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ULTRASOUND

A comparative study of color Doppler imaging and contrast-enhanced ultrasound for the detection of ulceration in patients with carotid atherosclerotic disease

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Abstract

Objectives To evaluate the diagnostic accuracy of color Doppler imaging (CDI) and contrast-enhanced ultrasound (CEUS) for diagnosing carotid ulceration, having multi-detector computed tomography angiography (MDCTA) as the reference method.

Methods Patients with carotid disease referred for ultrasound (US), either due to the occurrence of neurovascular symptoms or for screening purposes, were included in this study if at least one plaque causing moderate (50–69%) or severe (70–99%) internal carotid artery stenosis was detected. Carotid US with CDI technique, CEUS, and MDCTA were performed in all patients, investigating the presence of ulceration. The agreement between modalities was evaluated using kappa statistics.

Results The study population included 54 patients (median age 62 years, inter-quartile range 16.2) and 66 carotid arteries. The mean degree of stenosis was 68.5% (SD 12.2%) while 47.1% of plaques were symptomatic. MDCTA characterized 28.8% of plaques as smooth, 45.5% irregular, and 24.3% ulcerated. Flow reversal was detected with CDI in 65.5% of ulcerations, while swirling of the microbubbles and neovessels adjacent to the ulcer were detected with CEUS in 17.64%. The agreement for ulceration diagnosis was moderate between CDI and CEUS (kappa 0.473) and between CDI and MDCTA (kappa 0.473) and very good between CEUS and MDCTA (kappa 0.921). The sensitivity, specificity, and positive and negative predictive values of CDI for the diagnosis of ulceration were 41.2%, 97.95%, 87.5%, 82.8% respectively, while CEUS respective measures were 94.1%, 97.95%, 94.1%, and 97.95%.

Conclusion CEUS outperformed CDI in terms of agreement with MDCTA and diagnostic accuracy for the diagnosis of ulcerated carotid plaque.

Key Points

- *Superficial ulceration is a significant feature of carotid plaque vulnerability.*
- *Color Doppler imaging has the potential to demonstrate carotid plaque ulceration but is characterized by limited sensitivity and moderate agreement with the reference method of multi-detector computed tomography angiography.*
- *Contrast-enhanced ultrasound outperforms color Doppler imaging in terms of sensitivity for the detection of carotid plaque ulceration and in agreement with the reference method of multi-detector computed tomography angiography.*

Keywords Ultrasonography · Computed tomography angiography · Stroke · Contrast media

Abbreviations

CDI	Color Doppler imaging
CEUS	Contrast-enhanced ultrasound
MDCTA	Multi-detector computed tomography angiography
TIA	Transient ischemic attack
US	Ultrasound

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Introduction

Superficial ulceration represents an important feature of carotid atherosclerotic plaque vulnerability, strongly predicting the occurrence of transient ischemic attack (TIA) or stroke [1–3]. This has been shown through many publications evaluating different aspects of this entity. Carotid ulcerated plaques have been associated with the detection of micro-embolic signals on transcranial Doppler examination [4], while being more frequently detected in patients with TIA [5]. The estimated risk for stroke in patients with ulcerated carotid plaques may be more than three times higher compared to that in those with non-ulcerated plaques [1] while ulceration detected on histology was more than two times more common in symptomatic patients [6]. Similarly, ulcerations diagnosed with ultrasound (US) are also associated with increased risk for stroke occurrence and recurrence compared with smooth plaques, particularly in severely stenotic ulcerated plaques [2].

Based on the high clinical significance of ulceration, imaging modalities evaluating carotid plaques should also focus on the detection and characterization of plaque surface, with a particular interest in detecting ulceration [7]. US constitutes the first-line imaging modality for the diagnostic approach of carotid disease, having the potential not only to accurately grade stenosis but also to provide information regarding plaque composition and surface characteristics. Nowadays, non-invasive cross-sectional modalities like multi-detector computed tomography angiography (MDCTA) and magnetic resonance angiography have gradually replaced the traditional reference method of invasive arteriography, providing valuable information both for the luminal narrowing and the characteristics of the wall and the atherosclerotic plaque. The diagnostic accuracy of US and MDCTA has been thoroughly studied leading to inconsistent results for US, with some studies attributing excellent diagnostic accuracy to US (sensitivity and specificity of more than 90%) [8], while others documenting a limited value, with less than 50% sensitivity [9]. Recent studies have concluded that MDCTA is characterized by excellent diagnostic accuracy, having the potential to be used as a reference method for the diagnosis of ulcerated carotid plaque [3, 10, 11]. Contrast-enhanced ultrasound (CEUS) is an advanced form of ultrasound, making use of intravenous ultrasonographic contrast agents in the form of microbubbles, valuable in the study of carotid plaque's neovascularization and surface characteristics, offering improved plaque delineation [3, 12]. The value of CEUS in the detection of carotid ulcerations has been previously studied in limited studies offering promising results [13–15].

The purpose of this study was to evaluate the diagnostic accuracy of color Doppler imaging (CDI) and CEUS for the detection of ulcerated carotid plaques in both symptomatic and asymptomatic patients with carotid disease, having MDCTA as the reference method. The agreement between CDI, CEUS, and MDCTA was also evaluated.

Methods

Patients and inclusion/exclusion criteria

The study was approved by the Institutional Ethics Committee and all patients provided written informed consent. Patients were recruited in a consecutive and prospective pattern for a period of 2 years (June 2016 to June 2018), from the Radiology and Neurology Department of our institution. Patients were referred for carotid US either because they suffered a TIA or stroke or for screening or other unrelated reasons (for example, for preoperative checkup). Both symptomatic and asymptomatic patients were included in the study. The main inclusion criterion was the identification of an internal carotid artery atherosclerotic plaque causing moderate (50–69%) or severe (70–99%) stenosis based on velocity criteria [16] and direct diameter measurements on B-mode and CDI images. Exclusion criteria included history of allergy or other contraindications to US or MDCTA contrast agent used or presence of extensively calcified plaques unsuitable for evaluation due to acoustic shadowing.

Imaging techniques

The ultrasonographic examinations were performed by a radiologist with experience in vascular ultrasound, with a GE Logiq S8 (GE Healthcare) with XDclear technology device and a linear-array probe (type 9L) with a 3–10-MHz bandwidth. The examination was carried out with the patient in the supine position and the head turned to the side contralateral to the carotid system examined, using B-mode and CDI techniques for the detection of atherosclerotic plaques and grading of stenosis, based on the Department's standard scanning protocol and using the manufacturer's scanning preset for carotid arteries. Based on this protocol, the common, internal, and external carotid arteries are examined in both axial and longitudinal views for evaluation of potential plaques. The frequency used was chosen based on the patient's body habitus, and the focus was placed at the center of the vessel's lumen. If the patient met the study's inclusion criteria, the CEUS part of the examination was performed immediately after the unenhanced part. An intravenous catheter was placed in an antecubital vein, the contrast mode of the device was set (both amplitude modulation and pulse inversion techniques were used) keeping a mechanical index of less than 0.1, and the gain was adjusted so that the target vessel was optimally visualized. The SonoVue contrast agent (Bracco SpA) was intravenously administered in one bolus of 2.4 ml, followed by a

saline flush of 5 ml NaCl 0.9% solution. The microbubbles were visualized in the target vessel's lumen approximately 20 s after the bolus administration, and the lumen's adequate enhancement lasted for approximately 4 min. Each internal carotid artery was examined in both axial and longitudinal imaging planes, while both cine clips and still frames were digitally stored in DICOM format for offline analysis.

MDCTA examinations were performed using a 128-slice multi-detector CT system (GE Optima CT660, GE Healthcare) and using both an unenhanced scan and an angiographic scan. The scan range extended from the ascending aorta to the intracranial circulation, up to the point of the frontal sinuses. Eighty milliliters of contrast agent (37% iodine, iopromide, Ultravist, Bayer) was intravenously administered in a bolus followed by 50 ml of saline bolus chaser, both administered at an injection rate of 4 ml/s. Real-time bolus tracking was performed at the level of the ascending aorta and used in order to synchronize contrast passage with the angiographic data acquisition. The slice thickness of the images reviewed was 0.625 mm for optimal isotropic imaging.

Image analysis

All cases were reviewed by two different radiologists, blinded to the patient's history and MDCTA findings. These two radiologists characterized each plaque as ulcerated or not on CDI and CEUS images and decided if the plaque should be excluded based on the presence of extensive calcification with acoustic shadowing. Consensus was reached in cases of discrepancy, while a third radiologist with experience in cardiovascular imaging was consulted if a consensus could not be reached. CDUS and CEUS images were separately reviewed. Carotid plaque ulceration was defined as the presence of one disruption of the plaque-lumen border of at least 1 × 1 mm size, which was filled with color Doppler blood flow signals on CDI or microbubbles in CEUS. The presence of flow reversal was examined in CDI images, swirling of microbubbles in CEUS [17], and intraplaque neovascularization in CEUS.

Two different radiologists with experience in cardiovascular imaging reviewed the MDCTA examination of the patients, being blinded to clinical history and US and CEUS findings. The examinations were carefully reviewed for the detection of atherosclerotic plaques, grading of stenosis, surface morphology characterization, and detection of ulceration, reaching consensus in cases of discrepancy. Again, a third experienced radiologist was consulted when consensus was not reached. The degree of stenosis was graded based on the European Carotid Surgery Trial (ECST) criteria [18]. The plaques were classified in terms of surface morphology as smooth, irregular, or ulcerated. Carotid plaque ulceration was defined as the presence of an extension of the contrast agent column, beyond the vascular lumen and within an atherosclerotic plaque, measuring at least 1 mm and confirmed in at least two projections. Similar definitions of carotid plaque ulceration in US, CEUS, and MDCTA were previously proposed and used in the literature [13, 14]. The diagnosis of ulceration was established based on both axial source MDCTA images and multi-planar reconstructed images. The differential diagnosis between calcification and ulceration was done by comparing precontrast and post-contrast images, with hyperdense structures imaged prior to contrast administration representing calcification and hyperdense structures visualized only on the angiographic study classified as ulcerations (Fig. 1) [3]. The ulcerations detected with MDCTA were classified into four types, as previously described in the literature [3, 19].

Statistical analysis

IBM SPSS Statistics version 23.0 was used for statistical analyses. Descriptive statistics included mean and standard deviation (SD) for variables normally distributed. Median and inter-quartile range of values were used for non-normally distributed variables. The normality of distribution was assessed based on the Kolmogorov-Smirnov test. Both carotid systems of each patient were studied and included in the study. The diagnostic accuracy was assessed after cross-tabulation of the results of the index and reference method, by calculating sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios. The agreement between different techniques for the classification of a plaque as ulcerated or not was done with the kappa (κ) statistics. Values less than 0.4 were considered to indicate poor agreement, values between 0.41 and 0.6 moderate agreement, values between 0.61 and 0.8 good agreement, and values above 0.81 very good agreement.

Results

Patients

All patients meeting the inclusion criteria underwent carotid US, CEUS, and MDCTA. In total, 54 patients (39 males, 15 females) were recruited for this study, with a median age of 62 years and an inter-quartile range of 16.2. Four plaques were excluded from further analysis due to calcification, leaving a total of 66 plaques. Mean degree of stenosis was 68.5% with SD 12.2%, based on US. Based on the occurrence of symptoms for the last 6 months prior to the examination, the plaques were characterized as symptomatic in 33 cases (47.1%) and asymptomatic in 37 cases (52.9%). Based on MDCTA, the plaques analyzed were classified as smooth in 28.8% (19/66) of cases, irregular 45.5% (30/66), and ulcerated in 24.3% (17/66). CDI detected ulceration in 12.1% (8/66), CEUS in 25.8% (17/66), and MDCTA in 25.8% (17/66) of

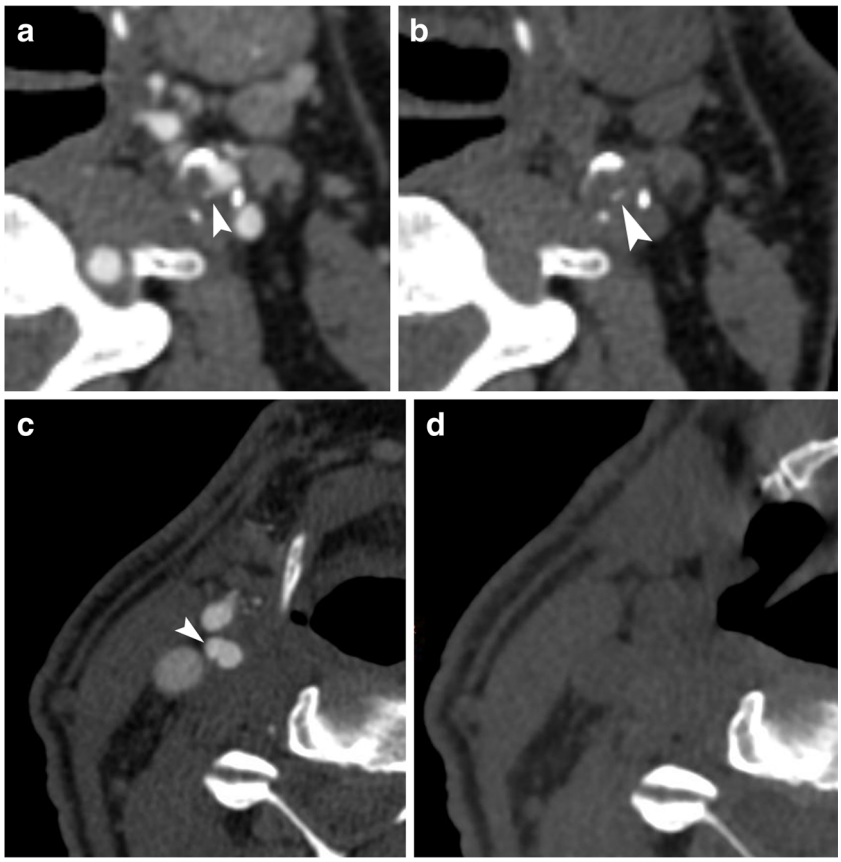

Fig. 1 Differentiation between ulceration and focal calcification with pre- and post-contrast MDCTA. Axial angiographic image (**a**) showing a suspected small superficial ulceration (arrowhead). The respective precontrast image (**b**) shows that this hyperattenuating structure truly corresponded to a focal calcification (arrowhead). Axial angiographic MDCTA (**c**) demonstrating an ulcer (arrowhead). The corresponding precontrast MDCTA (**d**) image confirms the diagnosis by showing no calcification within this part of the carotid wall

plaques. Flow reversal (or yin-yang sign) was documented in 62.5% (5/8) of ulcers detected with CDI technique. Swirling of the microbubbles was visualized in 17.64% (3/17) of ulcers diagnosed on CEUS. Intraplaque neovessels adjacent to the ulcer's cavity were detected in 17.64% (3/17) of ulcers detected by CEUS. Based on MDCTA findings, the ulcerations were classified as type 1 in 41.2% (7/17), type 2 in 5.9% (1/17), type 3 in 35.3% (6/17), and type 4 in 17.6% (3/17) (Fig. 2). No adverse reaction to the contrast agents used was observed in this study.

Agreement between different imaging modalities

The kappa coefficient was 0.473 for the characterization of a carotid atherosclerotic plaque as ulcerated or non-ulcerated, between CDI and CEUS, indicating a moderate agreement between these two modalities. The kappa coefficient between CDI and MDCTA was 0.473, also indicating a moderate agreement. The kappa coefficient between CEUS and MDCTA was 0.921, indicating a very good agreement.

Diagnostic accuracy for the diagnosis of ulceration

The cross-tabulation for the results of CDI and CEUS vs the reference method of MDCTA is presented in Tables 1 and 2. Based on these tables, sensitivity was calculated as true positive/(true positive + false negative), specificity as true negative/(false positive + true negative), positive predictive value (PPV) as true positive/(true positive + false positive), and negative predictive value as true negative/(false negative + true negative). Positive and negative likelihood ratios (LR+ and LR−) were calculated by the following equations respectively: sensitivity/(1-specificity) and (1-sensitivity)/specificity. The diagnostic accuracy measures can be found in Table 3. Characteristic cases of ulcerated plaques examined with CDI, CEUS, and MDCTA can be found in Figs. 3, 4, and 5.

Discussion

The main findings of this study were that superficial ulcerations are not an uncommon finding in carotid plaques, with an estimated prevalence of 24.3% based on MDCTA. The agreement between CDI and CEUS was moderate for the detection of carotid ulceration while the latter outperformed the former in terms of agreement with the reference method of MDCTA, showing a very good agreement. Moreover, CEUS was significantly superior to CDI in terms of sensitivity and positive and negative predictive values while characterized by the same high specificity. Additionally, CEUS was better than CDI based on both positive and negative likelihood ratios. As a result, both CDI and CEUS were found to offer good

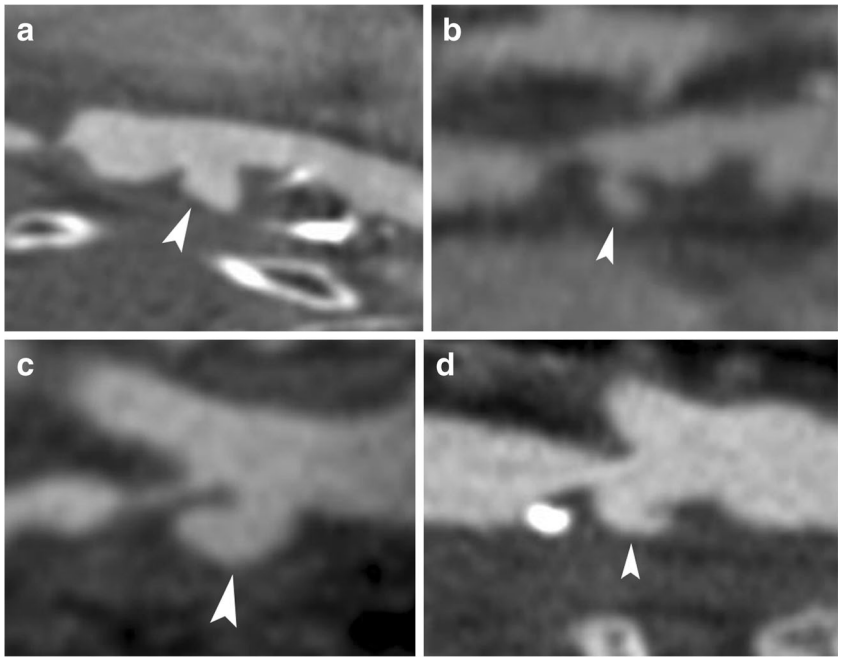

Fig. 2 Morphological classification of ulceration based on MDCTA findings. Type 1 ulcer (**a**) appears perpendicular to the vascular lumen. Type 2 ulcer (**b**) has a narrow neck. Type 3 ulcer (**c**) has a proximally situated neck and its cavity pointing distally. Type 4 ulcer (**d**) has a distally located neck and its cavity pointing proximally. Arrowheads showing the ulceration in all figures

results in this study, although the latter was significantly better. CDI should be thus considered inadequate for the diagnosis of an ulcerated carotid plaque, and CEUS offers a valuable complementary technique with superior diagnostic accuracy and shows a very good agreement with the reference method.

The clinical significance of ulceration has been well established throughout recent literature and is currently considered a major feature of carotid plaque vulnerability [3, 20]. In a study recruiting both asymptomatic and symptomatic patients, ulcerations were associated both with symptomatic disease and the occurrence of new symptoms in asymptomatic patients [21]. The ultrasonographic detection of ulceration within a hypoechoic carotid plaque is estimated to increase the risk for neurologic symptoms more than nine times [22] while a long-term follow-up study with multi-variable analysis has concluded that the presence of ulceration is significantly associated with the occurrence of ipsilateral TIA or stroke [23].

In the light of these findings, the evaluation of carotid plaque surface and investigation for the presence of superficial ulcerations should be incorporated in the examination of the carotid arteries with virtually every imaging modality [7]. US represents the primary modality for evaluation of carotid disease and has been extensively studied for the characterization of carotid plaque surface and ulceration, although with conflicting results regarding diagnostic accuracy. Some advocate the modality's value, reporting sensitivity and specificity of more than 80%, although inferior to MDCTA whose measures were close to 100% [8, 10]. On the contrary, different authors suggest that US is not sufficient for detecting ulceration due to low sensitivity and specificity and poor correlation with histology, while the accuracy of the diagnosis was influenced by the degree of stenosis with US being more accurate for diagnosing ulceration in plaques causing mild stenosis [9, 11, 24]. MDCTA has been found very accurate for the diagnosis of carotid ulceration, with excellent sensitivity and specificity, justifying its use as a reference method [3, 11, 25, 26]. CEUS has been recently established as a valuable complementary ultrasonographic technique offering improved delineation of the plaque surface, along with the potential to visualize and grade intraplaque neovascularization, an additional feature of vulnerability [12, 27–30]. It has been used to detect

Table 1 Cross-tabulation for the diagnosis of ulceration by CDI vs MDCTA

	Reference method		
Index method	Positive	Negative	Sum
Positive	7	1	8
Negative	10	48	58
Sum	17	49	66

Index method: CDI; reference method: MDCTA

Table 2 Cross-tabulation for the diagnosis of ulceration by CEUS vs MDCTA

	Reference method		
Index method	Positive	Negative	Sum
Positive	16	1	17
Negative	1	48	49
Sum	17	49	66

Index method: CEUS; reference method: MDCTA

Table 3 Diagnostic accuracy measures of CDI and CEUS for the diagnosis of ulcerated carotid plaque

Parameter	CDI	CEUS
Sensitivity	41.2%	94.1%
Specificity	97.95%	97.95%
PPV	87.5%	94.1%
NPV	82.8%	97.95%
LR+*	20.6	45.9
LR−*	0.6	0.06

CDI color Doppler imaging, *CEUS* contrast-enhanced ultrasound, *PPV* positive predictive value, *NPV* negative predictive value

**LR+* positive likelihood ratio, *LR−* negative likelihood ratio

ulcerated carotid plaques in diabetic patients, detecting a prevalence of 8% [14]. Ten Kate et al have compared US and CEUS for the diagnosis of ulcerated carotid plaque having MDCTA as the reference method in 20 symptomatic patients. This study found ulcerations in 44% of cases, a percentage higher than that found in the present study (24.3%). They concluded that color Doppler US was 29% sensitive and 73% specific and has a 46% positive and 57% negative predictive values. CEUS was 88% sensitive and 59% specific and had positive and negative predictive values of 63% and 87% respectively [13]. In keeping with these results, this study confirmed that CEUS outperforms CDI in terms of most measures of diagnostic accuracy. Furthermore, a better agreement with the reference method was determined for CEUS. Another recent study compared CEUS with histology to determine the accuracy for the detection of ulcerations, concluding that plaques with rupture, thrombus formation, and fibrous cap disruption showed more frequently findings of ulceration on CEUS than on CDI. Optimal cutoff values for ulceration were defined as 1.4 mm for neck width, 1.3 mm for ulcer depth, and 1.88 mm for ulcer width. Receiver operating characteristic (ROC) analysis was used to determine that the diagnosis of ulceration was more than 90% sensitive if one of these criteria was met [15]. Based on the literature available, CEUS appears superior to CDI for the diagnosis of carotid plaque surface irregularities. Further studies are needed to examine the exact place of CEUS in the diagnostic work-up of carotid disease and its implications on patients' treatment.

Regarding the ancillary findings of ulceration on US and CEUS observed in this study, the detection of flow reversal within an ulcer cavity, also termed the "yin-yang sign," has been previously incorporated into diagnostic criteria for the diagnosis of ulceration by de Bray et al and has been long used for this purpose [3, 8, 31]. It is evident that flow reversal demonstration depends on the geometric characteristics of the ulcer cavity and thus only a percentage of ulcerations may show this finding. In the present study, this finding was observed in 62.5% of ulcerations detected with CDI, while different studies have reported a frequency of more than 90%, during diastole [8]. Flow reversal is created by the swirling movement of blood cells within the cavity, as explained in an experimental study [32]. The same mechanism causes the swirling movement of microbubbles in CEUS [17]. Swirling of microbubbles was demonstrated in only 17.64%

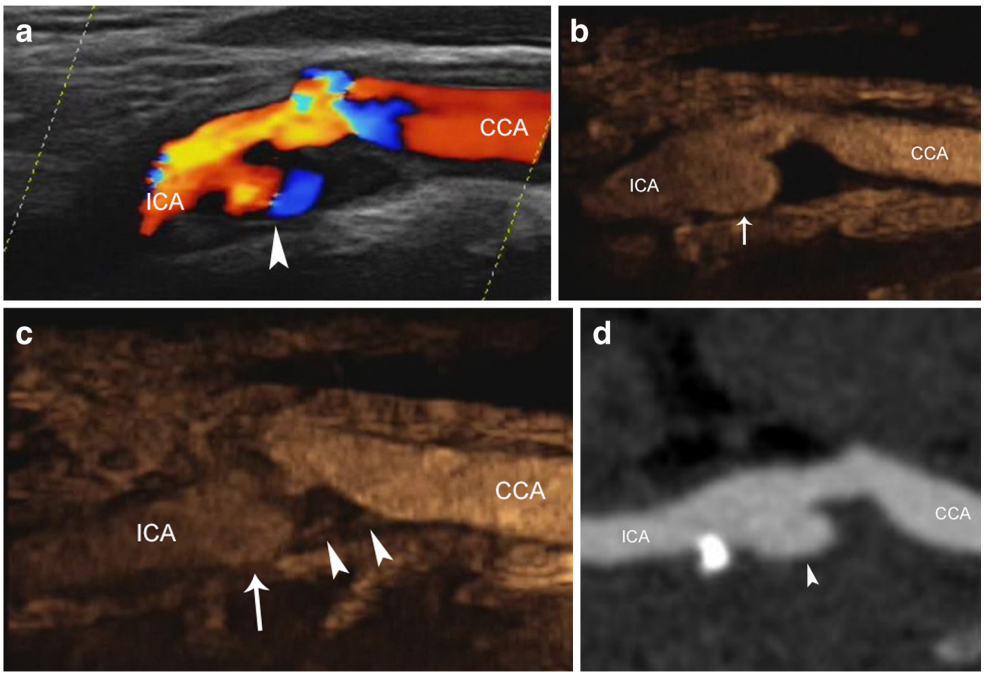

Fig. 3 A 73-year-old male patient diagnosed with an ulcerated left internal carotid plaque after presenting with stroke. CDI image (**a**) demonstrating the presence of a type 4 ulceration (arrowhead) within a hypoechoic plaque. Note the presence of flow reversal within the ulcer's cavity. Early (**b**) and delayed (**c**) CEUS image confirming the diagnosis of ulceration (arrow) while additionally demonstrating intraplaque neovascularization with microbubbles (arrowheads) flowing within the plaque and in close proximity with the ulcer. Corresponding MDCTA image (**d**) confirming the previous findings (arrowhead showing the ulceration) (*CCA* common carotid artery, *ICA* internal carotid artery)

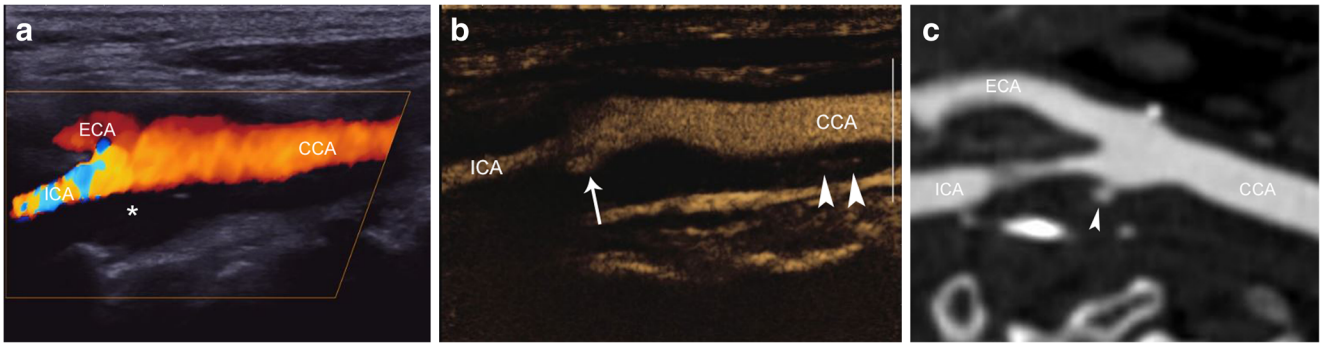

Fig. 4 A 76-year-old patient with a symptomatic ulcerated right internal carotid artery. CDI image (**a**) demonstrating severe stenosis caused by a smooth hypoechoic plaque (asterisk). CEUS (**b**) revealed the presence of a small superficial ulceration (arrow) and intraplaque neovessels (arrowheads). MDCTA image (**c**) confirming CEUS findings (arrowhead showing the ulceration) (*CCA* common carotid artery, *ICA* internal carotid artery, *ECA* external carotid artery)

of ulcers detected with CEUS, possibly due to the fact that high concentration of microbubbles may obscure this finding during most part of the examination. Intraplaque neovascularization is another finding commonly coexisting with ulceration [33], with small neovessels being delineated by microbubbles in proximity with ulcers (Figs. 3 and 4). In this study, this observation occurred in only 17.64% of ulcers detected with CEUS, although this percentage could be higher if a protocol optimized for the detection of neovascularization would be implemented.

Regarding the cost of CEUS as compared to other cross-sectional modalities such as CTA, it has been concluded that CEUS reduced the cost of the diagnostic process in the setting of focal liver lesion characterization and pediatric imaging including liver lesion characterization, trauma assessment, and other applications [34, 35]. The same benefit would apply in carotid disease imaging evaluation, and the exact cost reduction depends on each country's pricing policy.

In the light of this and other studies' results, CEUS could be justified for carotid disease investigation in symptomatic and asymptomatic patients having a plaque causing more than 50% stenosis as it is in these plaques that ulcerations and neovascularization are more likely to occur. Moreover, hospital where endarterectomy is performed based only on US findings with CTA not routinely performed [36], CEUS could be justified in order to increase both the physician's diagnostic confidence in grading of stenosis and increase the accuracy for detection of ulceration and neovascularization. Finally, patients with renal disease could benefit from CEUS as ultrasonographic contrast agents are not nephrotoxic, and in these patients, CEUS could replace CTA in the evaluation of carotid arteries.

Limitations of this study include a potentially small number of patients, with a prevalence of ulcerations potentially affecting diagnostic accuracy. A certain spectrum bias may have been observed, as only plaques causing more than 50% stenosis were included, as plaques causing mild stenosis would not substantialize the need for MDCTA for the diagnostic work-up of these patients. Some plaques with less than 50% stenosis have been included only if found in the contralateral side of a > 50% stenotic plaque. The diagnostic accuracy could have been a little different if mildly stenotic plaques have been included. False positive diagnosis of ulceration by US can be caused by technique inherent artifacts including overwriting artifact and the mirror image artifact where blood flow signals are falsely visualized within a plaque [37]. The

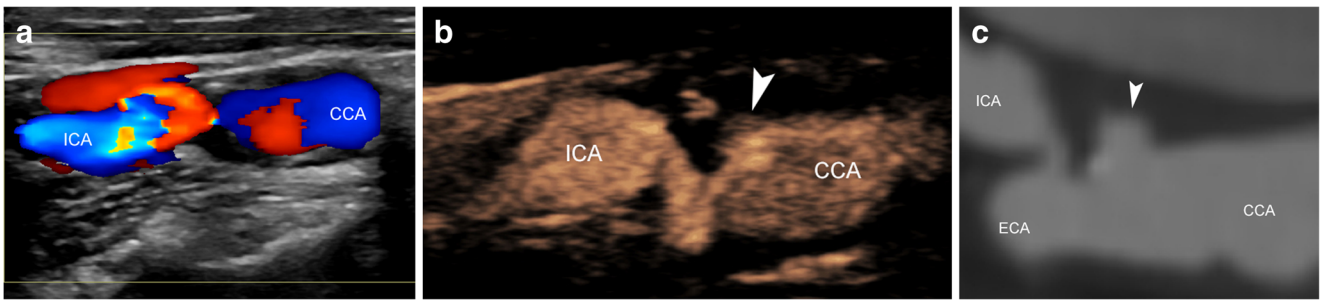

Fig. 5 A 63-year-old asymptomatic patient diagnosed with an ulcerated left internal carotid artery plaque during preoperative checkup. CDI image (**a**) showing severe stenosis of the internal carotid artery, although little information is provided regarding plaque surface due to overwriting artifact. CEUS image (**b**) accurately delineating the plaque surface and identifying an ulceration (arrowhead), proximal to the point of maximum stenosis. Corresponding MDCTA image (**c**) confirming the diagnosis and CEUS findings (arrowhead showing the ulceration) (*CCA* common carotid artery, *ICA* internal carotid artery, *ECA* external carotid artery)

saturation artifact may be caused by calcification or hyperechoic parts of the plaque in CEUS, potentially leading to false positive diagnosis of ulceration.

Conclusion

Ultrasound represents the primary modality for evaluation of carotid disease. Conventional techniques such as CDI are characterized by a limited sensitivity for the diagnosis of superficial ulceration, while CEUS offers improved sensitivity, constituting a valuable complementary ultrasonographic technique for the diagnostic work-up of carotid disease. Ancillary findings supporting the diagnosis of ulceration include flow reversal on CDI and the swirling of the microbubbles on CEUS.

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Compliance with ethical standards

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Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- Prospective
  - Diagnostic or prognostic study
  - Performed at one institution

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