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New Ultrasound Methods of Carotid Artery Atherosclerotic Plaque Vulnerability Assessment

In this review, we analyzed the main methods of ultrasound assessment of the atherosclerotic plaque vulnerability.

V tomto review sme analyzovali moderné metódy ultrazvukového hodnotenia nestability aterosklerotického platu.

Abstract
Cievna mozgová príhoda je treťou najčastejšou príčinou smrti a najčastejšou príčinou zdravotného postihnutia pacientov na celom svete. Avšak aj pri dôkladnom diagnostickom vyšetrení je až 30% prípadov klasifikovaných ako cievna mozgová príhoda neznámej etiológie. Tradične je stupeň stenózy karotických tepien hlavným rizikovým faktorom pre ďalšie komplikácie. Veľké množstvo štúdií ukazuje, že morfologické charakteristiky aterosklerotického platu môžu byť významným prediktorom nepriaznivých výsledkov v budúcnosti. V tomto review sme hodnotili moderné metódy ultrazvukového hodnotenia nestability aterosklerotického plátu. Pri opise aterosklerózy karotických tepien je potrebné komplexné posúdenie morfológie a štruktúry aterosklerotického plátu a použitie moderných klasifikácií, ktoré uľahčí komunikáciu medzi lekármi a umožní im porovnávať údaje získané pomocou rôznych vizualizačných techník.
Kľúčové slová: karotická ateroskleróza, ultrazvuk, nestabilný aterosklerotický plát, cievna mozgová príhoda.

Abstract
Stroke is the third leading cause of death and the most common cause of disability worldwide. However, even with a thorough diagnostic examination, up to 30% of stroke cases are classified as strokes of unknown cause. Traditionally, the degree of stenosis, assessed by ultrasound diagnosis, has been the main risk factor for further complications. However, a large number of studies show that the morphological characteristics of atherosclerotic plaque may be a more significant predictor of adverse outcomes in the future. In this review, we will look at the main methods of ultrasound assessment of the vulnerability of atherosclerotic plaque. When describing atherosclerosis of the carotid arteries, a comprehensive assessment of the morphology and structure of the atherosclerotic plaque is necessary. The use of modern classifications will facilitate communication between doctors and allow them to compare data obtained using various research methods.
Keywords: carotid atherosclerosis, ultrasound, vulnerability plaque, stroke.

Introduction

Stroke is the third leading cause of death and the most common cause of disability worldwide. (**1**) According to Trial of Org 10172 in Acute Stroke Treatment (TOAST), its five main subtypes are distinguished: large artery atherosclerosis, cardioembolism, small artery occlusion, a stroke of other determined cause (hyperhomocysteinemia, thrombophilia, cerebral artery dissection, Fabry disease), and stroke of undetermined cause. (**2**) However, even with a thorough diagnostic examination, up to 30% of stroke cases are classified as a stroke of undetermined cause, that is, the probable cause was not found, or the patient with two or more potential causes of stroke, which impeded the final diagnosis (for example, a patient with atrial fibrillation and 50% ipsilateral carotid artery stenosis). As a result, these patients are left without special treatment. (**3**) Suppose an ischemic stroke occurred as a result of large artery atherosclerosis when an ipsilateral atherosclerotic plaque narrowing the arterial lumen by more than 50% was detected. In that case, early diagnosis and timely treatment of carotid atherosclerosis can prevent a recurring stroke. (**2**) The main indications for carotid artery intervention are based on the neurological status and degree of carotid artery stenosis. However, it is becoming increasingly clear that the degree of lumen stenosis is not the best indicator for assessing stroke risk, while plaque morphology plays a more important role. Consequently, research in carotid artery atherosclerosis imaging focuses on identifying characteristics that will help identify vulnerable atherosclerotic plaque. Based on histopathological studies, the following components were recognized as critical structural features of vulnerable plaque: thin/ruptured fibrous cap (TRFC), lipid-rich necrotic core (LRNC), intraplaque hemorrhage (IPH) or thrombus, and intraplaque neovascularization (IPN). (**1**) For example, in the meta-analysis of Rizvi et al., 2020 IPH, LRNC, and TRFC detected on Magnetic Resonance Imaging (MRI) correlated directly with an increased risk of ischemic complications in the future. (**4**) Thus, the main task facing various imaging methods is identifying patients at high risk of neurological complications and vulnerable plaques before they occur. (**5**) Plaque assessment in the carotid artery is of exceptional importance for preventing the occurrence and recurrence of ischemic cerebral circulation disorders. (**6**) This review aims to evaluate the main methods of ultrasound assessment of atherosclerotic vulnerable plaques.

Two-dimensional ultrasound (2D ultrasound.)

The primary method for assessing atherosclerotic plaques is 2D ultrasound, a fast, cheap, and reproducible method used to estimate the degree of plaque stenosis and morphology, its echogenicity, and thickness of the intimate media (TIM) assessment. (**7**). To create a universal description of the plaque structure and in order to compare the results of different research methods, two scale stratifications are used: Plauqe-RADS (JACC Cardiovasc Imaging 2024) and GRADE (Recommendations for the Assessment of Carotid Arterial Plaque by Ultrasound for the Characterization of Atherosclerosis and Evaluation of Cardiovascular Risk: From the American Society of Echocardiography). As it is known, an anechoic plaque on ultrasound is considered vulnerable, and its anechoic center is an LRNC or IPH. For example, the study by Anna Kopczak et al. 2022, examined the contribution of complicated (type VI plaque, according to the American Heart Association, according to MRI, which corresponds to an anechoic plaque on ultrasound) non-stenotic plaques in the carotid arteries to the development of stroke of undetermined cause. According to the results of the study, in patients with stroke of undetermined cause, the prevalence of vulnerable atherosclerotic plaques was significantly higher on the ipsilateral side of the lesion compared with the contralateral side. Moreover, the prevalence of ipsilateral vulnerable plaque was significantly higher in patients with stroke of undetermined cause compared to cardioembolism. At the same time, when comparing stroke causes of undetermined cause with strokes caused by large artery atherosclerosis, a lower level of vulnerable plaque was seen in the latter. The most common sign of a vulnerable plaque was an intraplaque hemorrhage. (**3**) It is worth noting that in women, the presence of intraplaque hemorrhage is associated with the occurrence of cardiovascular diseases within the next 5 years; in men, such correlation was found only with the degree of stenosis. The disadvantages of ultrasound include operator dependency. (**8**). **Figure 1.**

The grayscale median method

The following contrast-free technique based on the degree of echogenicity of the plaque is the GSM (the grayscale median), which refers to the average value of all gray levels in pixels in the plaque. The software uses post-processing to map plaque pixels according to their degree of intensity, where black is located at the lower boundary of the gradient (GSM = 0) and white at the upper (GSM > 190), GSM < 30, is considered a sign of vulnerable plaque. (**9**) One of the disadvantages of this method is the difficulty of adjusting the image for further post-processing because it has to be normalized by the echogenicity of blood and adventitia. Statin treatment is believed to increase echogenicity, i.e., the GSM of plaques. However, no significant difference in GSM of carotid plaques was found upon examining patients who took statins and the ones with no treatment. (**10**) **Figure 2.**

Three-dimensional ultrasound (3D ultrasound.)

3D ultrasonography is a promising technique, although it is time-consuming and laborious. 3D visualization showed a significant correlation between atherosclerotic plaque volume and histological samples after carotid endarterectomy (CEA). However, the validity of using three-dimensional sonography for assessing hemodynamically insignificant stenoses is still argued. Plaques with less than 50% stenosis cannot be compared with histological samples. Beatriz Lopez-Melgar et al. conducted a study in 2022 to examine non-hemodynamically significant plaques. The experimental model created used histological samples from a pig's carotid and femoral arteries. As a result, a statistically significant correlation with three-dimensional ultrasonography was found. (**11,12**) In addition, in assessing plaque morphology, 3D ultrasound showed better results than 2D ultrasound and was comparable to computed tomography angiography (CTA) and contrast-enhanced MRI. Three-dimensional ultrasound with contrast enhancement had a higher diagnostic accuracy in assessing the degree of stenosis compared with CTA, which was used as the standard procedure before surgery. In assessing plaque vulnerability, the two methods were comparable. The disadvantages of three-dimensional sonography include the large size of the sensor and the need for special software. (**1**) **Figure 3.**

Shear wave elastography

Shear wave elastography (SWE) uses the power of acoustic radiation to generate shear wave propagation in tissues, which makes it possible to assess the stiffness of tissues by quantifying Young's modulus (a value characterizing the ability of an object to resist stretching and compression during elastic deformation). It is known that the plaque ruptures when the maximum stress in the fibrous cap exceeds a certain level; it can identify vulnerable plaques. In a study by M. Zamani et al. 2020, the average value of Young's modulus in unstable plaques was 29 kilopascals lower than in stable plaques. Shear wave elastography is less dependent on the operator and has better reproducibility than ultrasonic elastography methods based on tissue compression by the researcher. (**13**). Similar data was obtained in the Miao LI et al. study, 2019, in patients with atherosclerotic plaques in the carotid arteries. The study showed a significant negative correlation between the deformation rate over time and the degree of activity of the inflammatory process in the atherosclerotic plaque, which was assessed using positron emission tomography (PET). (**14**). **Figure 4**

Superb microvascular imaging

One more contrast–free technique based on hypersensitive Dopplerography, which can assess the presence of blood flow in unstable atherosclerotic plaques penetrated by small vessels with low blood flow velocity, is superb microvascular imaging (SMI). With conventional color Doppler mapping, wall motion artifacts are suppressed, which leads to the suppression of signals from small-diameter vessels with low velocity. SMI is a simple, safe, and non-invasive method that helps to visualize plaque neovascularization without a contrast agent. In addition, a positive correlation has been proven between SMI and contrast-enhanced ultrasound results. (**15**). The visualization of a hypoechoic plaque in the B-mode is limited by the low sensitivity of ultrasound due to anechogenicity. (**16**) However, stroke risk associated with the degree of visual assessment of plaque echogenicity during 2D sonography is insufficient for clinical practice implementation as 2D is unable to distinguish intraplaque hemorrhage from a lipid-rich necrotic nucleus, both of which, according to the Plaque-RADS classification, represent varying degrees of plaque vulnerability. (**5, 17**) Contrast-enhanced ultrasound (CEUS) provides a better understanding of plaque anatomy, including its ulceration, and enables the evaluation of neovascularization. The degree of neovascularization in the plaque correlates with the intensity of contrast agent accumulation. (**1**) In a study conducted by N.K. Jain et al., in 2022, a statistically significant association was found between symptoms of cerebral vascular ischemia and plaque hyperechogenicity during contrast-enhanced ultrasound. Before carotid endarterectomy (CEA), patients underwent CEUS, and the results were compared with those from MRI and histological examinations. In asymptomatic patients who underwent elective CEA, contrast ultrasound showed minimal contrast agent accumulation. At the same time, plaques in patients with neurological symptoms exhibited a more pronounced accumulation of the contrast agent. Additionally, the presence and degree of neovascularization correlated with the findings from histopathological studies. (**5**) Similar findings were reported in a study by Rie Motoyama et al. in 2019, which used magnetic resonance imaging to analyze plaques. Plaques that exhibited intraplaque hemorrhage were categorized as vulnerable atherosclerotic plaques. Significant neovascularization was observed in a group of asymptomatic patients during the contrast ultrasound examination. Subsequently, histological analysis classified these atherosclerotic plaques as having extensive neovascularization. The authors noted that MRI could not identify all vulnerable plaques, as some plaques with a lipid-rich necrotic core may appear iso- or hypointense and could be indistinguishable from nonvulnerable plaques. This limitation may result in an underestimation of their vulnerability. (**18**) **Figure 5.**

Contrast-enhanced ultrasound with subharmonic micro-bubble signals (SHAPE)

Contrast-enhanced ultrasound is based on the nonlinear vibration of contrast microbubbles. When exposed to ultrasound, these microbubbles vibrate non-linearly, generating subharmonic vibrations. There is an inverse relationship between the amplitude of these subharmonics and the blood flow pressure. When the internal stress within a plaque exceeds the resistance of its fibrous cap, the cap may rupture. (**6**) An optimization algorithm is activated during the infusion of an ultrasonic contrast agent. Following this calibration, the subharmonic microbubble signals (SHAPE) exhibit the highest sensitivity to pressure changes and can be used for non-invasive quantitative pressure assessment. (**19**). It is known that the components of a plaque can easily deform under the pressure of blood flow, resulting in an uneven distribution of pressure within the plaque. The subharmonic gradient across the entire plaque surface negatively correlates with the plaque's thickness and the degree of lumen stenosis. As the plaque thickens, the relative surface area increases, leading to an uneven and thinner fibrous cap, heightened neovascularization, and a greater degree of lumen stenosis. Concurrently, the kinetic energy from the blood flow further contributes to the instability of the fibrous cap. As a result, the load on the plaque significantly increases, making high-pressure areas more likely to rupture. The study by Rui Li et al. (2023) demonstrated through quantitative analysis of SHAPE that the subharmonic gradient within the plaque in the ischemic stroke group patients was higher than that in the control group. A threshold value of 3.95 dB was identified, with a specificity of approximately 77.27% and a sensitivity of about 66.67%. This threshold can be utilized for clinical monitoring of plaque development trends. However, it is important to note that in the SHAPE mode, the frequency used did not provide sufficient resolution to assess small plaques effectively. (**6**) **Figure 6.**

Using of artificial intelligent (AI)

Recognizing that ultrasound is an operator-dependent technique; artificial intelligence was employed to enhance the interpretation of results and mitigate this limitation. In the study by Yang Guang et al., 2021, the Xception artificial intelligence model, alongside experienced radiologists, manually analyzed contrast ultrasound films to diagnose and classify the vulnerabilities of carotid plaques. These assessments were then compared with histological findings. A significant innovation of this study was that, unlike previous work where artificial intelligence evaluated only static images, it utilized dynamic video as input data. By combining information from all frames, the AI could more effectively assess the vulnerability of carotid plaques. The results demonstrated that artificial intelligence performed well in evaluating plaque vulnerability. (**20**)

Aterosclerotic plaque changes

It is important to note the dynamic changes of atherosclerotic plaque. It is generally believed that a regression in the degree of stenosis indicates the stabilization of atherosclerotic plaques. Thus, in the study conducted by Faisal Khan et al. (2022), a controlled study over 36 months revealed some nuances. Despite a decrease in the percentage of stenosis, hypoechoic plaques retained their hypoechoicity, suggesting that the reduction in plaque size did not correlate with stabilization. Interestingly, size regression was more commonly observed in larger vulnerable plaques, specifically those identified as hypoechoic on sonography. In patients receiving statin therapy, the growth of carotid artery plaques was primarily attributed to hyperechoic plaques. It was associated with elevated plasma concentrations of stabilizing growth factors that stimulate growth through increased synthesis of fibrous material. In contrast, regression tends to occur mainly in larger plaques with a more vulnerable phenotype, linked to heightened expression of pro-inflammatory biomarkers and a lower concentration of growth factors that stabilize the plaque. (**10**). Notably, a separate study by Chen et al. (2021) observed a decrease in plaque volume in patients undergoing statin therapy compared to the control group not receiving statins, with reductions of +70 mm^3 versus +15 mm^3, respectively ($P < 0.05$). (**21**)

Discussion

Numerous studies have demonstrated that relying solely on the degree of carotid artery stenosis as the predictor of adverse events and subsequent management decisions is insufficient. A comprehensive assessment of atherosclerotic plaques is essential, particularly regarding their morphology and structure. Unfortunately, there is currently no single method for diagnosing vulnerable atherosclerotic plaques; thus, a combination of various imaging techniques is necessary. These techniques include ultrasound diagnostics, magnetic resonance imaging, and computed tomography. Many auxiliary ultrasound techniques require specialized, costly software or specific sonographic sensors, and they are not widespread among practitioners; instead, they are primarily employed in scientific research or large research centers. Consequently, 2D Doppler ultrasound can no longer be a sufficient method for diagnosing vulnerable atherosclerotic plaques. As previously mentioned, assessing the vulnerability of plaques is associated with several technical challenges, such as surface calcification, which creates echo interference during examinations and complicates assessment. Additionally, anechoic plaques can be challenging to detect using B-mode imaging, and managing hemodynamically insignificant vulnerable atherosclerotic plaques, which, as indicated by the literature, may be a hidden cause of strokes of undetermined cause, remains uncertain. From our point of view, superb microvascular imaging emerges as a promising technique for evaluating intraplaque neovascularization without the need for contrast agents; however, further research is required before it can be widely adopted in clinical practice. The recent development of Plaque-RADS 2024 by Saba et al. is a significant advancement, providing a standardized classification system that facilitates communication between ultrasound diagnosticians and clinicians while enabling the comparison of data obtained through various imaging modalities. Additionally, it has been established that plaques can transition between vulnerable and non-vulnerable states, highlighting the dynamic nature of atherosclerotic disease. The application of artificial intelligence as an adjunctive tool for interpreting imaging results also holds promise, though the process remains labor-intensive and requires expert oversight. Furthermore, while interventional therapies are currently guided by CT angiography and MRI findings, the literature suggests that sonography offers unique advantages in assessing plaque characteristics such as cap tension, mobility, and neovascularization—factors that are challenging to evaluate with other imaging techniques.

Conclusion

In conclusion, ultrasound techniques posses vast possibilities in identifying and evaluating carotid artery plaques. The ultrasound techniques mentioned above, together with AI modes, if available, should be considered in evaluating patients with stroke and in its prevention.

Conflict of interest statement: the author declares that there is no conflict of interest.

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Obrazová príloha

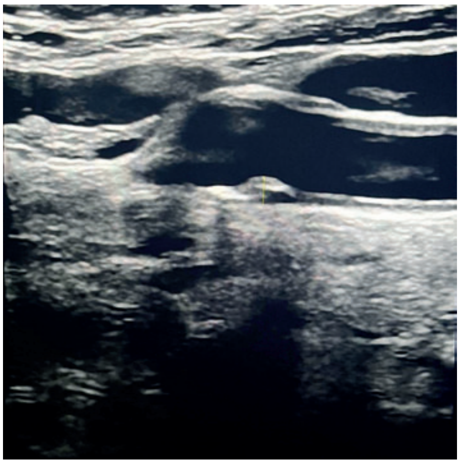

Figure 1. 2D methods of plaque assessment. Two-dimensional methods of quantifying arterial plaque in bifurcation common carotid artery. Anna Shevchenko. Nemocnica AGEL Bánovce

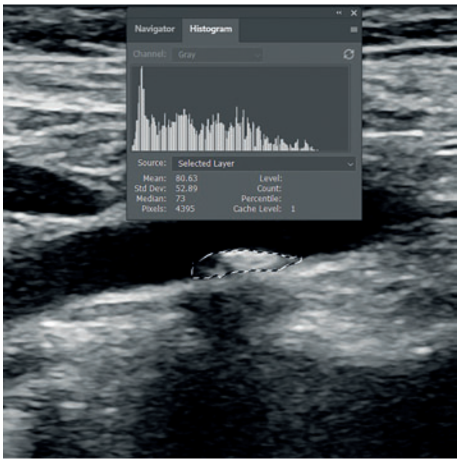

Figure 2. Selection and analysis of the histogram for the region of the atherosclerotic plaque, providing the grayscale median (**9**). (These images are used in accordance with the copyright statement and have been sourced from the public domain – This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.)

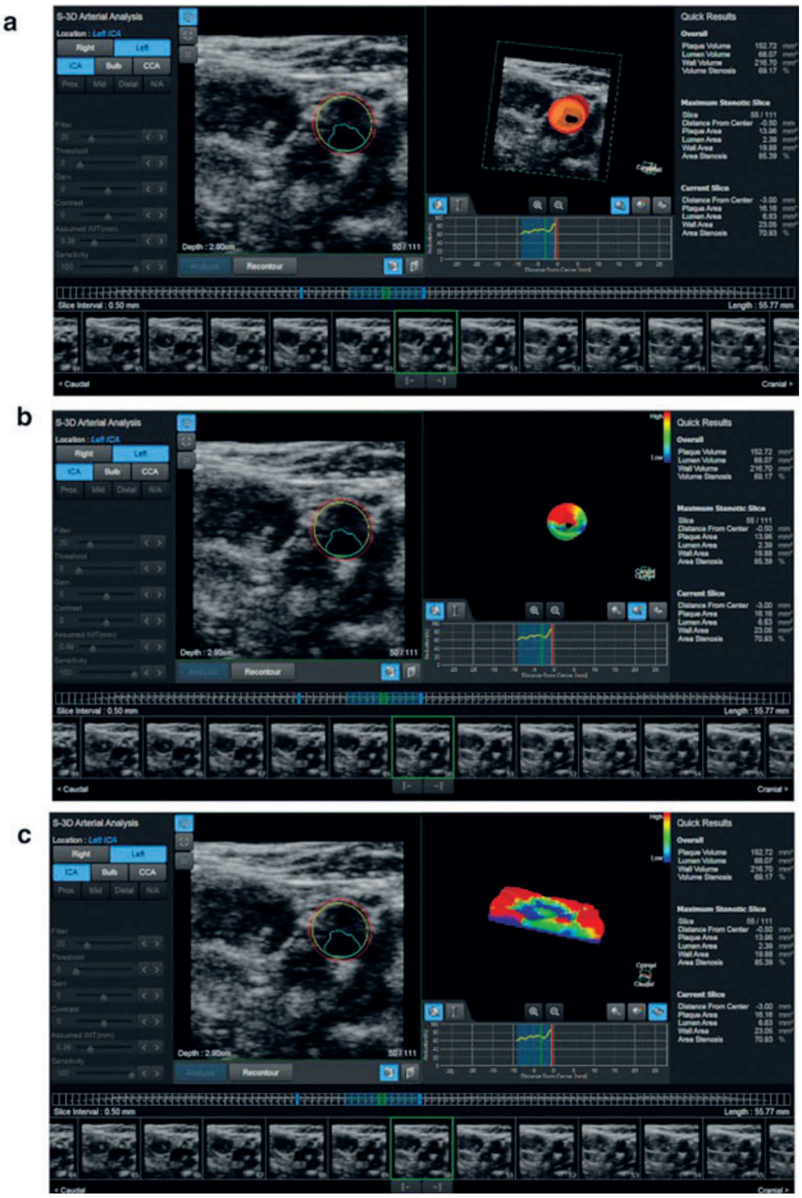

Figure 3. a 3D Arterial Analysis shows the mild/severe stenosis (69%) at left internal carotid artery in a volumetric evaluation. b 3D Arterial Analysis shows the plaque chromatic map according to the plaque vulnerability in a volumetric evaluation. The prevalence of the red areas indicates a soft and vulnerable plaque. c 3D Arterial Analysis shows the same plaque chromatic map in a superficial evaluation (**1**). (These images are used in accordance with the copyright statement and have been sourced from the public domain – This is an open access article distributed under the Creative Commons Attribution 4.0 International License.) (**1**)

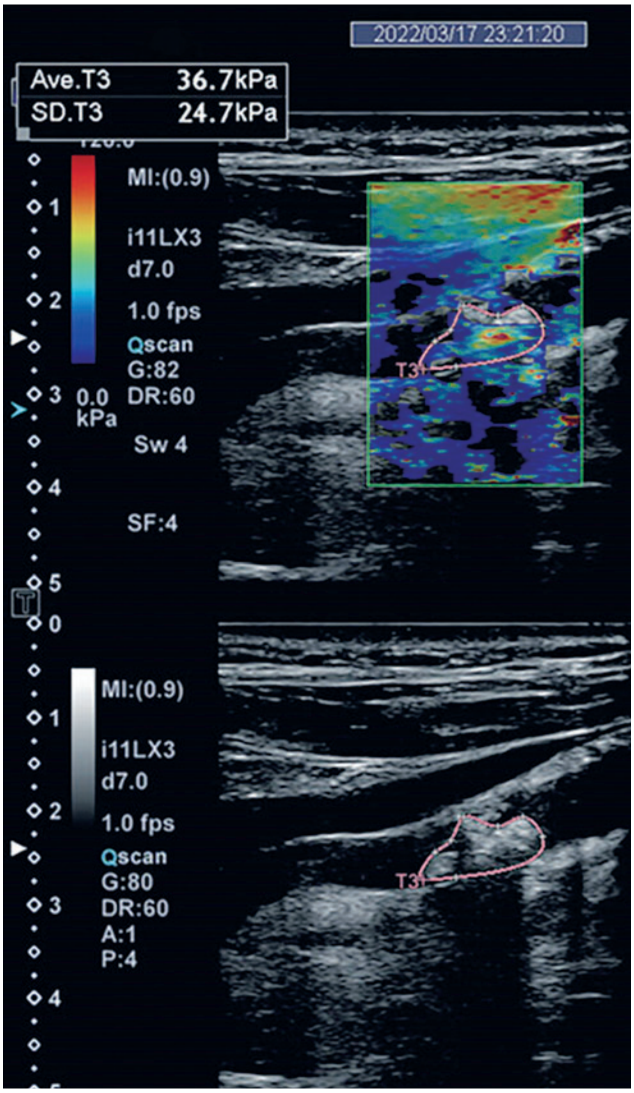

Figure 4. Shear Wave Elastography for the Assessment of Carotid Plaque Vulnerability (**22**).
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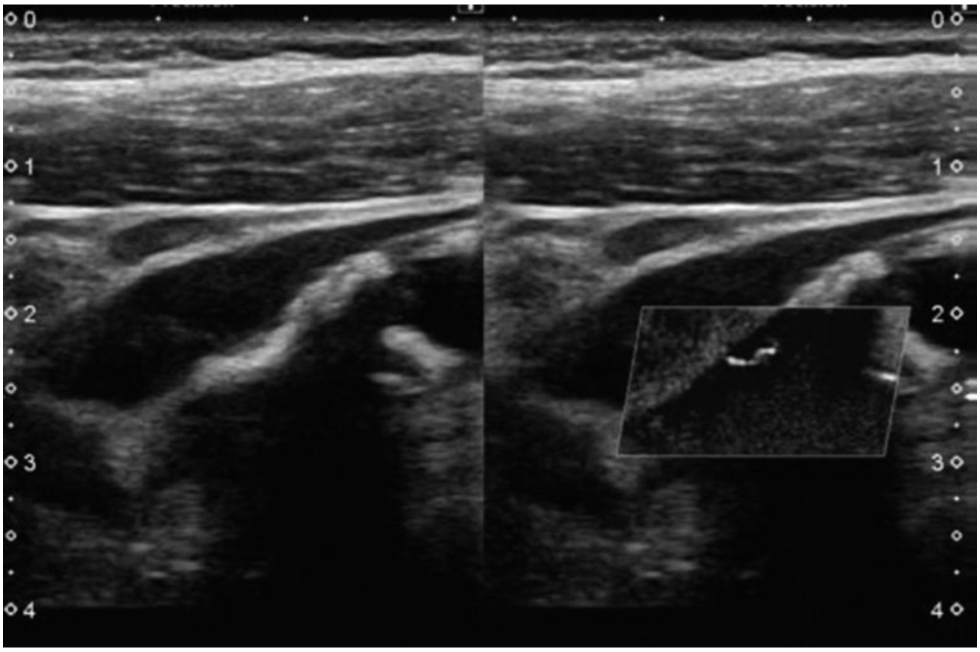

Figure 5. Neovascularization detected with SMI. Superb Microvascular Imaging (**23**). (with permission to use images – Nina Ondkova, INmed Slovakia s.r.o. official distributor of medical equipment Canon Medical System and Clarius Moblile Health)

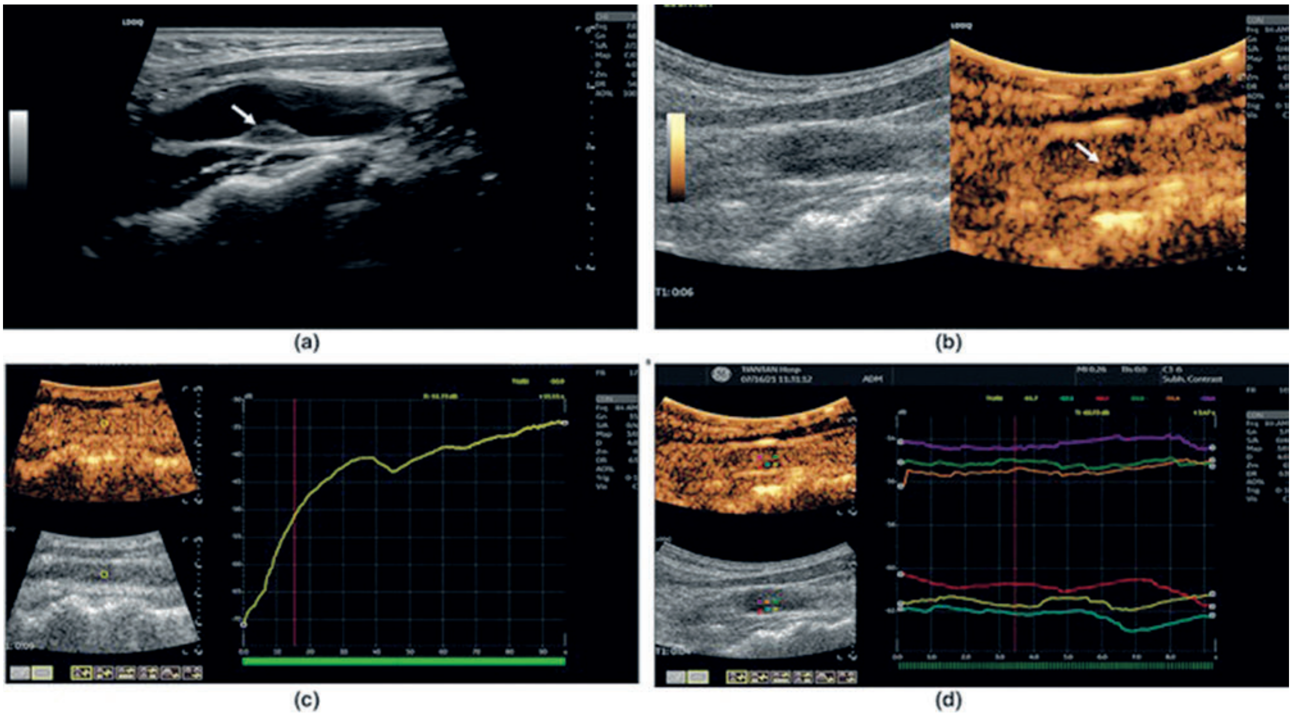

Figure 6. Routine US and SHAPE US Examination of atherosclerotic plaque. (a) 2D ultrasonography of carotid artery with atherosclerotic plaque, the white arrow indicates an isoechoic plaque; (b) CEUS of carotid artery with AS plaque, the white arrow indicates that the plaque can be clearly displayed in subharmonic mode. (c) The point (the intersection of red and yellow lines in the growth phase) was selected as the optimum mechanical index; (d) region of interest with 1 mm sampling frame were selected in the upstream shoulder, downstream shoulder, top section of atherosclerotic plaques, and the above three corresponding horizontal lumens of the plaque (**6**).