Ultrasound Elastography: another piece in the puzzle of carotid plaque vulnerability?

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Abstract

Recent literature has shown that various carotid plaque features, other than stenosis, contribute to plaque vulnerability. Features such as surface morphology and plaque composition with distinct components (e.g. intraplaque hemorrhage, lipid core) have been associated with the increased risk of future cerebrovascular events. Ultrasonography constitutes the first line modality for the assessment of carotid disease and has traditionally been used to grade stenosis with high accuracy. Recent technological advances such as contrast-enhanced ultrasound and elastography increased the diagnostic yield of ultrasound in assessing the morphology of carotid plaques. The purpose of this review is to present the available literature on ultrasound elastography of the atherosclerotic carotid. Strain and shear wave elastography allow for the characterization of plaque components, thus indicating its nature and importantly, the plaque’s vulnerability. Shear wave elastography indices appear more robust than Strain indices. Overall, elastography is a feasible method to distinguish vulnerable carotid plaques. There is, however, a need for larger and longer prospective controlled clinical studies in order to validate elastography as an imaging modality used for the detection of unstable carotid plaques.

Keywords: ultrasound imaging; carotid artery; elastography

Introduction

Carotid atherosclerotic plaque and its rupture are one of the most frequent causes of cerebrovascular events. Up to 80% of strokes are ischemic in etiology [1], with 10%-20% attributable to cerebral micro-embolism [2]. Carotid plaques have different histologic components, including lipid, fibrous, or calcified tissue. The quantification of these components and the resulting characterization of a plaque - as vulnerable or stable - represent a major field in current imaging research. They may predict the future stroke risks and open the opportunity for prevention by early plaque- and risk-specific treatments.

Features that render a plaque more prone to rupture, either partially or entirely, include a large fatty necrotic core surrounded by a thin fibrous cap, intraplaque hemorrhage and neovascularization. Magnetic resonance imaging (MRI) is highly sensitive for detecting these features and remains the gold standard non-invasive imaging method for characterizing carotid plaque vulnerability [3]. However, MRI is time-consuming, has relatively limited availability, a number of contraindications and is not cost-effective [3]. Moreover, MRI has a limited in-vivo resolution of 0.7 mm, even with dedicated coils [4]. On the contrary, ultrasound (US) is cheap, widely available and time-efficient with better patient tolerability. Efforts to develop ultrasound-based techniques that can identify and characterize unstable plaques have led to multiple carotid plaque characterization techniques. They are now widely available in the context of multi-parametric US [5]. One of these techniques, elastography, assesses the carotid plaques’ mechanical properties by measuring their deformation (strain). In general, a tissue’s mechanical property such as elasticity is a function of its physi-
cal properties. Young’s modulus (YM), bulk modulus, or shear modulus quantifies the amount of stress needed to achieve a unit of strain and measures the tissue’s elasticity or elastic modulus. Two methods exist for the measurement of the elastic deformation of a tissue; strain (SE) and shear wave elastography (SWE) [6,7]. SE measures the plaque’s displacement caused by an external force, such as blood pressure oscillations.

Through deformation estimating algorithms (e.g., cross-correlation measurements or optical flow methods), strain elastography calculates semi-quantitative parameters such as strain, strain velocities or strain rate.

In SWE, the transducer emits shear waves through an acoustic radiation force impulse (ARFI) [8]. These waves disseminate perpendicularly to the impulse. The technique measures the velocity by which shear waves propagate through the tissue, expressed as YM [6]. YM defines the tissue’s resistance to elastic deformation and depends on its composition. Soft tissues, such as a plaque’s lipid core, demonstrate significant elastic deformation, a lower YM and lower shear wave velocities; more rigid tissues and lesions demonstrate less elastic deformation [9].

Unstable plaques show various displacement patterns [10-12] depending on the plaque composition. In general, fatty elements are softer than fibrous tissue [9-13]; hence soft plaques (e.g., plaques with an extensive fatty nucleus, intraplaque hemorrhage) show more extensive deformation. The distribution of deformation in a plaque is directly related to its composition. Even small foci of soft areas demonstrate higher deformation values [14-16]. Vulnerable carotid plaques are softer than stable ones [16,17], a hypothesis currently explored with quantitative evaluation indices. Elastic or structural heterogeneity [18,19] is another index, where the deformation detected by elastography depends on the plaque heterogeneity and differences between the carotid’s blood pressure and the plaque’s structure.

This review aims to summarize the available literature on elastography of atherosclerotic carotid, to present evidence on the efficacy of Strain and SWE elastography to characterize carotid plaques’ vulnerability and the potential of elastography as a prognostic tool to stratify stroke risk.

Material and methods

The literature search was performed with MEDLINE via the PUBMED search engine on January 20, 2021. The following keywords were applied: “carotid” AND “plaque” AND “ultrasound” AND “elastography.” The original list consisted of 103 articles. Figure 1 depicts the PRISMA flow chart. We excluded 18 articles because of irrelevant article titles and one because of duplication. The remaining articles’ exclusion criteria were: editorials, case reports or series with less than five patients, letters to editor, literature reviews, animal studies, studies performed in phantom vessels, studies on intravascular US, and studies on mathematical optimization of elastography parameters. Furthermore, after reading the abstracts, articles not related to carotid plaques’ vulnerability studied in elastography in human subjects were excluded, as well the non-English language articles.

The cases presented as images in this review were examined in our department.

Twenty-one articles met the inclusion criteria and reported on elastography ability to characterize a carotid plaque as stable or unstable or distinguish between asymptomatic and symptomatic patients.

Results

We extracted the following data: a) study design, b) the total number of patients, c) the total number of plaques, d) elastography technique, e) reference method, f) conclusion (Table I).

All included articles were comparative studies and concluded that elastography is efficient in assessing carotid atherosclerotic plaques. Articles compared indices of SE or SWE/ARFI elastography for the non-invasive identification of vulnerable carotid plaques in patients with or without ischemic stroke symptoms. The reference was either another imaging modality (n=7), the clinical
<table>
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<td>Huang, 2015 [27]</td>
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<td>Huang, 2017 [26]</td>
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<td>Liu, 2014 [29]</td>
<td>19</td>
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<td>Hansen, 2016 [30]</td>
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<td>Lou, 2017 [32]</td>
<td>61</td>
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<td>Shang, 2018 [33]</td>
<td>142</td>
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<td>Doherty, 2015 [36]</td>
<td>5</td>
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<td>Correspondence of increased ARFI displacements in regions identified as lipid on MRI.</td>
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<td>Torres, 2019 [37]</td>
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<td>25</td>
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<td>Developing a new outcome metric (log(VoA)) that can differentiate components of the same stiffness (NC from IPH, COL from CAL)</td>
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<td>Czernuszewicz, 2017 [38]</td>
<td>25</td>
<td>17</td>
<td>ARFI</td>
<td>Histology</td>
<td>ARFI is feasible to distinguish soft from stiff plaque components and measure FC thickness.</td>
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<td>Garrard, 2015 [39]</td>
<td>25</td>
<td>25</td>
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<td>Lower mean YM in vulnerable plaques than in non-vulnerable. YM not correlated with GSM</td>
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<td>Di Leo, 2018 [40]</td>
<td>43</td>
<td>43</td>
<td>SWE (Multiparametric US)</td>
<td>Histology; CTA</td>
<td>High sensitivity (87.1%) of SWE and higher specificity compared to CEUS (66.7% vs.58.3%) in identifying vulnerable plaques.</td>
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status of the patients (n=7) or histopathology alone (n=4) or combined with imaging modalities (n=3).

Eleven articles studied semi-quantitative SE. Three of them [20-22] validated elastography against ischemic symptoms and found that specific parameters (e.g., maximum strain indices) correlate with neurological symptoms and may predict cognitive impairment [21]. Higher values of some indices (e.g., axial and lateral strain) were associated with a more significant cognitive function decline [20]. Furthermore, by including the adventitial layer in the plaque’s demarcation, Wang et al. [23] found an improved correlation between strain and cognition as the method provided more information on the strain distribution inside and around the plaque. However, another study found higher maximum values of indexes (axial strain, axial shear strain) in asymptomatic patients’ plaques, raising questions on SE value for plaque vulnerability characterization [22].

Five studies compared SE with MRI [24-28]. One study validated the inter-operator reproducibility in the detection of unstable, vulnerable plaques with the use of a specific index of strain (axial strain rate - ASR) and showed high sensitivity (71.4%), specificity (87.1%), and accuracy (82.2%) for the method [28]. Other studies examined different strain elastography parameters (local strain rate, cumulated axial strain/cumulated axial translation, axial strain) and found that higher values are associated with unstable plaques [24,26,27]. Unstable plaques also showed higher deformation values and a higher degree of heterogeneity [26]. Moreover, Huang et al. compared strain indices with plaque textural analysis and found that the method is feasible and may distinguish vulnerable from nonvulnerable carotid plaques [26]. Another study reported lower strain elastography values for unstable carotid plaques [24]. However, this is not corroborated by studies that used non-invasive strain measurements and endovascular elastography.

The concept that unstable plaques demonstrate increased strain indices has gathered strong support by studies using histopathology as a reference [7,29-31]. Histopathology classifies plaques according to the AHA classification and composition. Increased strain indices corresponded to plaques or plaques’ areas characterized histologically as unstable, while low values corresponded to plaques rich in fibrous tissue and collagen [30]. With histology as the reference method, elastography was superior to conventional ultrasound for unstable plaque identification, with a sensitivity of 50%, a specificity of 100%, and an accuracy of 89.4% [30]. Finally, unstable plaques with a high degree of elastic heterogeneity showed significant intraplaque neovascularization [31], attesting to the multifaceted nature of plaque vulnerability.

Nine articles [32–40] studied quantitative parameters of SWE, of which three studied ARFI indices [36–38], and one assessed quantitatively and qualitatively carotid atherosclerotic plaques [38]. The most important index of SWE, Young’s modulus (YM), showed lower mean values in plaques of symptomatic compared to asymptomatic patients (fig 2) [32,34]. Other SWE indices, such as the shear wave propagation velocity (SWV), showed lower mean values in symptomatic patients and hypoechoic plaques [33]. The same study compared SWV values to homocysteine serum levels, a stroke biomarker in patients with cerebrovascular accidents, and found negative correlation between them: the higher the homocysteine serum levels, the lower the values of SWV in plaques of patients with strokes.

Fig 2. SWE quantitative assessment of three different types of atherosclerotic carotid plaques: (a) After plaque’s segmentation, YM is measured. The lower values of YM corresponds to the hypo-echoic nature of the plaque (type II, according to Geroulakos-Nikolaides (G-N) categorization), indicating plaque’s vulnerability. Note plaque’s heterogeneity and irregular contour; (b) Type III plaque, according to G-N categorization, at carotid bulb. YM value and color map of the plaque agree with plaque’s echogenicity; (c) Type IV plaque, according to G-N categorization. SWE indices values (YM, SWV) are compatible with plaque’s echogenicity. E1: YM, V1: SWV
Another article compared SWE and ARFI elastography to MRI findings in unstable plaques and introduced two new biomarkers; group velocity and frequency-dependent phase velocities [35]. Following AHA classification, these indices distinguished unstable plaques from other carotid plaques, particularly type IV. Moreover, areas characterized as fatty on MRI were identified on ARFI elastography as areas of increased tissue deformation, enhancing the method’s ability to detect unstable plaques [36].

There are studies that compared SWE with histopathological features of carotid plaques [37–40]. Low YM values and low mean YM values were associated with plaques characterized histologically as unstable [40]. Czernuszewicz et al found that ARFI elastography might measure the fibrous cap and differentiate the plaque composition [38]. A new outcome metric of ARFI, log(VoA), allows the distinction of fibrous tissue from calcifications, and fatty necrotic core from intraplaque hemorrhage, essential elements of unstable plaques [37]. Correlated to histology, SWE shows high sensitivity (87.1%) – same as CT angiography – and higher specificity compared to CEUS (66.7% vs.58.3%) for the identification of carotid plaques prone to rupture (fig 3) [40].

**Discussion**

Quantifying a plaque’s composition and further characterizing the plaque as unstable or stable - before a stroke occurs - is currently an important research topic that may contribute to the prevention and treatment of atherosclerosis. Plaques with a large fatty necrotic nucleus coated by a thin fibrous cap, intraplaque hemorrhage, neovascularization, or inflammation, are more prone to rupture [41,42]. Ultrasound-based elastography assesses the mechanical properties of the carotid plaque by measuring the plaque displacement and deformation. Several research studies have highlighted elastography as a method able to characterize the carotid plaque and categorize it according to the risk of rupture [14,16,43–46]. The distribution of plaque deformation is directly related to its local composition [14–16]. Elastography was useful for assessing carotid atherosclerotic plaques, especially in combination with other ultrasound techniques in multi-parametric ultrasound settings (fig 4) [40]. Results are unequivocal for SWE but less so for strain elastography. Indices of SWE, mainly YM and SWV, were reliable for evaluating carotid plaque against any reference (clinical status, laboratory markers, imaging, histology). SWV demonstrated a negative correlation with laboratory markers, such as homocysteine serum levels [33]. Diagnostic accuracy increased with the inclusion of the fibrous cap’s thickness in the measurements, with a
smaller thickness associated with a higher rupture risk at a cut-off value of 0.5 mm [38]. However, this particular study’s limitation was the small number of samples with a fibrous cap thickness <0.5 mm. ARFI elastography identified unstable plaques and even differentiated elements of similar texture, such as fatty nucleus from intraplaque hemorrhage [37].

The correlation of strain elastography with ischemic stroke symptoms implies a potential role in evaluating carotid plaques in ischemic stroke patients [21]. The negative correlation of strain indices with the patients’ cognitive function [20] could be potentially significant in managing this subgroup of patients. Comparison of strain indices with other imaging indices of carotid plaque instability (e.g., MRI, CEUS) suggests that elastographic strain indices may be able to differentiate unstable plaques by identifying unstable focal areas or whole unstable plaques [27], increased heterogeneity, or a high proportion of soft texture [31]. Elastography was also able to identify histologically characterized unstable plaques. Not in line with these results, Cloutier et al. found that the maximum values of strain indices are lower in symptomatic than in asymptomatic patients. However, this study examined plaques with small fatty regions in patients who underwent ultrasound examinations three weeks after the onset of symptoms, factors that may have affected the strain parameters. Another equivocal study [25] reported lower strain values in the plaques’ fatty nuclei. However, this study measured strain with a non-commercially available method. These findings are at odds with the studies mentioned above and other studies that used intravascular ultrasound [47].

The heterogeneity of strain indices values [22,25] raises doubts as to the efficacy of strain elastography in assessing carotid atherosclerotic plaques (semi-quantitative assessment) and reflects the lack of unanimity for the assessment of carotid plaques. Unlike strain, SWE appears more reliable for distinguishing vulnerable carotid plaques, as the results are more homogeneous and quantifiable [33,37,38,40].

As an overview, the studies included showed heterogeneity, and in some cases, contradictory findings [22,25]. No validated cut-off values for carotid plaque elastography exist and values among ultrasound manufacturers may be different. The number of patients in studies varied significantly and was too small to evaluate the clinical value of elastography.

Despite the limitations mentioned, elastography has many advantages. It is a non-invasive, easily accessible, safe, and technically easy imaging modality, with high sensitivity and greater specificity than conventional ultrasound. Elastography is a potential diagnostic tool that may improve vulnerable plaque detection and stroke risk stratification.

More extensive prospective controlled studies on the elastography of carotid plaques are required, as are clinical trials assessing the technique’s ability to monitor plaque-reducing treatments. Studies with longer follow-up periods will add more information on the carotid plaques’ development and accurately evaluate strain and shear wave indices’ predictive value.

**Conclusion**

Ultrasound elastography is a promising method for the assessment of atherosclerotic carotid plaques. It allows for the distinction of vulnerable carotid plaques in patients with or without cognitive disorders secondary to stroke. SWE indices seem to be more robust compared to strain elastography indices in identifying vulnerable carotid plaques. There is a need for more extensive and longer prospective controlled clinical studies to validate elastography as an imaging modality for detecting unstable carotid plaques with the potential to prevent and guide stroke treatment.

**Conflict of interest:** none

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