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The Efficacy of Emerging Ultrasound Applications in Characterizing Vulnerable Carotid Plaques

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Abstract

The emergence and integration of nonconventional ultrasound applications into the vascular diagnostic armamentarium offers the opportunity for answering a long-standing question about the morphological makeup of focal carotid atherosclerotic lesions, that is, is this particular plaque vulnerable or not? Vulnerable lesions are those which, based on their histological and morphological features, predispose a patient to an increased risk of a cerebral ischemic event (CIE) secondary to plaque or thrombus embolization. The ability to reliably differentiate plaque types using readily available noninvasive imaging methods facilitates risk stratification in both symptomatic and asymptomatic patients. Improved identification of at-risk lesions makes more targeted patient management and/or interventional decisions possible. Three emerging ultrasound applications that have demonstrated efficacy in offering this enhanced diagnostic capability are point shear wave elastography (pSWE), contrast-enhanced ultrasound (CEUS), and microvascular ultrasound imaging (MUI).

Keywords

Carotid pathology, contrast-enhanced ultrasound, microvascular ultrasound imaging, and point shear wave elastography

Emerging ultrasound applications share some characteristics with, but are distinct from, the general concept of emerging technologies (ETs). While there are differing definitions of what exactly an ET is, several generally accepted attributes are associated with this notion. Specifically, an ET is one that is radically novel, relatively fast growing, and possesses the potential to exert a considerable impact on its parent domain.[1] ETs are not necessarily new and are still considered emerging if they are not yet a "must-have."[2] An example in the medical sonography domain is color Doppler imaging (CDI). Several decades ago, when it was first introduced, CDI was a novel and optional sonographic application that was technologically captivating but had not yet proven its value in routine use. Today, CDI is a "must-have." It has become a standard of care technique in virtually all diagnostic medical sonography specialties.

Similarly, emerging applications do not necessarily represent new diagnostic capabilities. The specific techniques, or applications, provided in this symposium have been available and have proven clinically efficacious for, in some cases, decades. However, their integration and routine use in the evaluation of carotid plaques has lagged in their assimilation into other diagnostic protocols. Shear wave elastography (SWE) has a proven role in enhancing the detection and staging of liver fibrosis and in improving the specificity of an sonographic diagnosis of breast cancer.[3,4] Contrast-enhanced ultrasound (CEUS) is ubiquitously used, particularly in European and Asian medical practices, to characterize and differentiate innumerable pathological entities in virtually all sonographically accessible organ systems.[5] And, while relatively new to the pack, microvascular flow imaging (i.e., microvascular ultrasound imaging [MUI]) is proving its efficacy as a CEUS-equivalent in assessing the perfusional characteristics in a number of pathological entities.[6] The integration of these established imaging techniques to carotid plaque evaluation, then, is a reasonable progression in bringing them to "must-have" status within the sonographic armamentarium.

Determination of Plaque Vulnerability

Carotid atherosclerotic disease is responsible for approximately 20%–25% of all cerebral ischemic events (CIEs) in

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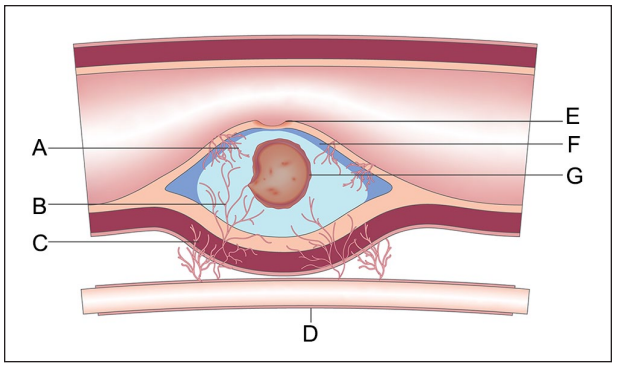

Figure 1. A diagram of vulnerable plaque with anatomical notations. (A) Neovessels—epithelial origin. (B) Neovessels—vasa vasorum origin. (C) Vasa vasorum. (D) Capillary. (E) Fibrotic cap fissure (plaque ulceration). (F) Thin fibrous cap. (G) Intraplaque hemorrhage.

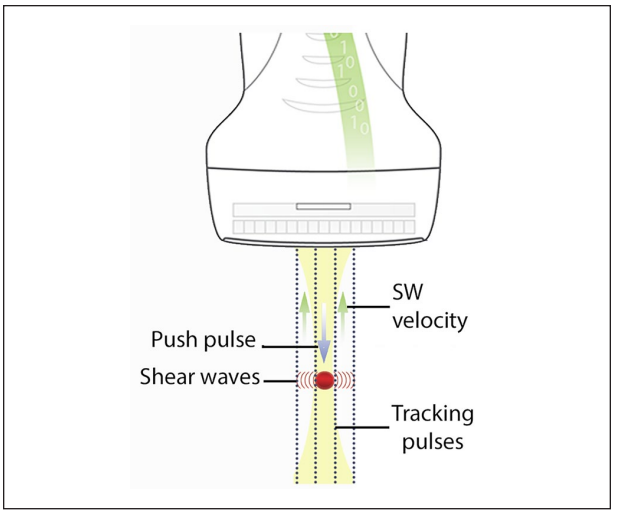

Figure 2. A diagram of shear wave ultrasound. An acoustic push pulse generates shear waves in an insonated region of soft tissue. Several tracking pulses measure the velocity of these transverse waves, which is used in calculating and quantifying tissue stiffness.

the United States.[7] These events result from reduction or cessation of perfusion to localized regions of the brain made manifest by neurological, typically stroke-like, symptoms. The passing and lodging of detritus arising from atherosclerotic lesions in the carotid bifurcation is the predominant etiology of focal cerebral ischemia. There is ample evidence in the medical literature that particular structural types of plaque are predictive of an increased risk of both cerebral and cardiac ischemic sequelae.[8,9] These plaques, termed "vulnerable" plaques, share distinct histological properties, which make them particularly amenable to differentiation using the three emerging sonographic applications highlighted in this article. These morphological attributes include surface disruptions (ulcerations), and an internal amalgamation of lipids, inflammatory cells, cellular debris, thrombus, and neovascularization all of which contribute to corresponding ultrasound findings[10-12] (see Figure 1). Characteristically, vulnerable plaques are "softer" and more highly vascularized than their fibrotic and calcified nonvulnerable counterparts. The relative softness of vulnerable plaques makes them amenable for evaluation with ultrasound SWE; their increased vascularization makes them ideally suited for imaging with both CEUS and MUI. In fact, identification of microvascularization within a plaque is pathognomonic for vulnerability.[13]

Shear Wave Elastography

Physics and instrumentation. Ultrasound elastography, in general, is a noninvasive method of evaluating the stiffness, or elastic properties, of a sampled tissue. SWE acquires elastographic data based on the combined use of a transmitted acoustic push pulse and an ultrafast imaging sequence capable of following in real-time the propagation of the resulting shear, or transverse, waves. The measured velocity of the shear waves is used to calculate tissue stiffness through a mathematical restatement of Young's modulus formula. The resulting values expressed in kilopascals (kPa) provide a metric of tissue stiffness (see Figure 2).

It is important to remember that there are two iterations of SWE capabilities available on most premium level ultrasound imaging platforms: two-dimensional SWE (2DSWE) and point SWE (pSWE). The former generates a 2D color-coded image representing relative stiffness values within the region of interest (ROI). 2DSWE is a semi-quantitative method and is not useful in characterizing vulnerable plaques. The latter, pSWE, measures plaque stiffness at a single point within the interrogated lesion using a single, fixed-dimension, operator-defined cursor location (see Figure 3). This technique permits acquisition of precise quantitative stiffness values from a very small interrogation point and is the method of choice in aiding in the determination of plaque vulnerability. Some manufacturers couple both capabilities into a single on-screen display. In acquiring elastographic data points from within an atherosclerotic lesion, it is imperative that the pSWE focal point be small enough and controllable enough for exact placement into an operator-selected ROI.

Clinical application in plaque characterization. As outlined above, the content of a vulnerable plaque consists of proportionately greater quantities of physically "softer" substances. Liquified and semi-solid blood, thrombus, randomly interspersed neovessels, and lipid deposits are less stiff than the solid, dense fibrotic, and calcific components found in more stable, nonvulnerable lesions.

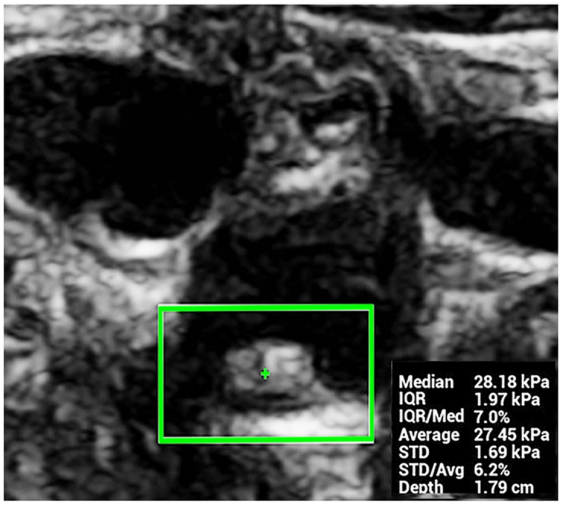

Figure 3. An example image of point shear wave ultrasound. A transverse pSWE image demonstrates placement of the data acquisition point within a focal carotid plaque (green cross) and display of quantitative metrics (lower right corner of image).

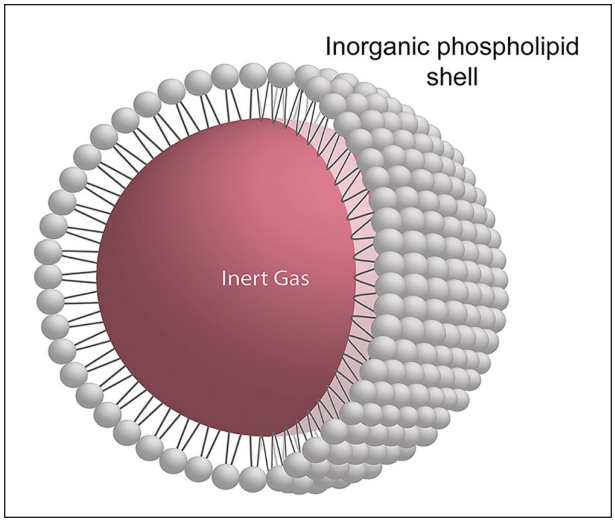

Figure 4. A diagram of an ultrasound contrast agent microbubble. This is a schematic illustration of a second generation ultrasound contrast agent microbubble. Inert gas microbubble encased in an inorganic phospholipid shell.

As SWE is a technique that appraises the stiffness, or softness, of a tissue sample, it is ideally suited for differentiating between the morphological composition of these plaque types. Numerous studies published in the medical literature have demonstrated the efficacy of SWE in providing information about the compositional features of carotid plaques.[14] As a rule, vulnerable plaques are "softer" and yield a significantly lower stiffness value (kPa) than those of stable plaques.[15,16] And while generally accepted absolute values have not yet been established across ultrasound imaging platforms, protocols maintaining internal consistency have been show to yield a sensitivity of 87% and a specificity of 67%, respectively, in differentiating plaque types.[17] In addition, the feasibility of incorporating SWE evaluation of plaques into routine vascular ultrasound examinations has been clearly established.[18] A pilot study conducted by Carter et al[19] showed the use of SWE added a little over 2 minutes to the total time of a diagnostic carotid ultrasound examination.

Contrast-Enhanced Ultrasound

Physics and instrumentation. Contrast imaging, in general, involves the introduction of an agent into the human body to enhance and differentiate anatomical structures and/or fluids. In CEUS, the pharmacological agent employed consists of inert gaseous microbubbles encased in an inorganic solid shell suspended within an aqueous solution (see Figure 4). Following intravenous injection, the bubbles remain intravascular as they course through the circulatory system and do not permeate into tissue parenchyma. As "blood pool agents," they are ideally suited for displaying and assessing both macrovascular and microvascular perfusional patterns within an interrogated region. The microbubbles eventually degrade as they pass through capillary beds. The inert gas becomes suspended in plasma and is ultimately cleared from the bloodstream via the lungs. The encasing shell material is engulfed by macrophages in the reticuloendothelial system in the liver and spleen.

The significant acoustic mismatch between the gas-containing ultrasound contrast agent (UCA) and the encompassing blood plasma results in dramatic and predictable physical responses when the microbubbles are exposed to an acoustic energy field. Reflection, backscatter, and nonlinear harmonic responses create a returning acoustic data set that can be processed in ways that permit the differentiation between bubble-bearing blood and adjacent soft tissue structures. Using specifically engineered contrast detection methods, anatomic grayscale information can be suppressed while the UCA-generated subset of the returning acoustic data set is enhanced permitting the creation of high-resolution, real-time images of microbubbles moving through the vasculature within the ROI.

Clinical application in plaque characterization. Numerous published clinical studies have demonstrated the efficacy of qualitative CEUS in detecting and differentiating vulnerable carotid plaques from their less risky stable counterparts. A study published by Iezzi et al,[20] reported a sensitivity of 94%, a specificity of 68%, and an overall diagnostic accuracy of 86%. Two particular sonographic findings are associated with this capability and have

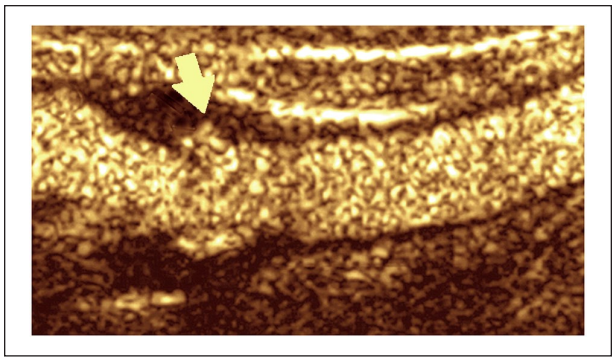

Figure 5. An image of carotid plaque ulceration, which is demonstrated with contrast-enhanced ultrasound imaging of the carotid artery lumen. It demonstrates enhanced visualization of a plaque surface ulceration (see arrow).

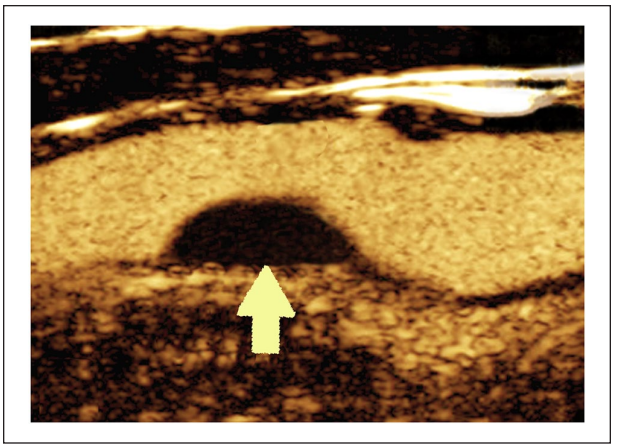

Figure 6. Neovascularization—longitudinal image through the carotid bulb demonstrating contrast-enhancement of blood flow in the vascular lumen with absent flow in a stable, nonneovascularized focal plaque (arrow).

demonstrated good correlation with plaque histology.[21-23] First, microbubble enhancement of the carotid lumen can reveal previously undetected plaque irregularities and morphology, particularly plaque surface ulcerations (see Figure 5). And, second, the enhanced spatial, contrast, and temporal resolution associated with high-frequency CEUS imaging permits real-time display of blood flow through arterioles and capillary beds. This feature is particularly efficacious in detecting tissue microperfusion; a hallmark of vulnerable neovascularized plaques[24,25] (see Figure 6). This ability to identify patients with greater potential for experiencing a CIE offers a new diagnostic standard for managing patients with carotid atherosclerotic vascular disease (ASVD).

While CEUS clearly offers improved efficacy as a noninvasive method for differentiating vulnerable carotid plaques and enhanced risk stratification, there are practical disadvantages for incorporating this application into every day, routine vascular laboratory practice. Additional requirements for performing CEUS studies include the availability of staff trained in phlebotomy and injection practices, imaging platforms with contrast-specific modes enabled on appropriate vascular transducers, and the availability of rapid response capabilities should an untoward clinical scenario arise. While UCAs are very safe and associated with a very low incidence of severe hypersensitivity events ($<$ .001% with no deaths in a series of 23 000 patients)[26] institutional risk management and legal considerations may require adequately trained personnel and equipment to be on site to cover emergent situations should they arise. In addition, performing a CEUS imaging pass after completing an initial conventional triplex ultrasound protocol increases overall examination time thereby reducing patient throughput in the vascular lab. In light of these considerations, CEUS may not be indicated for use in every carotid study but, rather, may be reserved for cases in which patient history, symptomatology, and grayscale imaging makes determination of plaque vulnerability more of a clinical imperative.

Microvascular Ultrasound Imaging

Physics and instrumentation. MUI is an emerging sonographic technique that overcomes the constraints of conventional Doppler imaging by enabling the display of arteriolar and capillary perfusional states in human soft tissue without the use of an intravenous contrast agent. While MUI images display information comparable with CEUS, the underpinning physical principles and engineering methods used to generate image frames differ. Unlike CEUS, which uses backscatter and nonlinear harmonic responses contained within the returning acoustic data set to create individual image frames, MUI is a Doppler-based modality that uses advanced adaptive filtering methods to reduce noise and clutter artifacts while simultaneously improving sensitivity to slower flow Doppler signals. Both methods also integrate flash and motion suppression techniques to eliminate fill-in of pixels with distracting and unwanted noise. The end result is an MUI image that is similar, in some respects, to a power Doppler image—a monochrome color map of blood flow superimposed on a grayscale image of adjacent anatomical structures. The difference, however, lies in the ability of MUI to detect and display microvascular perfusional states, a felicitous capability for characterizing neovascularization in vulnerable carotid plaques.

Clinical application in plaque characterization. As a new addition to the vascular sonographic lineup, MUI has yet to demonstrate unequivocal efficacy in aiding in

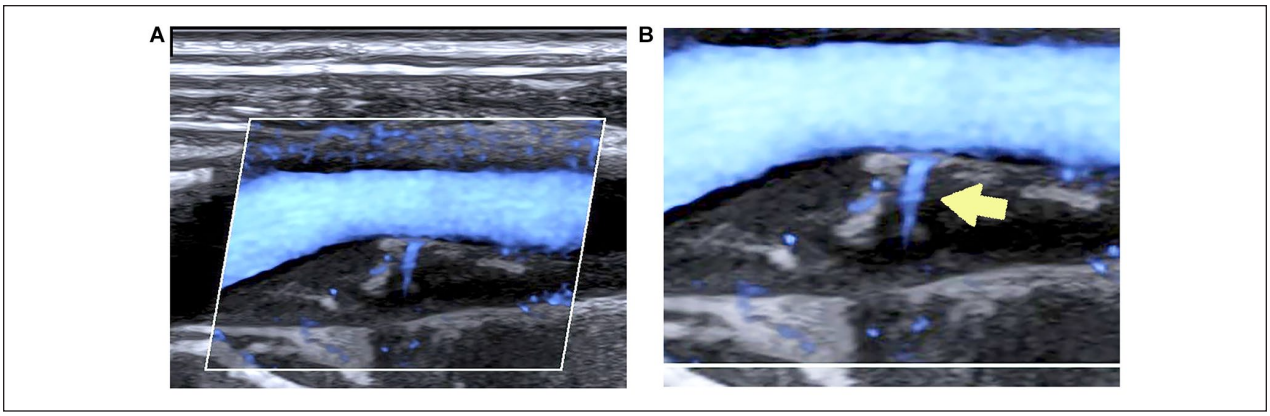

Figure 7. (A). An example of microvascular flow imaging that demonstrates blood flow into an atheromatous plaque. (B). A magnified microvascular flow image that demonstrates the same lesion showing a large neovessel arising from the intimal surface of the plaque.

the characterization of vulnerable carotid plaques. However, there are beneficial differences to this modality over its comparable perfusional modality, CEUS. First, and in most cases, foremost, MUI does not require the intravenous injection of a contrast agent. This obviates the rare and unlikely potential for any untoward hypersensitivity reaction and does not add additional procedural time to carotid ultrasound studies. Second, as the modality can be initiated by a simple touch of the console or soft screen, use of MUI could conceivable add a few minutes to examination time similar to that demonstrated in the SWE pilot study cited above. However, it is unlikely that an added 2 minutes to each carotid study that demonstrates the presence of plaque would significantly impact laboratory throughput. Finally, as of this writing, not all commercially available premium ultrasound imaging platforms offer an iteration of MUI that is sensitive enough to detect and display perfusional presence in small atherosclerotic plaques. However, as proprietary engineering methods continue to evolve and improve in sensitivity and spatial and temporal resolution, this modality certainly will become more widely available and evolve into a "must-have" for both vascular and nonvascular ultrasound applications.

Few peer-reviewed studies focused on the use and efficacy of MUI in histologically characterizing vulnerable plaques have been published to date. However, there are a several studies that do demonstrate MUI as equivalent to CEUS in correlating plaque neovascularization and in predicting CIE-related patient outcomes.[27,28] In the single study that assigned statistical metrics to MUI efficacy in predicting vulnerable plaquing demonstrated a sensitivity and specificity of 86.05% and 79.27%, respectively.[29] While these limited data are not robust enough to firmly establish its efficacy and reliability, MUI clearly offers the potential as a safe, cost-effective alternative to CEUS in differentiating plaque types. The singular microvascular ultrasound finding associated with plaque neovascularization is the demonstration of blood flow into the body of the lesion (see Figure 7). While the use of MUI in characterizing vulnerable carotid plaques is a good example of an emerging application still in its infancy, its use and efficacy in other diagnostic scenarios is well-established. Under the proprietary names of superb microvascular imaging (Canon Medical Systems, Otawara, Tochigi, Japan) and microvascular ultrasound angiography (Mindray Medical Systems, Shenzhen, China), MUI has proven efficacious in aiding in the diagnosis of placental infarctions and prediction of fetal growth restriction,[30] in characterizing malignant breast lesions,[31] in differentiating various types of focal liver lesions,[32] and in a number of other organ-specific applications.[33]

Conclusion

Emerging ultrasound applications capable of assessing carotid plaque vulnerability represent advances from the conventional sonographic approach that have long been used to exclusively detect and grade internal carotid artery stenosis. The traditional triplex method has provided the mainstay criteria for deciding intervention in most symptomatic patients for decades. It has, however, proven less efficacious in aiding in the management of asymptomatic patients with carotid disease. The ability to assess the histological characteristics of focal atheromatous lesions made possible by emerging ultrasound applications, such as SWE, CEUS, and MUI promise to be a game changer in patient management and ultimately in reducing clinical sequelae associated with CIEs.

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