ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ

ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΜΕΤΑΠΤΥΧΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΣΠΟΥΔΩΝ

ΥΠΕΡΗΧΟΓΡΑΦΙΚΗ ΛΕΙΤΟΥΡΓΙΚΗ ΑΠΕΙΚΟΝΙΣΗ ΓΙΑ

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Ειδικευόμενη Ακτινολογίας

Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

Διπλώματος Μεταπτυχιακών Σπουδών

«Υπερηχογραφική λειτουργική απεικόνιση για

την πρόληψη και διάγνωση των αγγειακών παθήσεων»

Λάρισα, 2023

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Τίτλος εργασίας στα αγγλικά:

"THE ROLE OF CONTRAST ENHANCED ULTRASOUND (CEUS) IN THE EVALUATION OF THE CAROTID SYSTEM"

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Περίληψη

Η χρήση των υπερήχου με σκιαγραφική ουσία (CEUS) αποτελεί σήμερα μία πολλά-υποσχόμενη, μη επεμβατική απεικονιστική μέθοδο που, σε συνδυασμό με το έγχρωμο Doppler υπερηχογράφημα, συμπληρώνει την απεικόνιση των αγγειακών παθήσεων. Πολυάριθμες μελέτες έχουν αναδείξει τον ρόλο των CEUS σε πολλαπλα πεδία των υπερήχων των αγγείων συμπεριλαμβανωμένων των καρωτίδων, της κοιλιακής αορτής, των λαγονίων, της πυλαίας και των ηπατικών φλεβών, όπως και των νεφρών και των νεφρικών αρτηριών. Ειδικότερα, όσον αφορά την απεικόνιση των καρωτίδων, τα CEUS μπορούν να χρησιμοποιηθούν για την ακριβέστερη διάγνωση απόφραξης ,διαχωρισμού ή και στένωσης, καθώς και για την διαφοροδιάγνωση μιας πλήρους από μία μερική απόφραξη (sub-occlusion). Επιπλέον τα CEUS μπορούν να αναδείξουν με περισσότερη ευαισθησία αλλοιώσεις του καρωτιδικού τοιχώματος όπως έλκη σε αθηροσκληρυντικές αλλοιώσεις και μαλακές -υπόηχες πλάκες. Επιπροσθέτως τα CEUS έχουν την δυνατότητα να προσφέρουν απεικόνιση σε επίπεδο μικροκυκλοφορίας και έτσι να αναδείξουν αυξημένη νεοαγγείωση εντός των αθηροσκληρυντικών πλακών συνεισφέροντας έτσι στον εντοπισμό ευάλωτων αθηρωματικών πλακών με αυξημένη πιθανότητα ρήξης. Τέλος, τα CEUS ενδείκνυνται και για την μετεγχειρητική παρακολούθηση και εκτίμηση της επαναστένωσης μετα από τοποθέτηση ενδοαυλικού stent στην καρωτίδα καθώς και για την εκτίμηση της φλεγμονής του καρωτιδικου τοιχώματος σε έδαφος αρτηρίτιδας.

Σε αυτή την μεταπτυχιακή διπλωματική εργασία θα πραγματοποιηθεί μία συστηματική ανασκόπηση της βιβλιογραφίας μεσω του PubMed σχετικά με την χρήση των σκιαγραφικών υπερήχων και την συμβολή τους στην εκτίμηση παθολογιών του καρωτιδκού συστήματος καθώς και την μετεγχειρητική παρακολούθηση των καρωτίδων μετά απο αγγειοπλαστική. Στην ανασκοπηση αυτή συμπεριληφθηκαν συνολικά 23 αρθρα.

Λέξεις-κλειδιά : σκιαγραφικό υπερήχων, καρωτίδες, καρωτιδικό σύστημα, αθηροσκλήρυνση, διαχωρισμός

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Abstract

Nowadays, contrast-enhanced ultrasound (CEUS) has evolved into a particularly useful, non-invasive and powerful diagnostic tool in vascular pathology. Many studies have pointed out the role of CEUS in multiple fields of vascular ultrasound such as the carotid arteries, abdominal aorta, iliac arteries, portal vein, hepatic veins, as well as the kidneys and renal arteries and veins. In particular, CEUS in the carotid system can be used for a more accurate diagnosis of occlusion, dissection or stenosis, while it can also be useful in differentiating a complete from a partial occlusion (near-occlusion). In addition, CEUS has the ability to demonstrate carotid wall lesions such as atherosclerotic ulcers and hypoechoic plaques. Furthermore, CEUS is able to offer information about the microcirculation and thus can be able to detect increased neovascularization inside carotid plaques, contributing to the identification of unstable atherosclerotic plaques that carry an increased risk of rupture. Finally, CEUS is also indicated for postoperative monitoring and assessment of restenosis after intraluminal stent placement in the carotid arteries as well as for the identification of carotid wall inflammation in patients with arteritis.

The aim of this thesis is to present and discuss the latest literature regarding the various applications of ultrasound contrast agents in the carotid system and the possibilities they provide, along with the applications of this alternative radiological technique in the daily clinical practice. A systematic review was performed using the literature data base PubMed including 23 full-text articles.

Key-words: contrast-enhanced ultrasound, carotid arteries, carotid system, atherosclerosis, dissection

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Introduction

1.1 Basic ultrasound principles

Ultrasound (US) is currently one of the most versatile and widely used radiological techniques in the everyday clinical practice. Medical US imaging is based on the transmission and reception of sound waves with frequencies ranging from 2 to 15MHz, although even higher frequencies may be needed in some situations [1].

1.1.1 Wave Terminology

Sound consists of longitudinal vibrations which propagate through a medium as a wave containing compressions (areas of increased pressure) and rarefactions (areas of decreased pressure) [2]. The characteristics of a sound wave can be defined using the following parameters:

1. Period (T) The time needed for the particle in the medium to complete on vibrational cycle

2. Frequency (f) The number of complete cycles in a unit of time performed by the particles in the medium. Frequency is measured in Hertz (Hz), while high frequencies can be expressed in kHz (1kHz=1000Hz) or MHz (1MHz=1,000,000 Hz)

3. Wavelength (λ) The distance of one wave cycle (e.g., between two compressions or two rarefactions)

4. Velocity (c) The speed that sound waves move through different mediums. The density and compressibility of a medium strongly affect the velocity of the sound wave. Therefore, propagation velocity differs in each material.

Sound is categorized according to its frequency. In the natural environment, acoustic frequencies vary from less than 1Hz to over 100,000Hz. Human hearing ranges from 20 up to 20,000Hz, while diagnostic US typically ranges from 2 to 15MHz.

1.1.2 The piezo-electric effect

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The waves are produced by a transducer consisting of piezo–electric crystals that transforms an electrical signal into an ultrasonic pulse. Therefore, the piezo-electric crystals within the transducer convert electrical energy into mechanical and vice-versa. The transmitted waves propagate through a medium until they encounter reflective or scattered objects, and then return to the transducer as reflected echoes. The transducer crystals convert the reflected echoes back into electrical impulses, which are then further prepared in order to build the US image that is visualized on the screen.

1.1.3 Interaction between sound and tissue

As sound moves though different tissues within the body, various factors result in energy loss and therefore a reduction in amplitude and intensity. Attenuation is defined as this loss of energy and it is determined by the medium involved, the distance traveled and the frequency of the beam. The attenuation of sound energy is significant since it affects how deep the tissue from which useful information can be collected can be. There are four main processes contributing to the attenuation of sound, which are: reflection, refraction, absorption and scattering [3].

Reflection

Reflection appears at the junction between tissues with a difference in their acoustic impedance (Z). A simpler definition of acoustic impedance is $Z = \rho c$, where ρ is the density of the tissue in kg/m and c is the speed of sound in m/s [3]. The amount of reflected sound increases and the amount of transmitted sound decreases accordingly as the density difference increases. The sound is entirely reflected if the tissues are very different regarding their density, which results in total acoustic shadowing. Bones, calculi (gallbladder, kidneys etc.) and air bubbles (gastrointestinal system) all exhibit acoustic shadowing. If variation between the tissues does not exist then echoes will not be produced. Blood, urine, bile, ascites, etc. are homogeneous fluids that are depicted on US as echo-free structures.

Refraction

Refraction is the alteration of the pathway of a sound wave, when it passes through tissues with different propagation velocities, when the angle of incidence to an interface is not 90°. Refraction is significant because it can cause misregistration of a structure in an US image.

Absorption

Absorption is the shifting of the energy of a sound wave into the material in which the sound is traveling. Absorption produces a heating effect and it increases with the increase in the frequency.

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Scattering

Scattering appears when a sound wave travels through an area with a different acoustic impedance than the tissue around it, with individual dimensions smaller than the wavelength of the sound wave. The echoes of these interfaces are scattered in all areas. Such structures are known as 'diffuse reflectors' and represent the echoes that create the distinctive echo patterns that solid organs and tissues display.

1.2 Ultrasound Contrast Agent

1.2.1 Historic overview

The use of CEUS begun in the last years of 1960s after discovering that the administration of agitated saline causes a distinguishable change in the signal amid US examination [4]. Contrast enhancement occurred due to the compressible gas center of saline bubbles, allowing the bubbles to backscatter the applied US wave. The high surface tension of those first bubbles caused instability. In the decade of 1970s, the area of ultrasound contrast agents (USCA) developed further and it primarily involved applications in cardiology. Nonetheless the full potential of CEUS could still not be investigated, due to the insufficient lifetime and non-defined size of the bubbles [5]. Circulation time was efficaciously evolved by substituting air for perfluorinated gases that have low solubility in water, such as sulfur hexafluoride [6], perfluoropropane [7] or perfluorobutane [8], resulting in sufficient lifetime enough for clinical use. Mored thatn 20 years were needed in order to create the first stable and commercially accessible ultrasound contrast agent, Albunex®, a microsphere covered with albumin and filled with air. [9]. In the following years, persistence and clinical effectiveness of USCA have been improved and micro-bubbles targeting specific surface molecules expressed in pathologic conditions have been developed.

1.2.2 Basic characteristics of Ultrasound Contrast Agents

USCA can be defined as exogenic substances which can be injected either intravenously or inside a cavity. USCA increase the backscattered signal intensity and thus improve the Doppler analysis and highlight the details of the anatomical structures [10]. The majority of USCA in use are composed of microbubbles (typically 3μm in diameter) of gas, such as sulphur hexafluoride, perfluorohexane, air or nitrogen [10,11]. Air was the gas of choice in the earlier USCA as well as in some of the latest ones. However, inert gases with higher molecular weight may be superior due to the fact that they have a low solubility in blood and thus can have a longer half-life [5]. Microbubbles are surrounded by a shell in order to improve the stability in the bloodstream and create a standardized size. The shell consists of stabilizing materials such as phospholipids, albumen or galactose [12, 13]. Microbubbles have the same osmotic pressure as the human plasma and are removed from the body through the lungs [10].

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1.2.3 Classification

USCA can be categorized into two types depending on the type of gas that is used inside the microbubbles. First- generation contrast agents, launched in 1996, contained microbbules of air within thin shells consisting of protein, polymer or phospholipids [5, 14]. However, air presents high solubility in blood and thus first-generation contrast agents had a very short circulation time during exposure to the acoustic pressure of the ultrasound field [14]. Therefore, their presence in the blood was limited and only intermittent scanning was feasible. In order to improve the lifespan of the microbubbles, air was replaced by inert gases with low diffusion coefficients and low solubility in blood [15]. Gases that were mostly used for this purpose were sulfur hexafluoride and perfluoroboutane and thereby second-generation contrast agents were introduced [14,15]. Inert gases used in second-generation contrast agents were also surrounded by a shell consisting of lipid, proteins or biopolymers in order to control their size distribution and achieve firmness [14]. A partial list depicting first and second generation USCA is demonstrated in Table 1.

Table 1 Ultrasound contrast media: first and second generation in comparison

	First generation	Second generation
Ultrasound contrast media	Levovist (Schering AG, Berlin, Germany)	SonoVue (Bracco Imaging Spa, Colleretto Giacosa (TO), Italy)
Structural characteristics	Air microbubbles with casing of galactose and palmitic acid	Sulfur hexafluoride microbubbles stabilised by membrane phospholipid
Physical properties	Stimulated acoustic emission	Nonlinear oscillation

Table 1. Πηγη: (Esposito F, Di Serafino M, Sgambati P et al. Ultrasound Contrast Media in Paediatric Patients: Is It an Off-Label Use? Regulatory Requirements and Radiologist's Liability. Radiol med. 2011;117(1):148-59.)

1.2.4 Adverse reactions and Contraindications

In general, USCA are quite safe carrying a low rate of complications. USCA that have been approved for clinical practice are all microbubble-based (Table 2). Unlike iodinated contrast agents, microbubbles do not have renal toxicity and do not interact with the thyroid [16]. The adverse effects are uncommon and of mild intensity and usually do not require any treatment. Most common side effects reported in clinical trials include mild nausea or emesis, flushing, pruritus, mild urticaria, injection site pain and cephalalgia. [12, 17, 18]. More serious adverse reactions of USCA are quite rare, especially when comparing to CT and MRI contrast agents [19]. In a study of 23,188 cases of USCA the incidence of serious side effects was only 0,0086% (n=2) while the total cases with an adverse effect were 29 [20]. Although very rare, temporally related fatal adverse events have been recorded in the literature in patients with coexistent coronary artery disease

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[21, 22]. Following these events, in 2007 the US Food and Drug Administration (FDA) released a black box warning for Definity and Optison including contraindications such as aggravated or unstable heart failure, acute myocardial infarction, acute coronary syndrome, severe ventricular arrhythmia or high risk for arrhythmia and pulmonary hypertension [23]. It also required a 30-minute monitoring period after the injection of USCA. Since then, many investigators started publishing studies about the safety and improved efficacy of USCA. The low incidence of severe complications has remained stable in these following studies. At present, hypersensitivity to any of the contrast agents is listed as the only contraindication in Lumason, Definity and Optison [24, 25]. However, all USCA still have a warning of the rare event of severe cardiopulmonary events. Despite the low incidence of adverse effects, USCA should always be used with caution along with readily available resuscitative equipment and experienced professionals on site.

Table 2. Clinically approved ultrasound contrast agents.

Name	First approved for clinical use	Shell material	Gas	Application (examples)	Producer/distributor	Countries
Optison	1998	Cross-linked serum albumin	Octafluoropropane	Left ventricular opacification, endocardial border delineation, Doppler	GE healthcare, Buckinghamshire, UK	USA, Europe
Sonazoid	2006	Hydrogenated egg yolk phosphatidyl serine (HEPS)	Perfluorobutane	Myocardial perfusion, liver imaging	GE healthcare, Buckinghamshire, UK/ Daiichi Sankyo, Tokyo, Japan	Japan, South Korea, Norway, Taiwan, China
Lumason/SonoVue	2001/2014	Phospholipid	Sulphur hexafluoride	Left ventricular opacification, microvascular enhancement (liver and breast lesion detection)	Bracco Diagnostics Inc., Monroe Township, NJ, USA/Bracco Imaging S.p.A., Colleretto Giacosa, Italy	USA, Europe, China, Brazil
Definity/Luminity	2001/2006	Phospholipid	Octafluoropropane	Echocardiography, liver/kidney imaging (Canada)	Lantheus Medical Imaging Inc, North Billerica, MA, USA	North America, Europe
Imagent/Imavist	2002, withdrawn	Phospholipid	Perfluorohexane, Nitrogen	Echocardiography, heart perfusion, tumor/blood flow anomalies	Schering AG, Berlin, DE	USA
Echovist	1991, withdrawn	Galactose microparticles	Air	Right heart imaging	Schering AG, Berlin, DE	Germany, UK
Levovist	1995, withdrawn	Galactose microparticles, palmitic acid	Air	Whole heart imaging, Doppler imaging	Schering AG, Berlin, DE	Canada, Europe, China, Japan
Albunex	1993, withdrawn	Sonicated serum albumin	Air	Transpulmonary imaging	Molecular Biosystems Inc., San Diego, CA, USA	Japan, USA

Adapted from Paefgen et al. 2015.

Table 2.

Πηγή:Frinking P, Segers T, Luan Y, Tranquart F. Three Decades of Ultrasound Contrast Agents: A Review of the Past, Present and Future Improvements. Ultrasound Med Biol. 2020 Apr;46(4):892-908.

1.2.5 Imaging of ultrasound contrast agents

Microbubbles act by enhancing the echoes, causing the echo intensity to increase depending on the difference in the acoustic impedance between the blood and the microbubbles [5]. The difference in the acoustic impedance at this interface is increased

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which means that all of the incident sound is reflected, even though not all of it will reach back the transducer. However, even though the acoustic reflection of the wave is almost complete, it would not be enough in order to retain a strong enhancement due to the small dimensions and sparsity of the microbubbles in the blood. By a fortunate coincidence, microbubbles display a high echogenicity, which originates from the fact that they vibrate very strongly at the frequencies that are used for diagnostic US exams [11]. It is due to this fact that microbubbles can be extremely more reflective than human tissues. If microbubbles were the same size but rigid which would result in a loss of the ability to resonate, they would be a lot less echogenic [26]. Of course, microbubbles must retain small dimensions to be able to travel through the capillaries (7.5μm) and the critical frequency depends on the diameter of the bubbles. Once again, the fortunate coincidence constitutes on the fact that the frequency in which microbubbles 1-7μm in diameter resonate ranges within 2-15MHz, which is the frequencies that are used in US [5].

1.3 Evaluation of carotid artery stenosis and plaque morphology with carotid duplex ultrasonography

Carotid Duplex ultrasound (CDU) is a widely used imaging tecnhique for estimating the degree of carotid artery stenosis as well as measuring the intima-media thickness and aiding in the characterization of the plaque morphology.

Carotid artery stenosis is an important risk factor for ischemic events, accounting for 10-20% of strokes or transient ischemic attacks (TIA) [27]. The standard CDU combines grayscale B-mode imaging along with Colour Doppler and pulsed wave Doppler imaging. The degree of stenosis is measured by evaluating the waveform at the narrowest site of the lumen. Recommended measurements include the peak-systolic (PSV) and end-diastolic velocity (EDV) at the distal part of the common carotid artery (CCA) and the internal carotid artery (ICA) [28]. Many criteria have been used for the evaluation of the degree of the ICA stenosis. The most widely applied are those of The Society of Radiologists in Ultrasound (SRU) which are shown in Table 3 [28].

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Degree of Stenosis (%)	Primary Parameters		Additional Parameters	
	ICA PSV (cm/sec)	Plaque Estimate (%)*	ICA/CCA PSV Ratio	ICA EDV (cm/sec)
Normal	<125	None	<2.0	<40
<50	<125	<50	<2.0	<40
50–69	125–230	≥50	2.0–4.0	40–100
≥70 but less than near occlusion	>230	≥50	>4.0	>100
Near occlusion	High, low, or undetectable	Visible	Variable	Variable
Total occlusion	Undetectable	Visible, no detectable lumen	Not applicable	Not applicable

* Plaque estimate (diameter reduction) with gray-scale and color Doppler US.

Table 3. Πηγή: SRU- criteria for estimating the degree of ICA stenosis [28]

Intima-media thickness (IMT), which is measured on grayscale B-mode ultrasound, has been established as a biomarker for atherosclerosis. IMT should be measured at the distal part of the CCA, in a segment without a focal lesion [29]. A measurement >1mm is taken as abnormal.

A carotid artery plaque is defined as a focal thickening of the vessel wall that extends into the lumen >1,5mm or has a thickness exceeding the surrounding IMT by >50% [30]. The characteristics of the plaque including the echogenicity, location, thickness, surface and the presence of ulceration or possible stenosis are crucial for predicting upcoming cardiovascular events [29]. The plaque echodensity can be classified from 1 to 4, from echolucent to almost entirely echolucent, almost entirely echogenic and echogenic [29]. Plaque echolucency is a strong marker of plaque instability. The plaque surface could be described as smooth, irregular or ulcerated. Patients with ulcerated carotid plaques carry a high risk for cerebrovascular events. Large plaque ulcerations can be demonstrated as craters inside the plaque with reversed or stagnated flow. However, CDU has a low sensitivity for the identification of carotid plaque ulceration while it can also be operator dependent. The diagnostic accuracy of CDU ranges from 30 to 80% when compared to histopathological specimens [31].

Materials and Methods

2.1 Search strategy

This systematic review included reports regarding the use of CEUS in the assessment of carotid artery pathology. Data were collected from the literature data base PubMed. The

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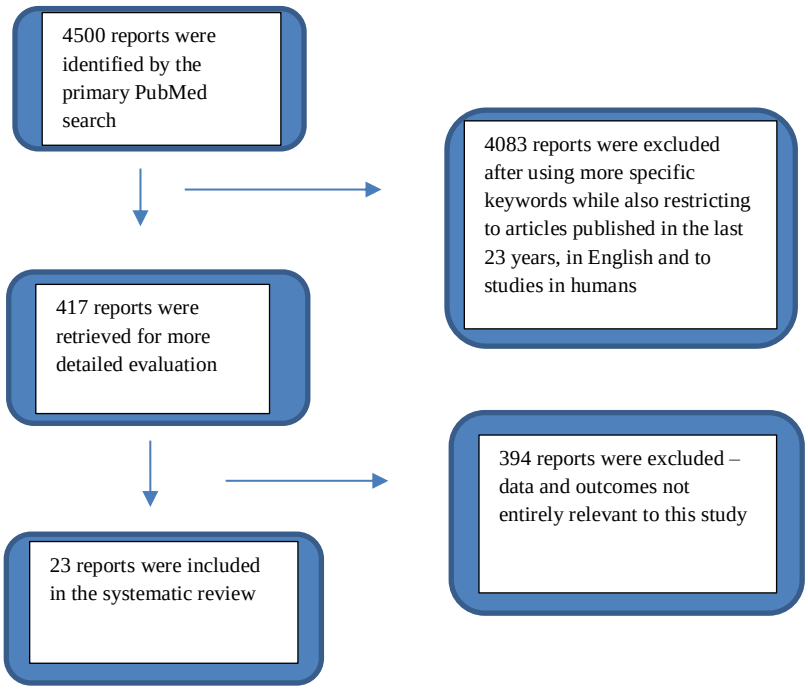
keywords ultrasound contrast agents, carotid system, carotid plaques, Intima-media thickness, contrast-enhanced ultrasound, CEUS, carotid, atherosclerosis, occlusion and stenosis, as well as combinations of the above, were used as appropriate. The search was limited to articles published in English and to studies examining humans.

Results

3.1 Study selection

Searching PubMed with the aforementioned key-words yielded numerous records (up to 4500). A more specific search was conducted using the keywords that were more closely associated with the title of the thesis while also restricting to articles published in the last 23 years, in English and to studies in humans. For example, using the key-words 'contrast-enhanced ultrasound' and 'carotid'. This time searching PubMed yielded 417 results, published in the last 23 years. Abstracts were reviewed in order to detect relevant information which were then examined in detail in the full-text. References of the papers were assessed in order to find further studies in the literature. After elimination of all articles not entirely relevant to the topic of our search, the final selection included 23 articles found to be closely related to the applications of CEUS in the carotid system (Figure 1).

Figure 1. Flowchart demonstrating the pathway that was followed for the selection of the final reports.



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3.1.1 Results of studies included

Through this review of the literature, articles about the applications of contrast-enhanced ultrasound in the carotid system over the last decade were reviewed. The majority of the published articles in the field of the applications of CEUS in the carotid system were about atherosclerotic plaque and intraplaque neovascularization as well as carotid artery stenosis. There was also as significant number of studies investigating the role of CEUS in differentiating between occlusion and pre-occlusion stenosis of the carotid artery. A smaller number of articles discussed the application of CEUS in evaluating disease activity in Takayasu disease as well as identifying carotid artery dissection. One published article about the role of CEUS in the follow-up of carotid stenting and endartectomy was included in the study. The results are demonstrated in table 4.

Table 4. Summary of the selected articles on the applications of CEUS in the carotid system.

Author(year)	Study subject	No. of patients	Population/inclusion criteria	Results/Conclusion
J M Baud (2020) [32]	Carotid plaque instability	33	Stroke<10days, carotid plaque thickness ≥2,5mm	Contrast enhancement of the carotid plaque ipsilateral to a recent ischemic event in 34% of patients
Clevert DA (2011) [33]	Carotid plaque instability	33	Patients with carotid atherosclerotic plaques	CEUS allows the dynamic evaluation of neovascularization within carotid plaques
Kono Y (2004) [34]	Degree of carotid artery stenosis	20	ICA stenosis ≥70%	CEUS provides accurate depiction of carotid stenoses, plaques and ulcerations
A Holden (2000) [35]	Degree of carotid artery stenosis	28	Patients with equivocal carotid duplex ultrasound	CEUS improved diagnostic confidence in equivocal carotid ultrasound exams

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CJ Hammond (2008) [36]	Degree of carotid artery stenosis	31	carotid occlusion on conventional ultrasound and with recent ipsilateral hemispheric TIAs	CEUS superior to 2D-TOF MRA in identifying carotid occlusion
Venture CA (2015) [37]	Degree of carotid artery stenosis	72	Suspected ICA occlusion	CEUS is as effective as DSA in differentiating between a total occlusion and a pre-occlusion stenosis of the ICA
Van den Oord SC (2013) [38]	Carotid plaque instability	69	Asymptomatic patients with heterozygous familial hypercholesterolemia	Quantification of intraplaque neovascularization with CEUS is feasible
Xiong Li (2009) [39]	Carotid plaque instability	104	At least one atherosclerotic plaque thicker than 2mm	Symptomatic patients had a stronger intraplaque enhancement than asymptomatic - CEUS can be used for plaque risk stratification
Ten Kate GL (2013) [40]	Carotid plaque instability	20	Symptomatic stenosis of ICA	CEUS is an effective method for identifying carotid plaque ulceration
Varetto G (2012) [41]	Carotid plaque instability	51	Patients with indication for internal carotid endarterectomy	CEUS is as significant tool for the stratification of carotid plaque instability
Macioch JE (2004) [42]	IMT measurement	26	Patients referred for standard carotid ultrasound	CEUS is superior to conventional ultrasound in estimating CCA IMT
HFJ Muller (2014) [43]	Intraplaque neovascularization	33	Symptomatic stenosis >50%, Asymptomatic stenosis >60%	Visual analysis of neo-vascularization with CEUS is accurate
Coli S (2008) [44]	Intraplaque neovascularization	32	At least 1 atherosclerotic carotid stenosis>30%	CEUS provides valuable findings for plaque risk stratification and for evaluating the response to the treatment of atherosclerosis
Y Zhou (2013) [45]	Intraplaque neovascularization	46	Carotid stenosis >50%	Intraplaque neovascularization detected with CEUS is associated with the presence

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				of microembolic signals -CEUS may detect high risk plaques
GL Faggioli (2011) [46]	Intraplaque neovascularization	22	Symptomatic or asymptomatic carotid artery stenosis >70%	CEUS can be used as a tool for identifying vulnerable plaques
Hoogi A (2011) [47]	Intraplaque neovascularization	27	Patients with indication for internal carotid endarterectomy	Quantification of intraplaque neovascularization detected with CEUS is a promising tool for assessing the vulnerability of the plaque
MF Giannoni (2009) [48]	Intraplaque neovascularization	77	Patients with indication for internal carotid endarterectomy	CEUS allows the detection of microvessels with neoangiogenesis within a carotid plaque
Owen DR (2010) [49]	Carotid plaque inflammation	37	Atherosclerotic plaque causing a stenosis >30%	Late-phase enhancement of the carotid plaque was higher in the symptomatic group of patients-CEUS can be used as a tool for identifying inflammation and for assessing risk stratification of carotid plaques
LY Ma (2019) [50]	Takayasu arteritis	84	Active Takayasu disease	CEUS can be used as an alternative tool in assessing disease activity in Takayasu patients
Magnomi M (2011) [51]	Takayasu arteritis	1	-	CEUS allows the detection of inflammation-driven hyperaemia and neovascularization, a marker of disease activity
AFL Schinkel (2014) [52]	Takayasu arteritis	7	Patients with established large-vessel vasculitis	CEUS improves the visualization of the lumen border and allows the evaluation of wall vascularization,

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				a potential marker of disease activity
Clevert DA (2011) [53]	Restenosis after carotid stenting	30	Follow-up after carotid artery stenting	CEUS is a valuable tool for detecting in-stent restenosis after carotid stenting
Li ZJ (2015) [54]	Carotid artery dissection	1	-	CEUS improves the sensitivity of conventional US in the detection of carotid dissection

3.2 The role of CEUS in the grading the degree of carotid stenosis

CDU is essential both for screening and diagnostic evaluation of carotid disease and it can be a great imaging method for demonstrating the blood flow inside the vessel and identifying segments with stenosis. However, its value is significantly limited by pitfalls which can lead to a misdiagnosis. Firstly, CDU can be insufficient in the assessment of low-velocity blood flow, particularly in cases of severe carotid stenosis [55]. Secondly, in cases of heterolateral carotid artery stenosis, the PSV can be falsely increased without an actual hemodynamically important stenosis [29]. Moreover, vessels with an oblique direction may demonstrate poor filling of the vascular lumen, due to the Doppler angle dependence [55]. Finally, the aliasing artefact which is related with pulse repetition frequency is another pitfall of CDU that lowers the quality of flow visualization [55].

The introduction of CEUS aims to overcome these limitations. Sirlin [56] and Kono [34] were among the first to explore the possible applications of CEUS in the asessment of carotid stenosis, proving that it can be superior to Color-Doppler in terms of accurately grading a stenosis. CEUS offers simultaneous depiction of the flow in the pre-, intra- and post-stenotic part of the lumen, even in elongated plaques and stenotic segments [57, 58]. This is also possible because the high-velocity and low-velocity flow areas are detected simultaneously without aliasing and blooming artefacts and without an angle dependence. CEUS has been proved to enhance and surpass the performance of CDU by accurately delineating the plaque surface and highlighting wall irregularities thus resulting in an accurate visualization of vessel stenosis (Figure 2).

Figure 2. (A) 69-year-old female patient with recent ischemic event. B-mode ultrasound reveals a significant ICA stenosis (yellow arrow) with soft plaque (white arrow. (B)

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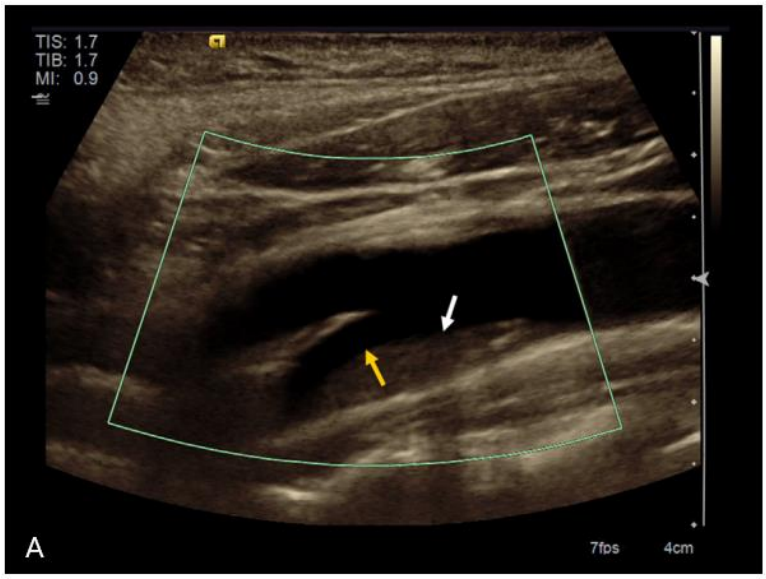
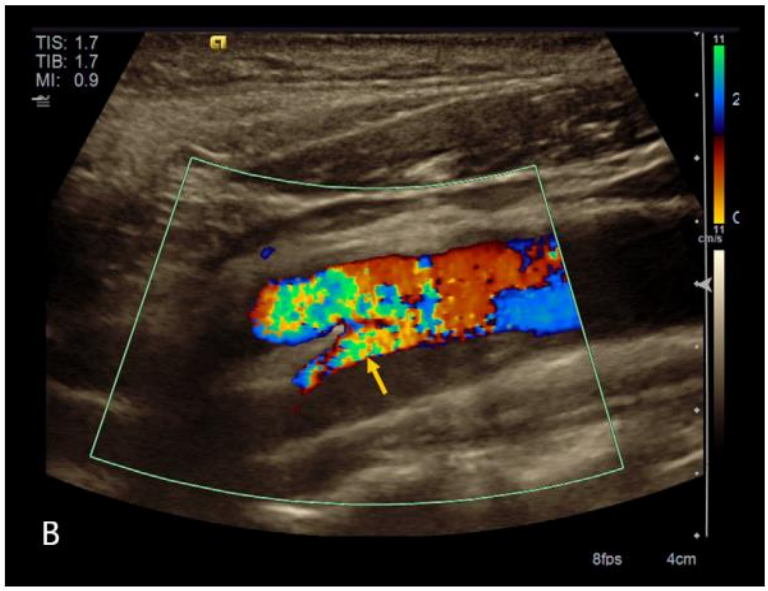
Colour Doppler Ultrasound demonstrates the high-grade stenosis of the ICA. However, the full extent of the stenotic segment is not clearly visualized. (C) CEUS visualizes the flow inside the stenosis (yellow arrow) without the aliasing artefact and clearly demonstrates the residual stenotic segment of the lumen as well as the extentof the stenosis and the plaque.





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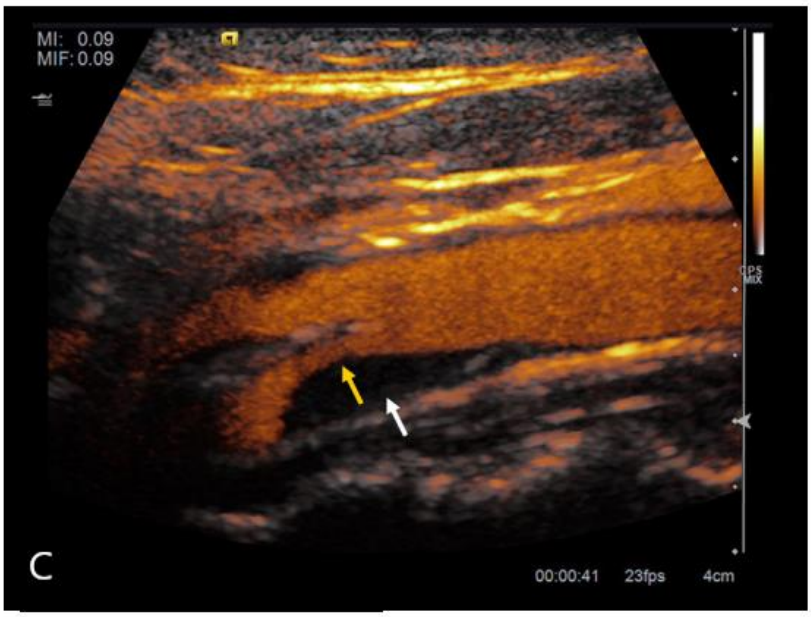

Πηγη: Clevert DA, Helck A, Paprottka PM, et al: Contrast-enhanced ultrasound imaging of the carotid artery. Radiologe 51 (6):483-489, 2011

3.2.1 Differential diagnosis of total occlusion and near-occlusive stenosis

ICA stenosis is the leading risk factor for ischemic strokes, with the risk dictated by the degree of the stenosis. Norris et al [59] demonstrated that patients with an asymptomatic carotid stenosis of <75% had an annual risk of 1,3% while patients with a stenosis more than 75% had an annual risk for TIAs and strokes combined of 10,5%. Although ICA stenosis is the main cause of ischemic episodes, total ICA occlusion rarely leads to ischemic events. Therefore, total ICA occlusion does not require intervention. On the other hand, high-grade stenosis of ICA should be treated surgically or interventionally order to prevent a possible embolization leading to an ischemic event [58]. Thus, differentiating a near-occlusion stenosis (at least 90%) of the ICA from a total ICA occlusion is crucial due to the different treatment pathways. Near occlusion of the ICA is a relatively rare clinical entity with an incidence ranging from 0,5% to 2% [60]. Digital subtractive angiography (DSA) is the gold standard for the evaluation of the degree of the stenosis of the ICA but it is an invasive method associated with post-procedure complications [55]. CTA and MRA are non-interventional methods that also offer an alternative pathway for the diagnosis of carotid occlusion. Colour Doppler Ultrasound is effective in grading the degree of the stenosis but it can lead to a misdiagnose in cases of near-occlusion ICA stenosis with a slow flow. CEUS has been proved to be accurate in differentiating between occlusion and near-occlusion of the ICA and has been proved even more sensitive than time-of-flight (TOF) MRI and equal to contrast-enhanced MRA. It has been concluded that CEUS can replace DSA in the assessment of cases with a suspected near-occlusion stenosis of the ICA [35, 36]. (Figure 3)

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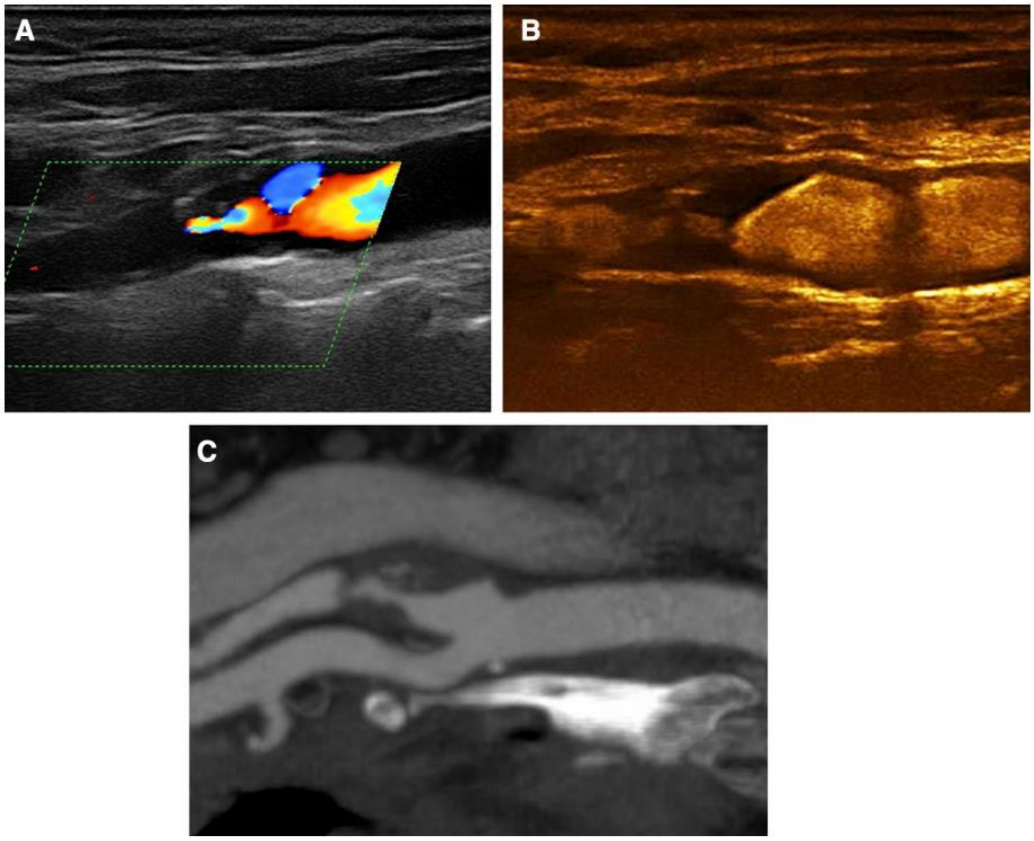
Figure 3. A 66-year-old male patient without any symptoms presented with an irregular ICA plaque. (A) Colour Doppler ultrasound demonstrated atherosclerotic lesions in the origin of ICA with absence of blood flow distally, arousing suspicion of total occlusion (B) CEUS depicted the presence of flow inside a segment with a high-grade stenosis due to plaques. (C) CTA revealed the same findings as CEUS.



Πηγη:Rafailidis V, Charitanti A, Tegos T, Destanis E, Chryssogonidis I. Contrast-enhanced ultrasound of the carotid system: a review of the current literature. J Ultrasound. 2017 Feb 9;20(2):97-109

3.3 Role of CEUS in characterizing carotid atherosclerotic plaques

As mentioned above, the most widely accepted predictor of the risk of an ischemic event is the degree of the carotid stenosis. Even so, it is becoming increasingly obvious over the last few years that additional factors besides the degree of the stenosis also correlate with the occurrence of stroke. Plaque morphology and composition have been considered to have a great impact on the pathogenesis of a stroke [61]. Atherosclerotic plaques may transform into unstable plaques, also characterized as ‘vulnerable’, which are more prone to rupture. These vulnerable plaques constitute a topic of great clinical significance, as numerous studies have demonstrated a strong association with the occurrence of neurological sequalae such as TIAs or cerebrovascular ischemic events. Due to inherent technical artefacts and limitations the accuracy of diagnosing unstable plaques by

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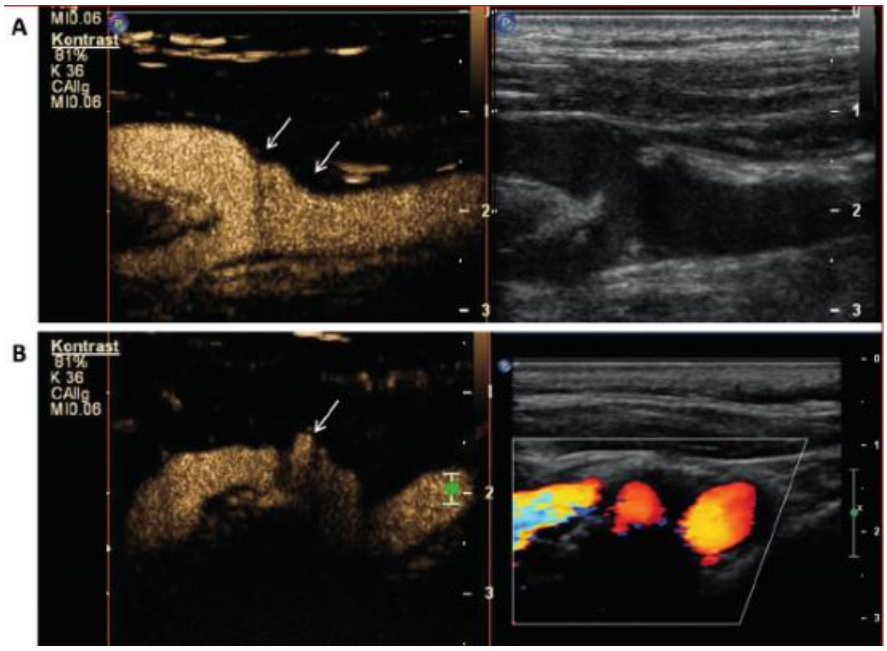
conventional ultrasound techniques may be occasionally limited. The introduction of CEUS during the last years has offered a solution to these limitations, yielding additional information compared to conventional ultrasound by allowing a better depiction of the luminal borders and a more precise delineation of plaque morphology and surface (Figure 4A). In a study by van den Oord et al [38] investigating asymptomatic patients with cardiovascular risk factors, it was revealed that CEUS accurately detected subclinical atherosclerosis by identifying plaques that were missed on CDU due to their low echogenicity. Intraplaque neovascularization, plaque ulceration and low echogenicity all contribute to the instability of the plaque [63, 64, 65]. Echolucent carotid artery plaques which represent a high content of lipids or an intraplaque hemorrhage have been correlated with an elevated risk of cerebrovascular disease, regardless of the degree of carotid stenosis [66].

Figure 4. CEUS allows for a better depiction of vessel wall irregularities. (A) Echolucent and echogenic plaques at the carotid bulb – the echolucent plaque is not identified as clearly on B-mode ultrasound (arrows) (B) CEUS revealing an ulcerated plaque (arrow) at the origin of the ICA that was not depicted on Colour Doppler Ultrasound.



Πηγη: Staub D, Partovi S, Imfeld S, Uthoff H, Baldi T, Aschwanden M, Jaeger K. Novel applications of contrast-enhanced ultrasound imaging in vascular medicine. Vasa. 2013 Jan;42(1):17-31.

3.3.1 Carotid plaque ulceration

Numerous imaging methods have been developed for the detection patient with carotid plaques that are in a risk of rupture. Early detection of these patient could prevent clinical complications such as TIAs and stroke. Plaque ulceration has been strongly associated

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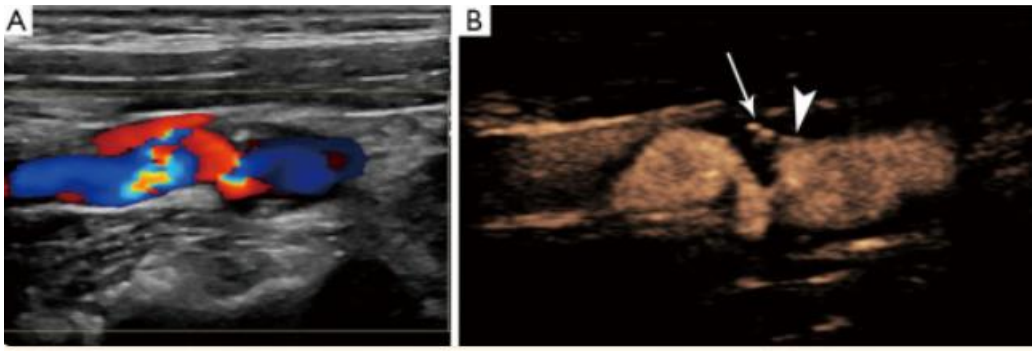
with atherosclerotic events. B-mode and Colour Doppler ultrasound have a high specificity but lack sensitivity for the detection of ulcerated plaques. Several studies have proved the superiority of CEUS compared to CDU for the identification of plaque ulceration [55, 40]. Ulceration constitutes the most dangerous plaque surface irregularity and it is defined as focal gap in the border between the plaque and the lumen that is at least 1mm or 2mm in depth according to different studies [40, 67]. Each ulcer is characterized by a neck and base that differ in their dimensions and shape [68]. The first criteria for the diagnosis of an ulcerated plaque, introduced by De Bray et al [69], defined it as a cavity ≥2 mm in depth and length with a clearly delineated posterior wall on grey-scale ultrasound and a reversed internal flow on Colour-Doppler. In 2012 Muraki et al [70] published new, more straightforward criteria that defined an ulcer as a gap located on the plaque surface that has a lower echogenicity compared to the adjacent intima border of the plaque on B-mode ultrasound. On CEUS a criterion that is used widely for the definition of an ulcer requires the discontinuation of the plaque lumen border for no less than 1x1mm [40] (Figure 4B), (Figure 5).

Figure 5. An asymptomatic 63-year-old female with a plaque ulceration in the origin of the ICA. (A) Colour Doppler Ultrasound reveals an echogenic plaque in the origin of the ICA. However, the exact borders of the plaque cannot be detected due to overwriting artifact. (B) CEUS clearly depicts an ulceration within the plaque (arrowhead) while also allowing for a better visualization of the stenosis. Note that calcifications (arrow) should not be confused with intraplaque enhancement of ulcers.



Πηγή: Rafailidis V, Li X, Sidhu PS, Partovi S, Staub D. Contrast imaging ultrasound for the detection and characterization of carotid vulnerable plaque. Cardiovasc DiagnTher. 2020 Aug;10(4):965-981

3.3.2 Carotid plaque enhancement and intraplaque neovascularization

Several histopathological reports have shown that the presence of intraplaque neovessels and inflammation both contribute to plaque instability [71, 72]. In comparison to normal micro-vessels, newly formed vasa vasorum often lack the essential pericytes that provide stability making them fragile and more prone to intraplaque hemorrhage [40]. Intraplaque hemorrhage may further destabilize an already vulnerable plaque increasing the risk of rupture. Moreover, inflammatory cells and lipids can penetrate their wall due to the wider

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gap junctions of the neo-vessels, leading to plaque enlargement [40]. Furthermore, macrophages release metalloproteinases such as MMP-9, that damage the connecting fibrous tissue, thus further encouraging the growth of these aberrant vasa-vasorum [73]. Therefore, intraplaque neovascularization constitutes a major feature of instability and has become an important target for the evaluation of plaque vulnerability.

CT and MRI have been used for the detection of the intraplaque vascularization but with poor outcomes [40, 74]. The role of CEUS in the evaluation of intraplaque microvasculature evaluation was first described by Feinstein in 2006, by presenting a case report demonstrating the detection of the neovessels with the use of CEUS [40]. Since then, multiple subsequent studies have investigated the possible correlation of ultrasound contrast enhancement with the presence and degree of intraplaque neovascularization. The intraplaque enhancement has been associated with histologically proven newly formed vasa vasorum after endarterectomy, with a correlation between the histological density of these aberrant neovessels and the degree of the enhancement [44]. In another study by Owen et al the usefulness of late enhancement (6 minutes after the intravenous administration) was investigated [49]. Owen et al concluded that the retention of contrast (late enhancement) in an atherosclerotic plaque may represent intraplaque inflammation (Figure 6). Furthermore, various studies have shown that ultrasound contrast enhancement and therefore intraplaque neovascularization is elevated inside echolucent or heterogeneous plaques when compared to echogenic or calcified, in accordance with the increased instability of hypoechoic plaques (44,39). Overall, CEUS is a readily available imaging tool that can provide crucial information about the vulnerability of atherosclerotic plaques by identifying ulcerations as well as intraplaque neovascularization.

Figure 6. Intraplaque neovascularization demonstrated with CEUS. A. B-mode ultrasound revealing atherosclerotic plaques in the bulb and the origin of the ICA - the distal plaque contains calcifications. B-D the arrowheads are demonstrating the shadowing due to the calcifications. B. Contrast enhancement within the plaque can be identified at 0,5sec prior to a high mechanical index flash in order to break down the contrast given. C. Image taken 1,5sec after the flash, showing the disappearance of the enhancement within the plaque. D. Image taken 6 seconds following the flash revealing retention of contrast within the plaque representing intraplaque neovascularization.

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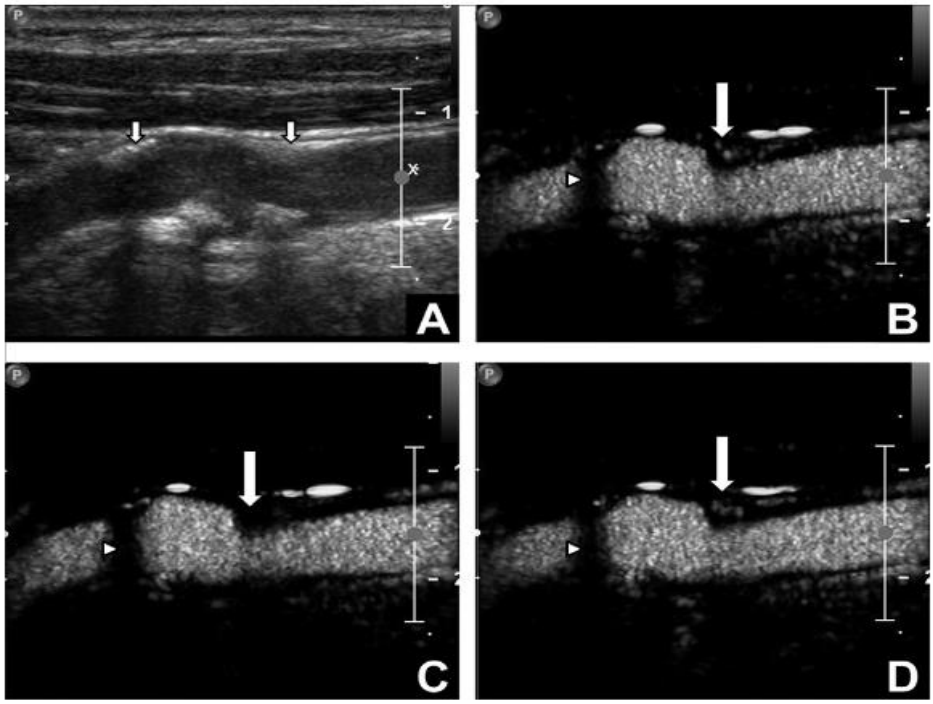

Πήγη: Ten Kate GL, van den Oord SC, Sijbrands EJ, van der Lugt A, de Jong N, Bosch JG, van der Steen AF, Schinkel AF. Current status and future developments of contrast-enhanced ultrasound of carotid atherosclerosis. J Vasc Surg. 2013 Feb;57(2):539-46.

3.4 Other uses of CEUS in the carotid system

3.4.1 Carotid dissection

Carotid artery dissection is an uncommon clinical entity with less than 3 cases per 100.000 patients every year [75]. However, it represents an important risk factor (15-20%) for stroke among young patients [75]. Carotid dissection can be either traumatic, iatrogenic or spontaneous and its clinical symptoms are often inconclusive mainly involving neurological symptoms depending on the affected brain territory. CDU may demonstrate the intramural hematoma and mobile intimal flaps that divide the vessel into a true and a false lumen. The blood flowing within the false lumen is slow thus leading to thrombus formation, occlusion or distal emboli [76]. B-mode ultrasound is the first-line imaging technique in the diagnostic work up of carotid dissection but it has a low sensitivity. MRI is considered the gold standard method for the diagnosis of carotid dissection. However, many patients may have contraindications for the above technique (i.e., pacemaker, old arthroplasty material or chronic renal disease). CEUS constitutes an alternative, readily available, imaging tool improving the diagnostic accuracy of CDU (Figure 7).

Figure 7. CCA dissection. A) CCA (white arrow) dissection and dissection membrane (red arrow) as demonstrated on gray-scale ultrasound. Colour (B) and power (C) doppler

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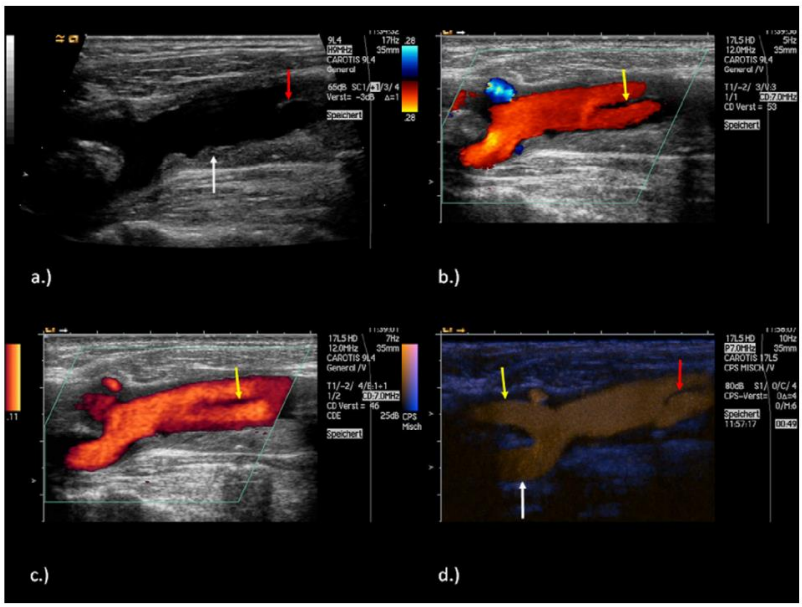
showing the true and the false lumen as well as the dissection membrane. (D) CEUS enabling better visualization of the vessel wall of the ICA(white arrow) and ECA (yellow arow) as well as the free floating, on-enhancing membrane that represents the intimal flap (red arrow).



Πηγή: Clevert DA, Sommer WH, Zengel P, Helck A, Reiser M. Imaging of carotid arterial diseases with contrast-enhanced ultrasound (CEUS). Eur J Radiol. 2011 Oct;80(1):68-76.

3.4.2 Follow up after stenting/endarterectomy

Patients undergoing endarterectomy (EA) or carotid artery stenting (CAS) for the treatment of carotid artery stenosis run the risk of restenosis. In particular, restenosis is estimated to occur in about 25% patients after endarterectomy and in 5% of patients after carotid artery stenting [76]. Several studies have demonstrated that CDU is a sufficient imaging technique for the surveillance of restenosis in patients with CAS. However, the various carotid stenosis criteria should not be used in patients with CAS, due to the fact that the arterial segment with the stent presents a significant elevation of the blood flow due to the different compliance between the stented and unstented part of the vessel wall [77]. The revised criteria for post CAS stenosis are demonstrated in Table 4. CEUS increases the sensitivity of CDU in the diagnosis of restenosis after EA or CAS, by offering a reduction of conventional US flow artefacts as well as better delineation of the whole length and morphology of the stenotic segment of the vessel [55] (Figure 8).

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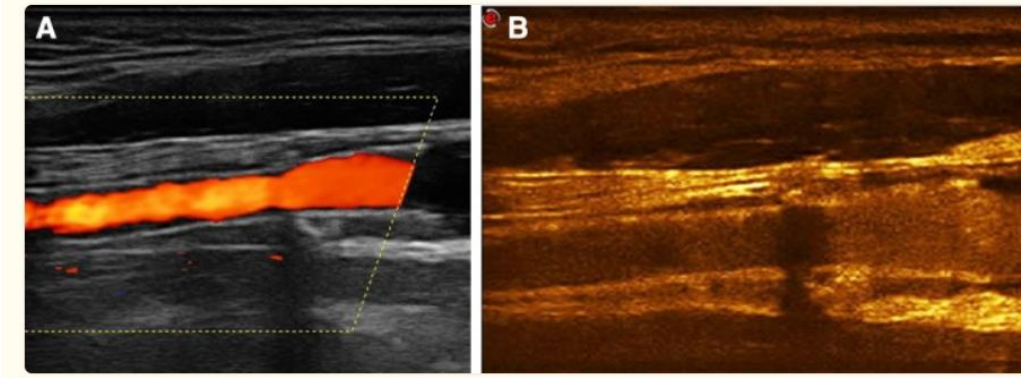
Modified velocity criteria for carotid stent stenosis.

Journal	Stenosis > 20%	Stenosis > 50%	Stenosis > 80%
J Vasc Surg 2008 Jan; 47 (1): 63–73	(PSV ≥ 150 cm/s and ICA/CCA ratio ≥ 2.15	PSV ≥ 220 cm/s and ICA/CCA ratio ≥ 2.7	PSV 340 cm/s and ICA/CCA ratio ≥ 4.15

Table 4. Modified criteria for post CAS stenosis. Πηγή: Swinnen J. Carotid duplex ultrasound after carotid stenting. Australas J Ultrasound Med. 2010 Aug;13(3):20-22.

Figure 8. A sixty-five year old male patient after CAS. (A)CDU demonstrates the patency of the stent although the inside of the stent is not entirely filled, probably due to restenosis or flow artefacts. (B) CEUS sharply demonstrating complete filling of the stent ruling out the possibility of restenosis.



Πηγή: Rafailidis V, Charitanti A, Tegos T, Destanis E, Chryssogonidis I. Contrast-enhanced ultrasound of the carotid system: a review of the current literature. J Ultrasound. 2017 Feb 9;20(2):97-109

3.4.3 Inflammatory conditions of the carotid artery system

Another application of CEUS in the carotid system includes the identification of inflammation of the carotid artery wall in patients with Takayasu arteritis (TA). TA is a granulomatous large vessel vasculitis, with a strong female predilection, that typically damages the aorta and its branches, as well as the renal arteries and the pulmonary artery. [78]. Typical pathological characteristics of TA include inflammation in the adventitia that moves to the intima and in the late stages completely surrounds the vessel resulting in concentric wall thickening leading to stenosis, thrombosis or aneurysm formation [79]. Clinical presentation may vary greatly depending on the degree of inflammation and the

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affected vessels. Due to the fact that biopsies in the large arteries are not easily performed, imaging techniques are crucial in order to provide the diagnosis in patients with a suspicion of TA. DSA used to be the gold standard imaging method but has been recently replaced by CTA and MRA, which both have a high sensitivity and specificity for the diagnosis of the disease, allowing the visualization of intramural inflammation [80]. Colour-Doppler ultrasound can also offer crucial information about the morphology of the arteries while it can also detect thrombosis or aneurysms, mainly in the carotid system [80]. The "macaroni sign" indicating the circumferential arterial wall thickening is highly specific for TA. Furthermore, some recent studies have demonstrated that CEUS can improve the quality of the visualization and the definition of the borders of the wall thickening. Contrast-images can clearly demonstrate the presence of contrast enhancement, indicating vascularization, within the affected arterial wall a potential market for disease activity [51, 52].

Discussion – Future Developments

CDU is the primary radiological technique for patients with suspected carotid arterial diseases. It provides a sufficient visualization of the carotid arteries but it is restricted due to low temporal or spatial resolution, angle dependency and vulnerability to artifacts. CEUS constitutes a safe, non-invasive, fast and valuable tool in the field of vascular pathology. The diagnostic and therapeutic applications of CEUS imaging have been growing rapidly, especially in the field of extracranial carotid arterial pathology. The use of USCA tends to increase the sensitivity of CDU, by overcoming its disadvantages and improving the visualization of the lumen borders, the plaque morphology and the blood flow within the vessel.

One of the most fascinating fields of application of CEUS is the study of the carotid atherosclerotic plaques and specifically the intraplaque neovascularization which has been associated with neurological symptoms. CEUS provided a novel method for the evaluation of intraplaque neovascularization which can be helpful in assessing risk stratification for future cerebrovascular events. Moreover, ultrasound contrast enhancement may indicate not only an elevated vascular density within the plaque but also a loss of vascular integrity which can be caused due to intraplaque hemorrhage, another significator factor of plaque instability. Furthermore, an important number of studies have showed that CEUS is superior to CDU in accurately grading stenosis, detecting vessel wall irregularities and differentiating occlusion from highly stenotic plaques. CEUS can also enable the detection of carotid artery dissection while also it can be used in order to identify carotid wall inflammation in patients with vasculitis. Following up patients after carotid intervention is a promising filed of CEUS in need for

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further research. Additionally, CEUS can be used as an effective alternative imaging technique in patients with a contraindication for the use of CT or MRI.

Nonetheless, CEUS also has some limitations. Firstly, it is a strongly operator dependent modality. Moreover, calcified plaques that create and acoustic shadow may not allow the complete visualization of the lumen and the plaques as with the conventional ultrasound techniques. Finally, due to the time limitation, it sometimes requires multiple administrations of contrast in order to establish the diagnosis.

On top of its diagnostic applications, CEUS is currently being investigated for its potential therapeutic uses. Recent advances in CEUS include the addition of ligands with a specific target to the contrast microbubbles so that the contrast concentrates on the area of interest, a technique that can be particularly useful in the delivery chemotherapeutic drugs [81]. It is also possible to place drugs or DNA plasmids within the microbubbles in order to be administered directly to a specific area of the body. This use may also extend to thrombolytic therapies by using microbubble thrombolysis with ultrasound waves [81]. Future research and application of this technology will undoubtedly uncover many more advantages and uses for the treatment of a variety of clinical conditions.

Conclusion

In conclusion, CDU remains the first-line imaging modality for the evaluation of carotid artery diseases, based on its diagnostic value, low cost and wide availability. CEUS constitutes a recent technological development and a complementary imaging technique improving the diagnostic of accuracy of conventional ultrasound. It offers better visualization of blood flow inside the lumen without artefacts. It can sharply delineate atherosclerotic plaques, even elongated, while also identifying plaque ulceration and echolucent plaques which can be easily missed with CDU. It can also be used as an alternative imaging technique with a high accuracy for differentiating occlusion and near-occlusion of the ICA while it can also be used for the detection of possible restenosis after carotid angioplasty. Finally, it can be used to visualize and grade intraplaque neovascularization, inflammation of the carotid artery wall and carotid artery dissection. The application of CEUS in the everyday clinical practice is constantly developing and it is expected that its use will be expanded even further in the near future.

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