Multiparametric 3D Contrast-Enhanced Ultrasound to Assess Internal Carotid Artery Stenosis: A Pilot Study

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ABSTRACT

BACKGROUND AND PURPOSE: Extracranial internal carotid artery stenoses (ICASs) may greatly differ with respect to morphological and hemodynamical aspects. The aim of this pilot study was to evaluate the use of multiparametric 3-dimensional (3D) contrast-enhanced ultrasound (3D-CEUS) to comprehensively examine ICAS.

METHODS: Fifteen patients with moderate to severe ICAS were examined with multiparametric 3D-CEUS, power-mode 3D ultrasound (3DUS), color-coded duplex sonography (CDS), and digital subtraction angiography (DSA) (n = 9). Multiparametric 3D-CEUS comprised the assessment of the morphology and the stenotic degree of ICAS and the measurement of the ipsistenotic cerebral circulation time (CCT).

RESULTS: Multiparametric 3D-CEUS reliably visualized even complex aspects of ICAS such as ulcerated or heavily calcified plaques with high spatial resolution. When comparing the different methods to quantify ICAS, the intermethod agreement was good (ranging from poor to excellent) between 3D-CEUS and CDS, moderate (ranging from poor to good) between 3D-CEUS and DSA, and poor (ranging from poor to good) between CDS and DSA. The CCT was significantly longer in patients with ICAS than in healthy subjects (8.2 ± 1.5 seconds vs. 6.5 ± 1.3 seconds, \( P = .026 \)).

CONCLUSION: In this pilot study, bedside multiparametric 3D-CEUS provided reliable estimations of different morphological and hemodynamical aspects of ICAS, thus ideally complementing CDS.

Keywords: 3D contrast-enhanced ultrasound, internal carotid artery stenosis, color-coded duplex sonography, cerebral circulation time.

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Introduction

The proximal internal carotid artery (ICA) is especially vulnerable to atherosclerosis with subsequent stenosis, which is explained by factors such as geometry and complex flow patterns at its origin that lead to an increased vessel wall shear stress.\(^{1-3}\) Because of the high risk of recurrent ischemic stroke, there is a strong recommendation to revascularize symptomatic high-grade (\( \geq 70\% \)) according to the North American Symptomatic Carotid Endarterectomy Trial [NASCET] criteria) ICA stenosis (ICAS).\(^{4,5}\)

While angiographic imaging modalities such as computed tomography angiography (CTA) or digital subtraction angiography (DSA) visualize and quantify ICAS by the intraluminal absence of a contrast agent, color-coded duplex sonography (CDS) assesses the stenotic value based on the hemodynamic changes caused by the stenosis.\(^{6,7}\) However, there is an ongoing debate about the intermethod agreement between CDS and the angiographic imaging modalities.\(^{8,9}\)

We previously demonstrated that 3-dimensional ultrasound (3DUS) based on B-mode or power mode was able to overcome some limitations of CDS when examining ICAS.\(^{10,11}\) An even further improvement to the visualization and grading of ICAS might be achieved by 3D contrast-enhanced ultrasound (3D-CEUS). In addition to quantifying ICAS, 3D-CEUS might also better identify morphological aspects of ICAS such as ulcerated plaques or neovascularization that are associated with an increased risk of subsequent cerebrovascular events.\(^{12}\)

Finally, 3D-CEUS would also allow for the assessment of the cerebral circulation time (CCT), which was repeatedly shown to be shortened in patients with intracranial shunts,\(^{13,14}\) but, as we hypothesize, might be prolonged in hemodynamically relevant ICAS.

Thus, the aim of this study was to evaluate a multiparametric 3D-CEUS protocol that comprised the assessment of the ICAS’s morphology, the quantification of ICAS, and the measurement of the ipsistenotic CCT.

Methods

The study was approved by the local Ethics Committee of the Medical Faculty of the University of Leipzig (reference number: 246/15-ek) and all participants gave their written informed consent.

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Study Population

We did not perform a power analysis prior to the initiation of patient recruitment but aimed to examine at least 30 patients for an adequate intermethod comparison of 3D-CEUS with the other imaging modalities. However, because of slow recruitment, we terminated this study after 15 patients.

Fifteen patients (6 females; median age 67 years; age range 48–80 years) with at least moderate (50% NASCET) stenosis or occlusion of the proximal extracranial ICA according to an in-depth CDS examination were consecutively recruited from our stroke unit (14 patients) and our neurovascular outpatient clinic (1 patient). The level of stenosis or occlusion of the ICA was confirmed by CTA (9 patients), magnetic resonance angiography (MRA; 7 patients), and/or DSA (9 patients), or not confirmed by a second method in 1 patient. The exclusion criteria were a concurrent intracranial stenosis of the ICA or an at least moderate stenosis of the contralateral ICA. We also assessed possible confounders for the measurement of the CCT; no patient had a history of congestive heart failure. Eleven of the 14 patients from the stroke unit had a normal echocardiographic left ventricular ejection fraction. Moreover, no patient was hypotensive (arterial blood pressure below 110/70 mmHg) during the examination.

The CCT control group consisted of seven healthy subjects without any sonographic evidence of a stenosis or occlusion of the extra- or intracranial arteries supplying the brain.

All ultrasound data (3D-CEUS, power-mode 3DUS, and CDS) were anonymized upon examination. During data analysis, which took place at the end of this pilot study, the evaluating neurologists and the neuroradiologist were unaware of the results from the other imaging modalities.

Grading of ICAS by Color-Coded Duplex Sonography

All patients were examined by the same experienced vascular neurologist (JP) who was certified in neurosonology by the German Society of Ultrasound in Medicine and Biology (DEGUM) and the European Society of Neurosonology and Cerebral Hemodynamics (ESNCH). ICAS were graded with CDS by applying the multiparametric DEGUM ultrasound criteria, which are almost identical to the criteria of the Neurosonology Research Group of the World Federation of Neurology. The stenotic degree of ICAS was expressed in steps of 10 degrees.

Contrast-Enhanced Ultrasound

All ultrasound examinations, ie, the CDS and the 3D-CEUS examinations, were performed with a Siemens Acuson S2000 (Siemens, Erlangen, Germany) equipped with a 9 MHz linear transducer (9L4 Multi-D). For 3D-CEUS, this conventional ultrasound system was attached to the Curefab CS system (Curefab Technologies GmbH, Munich, Germany), which comprised a freehand magnetic field tracking system and a workstation equipped with special software (Curefab CS, version 1.91). Briefly, ultrasound images were grabbed from the video port of the Siemens Acuson S2000, concatenated with spatial and temporal information, and stored in a virtual 3D volume.

Practically, patients were lying in a supine position and were asked not to swallow during the examination. The ultrasound transducer was placed cranially to the clavicle and medially to the sternocleidomastoid muscle at the level of the thyroid gland, where the common carotid artery (CCA) and the adjacent internal jugular vein (IJV) could clearly be visualized in the transverse plane. To avoid compression of the IJV, the pressure of the ultrasound transducer was reduced until the venous lumen was clearly inflated. Then, parameters such as depth (30-35 mm), gain, and focus were individually optimized.

First, the ICAS was examined with power-mode 3DUS. Subsequently, the ultrasound transducer was moved back to the starting position, and a 2.4-mL bolus of the US contrast agent (Sonovue®, Bracco, Milan, Italy) was administered via a peripheral venous catheter in the median cubital vein followed by 5 mL of physiologic saline. Upon injection, a 45-second video was recorded to measure the CCT. After the IJV was clearly filled with the ultrasound contrast agent, the 3D-CEUS recording was started, and the ultrasound transducer was moved cephalad in the transverse direction while keeping the ICA lumen in the center of the monitor screen.

Measurement of Cerebral Circulation Time and Grading of ICAS by 3D Contrast-Enhanced Ultrasound

The CCT was measured with dedicated software (VueBox®, Bracco Suisse SA, Plain-les-ouis, Switzerland) according to the protocol of Schreiber et al. Briefly, a circular region of interest (ROI) was marked on the CCA and the IJV. Then, the time-intensity curves and maximum intensity values of the bolus arrival of the U.S. contrast agent were calculated for both ROIs. The CCT was defined as the time interval between the points on the time-intensity curves reaching 10% of the overall intensity increase. In this way, artifacts mainly caused by baseline variations were reduced (Fig 1).
Within the virtual 3D-CEUS and power-mode 3DUS volumes, the smallest diameter of the stenotic lumen and the normal diameter of the distal lumen of the ICA were measured perpendicular to the artery’s course in the coronal and/or sagittal plane. The stenotic degree was calculated according to NASCET: 100% * [1 – (diameterintrastenotic / diameterdistal)] and rounded to the nearest 10 degrees.¹

**Diagnostic Transarterial Angiography**

Diagnostic DSA was performed using either a biplane Siemens system (Axiom Artis, Erlangen, Germany) or a biplane Philips system (Allura, Best, The Netherlands). The selective catheterization of the respective CCA was performed. At least three different views (posteroanterior, lateral, and 45° oblique) were obtained for all patients. Iopromid (60-120 mL, containing 300 mg iodine per mL) was used as the contrast agent. Quantification of ICA stenosis was performed according the NASCET criteria using the narrowest diameter of the stenotic lumen and the normal lumen of the distal ICA for calculation.

**Statistical Analysis**

Statistical analyses were performed with SPSS version 24.0 (IBM Corporation; New York, NY, USA). The intermethod agreements between 3D-CEUS, power-mode 3DUS, CDS, and DSA were visualized and described by Bland and Altman analyses¹⁶ and the calculation of the intraclass correlation coefficient (ICC). The ICC estimates and their 95% confidence intervals were calculated using SPSS version 24.0 (IBM Corporation) based on an absolute agreement, two-way mixed-effects model. The ICC values (ranging from 0 to 1) were interpreted as follows: excellent agreement ICC ≥ .90, good agreement ICC ≥ .75, moderate agreement .75 > ICC ≥ .50, and poor agreement ICC < .50.¹⁵ For the CCT, the statistical significance between groups was assessed by a nonparametric test (Mann-Whitney U test) because of the small sample size. Moreover, the Spearman rank correlation was used to explore the association between the CCT and the stenotic value of ICAS. A P value < .05 indicated statistical significance.

**Results**

Three-dimensional CEUS could successfully be performed in all participants including patients with an in-stent stenosis (Fig 2C), complex and long-distance ICAS (Fig 2D), or heavily calcified ICAS (Fig 2E). In addition to measuring the stenotic degree, 3D-CEUS also facilitated the visualization of ulcerated plaques or neovascularization (Fig 2B).

As visualized in the Bland and Altman analyses, 3D-CEUS systematically underestimated the stenotic value of high-grade ICAS by approximately 10% in comparison with CDS (bias –8.0%) and DSA (bias –10.0%). Generally, there were wide confidence intervals for the ICC calculation because of the small sample size of this pilot study. Hence, the ICC values and their interpretation should be regarded as preliminary. We found good (ranging from poor to excellent) intermethod agreement between 3D-CEUS and CDS (ICC .80, range .15-.94, P < .001; Fig 3, Table 1) and moderate (ranging from poor to good) intermethod agreement between 3D-CEUS and DSA (ICC .50, range –.12 to .86, P = .014; Fig 3). For power-mode 3DUS, the intermethod agreement was moderate (ranging from poor to good) compared to 3D-CEUS (ICC .55, range .05-.83, P = .019), but poor (ranging from poor to moderate) compared to DSA (ICC .41, range −.06 to .75, P = .032), and moderate (ranging from poor to good) compared to DSA (ICC .50, range −.10 to .85, P = .025). There was poor (ranging from poor to good) intermethod agreement between CDS and DSA (ICC .44, range −.33 to .85, P = .12).

The CCT was significantly longer in patients with ICAS compared to healthy volunteers (8.2 ± 1.5 seconds vs. 6.5 ± 1.3 seconds, P = .026, Mann-Whitney U test). There was no correlation between the CCT and the stenotic value of ICAS assessed by either CDS, 3D-CEUS, or DSA (P > .05 for each).

**Discussion**

In this pilot study, we evaluated multiparametric 3D-CEUS to quantify ICAS and found good (ranging from poor to excellent) intermethod agreement with CDS when applying the DEGUM criteria and moderate (ranging from poor to good) agreement with DSA. Moreover, patients with ICAS exhibited longer CCT than healthy subjects.

While the established angiographic imaging modalities (CTA, MRA, and DSA) directly visualize the lumen of the vessel with a contrast agent, CDS derives the stenotic value on the basis of pre-, intra-, and poststenotic hemodynamical changes.¹² Since CDS is noninvasive and allows for bedside examination, it is routinely performed in patients with ischemic stroke to detect ICAS.¹⁷ However, CDS is of limited use in patients with heavily calcified plaques that lead to acoustic shadowing, in patients with short and obese necks, or in patients where the carotid bifurcation is located distally beneath the mandible.¹⁸ Moreover, unlike the angiographic imaging modalities, CDS is supposed to be subjective and dependent on the experience of the sonographer. As demonstrated previously, noninvasive freehand 3DUS based on power-mode imaging could overcome some of these limitations.¹¹ Here, 3D-CEUS showed good agreement with CDS for the grading of ICAS even in patients with heavy acoustic shadowing. However, probably, because of the small sample size, the confidence intervals of the ICC estimates were wide, which currently restricts a final evaluation of 3D-CEUS. Although the intermethod agreement between 3D-CEUS and DSA was moderate (ranging from poor to good), it was still better than that between CDS and DSA. This confirmed recent findings by Barlinn and colleagues who described an overall poor agreement between CDS and DSA in their multicenter study.⁹ They concluded that CDS alone does not eliminate the need for a confirmatory test to identify clinically relevant ICAS.⁹ Generally, ultrasound contrast agents are well tolerated, and thus, can be repeatedly applied in patients with hyperthyreosis, (chronic) renal failure, or a known hypersensitivity to CT contrast agents.¹⁹ Therefore, 3D-CEUS might prove to be such a confirmatory test and could easily be implemented into the routine ultrasound workup of ischemic stroke patients. Starting the examination with CDS and complementing it with 3D-CEUS rather than CTA or MRA to confirm a relevant extracranial stenosis might also be cost- and time-effective. These latter aspects would be of particular interest for patients with asymptomatic ICAS that require regular follow-up to detect a progression of the stenosis.

It is worth noting that 3D-CEUS systematically underestimated the stenotic value of high-grade ICAS in comparison with CDS and DSA. When assessing the stenotic value with
Fig 2. Visualization of complex morphological features of internal carotid artery stenosis with 3D contrast-enhanced ultrasound (3D-CEUS). (A) The common carotid artery (CCA), the bifurcation, and the internal and external carotid artery (ICA and ECA, respectively) of a healthy proband are visualized in the coronal plane. (B) A deeply ulcerated echolucent plaque (arrows; patient 1 [Table 1]) leads to a high-grade (80%) internal carotid artery stenosis (ICAS). Due to the lower spatial resolution, power-mode 3D ultrasound (3DUS) was unable to detect the echolucent ulceration, resulting in a low-grade (40%) ICAS. In the axial plane (B'), the thin border of the ulceration can be better distinguished, and there is evidence of a distinct area of neovascularization within the echolucent plaque (arrow). (C to C''') A high-grade in-stent stenosis, which is caused by a hyperplasia of the intima (patient 4 [Table 1]). While the contrast agent is difficult to detect in the computed tomography angiography because of the hyperdense stent (C'''), it can be better seen in 3D-CEUS (C', blue inlet = sagittal plane, green inlet = axial plane) and in digital subtraction angiography (DSA, C'). The arrows are marking the stent, while the echolucent hyperplasia is marked by an asterisk (C'). (D to D'') 3D reconstruction of a complex and long-distance ICAS (D, patient 3 [Table 1]). Unlike DSA (D''), 3D-CEUS shows both the original lumen (marked with arrows) and the eccentric stenosis (D'). (E to E') 3D-CEUS allows for the detection and grading of highly calcified ICAS (E', patient 5 [Table 1]) that are otherwise not detectable with 3DUS based on native B-mode (E) or power-mode imaging (E'). All scale bars: 1 cm. Stenotic values represent NASCET criteria.
DSA, the diameter of the narrowest lumen within the stenosis and the diameter of the distal normal lumen were measured in the same projection. Because DSA focuses on the narrowest stenotic lumen, small irregularities or a more oval shape of the distal lumen that were outside this plane might have been easily overlooked. Using 3D-CEUS, we measured the smallest diameter of the stenotic lumen as well as the smallest diameter of the distal normal lumen independently of each other. Thus, assessing both smallest diameters might have resulted in smaller values for 3D-CEUS according to NASCET.

In addition to the quantification of the stenotic value, 3D-CEUS also visualized ICAS with a high spatial resolution which, unlike power-mode 3DUS, facilitated the assessment of characteristics of the stenosis that are known to be associated with a higher risk of subsequent ischemic stroke, such as ulcerated and irregular plaques or neovascularization. Therefore, future studies should additionally focus on the use of 3D-CEUS to assess the ischemic stroke risk of asymptomatic ICAS.

The use of the contrast agent also enabled the measurement of the ipsistenotic CCT, which was significantly extended in
patients with an at least moderate ICAS when compared to healthy subjects. The CCT in the probands was similar to the values obtained previously.\textsuperscript{13,14,22} It is worth noting that we found no correlation between the CCT and the stenotic value of ICAS as assessed by either 3D-CEUS, CDS, or DSA. This might be due to the presence of collaterals within the arterial circle of Willis. This phenomenon can frequently be observed in severe (\textges 70\% NASCET) ICAS and is even a main CDS criterion to distinguish between moderate and severe ICAS.\textsuperscript{6,7} However, we only qualitatively assessed the presence or absence of collaterals. In the case of missing or insufficient collaterals, we hypothesize that the CCT might be further prolonged. Thus, future studies should examine the relationship between a prolonged CCT, the intracranial collateral status, cerebrovascular reactivity, and the risk for ischemic stroke in patients with asymptomatic severe ICAS. Finally, one might also include the measurement of the time interval from the injection of the US contrast agent bolus until its first appearance in the CCA (or middle cerebral artery), since this interval might be shortened in patients with a patent foramen ovale.\textsuperscript{23}

This study has several limitations: First, because of the small sample size of only 15 patients, the results should be regarded as preliminary. More patients with a wider age range, different ethnicities, and different stenosing pathologies of the ICA (for example, with stenosis due to atherosclerotic disease, dissection, radiation, or in-stent thrombosis/intima hyperplasia) should be included in future studies. The small sample size might be even more important when regarding the intermethod agreement between 3D-CEUS and DSA, as only 9 patients received both diagnostics. It is worth noting that the small sample size might also have resulted in lower ICC values and wider confidence intervals when calculating the intermethod agreement between

\textbf{Fig 2.} Continued.
Fig 3. Intermethod agreements between 3D-CEUS, CDS, and DSA. The intermethod agreements for the stenotic values of internal carotid artery stenosis (ICAS) as assessed with 3D contrast-enhanced ultrasound (3D-CEUS) and color-coded duplex sonography (CDS, left side), as well as for 3D-CEUS and digital subtraction angiography (DSA, right side) are visualized by Bland and Altman analyses. In direct comparison with CDS and DSA, 3D-CEUS systematically underestimates the stenotic value of high-grade (≥70% NASCET) ICAS by approximately 10%.

Table 1. Cerebral Circulation Time and Stenotic Values of the Internal Carotid Artery using DSA, 3D-CEUS, Power-Mode 3DUS, and CDS

| Patient | DSA (% NASCET) | 3D-CEUS (% NASCET) | Power-Mode 3DUS (% NASCET) | CDS (% NASCET) | CCT (s) |
|---------|----------------|-------------------|-----------------------------|---------------|--------|
| 1  | - | 80 | 40 | 90 | 8.4 |
| 2 | - | 60 | 50 | 50 | 7.6 |
| 3 | 90 | 80 | 65 | 90 | 8.2 |
| 4 | 70 | 70 | 70 | 90 | 9.9 |
| 5 | - | 50 | Not visualizable | 50 | 7.1 |
| 6 | 80 | 70 | 90 | 80 | 9.9 |
| 7 | 70 | 50 | 55 | 50 | 8.6 |
| 8 | 100 | 90 | 100 | 100 | 7.8 |
| 9 | 90 | 70 | 70 | 80 | 9.9 |
| 10 | - | 60 | 70 | 60 | 11.7 |
| 11 | 90 | 70 | 75 | 80 | 7.9 |
| 12 | - | 40 | 40 | 50 | 6.3 |
| 13 | 70 | 70 | 50 | 90 | 7.8 |
| 14 | - | 80 | 80 | 90 | 6.9 |
| 15 | 80 | 80 | 70 | 90 | 6 |

Note. Number of patients = 15; s = seconds; CCT = Cerebral Circulation Time; DSA = Digital Subtraction Angiography; 3D-CEUS = 3D Contrast-Enhanced Ultrasound; 3DUS = 3D Ultrasound; CDS = Color-Coded Duplex Sonography.

3D-CEUS, CDS, DSA, and power-mode 3DUS. Koo and Li suggested that a reliability study should obtain at least 30 heterogeneous samples.15 Second, we recruited only patients with a single, at least moderate, stenosis of the extracranial carotid arteries. Therefore, the generalization to patients with ipsilateral tandem- and/or contralateral stenosis is limited. However, in patients with tandem stenoses or bilateral relevant ICAS, DSA grading might also be impaired by compensating blood flows. Moreover, imaging modalities that are based on the visualization of the vessel’s lumen are generally considered to yield more accurate stenotic values in these cases. Finally, as outlined above, to better understand the relevance of a prolonged CCT in patients with ICAS, the full status of arterial collateralization (either by transcranial and transorbital CDS or by time of flight MRA) and the cerebrovascular reactivity should be assessed.

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