinical data. Discrepancies in their evaluation were resolved by consensus. The image quality of CDUS and CEUS clips was independently scored based on a grading scale as (i) good, (ii) moderate, (iii) poor, or (iv) uninterpretable. In accordance with the previously published studies, the carotid intima-media thickness (CIMT) was measured in the far wall of the distal 1 cm of the CCA.[11] Semi-automated CIMT measurement was performed using the Qlab quantification software (Philips Healthcare, Best, the Netherlands). For each side, the CIMT measurement was performed three times on selected still frames on different R-peaks of the ECG signal. The mean value of three measurements from the left and right carotid artery was used in further statistical analysis. Using the CDUS clips, the CCA, carotid bulb, ICA, and ECA were extensively evaluated for the presence of lesions. The maximum lesion thickness was measured perpendicular to the luminal flow. The presence of lesions was recorded for each side. Stenosis severity was assessed using the criteria of the Society of Radiologists in Ultrasound.[12] In short, abnormal CIMT or lesion and peak systolic velocity (PSV) of $<$125 cm/s was considered indicative of $<$50% diameter stenosis, lesion and PSV of 125–230 cm/s as 50–69% stenosis, and lesion and PSV of $>$230 cm/s as $\geq$70% stenosis; no detectable patent lumen, and no flow at spectral, power, and colour Doppler, was considered to be total occlusion.

Using the CEUS clips, the carotid arteries were scored for the presence of wall vascularization. Carotid walls that could have been affected by pseudoenhancement, an artefact that hinders the evaluation of vascularization in the far wall or vascular wall below contrast pools, were excluded from analysis.[13,14] The presence and extent of wall vascularization was visually assessed using a previously published grading method.[15] Dynamic contrast enhancement in the carotid wall was considered to represent carotid wall vascularization. The presence of blood flow activity was identified on the basis of the movement of the echogenic reflectors (microbubble contrast agent) observed in the microvessels in the carotid lesions. Fixed echogenic signals were considered to be tissue acoustic reflectors. For each carotid artery, the presence of wall vascularization was graded as follows: Grade 0, no vascularization, was used to indicate no appearance of microbubble contrast agent in the carotid lesion; Grade 1, limited or moderate vascularization, was used to indicate limited to moderate visible appearance of moving microbubbles in the carotid lesion; or Grade 2, severe vascularization, was used to indicate extensive wall vascularization with a clear visible appearance of microbubbles. If there was a discrepancy in the scores of the independent readers, a consensus was reached.

Statistical analysis

Statistical analyses were performed using SPSS for Windows (version 17.0; SPSS, Chicago, USA) and Excel (Excel 2003; Microsoft, Redmont, USA). Continuous variables are reported as mean $\pm$ standard deviation. Categorical variables are expressed as number (%). The χ^2 test was used to evaluate differences between proportions. A P-value of $<$0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics

The patient characteristics (mean age 48 $\pm$ 14 years, all females) are summarized in *Table 1*. There were five patients with established Takayasu arteritis, and two with giant cell arteritis. Three (43%) patients had a history of previous vascular stenting, and 3 (43%) had previous vascular surgery. However, none of the patients had previous vascular stenting or surgery of the carotid artery. Five (71%) patients used some form of immunosuppressive therapy. All CDUS and CEUS studies were performed without adverse reactions.

Image quality

The image quality of the CDUS studies was good in 6 (43%), moderate in 8 (57%), and poor in 0 carotid arteries. CEUS resulted in significantly improved image quality ($P < 0.005$). All 14 CEUS studies were of good image quality, and none of moderate or poor quality. The use of contrast agent specifically led to an improved delineation of the carotid lumen and a better definition of the borders of carotid lesions. None of the ultrasound studies was judged to be uninterpretable; hence, 14 carotid arteries were available for the analysis.

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Table 1 Clinical characteristics

Case	Age, years	Sex	Disease	Vascular stenting	Vascular surgery	Aspirin	Clopidogrel	Oral anticoagulation	Prednisone	Methotrexate	Azathioprine	Blood pressure		Carotid bruit	
												Right	Left	Right	Left
1	31	F	Takayasu	+	+	+	+	+	0	0	0	150/90	150/90	0	0
2	64	F	Takayasu	+	+	+	0	0	0	0	0	110/80	NM	+	+
3	33	F	Takayasu	0	0	+	0	0	0	+	0	130/70	116/74	0	0
4	53	F	Giant cell	+	0	+	0	0	+	0	0	160/80	−	0	0
5	34	F	Takayasu	0	+	0	0	0	+	0	+	110/70	120/70	0	0
6	57	F	Takayasu	0	0	+	0	0	+	0	+	NM	NM	0	0
7	67	F	Giant cell	0	0	+	0	0	+	0	0	120/64	110/64	0	0
Summary	48 ± 14	100% (7/7)	71% (5/7)	43% (3/7)	43% (3/7)	86% (6/7)	14% (1/7)	14% (1/7)	57% (4/7)	14% (1/7)	29% (2/7)	130 ± 19/76 ± 9	124 ± 15/75 ± 10	14% (1/7)	14% (1/7)

+, present; 0, absent; −, not measured; F, female; NM, not measurable.

Table 2 Carotid ultrasound findings

Case	IMT (mm)		Lumen diameter at systole (mm)		Lumen diameter at diastole (mm)		Doppler peak systolic velocity (cm/s)		Lesion		Lesion thickness (mm)		Carotid wall vascularization	
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
1	0.54	0.58	5.3	6.0	4.8	5.2	66	69	0	0	−	−	+	+
2	1.10	1.32	3.1	3.6	2.8	3.4	283	126	+	+	3.1	2.4	+	+
3	0.51	0.48	5.9	5.7	5.3	5.2	98	106	0	0	−	−	0	+
4	0.60	0.59	6.0	5.9	5.2	5.4	74	73	+	0	1.7	−	0	0
5	0.48	0.51	4.8	5.5	4.1	4.6	136	137	0	0	−	−	0	0
6	0.84	0.89	6.4	5.8	5.8	5.2	74	92	+	+	1.4	1.7	++	++
7	0.63	0.70	6.9	6.4	5.9	5.9	40	57	+	+	2.1	1.8	++	++
Summary	0.67 ± 0.20	0.72 ± 0.26	5.5 ± 1.2	5.6 ± 0.8	4.8 ± 1.0	5.0 ± 0.7	110 ± 76	94 ± 28	57% (4/7)	43% (3/7)	2.0 ± 0.6	2.0 ± 0.3	57% (4/7)	71% (5/7)

+, present; ++, strongly present; 0, absent; −, not applicable; IMT, intima-media thickness.

Carotid ultrasound findings

The carotid ultrasound findings are summarized in *Table 2*. The CIMT was on average 0.70 ± 0.24 (range 0.48–1.32) mm. The lumen diameter at systole was 5.5 ± 1.0 (range 3.1–6.9 mm) mm, and the lumen diameter at diastole was 4.9 ± 0.9 (range 2.8–5.9 mm) mm. Seven (50%) carotid arteries demonstrated lesions, with an average lesion thickness of 2.0 ± 0.5 mm. According to the Doppler PSV, five carotid arteries had a <50% diameter stenosis, 1 had a 50–70% diameter stenosis, and 1 carotid artery had a ≥70% diameter stenosis. Carotid CEUS demonstrated vascularization within the carotid wall in 9 (64%) carotid arteries. Five (36%) carotid arteries exhibited mild-to-moderate vascularization, and 4 (29%) had severe vascularization of the carotid wall. *Figure 1* and Supplementary data online, *Movies S1* and *S2* demonstrate the CDUS and CEUS findings in a patient with Takayasu arteritis and vascular lesions with signs of wall vascularization. *Figure 2* demonstrates the CDUS and CEUS images in a patient with Takayasu arteritis without involvement of the carotid artery.

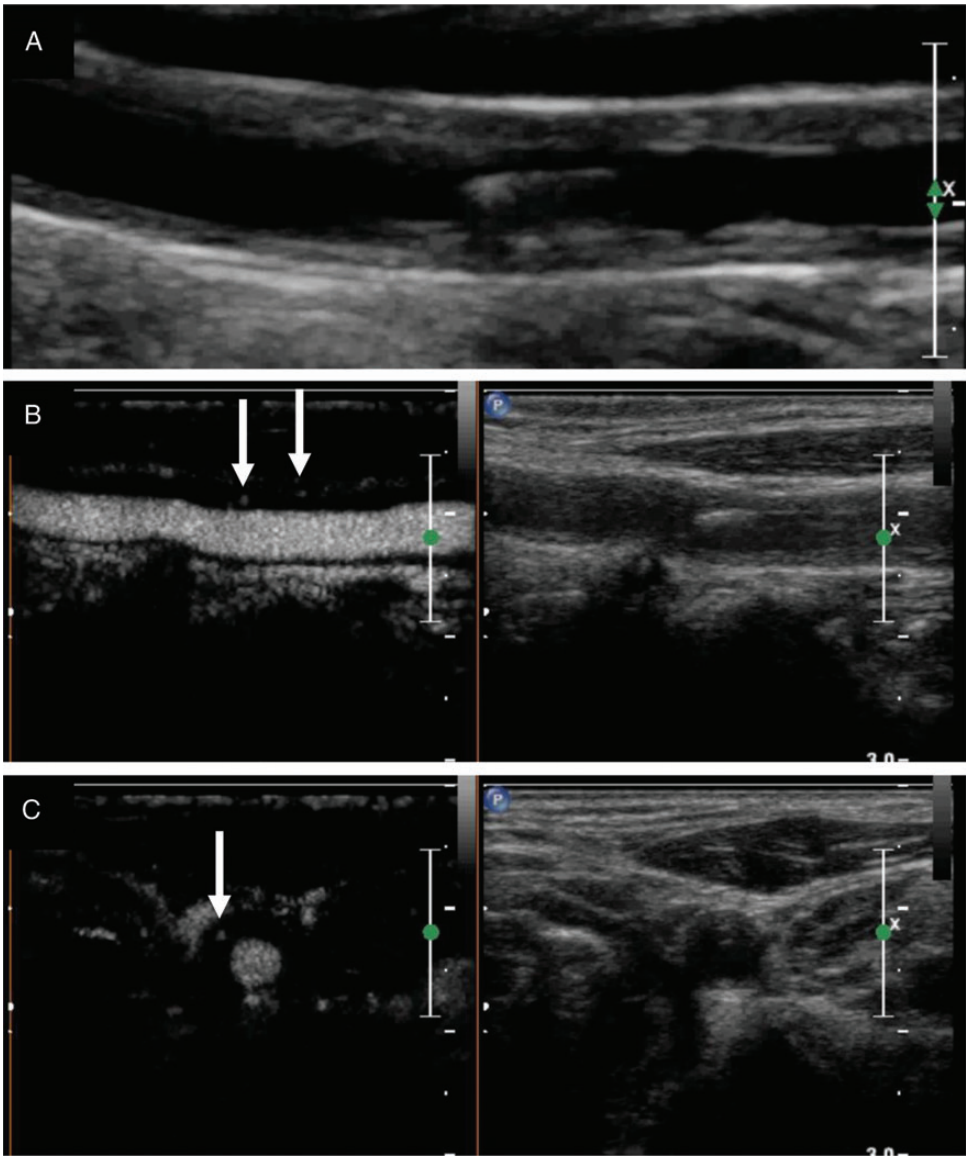

Figure 1 Carotid B-mode ultrasound and CEUS in a 64-year-old woman with Takayasu arteritis (Case 2 from *Table 1*). (*A*) Longitudinal B-mode ultrasound demonstrating marked carotid wall thickening. (*B*) Longitudinal side-by-side carotid CEUS (left panel) and B-mode ultrasound (right panel). The microbubble contrast agent improved the borders of the vascular lesion, and the arrows indicate microbubble contrast agent within the vascular wall lesions, indicating wall vascularization (vasa vasorum) (Supplementary data online, *Movie S1*). (*C*) Transversal side-by-side carotid CEUS (left panel) and B-mode ultrasound (right panel). The contrast agent improved delineation of the carotid lumen; there is marked circumferential thickening of the vascular wall. The arrows indicate microbubble contrast agent within the vascular wall lesions, indicating carotid wall vascularization (Supplementary data online, *Movie S2*).

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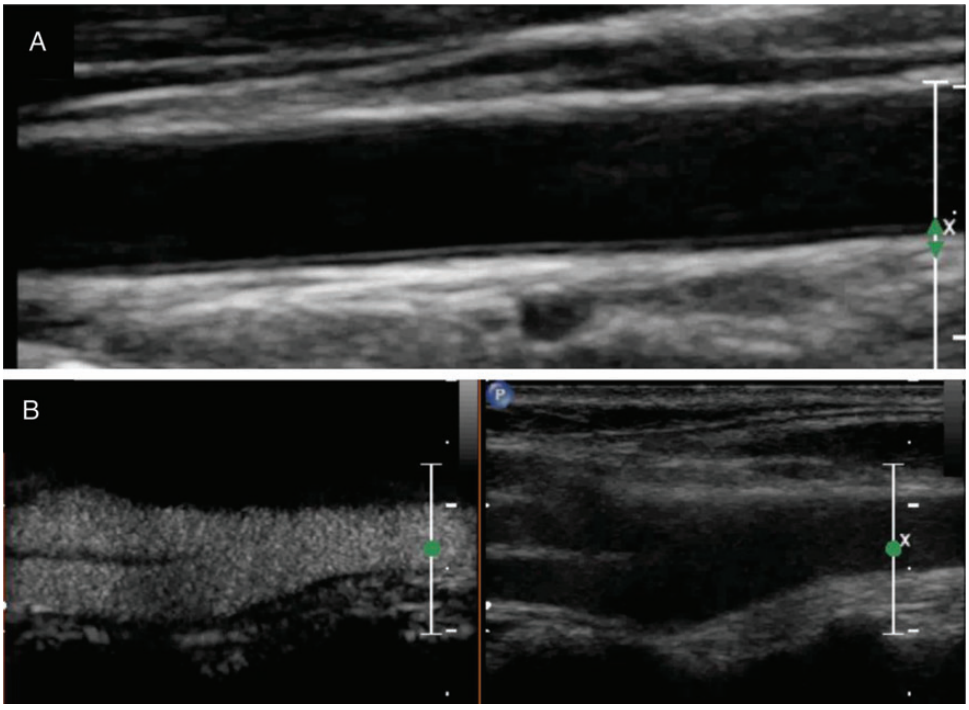

Figure 2 Carotid B-mode ultrasound and CEUS in a 34-year-old woman with Takayasu arteritis (Case 5 from *Table 1*). (*A*) Longitudinal B-mode ultrasound demonstrating a normal carotid wall thickness in the CCA. (*B*) Longitudinal side-by-side carotid CEUS (left panel) and B-mode ultrasound (right panel) of the carotid bifurcation. There were no vascular lesions, and no contrast enhancement at the vascular wall, suggesting the absence of pathological wall vascularization.

Discussion

The main findings of the present study are that carotid CEUS improves the visualization of the lumen border, and allows assessment of carotid wall vascularization, which is a potential marker of disease activity in patients with LVV. Takayasu and giant cell arteritis are relatively rare diseases, and the diagnosis and evaluation of disease activity may be challenging. Traditionally, invasive angiography has been used as the main imaging method in the diagnosis and management of LVV. Invasive angiography allows an accurate visualization of the vascular lumen; however, changes in lumen diameter occur relatively late in the disease. Additionally, the use of iodinated contrast agent and ionizing radiation are limitations of this technique. Recently, computed tomography angiography has replaced invasive angiography, but this method has similar limitations as invasive angiography.[3] 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) and magnetic resonance angiography (MRA) have overcome some limitations and also provide information on vessel wall thickness and disease activity. However, FDG-PET and MRA involve, respectively, ionizing radiation and gadolinium contrast agent. Repeated use of these imaging modalities in often young female patients with known or suspected LVV is not desired.

Recently, carotid CEUS has been proposed, in two case reports, as a potentially useful imaging modality in the assessment of disease activity in patients with Takayasu arteritis. In the report by Giordana *et al.*,[8] carotid CEUS was used in a 35-year-old woman to diagnose Takayasu disease and to monitor the response to treatment. The authors initially observed circumferential wall thickening of the right CCA with the multiple vasa vasorum before initiation of treatment. At 3 and 6 months after initiation of treatment, carotid CEUS was repeated, and a progressive decrease in inflammatory activity within the carotid artery wall under steroid treatment was observed. Next, Magnoni *et al.*[9] described a case of a 35-year-old woman with Takayasu arteritis. Using carotid CEUS, an improved image quality with a greater enhancement of vessel wall lumen and higher definition of the borders of the vascular lesion was observed. CEUS demonstrated the presence of a large amount of contrast signal within the carotid lesions, as visualized by moving bright spots and linear flow of microbubbles within the vascular lesions. This phenomenon was principally seen on the adventitial side of the vessels and was considered to represent the contrast agent's bubble signal coming from neovessels. This pilot study confirms and extends the results from these two case reports. Carotid CDUS and CEUS were used to evaluate seven patients (14 carotid arteries) with established LVV. Carotid CDUS allowed the assessment of anatomical features of LVV, including vessel wall thickening and degree of stenosis. CEUS was relatively easily incorporated into the standard carotid CDUS imaging protocol. Carotid CEUS improved the visualization of the lumen border, leading to a better definition of vascular lesions. CEUS allowed the assessment of carotid wall vascularization, by visualization of contrast microbubbles through the vascular wall and vascular lesions. The presence and intensity of the contrast

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enhancement within the vascular wall are potential markers of disease activity in patients with LVV. Additionally, if the described carotid lesions are detected in patients without known LVV, this has to be considered in the differential diagnosis.

In the present study, no histology was obtained to validate the carotid CEUS findings. Previous studies in patients with symptomatic carotid stenosis undergoing carotid endarterectomy have compared CEUS findings with histology. A recent overview[7] of the literature demonstrated that six studies[16–21] including a total of 95 patients have compared carotid CEUS findings with histopathological analysis of the plaque after surgery. It was shown that plaque with a higher amount of contrast enhancement had a significantly increased density of small diameter (20–30 μm) microvessels in the corresponding region on histology[18,19] Histological staining for specific vascular (CD31, CD34, hemosiderin, and von Willebrand factor) and angiogenic markers (vascular endothelial growth factor) showed a correlation between intraplaque contrast enhancement and the amount of staining.[17,19,21] Thus, contrast enhancement was shown to correlate with the presence and degree of intraplaque vascularization.

This study has several limitations. The number of included patients and carotid arteries was relatively small. After this pilot study, larger studies are needed to confirm the present findings. This study excluded the far wall of the carotid artery from the analysis of wall vascularization. The evaluation of the far wall vascularization may be influenced by the pseudo-enhancement artefact, leading to overestimation of the contrast activity at the far wall.[13,14] Currently, new ultrasound pulse sequences are being developed to overcome this limitation of CEUS.

In conclusion, carotid CDUS allows the assessment of anatomical features of LVV, including vessel wall thickening and degree of stenosis. Carotid CEUS improves the visualization of the lumen border, and allows dynamic assessment of carotid wall vascularization, which is a potential marker of disease activity in patients with LVV.

Supplementary data

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.

Conflict of interest: None declared.

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References

1. Weyand CM, Goronzy JJ. Medium- and large-vessel vasculitis. *N Engl J Med* 2003;**349**:160–9.
2. Grayson PC, Maksimowicz-McKinnon K, Clark TM, Tomasson G, Cuthbertson D, Carette S *et al.* Vasculitis clinical research consortium. Distribution of arterial lesions in Takayasu's arteritis and giant cell arteritis. *Ann Rheum Dis* 2012;**71**:1329–34.
3. Pipitone N, Versari A, Salvarani C. Role of imaging studies in the diagnosis and follow-up of large-vessel vasculitis: an update. *Rheumatology (Oxford)* 2008;**47**:403–8.
4. Direskeneli H, Aydin SZ, Kermani TA, Matteson EL, Boers M, Herlyn K *et al.* Development of outcome measures for large-vessel vasculitis for use in clinical trials: opportunities, challenges, and research agenda. *J Rheumatol* 2011;**38**:1471–9.
5. Feinstein SB, Coll B, Staub D, Adam D, Schinkel AF, ten Cate FJ *et al.* Contrast enhanced ultrasound imaging. *J Nucl Cardiol* 2010;**17**:106–15.
6. Staub D, Schinkel AF, Coll B, Coli S, van der Steen AF, Reed JD *et al.* Contrast-enhanced ultrasound imaging of the vasa vasorum: from early atherosclerosis to the identification of unstable plaques. *JACC Cardiovasc Imaging* 2010;**3**:761–71.
7. Ten Kate GL, van den Oord SC, Sijbrands EJ, van der Lugt A, de Jong N, Bosch JG *et al.* Current status and future developments of contrast-enhanced ultrasound of carotid atherosclerosis. *J Vasc Surg* 2013;**57**:539–46.
8. Giordana P, Baqué-Juston MC, Jeandel PY, Mondot L, Hirlemann J, Padovani B *et al.* Contrast-enhanced ultrasound of carotid artery wall in Takayasu disease: first evidence of application in diagnosis and monitoring of response to treatment. *Circulation* 2011;**124**:245–7.
9. Magnoni M, Dagna L, Coli S, Cianflone D, Sabbadini MG, Maseri A. Assessment of Takayasu arteritis activity by carotid contrast-enhanced ultrasound. *Circ Cardiovasc Imaging* 2011;**4**:e1–2.
10. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER *et al.* American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society Of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr* 2008;**21**:93–111.
11. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N *et al.* Mannheim carotid intima-media thickness consensus (2004–6). An update on behalf of the Advisory Board of the 3rd and 4th watching the risk symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. *Cerebrovasc Dis* 2007;**23**:75–80.
12. Grant EG, Benson CB, Moneta GL, Alexandrov AV, Baker JD, Bluth EI *et al.* Carotid artery stenosis: gray-scale and Doppler US diagnosis—Society of Radiologists in Ultrasound Consensus Conference. *Radiology* 2003;**229**:340–6.
13. Thapar A, Shalhoub J, Averkiou M, Mannaris C, Davies AH, Leen EL. Dose-dependent artifact in the far wall of the carotid artery at dynamic contrast-enhanced US. *Radiology* 2012;**262**:672–9.
14. ten Kate GL, Renaud GG, Akkus Z, van den Oord SC, ten Cate FJ, Shamdasani V *et al.* Far-wall pseudoenhancement during contrast-enhanced ultrasound of the carotid arteries: clinical description and *in vitro* reproduction. *Ultrasound Med Biol* 2012;**38**:593–600.
15. Staub D, Partovi S, Schinkel AF, Coll B, Uthoff H, Aschwanden M *et al.* Correlation of carotid artery atherosclerotic lesion echogenicity and severity at standard US with intraplaque neovascularization detected at contrast-enhanced US. *Radiology* 2011;**258**:618–26.
16. Vicenzini E, Giannoni MF, Puccinelli F, Ricciardi MC, Altieri M, Di Piero V *et al.* Detection of carotid adventitial vasa vasorum and plaque vascularization with ultrasound cadence contrast pulse sequencing technique and echo-contrast agent. *Stroke* 2007;**38**:2841–3.
17. Shah F, Balan P, Weinberg M, Reddy V, Neems R, Feinstein M *et al.* Contrast-enhanced ultrasound imaging of atherosclerotic carotid plaque neovascularization: a new surrogate marker of atherosclerosis? *Vasc Med* 2007;**12**:291–7.
18. Coli S, Magnoni M, Sangiorgi G, Marrocco-Trischitta MM, Melisurgo G, Mauriello A *et al.* Contrast-enhanced ultrasound imaging of intraplaque neovascularization in carotid arteries: correlation with histology and plaque echogenicity. *J Am Coll Cardiol* 2008;**52**:223–30.
19. Giannoni MF, Vicenzini E, Citone M, Ricciardi MC, Irace L, Laurito A *et al.* Contrast carotid ultrasound for the detection of unstable plaques with neoangiogenesis: a pilot study. *Eur J Vasc Endovasc Surg* 2009;**37**:722–7.
20. Shalhoub J, Monaco C, Owen DR, Gauthier T, Thapar A, Leen EL *et al.* Late-phase contrast-enhanced ultrasound reflects biological features of instability in human carotid atherosclerosis. *Stroke* 2011;**42**:3634–6.
21. Hoogi A, Adam D, Hoffman A, Kerner H, Reisner S, Gaitini D. Carotid plaque vulnerability: quantification of neovascularization on contrast-enhanced ultrasound with histopathologic correlation. *AJR Am J Roentgenol* 2011;**196**:431–6.

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