DOCTORATE OF HEALTH SCIENCE
EXEGESIS & PORTFOLIO

Diagnostic Efficacy of Enhanced Carotid Ultrasound Analysis for Atheromatous Plaques as a Risk Assessment for Strokes

VOLUME 2- PORTFOLIO

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STATEMENT OF AUTHENTICITY

I, Lysa Debbie Legault Kingstone, hereby declare that the all material presented in this submission is my own original work or fully and has not been accepted for academic recognition for any other subjects at Charles Sturt University or any other educational institution. To the best of my knowledge and beliefs, this submission contains no material previously published or written by another person nor material and all use of work or ideas of others has been accurately acknowledged in the text and cited or referenced, explicitly in the text.

This declaration is made on the 14th day of November 2014.

Signature: Lysa Legault Kingstone
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PREFACE

This exegesis documents the provenance of enhanced ultrasonographic analysis in carotid atherosclerotic lesions. The exegesis bonds the praxis of the body of work contained in this doctoral research, to the current evidence. The analysis in this exegesis makes significant contribution to the ultrasound discipline, and accomplished advanced professional practice. The analysis opens with historical results, relating to the current context and evidence, which provides insights into the examinable outcome of this exegesis. The extensive work contained in this exegesis and portfolio, is publicly available as published referencing throughout the document and to support the reader’s understanding of this exegesis, each of these are referenced in the doctoral candidate’s work by supplementing a footnote at the bottom of the page, providing full citations.

The associated portfolio is presented as an accumulation of full text versions of each published manuscripts cited in the exegesis as part of the doctoral work. In addition, color versions of conference presentations and posters are incorporated in the portfolio. Each manuscript and/or presentation is accompanied by a brief outline relating the particular work to the central theme of the doctoral work. To bring together the information gathered, all app applications, proposals and documents are included in the portfolio. The full breadth of this doctoral work and portfolio is presented via web based and a comprehensive version is presented as a hard copy compact disk (CD).
The following table provides a percentage breakdown of each author’s contribution for each manuscript presented in this body of work.

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<td>Kingstone, L., Castonguay, M., Torres, C. &amp; Currie, G. (2013). Carotid artery disease imaging: A home-produced, easily made phantom for two- and three-dimensional ultrasound simulation. Journal of vascular ultrasound; 37(2), 76-80.</td>
<td>90%</td>
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<td>The second to seventh authors’ contribution represented assistance with data collection/analysis and manuscript editing. The second and fifth author’s are supervisor for this doctoral work. The eighth author is a supervisor for this doctoral work.</td>
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The Pathogenesis, Analysis, and Imaging Methods of Atherosclerotic Disease of the Carotid Artery: Review of the Literature

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\textbf{ABSTRACT}

Cerebrovascular (CVA) accidents are the second leading cause of death worldwide and their numbers are increasing. Strokes can arise from several causes, with extracranial carotid artery atherosclerosis (CAS) being one of the leading causes. CAS causes these strokes either by diminishing blood flow directly to the diseased stenotic segment of the artery or, as more recently discovered, by a thromboembolic event of material from the plaque site itself. The specific etiology of CAS is unknown, but causative factors in the formation of atherosclerotic plaque of the carotid arteries have been linked to specific morphological areas within the plaque that may be vulnerable to rupture, leading to thromboembolic into the cerebrovascular circulation.

The current means for imaging and reporting CAS is through the measurement of the severity of luminal diameter stenosis caused by atherosclerotic disease. Recent developments in medical imaging techniques have expanded the role of early imaging and detection of CAS. Although current practice uses luminal narrowing as the surrogate marker to assess CAS, it has been recently discovered that plaque morphology and composition may help predict the clinical behavior of CAS and better determine the necessary medical intervention or risk of stroke. Although a single optimized imaging modality for standard CAS imaging has not been established or agreed on, various modalities can provide key elements to a successful exam. This review article will evaluate the most commonly used methods for CAS imaging along with the new and upcoming uses, advantages, and limitations for advanced CAS imaging.

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\textbf{RéSUMÉ}

Les accidents vasculaires cérébraux (AVC) sont la deuxième cause de mortalité au monde et leur nombre est en progression. Un AVC peut avoir plusieurs causes : l’athérosclérose de l’artère carotide extracranienne (AAC) est l’une des principales. L’AAC cause des AVC en diminuant le flux sanguin dans la portion distale du segment rétréci de l’artère affectée ou, comme on l’a constaté récemment, par un événement thromboembolique de matériel du site de la plaque. L’étiologie spécifique de l’AAC est inconnue, mais les facteurs de causalité de la formation de la plaque d’athérosclérose des artères carotides ont été reliés à des séries morphologiques spécifiques de la plaque qui peuvent s’avérer vulnérables à une rupture, conduisant à la formation d’un embol de circulation cérébrovasculaire.

La méthode actuelle d’imagerie et de présentation de l’AAC passe par la mesure de la gravité de la rétrose du diamètre luminal causé par l’athérosclérose. Les développements récents dans les techniques d’imagerie médicale ont élargi le rôle de l’imagerie et de la détection précoces de l’AAC. Bien que la pratique actuelle utilise le rétrécissement luminal comme marqueur de substitution pour l’évaluation de l’AAC, on a récemment découvert que la morphologie et la composition de la plaque pourraient aider à prédire le comportement clinique de l’AAC et à mieux déterminer l’intervention médicale nécessaire ou le dosage d’AVC. Bien qu’une modalité d’imagerie optimisée unique pour l’imagerie standard de l’AAC n’ait pas encore été établie ou convenue, différentes modalités peuvent fournir des éléments clés d’un examen réussi. Cet article d’examen bibliographique évaluera les méthodes couramment utilisées pour l’imagerie de l’AAC ainsi que les utilisations nouvelles et à venir, les avantages et les limites de l’imagerie avancée de l’AAC.

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\textbf{Introduction}

Cerebrovascular (CVA) accidents are the second leading cause of death globally [1] and the leading cause of death in North America [2]—and its numbers are increasing. An estimated...
one stroke every 10 minutes [3] occurs daily in Canada. Strokes can arise from several causes, with extracranial carotid artery atherosclerosis (CAS) being one of the leading causes. CAS is mainly caused by disease of the arterial vessel wall. The history of carotid disease spans many centuries, although observations influencing current practice were only described within the past 45 years [8]. Most reports received little or no attention until C. Miller Fisher published his first clinicoradiologic correlation article titled “Occlusions of the Carotid Artery” in 1951 [8]. Miller Fisher’s publications pioneered the use of lumenography and imaging to rule out suspected CAS, which at that time was believed responsible for strokes.

The specific etiology of CAS is unknown, but causative factors responsible for the formation of atherosclerosis of the artery include cholesterol deposits, extravasations of inflammatory cells, smooth muscle cell proliferation, increase in connective tissue, and calcifications [9-11]. Initially, the disease mechanism of atherosclerosis starts with damage to the endothelial layer of the vessel, followed by the infiltration of monocytes and thickening of the intimal-medial arterial layers [10]. This in turn forms fatty streaks, and eventually atherosclerotic plaques [11, 12] that ultimately cause narrowing or thrombosis of the vessel segment that may result in the reduction of flow in the vessel and impede vascular flow to the brain. Alternatively, recent discoveries have identified that certain types of plaques may contain areas with potential for rupture, which may lead to small blood clots, emboli, or fragments that propagate into the cerebrovascular circulation [13]. This leads to occlusion of a distal cerebral vessel, causing a stroke [14].

Plaques that are considered “vulnerable” have specific morphological features identifying their probability to rupture. These morphological characteristics include surface ulcerations, inflammation, microvascular formation, presence of a thin fibrous cap over the lipid core, and/or intraplaque hemorrhage [9]. Several studies have shown that the morphology of the plaque itself may play a critical role in the incidence of ischemic neurological events [12, 15]. Any of these interruptions of vascular flow to the brain can cause permanent injuries.

Biomarkers have been used as possible predictors in various physiological studies. These biomarkers were compared with cerebrovascular clinical outcomes, histopathological features, and relevant imaging findings. Among these studies, the specific biomarkers studied commonly included C-reactive protein (CRP) and matrix metalloproteinases [16]. At the molecular level, inflammation plays a key role in the pathogenesis of atherosclerotic plaques [17]. Increased serum concentrations of inflammation-sensitive proteins, such as CRP, have been shown to be a consistent, but nonspecific, marker of systemic atherosclerotic disease [18]. Elevated levels of CRP typically reflect the inflammatory process in the pathogenesis of atherosclerotic disease; however, levels of the protein are nonspecific.

Identifying patients at increased risk for CAS can be a challenging step for clinicians in the prevention of strokes because of the lack of specific risk factors or symptoms. Traditional risk factors such as smoking, hypertension, hyperlipidemia, decreased physical activity, obesity, poor dietary habits, and diabetes [1] can only aid in the prediction of 60-65% of cerebrovascular events [18]. Unfortunately, as with the identification of risk factors, the presence of clinical symptoms has limited value in the prediction of stroke. Clinical symptoms usually present after the atherosclerotic plaque has caused a major stenosis, thrombosed, or embolized distally, resulting in a clinically significant decrease in the cerebrovascular perfusion of the vascular territory in the affected arterial segment. Presenting symptoms depend on the affected vascular territory or blocked cerebrovascular segment and include amnesia, fugax, transient ischemic attacks, paraparesis, and neurological deficits [1].

Detection Methods of CAS

Patients with an increased risk of stroke typically have an association with CAS, most commonly a narrowing within
the internal carotid artery [19]. Current clinical imaging methods for the screening and assessment of CAS include both noninvasive and invasive diagnostic examinations, including digital subtraction angiography (DSA), US, MRI, and CT. Controversy exists, however, as to when clinicians should screen suspect CAS and what indications or tests are required for the diagnostic evaluation of the carotid artery [2]. The American Society of Neuroimaging [20] presented evidence-based guidelines regarding population-wide screening for asymptomatic CAS in the general population, and selected subsets of patients now commonly used as a reference for imaging referral. These guidelines include the recommendation to screen high-risk patients in the general population based on the prevalence of disease and anticipated benefits of identifying CAS. The indications include the high-risk population in general, symptomatic patients, and risk-associated groups. Patients who are at higher risk include those undergoing open heart surgery or having peripheral vascular disease, abdominal aortic aneurysms and/or renal artery stenosis; a history of radiotherapy for head and neck malignancies; prior endarterectomy or carotid stent placement; renal ischemic syndromes; a family history of vascular disease or hyperhomocysteinemia; and symptoms of syncope, dizziness, and vertigo [20].

Recent trends in the attempt to identify early or to predict predisposition to CAS include the intimal media thickness (IMT) measurement. IMT measures the thickness of an arterial wall, usually acquired using US (Figure 1). The increased IMT may be an adapted response of the medial layer, or from hypertensive stress resulting in intimal thickening reflecting early atherosclerosis [21]. Numerous large-scale studies have revealed that an elevated carotid IMT can independently predict future risk of cerebrovascular or cardiovascular events [22]. Consequently, carotid IMT has been established as an appropriate means of identifying, monitoring, and screening subjects at risk of cerebrovascular disease. Ongoing studies are underway to use US in the assessment of IMT in the application of future cardiovascular risks. It has not yet been applied worldwide as a standard protocol for screening, or routinely imaged on referred sonograms.

More recently, the specific composition of atherosclerotic plaque has been shown to be of significant importance in determining future cerebrovascular events. Atherosclerotic plaque comprises a variety of tissue matrices, including collagen, elastin, proteoglycans, lipids with foamy macrophages, and smooth muscle cells [23]. Inflammatory cellular components such as T-lymphocytes, macrophages, and basophils also exist within these lesions [23]. It is suspected that acute thrombus leading to arterial occlusion and/or distal emboli is triggered by the instability of certain molecules within the plaques, and this—rather than the traditional notion of arterial luminal narrowing—is responsible for cerebrovascular events [14]. Pathological studies have confirmed the association between specific morphological features and the vulnerability of plaques to rupture; however, statistical values relating the morphology and predictability of plaque are still questionable and are in the development stage in multiple large-scale studies worldwide [6]. Extensive studies have also been performed and are ongoing in the attempt to identify plaque composition and characteristics on imaging to determine the increase in risk of a cerebrovascular event [24].

In addition to traditional risk factors and recent insight into the role of plaque morphology on plaque vulnerability, the pathogenesis of atherosclerotic and subsequent cerebrovascular events is likely to involve additional factors and complex molecular interactions. Inflammatory molecular, cytokines, and homocysteine [1] have been examined as possible biomarkers accountable for the breakdown of atherosclerotic plaques. All of these disruptions cause a biochemical reaction within these normally balanced molecules, which may lead to irreversible changes within the vascular endothelial wall [1]. Trials studying specific molecular biomarkers such as CRP and matrix metalloproteinsases [30] are underway as the specific information on the predictive value of biomarkers and its relevance to vulnerable plaques is not yet available.

Another recent emerging factor in the prediction of atherosclerotic disease is the study of viscoelastic properties within an arterial segment. An increase in arterial wall stiffness is commonly related to atherosclerotic risk and is known to increase with age. However, the process is not necessarily pathological [4]. Studies have validated the alterations in elastic properties in correlation with atherosclerotic disease [4]; however, they are still preliminary. Additional studies are underway to further understand and validate this potential phenomenon.

Diagnostic Imaging Methods

CAS imaging and reporting occurs by measuring the severity of the luminal diameter stenosis caused by atherosclerotic disease. Imaging of luminal narrowing was determined by the European Carotid Surgery Trial (ECST) [25] and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [26] as referencing guidelines to...
In current clinical practice, DSA is largely reserved for problem-solving situations. For example, in cases in which other imaging modalities demonstrate near 70% stenosis, or if a discrepancy exists between two different imaging modalities, DSA is typically performed to corroborate the relevant findings. Angiography may only be done if further assessment is required, if treatment is needed, or if the stenosis is actually >70% and not definitive on other imaging studies. Although angiography remains an important tool in the assessment of CAS, newer, less invasive, and potentially more accurate technologies are available that can simultaneously assess both luminal stenosis and/or plaque morphology. US or MRI angiographic techniques are now employed as the primary screening tools for CAS over DSA with high accuracy, leaving the future role of angiography in question. These modalities can offer equivalents if not superior CAS imaging over DSA. DSA, being an invasive procedure, can have potential lethal complications and is an increased risk for any patient. Some of these side effects include hemorrhage, aneurysm, pain/discomfort, anaphylactic reaction to the dye, damage of blood vessels, nerve effect, thrombus, and/or renal damage. For historical and scientific purposes, the measurement of luminal narrowing with angiography remains the single validated method for identifying surgical candidates for intervention.

Carotid Duplex US

US offers an advantage in carotid artery assessment as it is capable of concurrently assessing the optimal anatomical details of the vessel wall, certain plaque characteristics, and hemodynamic and degree of luminal stenosis in real-time scanning. This combined advantage, coupled with its noninvasive nature, allows US to overtake other imaging modalities as a primary screening tool. In the past, US has been criticized for its inconsistencies resulting from variations in technical factors such as operator reliability and variance, or the inability to access the vessel segment in question because of technical or physiological restrictions. However, over the past two decades, considerable gains have been made in the quality of US examination as the technology, equipment, and resolution has improved significantly. US is by far the most common imaging examination requested worldwide to aid in the diagnosis of CAS, as it has proven to be an accurate and cost-effective means of carotid artery imaging and evaluation (without the risk of ionizing radiation and potential inadvertent contrast nephrotoxicity). The sensitivity of US for CAS is approximately 85% (range, 82–100%) with specificity close to 90% (range, 81–100%) [2].

In the detection of CAS, the arterial vessel in question is first scanned using the pulsed-echo B-mode, followed by pulsed spectral and color Doppler to assess blood flow. Two-dimensional (2D) or B-mode imaging provides anatomical as well as morphological information with regard to the vessel wall and plaque assessment. US has an additional advantage over other imaging modalities because it can accurately measure the carotid intima-media wall or IMT using...
high-frequency, high-resolution transducers [22]. The Doppler portion of the study enables the user to measure and recognize variations in blood flow velocities within the artery and estimate the degree of stenosis caused by atherosclerosis. Analysis of the Doppler signal is obtained via sound spectrum audio analysis and by observing color variations in the spectrum. Any changes in these parameters represent an alteration in mean blood flow velocities and require measurements at specific anatomical points, including the region of maximum stenosis to grade if it is hemodynamically significant. In addition to ratio measurements, peak systolic and diastolic velocities are used to grade and categorize any stenosis, as well as the lesion is hemodynamically significant and/or at a high-grade for therapeutic intervention.

Emerging trends using US to assess CAS involve the detailed assessment of plaque morphology, and characteristics using specific echogenicity criterion have been applied with high accuracy in recent studies [31]. US has the ability to identify and differentiate between hard and soft plaque, based on specific sonographic characteristics [24]. Hard plaques are identified as large and hypoechoic because they consist mainly of fibrous tissue (Figure 2). This type of plaque demonstrates more stability because of the presence of surface calcifications. Alternatively, soft plaques are hypoechoic to isoechoic because they contain more lipids and loss of texture (Figure 3). This form of plaque is more vulnerable to the altering hemodynamic effects and, according to recent literature, it is suspected that this type of plaque is more likely to rupture, shod, or hemorrhage, and to form a thrombus. Although plaque imaging is possible with US, it is not without limitations. Sonographic limitations, including complex plaque causing interference in the uniformity, heavy calcifications, and high anatomical bifurcation of the common carotid artery can impede the visualization of the anatomy in question or the internal contents of the plaque [31]. Research on US and its role in evaluating plaque morphology and characteristics is thriving and newer technological instruments are currently available to better assess the diagnostic value of US with respect to plaque vulnerability. One of these emerging methods is the application of three-dimensional US (3D-US) because morphological plaque progression is not limited to changes in one single direction and can progress in all three dimensions. 3D-US may thus be able to represent a more accurate measurement of plaque than the 2D assessment alone because all three dimensions can be visualized [21]. Recent studies on 3D plaque imaging have revealed the ability to directly visualize a plaque and to quantify better its features such as surface morphology, geometry, and distribution, as well as volume changes over time [21]. Despite the great progress of plaque assessment using 3D-US, its clinical applicability remains unproven and studies are ongoing.

Additional emerging technology using US to assess for CAS involves the study of tissue strain using the elastic properties of the vessel wall instead of the echogenicity of the plaque [32]. Elastography, or strain imaging, applied to the vessel wall or plaque itself demonstrates potential in the assessment of mechanical properties to better predict the risk of vulnerability or tissue rupture. Elastic arterial wall properties of in vivo plaque tissue studies using real-time US demonstrated that atherosclerotic lesions had amplified elasticity with progressive lipid deposition or fibrosis from histopathological changes within the plaque [33]. Most of the studies involving elastography have been performed using intravascular US and are largely limited in evaluation of the plaque in the coronary arteries. However, in recent trials noninvasive vascular elastography has been applied in the normal carotid arteries. Preliminary results have revealed a promising method in differentiating hard plaques and lipid cores from the normal carotid tissue characteristics [32]. This recent advancement in imaging requires further investigation as it has only been studied and applied in research—its use in a clinical setting has yet to be established.
MRI

MRI has become the widely preferred noninvasive diagnostic imaging alternative for angiography in CAS detection. MRI’s current major role in CAS assessment is luminal diameter and stenosis assessment. More recently, it has been employed in research to assess advanced plaque morphology and characteristics. MRI offers high-resolution anatomical imaging without exposure to radiation or iodinated contrast agents associated with DSA and CT. MRI’s foremost advantage is its ability to provide information from multiple tissue contrast weighting, which can be augmented using a natural gadolinium chelate contrast agent to improve or complement the information, such as the vascularity of an area or patency of a vessel [27].

The use of MRI in the assessment of CAS detection employs magnetic resonance angiography (MRA) to image targeted vascular segments. Initial MRA imaging used a phase-contrast (PC-MRA) method, which used the change in phase shifts of flowing protons in the artery to create an arterial phantom image. Although effective, and still used for certain imaging sequences, this method was quickly substituted by 2D Fourier transformation and 3D time-of-flight MRA (TOF-MRA). TOF-MRA uses gradient echo sequences and applies presaturation slabs to identify the difference between unsaturated and presaturated spins of the moving protons in a vessel segment, thus producing either an arteriogram or venogram. In the carotid artery, moving protons, such as the blood flowing within the artery, moves unsaturated spins from the outside of the slice and into the imaging plane. These spins produce a much higher signal than the stationary spins in the field of view, creating a bright signal and a lumino graphic effect on an image. MRI can also be used to image vessels without the use of contrast agents by using gradient echo (GRE) sequences and applying presaturation slabs to identify the difference between unsaturated and presaturated spins of the moving protons in a vessel segment, thus producing either an arteriogram or venogram. In the carotid artery, moving protons, such as the blood flowing within the artery, moves unsaturated spins from the outside of the slice and into the imaging plane. These spins produce a much higher signal than the stationary spins in the field of view, creating a bright signal and a lumino graphic effect on an image.

TOF-MRA uses no contrast to image the vessel, but it is associated with long scan times and signal voids that can lead to poor-quality imaging or overestimation of luminal stenosis [7]. Contrast-enhanced MRA (CE-MRA) application involves the use of a low-toxicity gadolinium chelate contrast agent. CE-MRA images the vessels by using a bolus-triggered sequence that coincides to targeting specific arteries such as the carotids (Figure 4). CE-MRA produces high-quality images in a short period and usually eradicates the drawbacks associated with TOF-MRA. Both TOF-MRA and CE-MRA offer 3D reformating capabilities of the arterial segments. The overall sensitivity of TOF-MRA for detection of severe stenosis is 91.2% with a specificity of 88.3%, whereas the sensitivity of CE-MRA was 94.6% with a specificity of 91.9% [7]. However, the accuracy of CE-MRA for moderate to severe stenosis is still subjective.

MRI is increasingly being studied as a risk stratification technique in carotid plaque morphological assessment. Among all current imaging modalities, MRI appears to be the most promising method in assessing plaque morphology and characteristics for CAS [34]. The use of high-resolution MRI to image plaque characteristics in the carotid artery is now possible using a combination of sequences, weighings, and, more recently, contrast enhancement (Figure 5). In addition, with the use of increased field-strength units in clinical use, such as the 3.0 Tesla scanner, along with dedicated phased-array surface coils designed specifically for carotid artery imaging, MRI’s capability of imaging CAS with high resolution has improved significantly. Recent published studies have demonstrated that MRI can help identify specific markers of vulnerable plaque associated with thrombotic events such as the fibrous cap thickness, lipid-rich necrotic cores, intraplaque hemorrhage, and other components such as calcifications and inflammation, all of which are perceived as increasing plaque vulnerability and the likelihood of a future rupture or emboli [28]. Recent studies involving CE-MRA have demonstrated that increased enhancement within a plaque’s fibrous cap and outer wall may reflect sites of active inflammation indicative of neovascularity and plaque instability [28]. Other MRI-specific contrast agents targeting certain plaque components such as endothelial or inflammatory cells and protease are being investigated in an attempt to better understand the pathophysiology of the disease and potentially provide further clinical risk assessment in CAS [6]. Nonetheless, most of these studies are ongoing and the risk stratification for each finding must be assessed to determine the specific risk of rupture, stroke, or death with each relevant finding.

MRI appears to be positioning itself to become the future modality of choice for CAS assessment and, more specifically, early plaque imaging and detection [27]. However, MRI is not without its limitations, and the cost can be prohibitive for widespread use [12].

CT

CT is currently the primary imaging modality recommended in the assessment of ischemic strokes [35]. With newer high-speed multidetector scanners, CT angiography (CTA) permits the anatomic evaluation of the carotid arteries by quantifying the carotid lumen diameter or using contrast luminography and 3D reformating capabilities [36]. CTA is evolving significantly with modern technological hardware and software. Current trends using CTA imaging include the use of multidetector, high-speed CT units using a near-isotropic spatial resolution and minimal sectional thickness slices as small as 0.75 mm [36], which is not possible with DSA. This creates the ability to directly measure carotid stenoses using a submillimeter dataset to better visualize the vessel segment in question. CTA’s 3D reformating capabilities can provide multiple viewing planes, which is currently limited with DSA, US, and to some extent, MRI. The use of faster, better imaging equipment with the use of minimal sectional thickness combined with the application of 3D image and multiplanar surface rendering may allow a unprecedented quantification in the assessment of carotid stenoses or disease, and further enable 3D or volumetric assessment of the vessel wall and artery [28] (Figure 6). Numerous institutions have now incorporated standardized CT imaging of the head with CTA of the carotid and cerebrovascular diseases to further assess the extent of stroke and to
CTA differs from all other methods in that it is capable of directly measuring millimeter segments of the contrast-filled vessels and the surrounding noncontrast soft tissues [36]. Similar to DSA, CTA results in exposure to ionizing radiation, but to a far lesser degree. It operates at higher speed, thus limiting the radiation burden without increasing the patient’s risk [36]. In a standard cranial-cervical CT angiographic examination using a 64-detector-row scanner, the mean effective radiation dose scan are typically acquired in the 0.57 mSv range [37], and head-CT doses up to approximately 75 mGy [38]. The dose from a 3D-DSA rotational acquisition is near 1100 cGy cm² per acquisition [37]; therefore, it is important to note that the radiation dose from DSA is higher than from CTA. Furthermore, CT is much less invasive than DSA because it only requires intravenous injection in lieu of intrarterial injection for contrast material [39]. Low-dose imaging can also be achieved with certain sequences in CT, coupled with the additional use of new software algorithms that enhance the CT image quality and cut the radiation dose without compromising the value of the examination. CTA is now considered the optimal imaging modality in luminal assessment for CAS and has proven to be beneficial with respect to safety, time, and cost over DSA [38]. CTA has a very high negative predictive value (100% for 70% stenosis, and 99% for 50% stenosis) and a high sensitivity (100% for 70% stenosis, and 86% for 50% stenosis) signifying that the test is unlikely to overlook important CAS [35]. However, CT still has associated variability of stenosis calculations, high cost, and certain sectional viewing limitations.

With the recent trends in plaque imaging, in addition to the standard parameter of luminal narrowing, CT’s ability to evaluate both the carotid wall and adherent plaque has evolved in recent years. It has been shown to detect ulcerations, large lipid cores, hemorrhages, and ulcerations, and to measure the specific fibrous cap thickness changes—all of which are biological features assumed to be associated with plaque vulnerability [40] (Figure 7). CTA does, however, have its limitations in plaque characterization, as it has difficulty identifying smaller lipid-rich necrotic cores, connective tissue, and hemorrhages due to the overlap in Hounsfield unit densities [41].
Although the literature on CT plaque imaging appears promising, additional research is required regarding its validity for plaque imaging. The risk stratification has yet to be validated prospectively in large-scale studies, which are under way.

**Molecular and Functional Imaging of CAS**

Nuclear medicine imaging can provide physiological information of the tissue instead of anatomical information commonly provided with other imaging modalities. Advanced molecular imaging methods include the use of positron emission tomography (PET), PET/CT, PET/MRI, single photon emission computed tomography (SPECT), SPECT/CT, and near-infrared fluorescence (NIRF). Although the application of nuclear medicine is not used clinically in the detection of CAS, functional or molecular imaging appears promising in identifying vulnerable plaque and its applicability to CAS. Various advanced imaging research methods are currently being performed to possibly identify plaque morphology and the molecular process in vulnerable plaques. Inflammatory processes or similar biologic changes could possibly be the key in the early identification of potential pathophysiological process of vulnerable plaque and may be beneficial in earlier prediction of the risk of stroke.

Research is under way to identify potentially important molecular processes in CAS associated with plaque vulnerability such as inflammation, lipid accumulation, proteolysis, apoptosis, angiogenesis, and thrombosis. These molecular-specific imaging tools may prove to be extremely beneficial in identifying early stages of unstable plaque by allowing early characteristics of plaque vulnerability, and permitting proper selection for therapeutic strategies by imaging molecular changes. The future of molecular and functional imaging for CAS may create the possibility of identifying early plaque vulnerability and shift the paradigm toward identifying biochemical constituents and cellular components within living plaques over stenotic lesions.

**Discussion**

Stroke is the most common serious neurological problem worldwide and is anticipated to become an epidemic.
Approximately 16% of all ischemic strokes are due to carotid atherothrombotic disease, with the extracranial artery most frequently involved [47]. Identifying carotid atherosclerotic plaque and arterial stenosis is a well-established risk factor associated with strokes [47]. Several studies in imaging support the notion that carotid artery assessment should include the degree of carotid stenosis and additional elements of the plaque, such as the morphology and surface features, which may be pathogenetically important in the production of cerebral ischemia [47]. Recent research on plaque pathogenesis and biology has discovered that its composition is responsible for vascular events, and the importance in the early identification for vulnerability is required. US has had limited success in determining plaque stability and plaque composition [48]. With emerging sono graphic methods such as 3D-US, plaque characteristics, and elastography, US may be the future noninvasive imaging method to provide better information on the plaque components. MRI has proven to be a valuable tool in CAS imaging and is now presumed capable of distinguishing atherosclerotic plaque composition, including lipid pools, fibrous caps, and hemorrhage. Research studies using MRI for plaque characterization are ongoing, and additional studies are required to confirm these preliminary findings. CT provides excellent arterial segment imaging and appears to be a promising tool in the future of CAS assessment. Trials are under way to investigate the sensitivity of CT in plaque morphology and the surrounding tissue analysis using CT. More sophisticated functional or molecular imaging is being investigated as possible means for identifying CAS and plaque vulnerability with the use of nuclear medicine. Both PET and SPECT appear to identify specific molecular components found in vulnerable plaques and NIRF is emerging as a potential imaging candidate in detecting specific chemical composition of vulnerable plaques. Although plaque features such as the characteristics, surface irregularities, and ulcerations appear promising in identifying
early plaque vulnerability using multiple imaging modalities, at this time no large clinical prospective trials have been completed in vivo, and further studies involving the relation to plaque stability and correlation are ongoing. Further information is required from these studies prior to shifting the paradigm in carotid imaging.

Patient clinical symptomology, life expectancy, and the extent of CAS are important factors when considering therapeutic interventions [49]. Besides preventive and medical treatment, the current therapeutic remedy for CAS is carotid endarterectomy or vascular stenting. Nonetheless, presently endarterectomy is only being done in specific patients, and stratification regimens are only done because of the luminal stenotic percentage based on interventional trials such as NASCET, ECST, and Asymmetric Carotid Atherosclerosis Study (ACAS), and identified on relevant imaging [50]. These pivotal trials were undertaken in the 1980s and early 1990s; since then, techniques such as US, CT, and MRI have gradually replaced intra-arterial angiography. However, their efficacy has not been studied in context with regard to their effect in therapeutic applications. Therapeutic interventional trials such as NASCET should be repeated using newer, noninvasive imaging techniques to ultimately determine the new “gold standard” for CAS imaging.

Conclusion

Stroke is the most common serious neurological problem worldwide and is anticipated to become an epidemic [45]. Two types of strokes exist: hemorhagic and ischemic strokes, with ischemic being the most common. Sixteen percent of ischemic strokes are due to a carotid atherosclerotic disease [47]. Early detection is a key to avoiding a potential stroke. Although current imaging can distinguish certain carotid atherosclerotic disease by luminal grading, early identification of specific plaque alterations could be of further benefit for early detection. Several studies in imaging support the idea that the carotid arteries should be assessed using both the degree of stenosis, plus additional elements such as the morphology and surface features, which may be pathogenically important in the production of cerebral ischemia [47].

Imaging modalities such as US, CT, and MRI are increasingly being studied as potential modalities in imaging early plaque formation and stability. To date, US has had limited success in determining plaque stability and plaque composition [48] using 2D technology, but shows promising methods using 3D-US and elastography. US may be the future noninvasive imaging method of choice for plaque characterization. MRI has increasingly become the most valuable tool in CAS imaging and can now distinguish atheromatous plaque compositions with newer, powerful magnets and designated carotid imaging coils being used in research. CT imaging provides optimal segment imaging, and trials investigating the sensitivity of CT in plaque morphology and surrounding tissue analysis are ongoing. Finally, functional or molecular imaging is being investigated as possible means of identifying CAS using both PET and SPECT, by identifying specific molecular component found in vulnerable plaques. Moreover, NIRF is emerging as a potential imaging candidate in detecting specific chemical composition in vulnerable plaques. Although all of these imaging features appear promising in identifying early plaque vulnerability, clinical trials are underway to correlate the imaging findings with plaque stability, thus further information is required from these studies prior to shifting the paradigm in carotid imaging.

With newer and noninvasive imaging software and technologies such as 3D and early molecular imaging, advanced CAS imaging and assessment may overpower conventional luminoigraphy in risk valuation and possibly reconsider current criteria for therapeutic interventions. Various imaging techniques, alone or combined, could be a more appropriate tool in detecting and monitoring the progression of carotid artery disease, and potentially be used as the new “gold standard” in CAS imaging. These imaging modalities’ capabilities of detecting vulnerable plaque may prove to be an important milestone in the prevention of future cerebrovascular events in efforts to shift the paradigm in everyday carotid artery imaging.

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Enhanced Plaque Ultrasonography

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CURRENT ARTICLE

Enhanced Plaque Ultrasonography

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Doctorate of Health Science

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A Systematic Literature Review of Ultrasonography for Morphology and Characterization of Vulnerable Carotid Artery Plaques

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ABSTRACT
Background and Purpose.—Although ultrasound (US) evaluation of the carotid artery for stenosis is the accepted method for identifying risk factors for cerebrovascular (CV) events, patients with specific plaque morphology may be at increased risk. Plaque characterization via US is a potentially useful adjunct to stenotic grading for identifying vulnerable carotid disease. The aim of this study was to systematically review published clinical trials via the use of US to identify vulnerable plaques among both symptomatic and asymptomatic plaques.

Methods.—We used a systematic search using Medline, Embase, and the Cochrane Library databases to find relevant studies published between 2001 and 2011. We reviewed randomized, controlled human clinical trials that validated the applicability, diagnostic accuracy, and diagnostic impact of US carotid plaque characterization. For studies reporting qualitative findings, we abstracted information about the study design and technique and the quality of the methodology and analyzed the data using a modified Jadad scale.

Results.—In this review, we identified 12 studies related to the evaluation of carotid plaque using US. The studies used a wide range of methodologies to quantify and image the plaque morphology. Published literature on this subject is lacking; however, this deficit may be because current studies are ongoing. Specific plaque characteristics identified as vulnerable included particular echo texture, the presence of echolucency and/or ulceration, surface alterations, and volume assessment using 3-dimensional US (3D US). In a minority of studies investigators used histopathology as the reference standard, and in most they used subsequent clinical observations. All studies demonstrated that US has good accuracy and specificity in identifying possible imaging characteristics related to vulnerable plaques.

Conclusion.—The collected evidence shows that US is effectively able to detect specific carotid plaque characteristics related to high-risk plaques vulnerable for CV events. We anticipate that additional well-designed prospective studies will provide more definitive evidence and distinguish specific distinctive findings that may serve as indicators of vulnerable plaques. Our findings must be extended to demonstrate the accuracy and validity in everyday clinical imaging findings.

Introduction
Ischemic carotid embolic strokes are associated with cerebral embolisms originating from a carotid atheromatous plaque or from a thrombus originating from the site of rupture.1 The vulnerability of the carotid plaque is dictated by its morphologic composition, which plays an important role in the risk for embolization or stroke. Studies have demonstrated that specific plaque characteristics often are associated with neurologic events.2-4 Postulated morphologic criteria of vulnerable plaque include a thin or fissured capsule, large lipid core(s), active inflammation, severe stenosis, or a combination of these findings.5

Emerging approaches in identifying early morphologic features and characteristics of vulnerable carotid plaque have opened up new avenues in the field of carotid artery imaging for stroke. Imaging modalities that offer possible identification of these features include magnetic resonance imaging (MRI), computed tomography (CT) and ultrasound (US). Duplex, high-resolution US imaging is currently the most common noninvasive imaging study performed to diagnose carotid artery disease. Until recently, US carotid imaging was limited to grading specific stenotic lesions within the carotid plaque segment; however, any atheromatous lesions may contain unstable plaques that can...
rupture, exposing the highly thrombogenic core to the bloodstream and causing a distal embolus, resulting in a cerebral infarct. US generally is effective in the evaluation of plaque morphology by identifying internal components and the structure of specific plaque appearance. Specific markers include echo texture, the presence of echolucency, and surface alterations or ulcerations. The increased interest in using US to image plaque morphology may present a paradigm for finding a relationship between morphologic characteristics and additional risk factors and identifying atherosclerotic plaques at greater risk for cerebrovascular events to prevent stroke.

The objective of the present systematic literature review was to evaluate the clinical data via US to identify and characterize vulnerable carotid artery plaque. On the basis of these findings, we aimed to use these data to measure plaque-imaging efficacy and create a methodological, systemic guideline for US use in the assessment of plaque, thereby helping to focus future research in this area.

Methods

For the purpose of this systematic review, we included all studies of the applicability and diagnostic accuracy and performance (i.e., sensitivity and specificity) of US carotid plaque assessment. Our review method involved a systematic search and investigation from selected databases and combining various medical keywords or terms such as “ultrasound plaque characterization” and “ultrasound carotid plaque.” We interchanged the words “ultrasound” and “sonography” in our search.

Search Strategy and Selection Criteria

Published reports were searched using the database of Medline via the PubMed interface, Embase via the Dialog interface, and the Cochrane Library for relevant articles. Because the primary focus of this project was to improve previous technological assessments, we limited our search strategy to articles published between January 1, 2001, and December 31, 2010. We limited our studies to human clinical trials published in the English or French language. Our search yielded 26 related articles. All selected article abstracts were reviewed and independently screened according to the following exclusion criteria: (1) not focused on plaque vulnerability or characterization; (2) included plaque assessment for the purpose of treatment or progression assessment; (3) used coronary plaque imaging studies in plaque assessment; (4) used commercially available software for the analysis or grayscale quantification or assessment of plaque; and (5) used intimal medial thickness, total plaque volume, or vessel wall volume. Of the 26 eligible abstracts, 12 studies were considered technically feasible for the purpose of this review.

Once excluded articles were omitted, the final articles were read in full. They included six papers identified by our Medline search and one from the Cochrane Library database. We excluded all Embase titles already identified by the Medline search; thus, no other articles were found. The reference lists of the selected review articles were cross-referenced to detect any articles missing from our search. An additional five secondary references were chosen for this review. All resulting articles found were evaluated for the use, efficacy, and assessment of plaque characterization using US imaging. The reviewer abstracted each study’s information in a Microsoft Excel spreadsheet, detailing the patient clinical subgroup, sample size, reference standard, start/end year, sonographic marker, diagnostic categorization and plaque visualization technique modality used. A summary of the findings is included in Table 1.

Data Analysis

For each study, a modified Jadad scale called the Jadad-Kingstone scaled was used to report the quality of relevant clinical trials (Table 2). One observer independently rated the quality assessment of each paper, and papers with an acceptability scale of 50% (or eight points of 15) were used.

Results

Our search strategy identified 26 articles evaluating the diagnostic application and efficacy of US in carotid plaque morphology imaging. Fourteen of these articles were eliminated because of the aforementioned exclusion factors listed, leaving 12 clinical trials for inclusion. All 12 of these clinical trials had an overall quality rating greater than 50% on the modified Jadad scale. B-mode imaging was used most frequently to evaluate plaque characteristics such as echogenicity, echolucency and echo texture in known carotid atherosclerotic disease. Other morphologic specifics imaged with US included surface alterations, the presence of ulcerations, and volume assessment, which was commonly analyzed using 3D US. The studies did not identify the specific pathology behind each individual characteristic in relation to the stroke location or symptoms, thus making it difficult to determine whether particular sonographic characteristics were related to specific neurological patterns. Studies using surgical specimen resected by carotid endarterectomy (CEA) as the outcome measurement were limited; only three fully published papers identified doing so. CEAX is considered the gold reference standard, and its use as a comparison enhanced the imaging findings of these three studies. Six of the articles confirmed their findings with observation periods and/or other cross-sectional imaging follow-up to determine the outcome. A majority of the studies focused on interobserver reliability and analysis to validate their findings. Although the related clinical findings and interobserver results did not relate to the methodology of plaque morphology, the studies were still included in this article for the purpose of reporting on their diagnostic accuracy. No articles were identified for cost-effectiveness analysis.
<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical Subgroup</th>
<th>Start/End Year</th>
<th>No. Patients</th>
<th>Reference Standard(s)</th>
<th>Diagnostic Feature for RISK STRATIFICATION</th>
<th>US Imaging Modality</th>
<th>Jadad-Kingstone Score</th>
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<tr>
<td>AbuRama et al., 2002</td>
<td>Asympto-matic 60-69% stenosis</td>
<td>July 1997-June 1999</td>
<td>382</td>
<td>Clinical observation</td>
<td>Heterogenous plaque</td>
<td>B-mode</td>
<td>11</td>
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<td>Verhoven et al., 2005</td>
<td>Asymptomatic and symptomatic</td>
<td>n/a</td>
<td>404</td>
<td>Carotid endarterectomy</td>
<td>Increase atheroma size</td>
<td>B-mode</td>
<td>13</td>
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<td>Carra et al., 2003</td>
<td>Asymptomatic</td>
<td>January 1990-January 2000</td>
<td>230</td>
<td>Clinical observation</td>
<td>Heterogenous, irregular surface</td>
<td>B-mode</td>
<td>9</td>
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<tr>
<td>Nicolaides et al., 2010</td>
<td>Asymptomatic</td>
<td>January 1990-January 2000</td>
<td>1121</td>
<td>Clinical observation</td>
<td>Heterogenous, DWA, ulceration, increased plaque area</td>
<td>B-mode</td>
<td>13</td>
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<tr>
<td>Baroncini et al., 2007</td>
<td>Asymptomatic and symptomatic</td>
<td>February 2003-July 2005</td>
<td>31</td>
<td>Carotid endarterectomy</td>
<td>Plaque classification, surface alterations, hemorrhage or thrombotic deposits</td>
<td>B-mode</td>
<td>13</td>
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<tr>
<td>Crossboli et al., 2001</td>
<td>Asymptomatic and symptomatic</td>
<td>1994-1996</td>
<td>111/135</td>
<td>Clinical observation</td>
<td>Echolucency</td>
<td>B-mode</td>
<td>11</td>
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<td>Methiesen et al., 2001</td>
<td>n/a</td>
<td>3 years</td>
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<td>Clinical observation</td>
<td>Echolucency</td>
<td>B-mode</td>
<td>11</td>
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<td>Saba et al., 2006</td>
<td>Asymptomatic and symptomatic</td>
<td>January 2004-October 2005</td>
<td>237</td>
<td>Carotid endarterectomy</td>
<td>Surface irregularities, plaque echotexture, classification, ulceration</td>
<td>B-mode</td>
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<tr>
<td>Heliopoulos et al., 2006</td>
<td>Symptomatic</td>
<td>2003-2004</td>
<td>284</td>
<td>Inteobservation</td>
<td>Ulceration</td>
<td>2D and 3D US</td>
<td>13</td>
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<tr>
<td>Landry et al., 2004</td>
<td>Asymptomatic and symptomatic</td>
<td>n/a</td>
<td>40</td>
<td>Inteobservation</td>
<td>Variability with smaller plaque volume</td>
<td>3D</td>
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<td>Ludwig et al., 2006</td>
<td>n/a</td>
<td>n/a</td>
<td>45/60</td>
<td>Inteobservation</td>
<td>Volume measurement</td>
<td>3D</td>
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<td>Nicolaides et al., 2003</td>
<td>Asymptomatic</td>
<td>n/a</td>
<td>n/a</td>
<td>Clinical observation</td>
<td>Specific parameters for reproducibility</td>
<td>3D</td>
<td>11</td>
</tr>
</tbody>
</table>
Table 2
Jadad-Currie-Kingstone Scale Questionnaire

1. Was the protocol detailed and appropriate? (+1 point)
2. Were there adequate exclusion criteria? (+1 point)
3. Was there a description of withdrawals and dropouts? (+1 point)
4. Were the data clearly and adequately reported? (+1 point)
5. Is the sampling method appropriate, free of sampling bias and valid externally? (+1 point)
6. Is the report current? Are the results and instruments valid today? (+1 point)
7. Is the sample size sufficient to be statistically valid? (+1 point)
8. Are the outcomes of interest identified and appropriately evaluated? (+1 point)
9. Are statistical methods appropriate and adequately explained? (+1 point)
10. Was data collected prospectively? (+1 point)
11. Is an appropriate gold standard used and justified? (+1 point)
12. Were study limitations identified and discussed? (+1 point)
13. Is the study sample sufficiently broad that the results are valid to other populations? (+1 point)
14. Are the conclusions consistent with the actual results? (1 point)

Study Quality
Taking into consideration the purpose of each study, the reviewer determined that 92% of the studies used an accurate reference standard. Few studies were criticized for inadequately addressing the issue of interobserver variation. Major pitfalls and areas of weakness identified included outdated equipment and technological use, limited information on the plaque grading system used or variability among studies, failure to use an appropriate gold reference standard, and lack of correlation with patients’ symptoms or neurological events. One report was criticized as poorly written.

Plaque Echo Texture
Plaque echogenicity as assessed by B-mode US reliably predicts the soft-tissue content and amount of calcification in carotid plaques. Specific plaque echo texture assessment for increased risk factors for CV events was the basis for univariate analysis in previous studies conducted in the 1990s. A plaque consisting of mixed high-, medium-, and low-level echoes and containing zones with echolucency is labeled “inhomogeneous” or “heterogeneous,” whereas “homogeneous” plaques present uniformly high-level echoes and are more echogenic.13

Plaques with identifiable echo texture have been associated with an increased prevalence of stroke rate compared with homogenous plaques. Two studies included in this review reported on plaque echogenicity. The first study, by AbuRama et al. (2002),14 reported on 382 asymptomatic patients and detailed the specific plaque appearance for >60% stenotic lesions using duplex US. Two different observers categorized the plaque as hyperechoic, isoechoic, or hypoechoic and classified the atheroma as either heterogeneous or homogenous. A third observer was integrated into the study to make the final determination if differences between the first two observers persisted. The study concluded that there was a greater incidence of neurologic events in the heterogeneous cohort than in the homogenous group. Progression was also more common in the heterogeneous group.

In a second, comparable study, Verhoven et al. (2003)15 assessed the characteristics of plaques in both asymptomatic and symptomatic patients. Although both studies demonstrated similar outcomes for the asymptomatic patients, Verhoven et al. found that patients with amaurosis fugax displayed characteristics similar to those characteristics found in asymptomatic patients. Despite this important finding, this patient population still had a decreased prevalence of atherosomatous plaques and an increased presence of collagen-rich, more fibrous plaques compared with the symptomatic population. Verhoven et al. also found that the incidence of atheroma size increased with symptomatic stroke symptoms. Both studies concluded that the use of imaging to determine the specific plaque characteristics associated with vulnerability of the morphology may be useful for selecting therapy for this at-risk population.

Plaque Characterization with US
Carotid plaque characteristics have been analyzed previously in relation to symptomatic and asymptomatic carotid patients. Throughout our literature search, various methods of echographic image standardization were described. Standardized plaque analysis and characterization is lacking, and, to our knowledge, no global classification system or form of image standardization exists. Currently, the only standardized form of carotid disease assessment is stenotic grading. Carra et al. (2003)16 reported on 230 asymptomatic patients (460 carotids) with stenotic internal carotid artery lesions and analyzed the internal carotid artery stenotic lesion (n = 396) to correlate the degree of stenosism with the echographic pattern and endoluminal surface appearance. Plaque characteristics were classified by the use of Gray-Wolfe criteria, with subcategories for the endoluminal surface. Like the preceding reports, this study found that inhomogeneous lesions had an increased association with clinical events compared with homogenous lesions (p < 0.001), and neurologic events were observed more often in patients with plaques with irregular surfaces (5.8%) than those with regular surfaces (0.9%).15 The surface irregularity also correlated with progression of the stenosis (p < 0.001), and an increased association with neurologic events was reported with each progressive plaque classification: Type I, 16%; Type II, 19%; Type III, 19%; Type IV, 10%; and Type V, 19%.16 The study did have two major
enhanced plaque ultrasound to identify lipid-rich core lesions and to predict the risk of stroke. This study found a strong correlation between plaque echolucency and the risk of stroke, with a 5-fold increase in the risk of stroke for patients with >50% stenosis and echolucency compared to those with >50% stenosis without echolucency.

Plaque Echolucency

Plaques appearing with an area of echolucency on B-mode imaging are associated with a greater risk of stroke and other cardiovascular events. This finding is consistent with previous studies that have shown a correlation between plaque echolucency and the occurrence of stroke, particularly in patients with high-grade carotid stenosis.

Two studies evaluated the specificity of plaque echolucency in vulnerable carotid plaque analysis. Both studies used B-mode imaging to identify specific plaque changes and early echolucency within the plaques to prospectively test the hypothesis that stroke development could be predicted by echolucency in carotid atherosclerotic plaques in both symptomatic and asymptomatic patients with significant stenoses. Gronhold et al. (2003) prospectively recruited 111 asymptomatic and 135 symptomatic patients with >50% relevant carotid artery stenosis. The authors focused on US measurement of plaque echolucency to indicate lipid-rich cores using the standardized method of B-mode imaging.

Results indicated that the objective measurement of echolucency in vulnerable carotid plaque plaques compared to echo-rich plaques predicted a 3.1-fold risk of ipsilateral ischemic strokes (95% CI: 1.3-7.3) in previously asymptomatic patients. In these patients, the echolucency in 80-90% stenotic lesions predicted an 8-fold risk compared with echo-rich areas in 50-79% stenotic plaques. The major weakness in this study was the lack of information to rule out origins other than the carotid plaque as a source of embolism. Deficient B-mode optimization, such as harmonics or compound imaging to reduce the limitations of low spatial resolution and artifacts, was another weakness; however, this technology was most likely unavailable at the time of the study.

In contrast to the preceding work, Mathiesen et al. (2001) observed and followed 223 subjects with moderate-to-severe carotid stenosis and 215 control subjects for 3 years to examine the identification and progression of echolucency. This study first used echographic plaque assessment with a modified version of the Gray-Wade grading system to develop a scoring system for echolucency; this scale ranged from 1 to 4, with 1 being predominantly echolucent and 4 being predominantly echogenic. The vessel lumen was used as the reference structure to define echolucency, and the far wall media-adventitia was used as the reference structure to define echogenicity. Similar to Gronhold et al.’s (2001) study, subjects with echoluent carotid plaques had a much greater risk of CV events than subjects with other plaque types, thus supporting the existence of increased risk of stroke in subjects with echoluent plaques.

Plaque Ulceration

Identification or evidence of ulceration in plaque signifies an important risk for CV events. This finding...
plus a high-grade stenosis increases this risk even more. Conventionally, ulceration is more frequently imaged with CT, but it can also be imaged with US. Saba et al. (2006) evaluated the role and diagnostic efficiency of CT and US in a study cohort of 237 patients with ulcerated carotid plaques and compared it with surgical specimen. In addition to the degree of stenosis, three major parameters were used to evaluate plaque characteristics using US: plaque echogenicity using a modified Gray-Weale classification, plaque surface irregularities, and plaque echo texture. The results of this study indicated that although CT identified 31 ulcerations (93.75% sensitivity, 98.59% specificity), US detected 12 of the 32 ulcerations, resulting in a sensitivity of 93.75% sensitivity, 91.5% specificity, positive predictive value of 66.5%, and negative predictive value of 76.5%. Of these 12 ulcers, 75% were found in Type 2 plaques, and the majority of these ulcers were heterogeneous (83%). Ulceration was more commonly found in fatty plaques than in calcified plaques. The lower sensitivity of US in this study may have been attributable to several factors, one in particular being that the US was performed by vascular surgeons and residents as opposed to experienced sonographers or radiologists. In addition, CEA was not performed in all 237 patients, so it was impossible to evaluate the presence of ulceration in 134 patients. Saba et al.’s (2006) study revealed that the number of ulcerations increased with the severity of the stenosis (16.6% with a stenosis degree of 50–69% and 33% with a stenosis degree of 85–99%). Although this study showed that CT was optimal for detecting ulceration, US still had a fairly good outcome in uncovering ulceration; therefore, it should still be used to attempt to identify ulcerations on plaques, especially in high-grade stenoses.

**Advanced Method Using 3D US for Plaque Characterization**

Improving US’s eminence for plaque imaging is important for allowing additional information acquisition and elucidating the possible pathophysiology of stroke, leading to better stroke prevention. Newer US techniques, such as 3D US, are showing great potential to maximize the information traditionally gathered by B-mode. B-mode has its limitations, because of its single-plane projection and its inability to identify the true plaque circumferential asymmetrical development, which can be minimized using 3D US. In addition, 3D US may improve the quality of characterization for plaque surface morphology, volume and echo texture. Although at the time of the review, specific studies using 3D US for echo morphology were lacking, we anticipate a surge of studies in the next few years. Only one identified study used 3D US for plaque characterization. Helipoulous et al. (2009) examined a total of 284 carotid arteries with >50% stenosis in symptomatic patients, using a combination of 2D plaque extension and morphology and 3D US for plaque ulceration. Ulceration was defined if a recess at least 2 mm in length and 2 mm in depth was identified and flow vortices using color Doppler were present. Sixty-two of the arteries had plaques that were accessible for visibility and thus characterizable using the 3D technique. Study results indicated that 3D US was reliable in characterizing the surface morphology of the carotid plaque and that 3D US identified ulceration more frequently than 2D US, particularly in the proximal upstream portion of the plaque. Although this study did identify a positive step towards 3D US imaging, its failure to validate its results with surgical histological specimens represents a major weakness. A major pitfall with 3D US imaging is the probe technology and the use of freehand manual manipulation for imaging. Unfortunately, this technology can cause considerable variations in the angular relationship of skin, sweep speed, and image lanes to remain parallel to each other, which in turn can increase the interobservation variability. We identified two small studies in which the authors examined the diagnostic performance and utility of 3D US for morphologic plaque assessment. Landry et al. (2004) presented 3D US data on 40 patients who were followed for carotid stenosis. Plaque geometry and distribution of the plaque was not used for the selection criteria for this study. Five or six 3D US scans were performed bilaterally for each patient, and five observers reviewed the best 3D images. The observers were trained during several tutorial sessions to manipulate the images to identify and measure the plaque, using manual planimetry for volume with the 3D US. Each observer sliced the 3D image with a thickness of 1.0 mm from one endpoint of the plaque to the other and traced the plaque boundaries; then each slice was summed and multiplied to calculate the plaque volume. The study results indicated that the intraobserver and interobserver measurement reliabilities were 94% and 93.3%, respectively, and that plaque volume measurement variability decreased with increasing plaque volume (range: 27.1–2.2%). The repeated 3D US scans determined no significant differences compared with single-scan measurements (p = 0.867). The identification of dropouts and shadowing caused by calcification in the plaque caused the US beam to attenuate and could hinder the identification of plaque boundaries. Landry et al. (2004) suggested the use of Sono-CT to minimize this effect.

In a similar study, Ludwig et al. (2008) measured intraobserver variability in the evaluation of plaque volume measurement using 3D US. Two separate data sets of 45 and 60 were used for assessment with manual planimetry. Trained sonographers imaged the plaque by using a mechanical 3D-probe and an axial resolution of 0.1 mm. Each of the readers reporting the volume performed two independent evaluations. Intrarater variability, reflected by the intraclass correlation coefficient, was 0.985, 0.967, and 0.969 for three appointed readers and was 0.964 among the three readers, indicating that it was small. A subgroup analysis indicated that the intra- and interreader variability were lower for larger plaques than for smaller ones, as indicated by the coefficient of variation. The final results indicated that using a standardized, central 3D US reading protocol and applying strict quality control
procedures provided high-quality, reliable US readings of plaque imaging using 3D. The use of an increased number of slices in smaller plaques to account for the higher variability in smaller plaques could have reinforced this study.

Diagnostic Performance: Quality Control and Operator Dependency of US

With the increasing concern about US and its reproduction quality, variability, and interobservation unevenness, the quality and consistency of examination is an important aspect in assessing imaging techniques. In the study by Nicolaides et al. (2003),10 the quality of collected data and quality control of the Asymptomatic Carotid Stenosis and Risk of Stroke Study were evaluated in the standardization of plaque imaging and characterization. The Asymptomatic Carotid Stenosis and Risk of Stroke Study was the first scientific study to assess high-grade (>50%) stenotic lesions and plaque characterization with clinical risk factors. This arm of the study adequately collected information on the methodology, such as the instrumentation settings, method of recording date, standardization of the method of scanning and personnel training. A high-quality level of data collected from this study identified that applying prerequisites is essential to adding credibility to the study results. Recommended prerequisites include low persistence setting, high frame rate, maximum dynamic range, time-gain compensation, sloping through tissues positioned vertically through the vessel lumen, overall gain to optimize image and having the US beam perpendicular to the artery wall so the plaque occupies a large portion of the image.10 Scanning specifics identified in this quality control study provides guidance and perhaps standards for plaque imaging and characterization.

Discussion

We conducted a systematic review of studies published between 2001 and 2011 in which the authors used US for the characterization of carotid atherosclerotic disease. Many relevant studies on US plaque characterization were published before 2001; however, we elected to focus our review on research published after this time frame because technological changes and advancement have renewed, if not replaced, previous applications for plaque imaging. Our search was restricted to articles published in peer-reviewed medical journals because we believe that this evidence carries the most weight.

The value of US for plaque assessment and characterization appears to remain underresearched. This lack of research may be because many trials are ongoing, considering the new emergence of this imaging procedure. Despite the steady accumulation of evidence, we believe future research could be valuable by providing the following suggestions:

- Diagnostic performance studies should be undertaken in which investigators evaluate the accuracy, sensitivity, and specificity of US plaque imaging and characterization by using myriad techniques in combination and, if relevant, surgical specimens as opposed to other imaging modalities to confirm findings.
- Several features of plaque echomorphology should be included to increase the potential risk stratification.
- Image standardization, classification criteria, and thresholds should be used to aid in the interpretation of quantitative grading.
- Radiologists or observers who are interested in the evaluation of plaques should be blinded to the stenotic or clinical assessment results to remove all biases from the study.
- Information about whether extra imaging or sequential interpretation time is justified to improve diagnosis and patient care and provide a diagnostic impact study.
- A pilot study could be used first and foremost to attempt the above; however, for statistically precise conclusions, studies on US plaque assessment should include a large sample size and recruit sufficiently large patient cohorts from various clinics or hospital settings as in some clinical subgroups, there were no large studies.
- A time frame of less than 3 months should be applied from the onset of imaging to the final surgical specimen to minimize the alteration of plaque changes.
- There has been little to no discussion of the cost-effectiveness of US plaque imaging; therefore, it should be calculated in various ways, including cost per additional case correctly diagnosed, cost per additional examination avoided, and cost per year of survival and quality of life.
- The inclusion of both symptomatic and asymptomatic patients should be considered for stratifying the risk of stroke because this factor has not been investigated, and previous US studies of plaque primarily included asymptomatic patient cohorts.
- The nature of DWA remains undetermined and because of these areas being at risk for CV events, they merit further investigation.

Conclusion

The 12 studies found in our search for US carotid plaque imaging provided encouraging findings that plaque characterization can make a significant contribution to the diagnosis and management of patients with potentially vulnerable plaque, providing early identification of CV event risk. We anticipate that additional well-designed, prospective studies integrating some of these studies’ components will provide more definitive evidence that other policy makers may be seeking prior to making coverage decisions. A number of small studies has demonstrated that US plaque imaging with the simultaneous use of B-mode and 3D US can accurately distinguish specific distinctive findings that are may be indicators of vulnerable plaques. This work must now be extended to demonstrate its
use, accuracy, and validity in everyday clinical imaging findings. It would be of interest to analyze plaque echogenicity, echolucency, and surface morphology with a consistent plaque characterization classification system without complex computer software and to minimize the discrepancy between imaging sites by using standard commonly used US equipment available in most vascular labs.

References
Carotid Artery Disease Imaging: A Home-Produced, Easily Made Phantom for Two- and Three-Dimensional Ultrasound Simulation

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ABSTRACT
Background and Purpose.—Ultrasound (US) plaque characterization has great potential with regard to maximizing the information traditionally gathered with spectral Doppler examination. It can directly visualize plaque and quantify better features such as surface morphology, geometry, volume, and echotexture via B-mode and the three-dimensional (3D) imaging mechanism. One of the major pitfalls of carotid imaging is the use of freehand manual manipulation. The application of angling, steering, as well as variability in the technical parameters, can increase the interobservation inconsistency. A limited number of commercial phantoms are available to teach this advanced technique but come at a high cost. We developed a home-produced phantom model to practice and teach carotid atherosclerotic disease imaging. We also investigated interobservation variability using two-dimensional (2D) characterization and 3D mechanical planimetry. This study presents a recipe to create an ultrasonic phantom that simulates a diseased carotid artery segment and how it can be used in identifying the 2D and 3D US interobservation variability.

Methods.—We created five tissue-like phantoms to simulate various types of diseased plaque segments. To simulate the plaque, a piece of frankfurter was cut and detailed to represent various forms of diseased plaque. Each mould contained dissimilar types of mimicked-plaque, including a soft-plaque, fissured, ulcerated, irregular surfaced, and calcified segment. We used a mixture of gelatin and Metamucil to mimic a previously published soft-tissue mixture. To create a vessel, we used a powder-free, nitrile examination glove. The frankfurter was held in place inside the middle finger of the glove using adhesive gel and filled with mineral oil. Preparation included interval refrigeration of the concoction of the mould. Trained sonographers imaged the plaque using a linear small parts probe for 2D and a mechanical 3D probe for 3D US. Two neuroradiologists assessed the corresponding images and reported their findings including the internal plaque contents, volume, and geometry. Analysis was performed on the inter-observation and inter-reading variability.

Results.—Interobserver and interreader reliabilities were high, and plaque volume measurement variability decreased with increasing plaque volume. There was increased sensitivity and specificity for each plaque phantom with the use of 3D versus 2D alone. Neuroradiologists reports were 96% sensitive and 97% specific, respectively, when they used combined 2D and 3D US.

Conclusion.—We created a 2D and 3D vascular US carotid phantom. This phantom is an excellent educational tool to simulate various degrees of diseased carotid segments; moreover, it can be made easily and inexpensively and is reusable. This phantom represents the vessel anatomy and pathology extremely well. We implemented a standardized scanning protocol and created a plaque morphological worksheet to cover all plaque characterization criteria and achieve optimal imaging. Results indicated minimal interobservation and interreader variability. Additional studies are required to address the phantom’s longevity and whether or not it can improve the sonographer’s skills.

Introduction
Ultrasound (US) carotid plaque characterization has shown great potential to maximize the information traditionally gathered with spectral Doppler examination by demonstrating the ability to directly visualize plaque and to quantify features such as surface morphology, geometry, volume, and echotexture via the use of the B-mode and three-dimensional (3D) US imaging mechanisms. Carotid two-dimensional (2D) and 3D US plaque imaging is emerging as the predominant approach in identifying and evaluating the progression of carotid atherosclerosis. This, in turn, maximizes the information quality traditionally gathered by B-mode.
Carotid plaque imaging can be challenging for any novice learner because of the high variability in plaque types, location, and imaging challenges. A major pitfall with carotid plaque imaging is the use of freehand manual manipulation for angling, steering for imaging, as well as the variability with technical parameters, which in turn can increase the interobservation variability. A limited number of commercial phantoms are available to teach this advanced technique but are expensive. We developed a phantom model to practice and teach carotid atherosclerotic disease imaging and to investigate the interobservation variability by using 2D characterization and 3D mechanical planimetry. This study presents a homemade recipe for an ultrasonicographic phantom simulating a diseased carotid artery segment and its use in identifying interobserver variability in 2D and 3D US. We describe an easily made, low-cost preparation of a carotid phantom that has proven to simulate a diseased vessel extremely well.

**Methods**

We created five tissue-like phantoms to simulate various types of diseased plaque segments. To simulate the plaque, we tested various items—corn, olives, Play-Doh, and compound putty—in an attempt to recreate the specific appearance of carotid atheroma (Figure 1A and B). After several trials, we determined that a piece of frankfurter was the substance that best mimicked the plaque. To simulate various diseased components of plaque, a piece of frankfurter was cut and detailed to represent the pathology. Each mould contained dissimilar types of mimicked-plaque including a soft-plaque, fissured, ulcerated, irregular surfaced and calcified segment (Figure 2A and B).

To create a vessel, a powder-free, nitrile examination glove was used. The frankfurter was held in place inside the middle finger of the glove with the use of superglue adhesive gel. Once sufficient drying time was applied, the glove was flipped inside out and filled with the mineral oil to create a tubular structure. The original design consisted of the use of ultrasound gel to fill these hollow tubes; however, after the trial, we quickly realized that the gel trapped air bubbles in the vessel, which impeded the visibility of the plaque. We discovered that mineral oil was the best substance to use as it left a smooth, anechoic filling to the structure. Special care had to be taken when filling the finger with the oil to minimize the amount of trapped air. The fingers were tied together in a knot at the upper end of the fingers to create a tubular-like structure in the distal portion of the middle finger. The remainder of the glove was then cut off resulting in a representative-sized carotid segment. The oil was washed off the tip using dish soap to remove any residue. The creation was placed aside.

Each phantom was formed combining the following from previously published mixture for soft-tissue: 250 mL of water, two packets of Knox brand gelatin, and one tablespoon of sugar-free psyllium hydrophilic muciloid fiber (brand name Metamucil). Powdered ingredients were combined and dissolved in one-fourth of the final volume of iced water. The remainder of the water was then heated to near boiling and added to the mixture and gently whisked to avoid introducing any air bubbles. The concoction was then poured into a bowl to form the base layer of the mould. The tubular structure was then placed in the middle of the mixture bowl and set to refrigerate until firm (approximately 1–2 hr). This base layer of the mould trapped the inclusion (Figure 3A). Once the moulds congealed, another gelatin-Metamucil mixture was prepared and poured on top of the base layer until the container was filled to the point that the tubular structures were no longer visible. The mould was then chilled a second time until firm (Figure 3B). At this point the phantom was ready for use.

We found this mixture quick and easy to make, and the cost per phantom was less than $2.00 each. Experienced registered sonographers imaged each plaque phantom using a linear small parts probe for 2D and a mechanical-3D probe for 3D US. All sonographers were trained and experienced in carotid sonography; however, they did not have plaque imaging morphology experience or training. Two neuroradiologists assessed the corresponding images and reported their findings, including the plaque volume and geometry. Analysis was...
performed on the interobservation and interreading variability.

Results

Five sonographers scanned the phantoms by using a set protocol provided and reported their findings using a standard report form for each mould. All sonographers were trained and experienced in carotid sonography; however, they did not have plaque-imaging experience.

The use of 2D imaging alone yielded the following: interobservation reliability was significantly high in identifying each specific pathology. In each case, high reliability was also identified in plaque location and twinkling artifact. Consistency was moderately high in the agreement for echotexture, type of classification, and surface alterations despite the sonographers’ lack of experience in plaque morphology. Fissures yielded poor reliability; moreover, fissures and surface irregularity on 2D alone were poorly identified because the sonographers had difficulty distinguishing between them and a true ulceration (Figure 4A and B). The largest areas of weakness identified were in the subcategorical plaque classifications such as the intensity analysis and areas of echolucency. We strongly suspect this may be attributable to the sonographers’ inexperience in plaque morphology, and it would be of interest to repeat this study post-training.

3D US interobservation reliabilities were significantly high for all phantoms. Minimal interobservation discrepancies occurred. 3D US was easily able to distinguish between fissures and ulcerations, commonly missed on 2D alone (Figure 5A and B). All plaque volume measurements differed slightly, but the variability decreased with increasing plaque volume. Results indicated an increase in sensitivity and specificity of each plaque phantom with the use of 3D versus 2D alone.

Discussion

Five tissue-like carotid atheroma phantoms were produced using widely available materials and a previous reported formula for soft tissue. A detailed frankfurter, submerged in mineral oil in a tip of a glove...
finger was used to mimic carotid atheroma, creating a "vessel." A psyllium hydrophilic mucilloid fiber mixture was used to produce a soft tissue appearance and encase the tubular structure. The echotexture of this material simulated a carotid artery segment within soft tissue and was easy to reproduce and create various forms of pathology within the tubular segment. The top layer of the gelatin mixture further coats the scanning surface and prevents any lacerations, prolonging the life of the phantom. These phantoms demonstrated an excellent carotid segment representation and were created quickly and inexpensively, costing less than $2.00 per unit volume. The phantom recipe was very simple and allowed for deviations while still producing acceptable results. We did not encounter any failures in our multiple phantoms creations.

The purpose of our phantom study was to use the tool as performance evaluation for sonographers learning carotid plaque imaging and for reporting radiologists. Because the phantoms were created for educational purposes only, we did not measure the speed of sound in the mediums, scatter coefficients, or attenuation coefficients. The phantoms lasted for several weeks when refrigerated. Optimal scanning was observed at 1-week time intervals because of the reduction of air bubbles or debris within the “vessel" and the maximum signal intensity from the frankfurter piece. We did not assess whether any significant microbial degenerations were present several weeks after the phantoms were created and subsequently disposed. We did not test the phantom longevity at room temperature.

Vascular experienced sonographers yield a high interobservation reliability using both 2D and 3D US for plaque assessment, despite the lack of training in plaque morphology. There appeared to be a lack of consistency between sonographers with regard to agreement in the subcategorical plaque classifications such as echotexture, type of classification, and intensity analysis; however, upon reviewing our standardize worksheet, it would have been beneficial to further explain the plaque classification type to better quantify the imaged segment. We strongly suspect this may be a result of the lack of education in plaque morphology, and it would be of interest to repeat this study post-training. The fissured segment yielded poor reliability when only 2D was used but was significantly enhanced when 3D US was used, thus enforcing the use of 3D US to better quantify plaque morphology. This study confirmed that the use of 3D US reduced the interobservations and interreader variability to next to none, and increased the sensitivity and specificity of each plaque phantom with the use of 3D versus 2D alone.

Conclusion

US carotid plaque characterization and morphology is increasingly being applied in everyday clinical applications of carotid imaging using US. With the use of 2D and 3D US, plaque imaging is emerging as the leading

Figure 4

(A) and (B) 2D and 3D imaging of a simulated irregular surface of a plaque.

Figure 5

(A) and (B) right and left: 2D- and 3D-reformatted imaging of a simulated ulcerated plaque.
approach to identify and evaluate the progression of carotid atherosclerosis and has great potential to maximize carotid plaque information.

We created a 2D and 3D vascular home-produced US carotid phantom. Previously educational tools such as these phantoms are limited or costly. This phantom is an excellent educational tool to simulate various degrees of diseased carotid segments: it can be made easily and inexpensively, and is reusable. This reusable phantom represents the vessel anatomy and pathology extremely well and can serve as a great teaching tool to enrich novice and experienced students, sonographers, residents and fellow staff learning carotid plaque morphology. We implemented a standardized scanning protocol and created a plaque morphological worksheet to cover all plaque characterization criteria and achieve optimal imaging. Results indicated minimal inter-observation and inter-reader variability. Additional studies are required to address the phantom’s longevity and whether it can improve the sonographer’s acquisition of skills.

References

Comparison and Accuracy of Carotid Plaque Analysis Between Two- and Three-Dimensional Ultrasound Imaging

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Abstract

Plaque characterization using traditional two-dimensional (2D) imaging and/or three-dimensional (3D) ultrasonographic (US) techniques is a new method for evaluating artery wall morphology and plaque risk stratification. The purpose of this study was to assess and compare 2D and 3D US, measuring the interobservation differences for specific plaque-imaging analyses. Phantoms that simulated various types of atherosclerotic plaque pathology were imaged and findings reported by three experienced sonographers. Interobservation agreement and subanalyses were created. For each type of plaque pathology, agreement was moderate; however, conformity increased with the application of 3D US versus 2D US alone. Agreement was best for the identification of fissures, ulcerations, and irregular plaque surface. Advanced sonographic techniques for carotid plaque imaging provide a reproducible method in the analysis and morphologic assessment of simulated carotid atheromatous lesions, with superior interobserver variability. Three-dimensional US improves visualization of some pathologies and may provide additional information in the evaluation and risk stratification of vulnerable carotid plaque.

Keywords

sonography, plaque, characterization, vulnerable

Characterization of carotid atherosclerotic plaque morphology by sonography has shown great potential to increase the amount of diagnostic information traditionally gathered with routine carotid Doppler examinations. Sonographic imaging has shown the ability to visualize plaque directly and quantify certain features such as surface morphology, plaque geometry, and echotexture, using two-dimensional (2D) gray-scale B-mode imaging. Improved methods are being investigated to identify potential markers of high-risk plaques, in the hope of identifying specific imaging parameters to help describe a patient’s overall vascular risk. These modalities include the use of high-resolution sonography using newer high-frequency probes and volumetric three-dimensional (3D) imaging. Studies have reported that 3D sonography used as a complementary imaging technique may provide additional information in the evaluation and risk stratification of vulnerable carotid plaque beyond traditional 2D imaging.1–3

Carotid 2D and 3D plaque imaging is emerging as the predominant approach in identifying and evaluating the progression of carotid atheromas.1 To our knowledge, no published studies have measured the interobserver analysis of various plaque pathologies and assess the value of 3D sonography, in addition to the routinely used 2D plaque imaging. The purpose of this study was to evaluate the utility of advanced sonographic plaque imaging for carotid plaque analysis.
characterization using high-resolution 2D and 3D imaging for morphologic assessment of simulated diseased carotid artery segments. In addition, the interobservational differences of 2D and 3D sonography, respectively, were assessed for specific simulated plaque pathologies.

Materials and Methods

Phantoms

Twelve tissue-like phantoms, with five simulated carotid specimens each, were created using a previously published method to mimic various types of diseased atherosclerotic plaque segments. To simulate the internal echotexture of the plaque, a number of items were tested including whole corn kernels, olives, modeling compound (Play-Doh, Hasbro, Pawtucket, RI), and compound putty, in an attempt to re-create the specific appearance of internal carotid artery atheromatous lesions. We determined that a segment of animal meat protein with internal coagulated milk casein provided the best tissue-mimicking echolucency within the model. Mustard seeds were added to some specimens to simulate calcifications. Each phantom specimen was shaped and precisely cut to represent specific pathologies within types of atherosclerotic plaque, with model characteristics including fissured, ulcerated, irregularly surfaced, internally echolucent, and calcified segments. Each prepared specimen was placed on the small finger of an examination glove and held in place using adhesive gel. Once the adhesive had been allowed to dry, the glove was turned inside out, and the finger with the specimen was filled with mineral oil to create a tubular structure that simulated a blood vessel, within the distal portion of the finger (Figure 1). Special care was taken when filling the glove finger with mineral oil to minimize the amount of trapped air and/or small air bubbles. The remainder of the glove was then cut off, resulting in a model with a representative sized (1.0-1.5 cm) segment simulating an atherosclerotic plaque.

These models of atherosclerotic plaque were then suspended in tissue-mimicking molds made from a mixture of gelatin, water, and psyllium hydrophilic mucilloid fiber to provide echogenicity comparable to soft tissue (Figure 2). In previous analysis of these phantoms for image quality, plaque representation, and reporting of findings were assessed and showed minimal variability between sonographers and interpreters, with appropriate representation of vessel anatomy and/or pathology by sonography.

Sonographic Examination and Analysis

Detailed sonographic examinations were performed on the phantoms using an iU22 ultrasound system (Philips Healthcare, Bothel, WA) equipped with a linear high-resolution, small-parts probe (L-12 MHz) for 2D sonographic imaging and a volumetric mechanical, high-resolution linear-array transducer (VL-13 MHz) for 3D imaging. The assessment began with a systematic overview of the carotid artery phantom specimen using high-resolution 2D imaging. Each sample was evaluated for specific morphologic features: internal echolucency, presence of fissure(s), presence of surface ulceration(s), surface irregularity, internal calcification(s), and no abnormality detected (NAD). All of the phantoms were of fairly equal size, thus the lead sonographer preset the unit’s primary imaging parameters (depth, focus, resolution, gain) to maintain consistency between scans. Time gain
compensation was not preset but was adjusted manually by each sonographer to optimize image quality for each specimen.

Each of the three registered vascular sonographers, blinded to the phantom’s simulated pathology (if any) and any other sonographic data, independently performed a high-resolution 2D evaluation of the specimens. All three sonographers were trained and experienced in carotid duplex sonography; however, the sonographers varied in their level of experience in the sonographic evaluation of carotid plaque morphology. The senior sonographer had more than 10 years of experience, the second sonographer had 5 years of experience, and the third was a novice sonographer with less than 1 year of experience. Each sonographer reported their 2D findings independently on a worksheet.

The imaging process was repeated using the volumetric 3D probe. On switching to the 3D volumetric imaging mode, scanning parameters such as volume angle, acoustic output power, gain compensation, focus, zoom, and imaging depth were preset for each case by the lead sonographer prior to the acquisition of the 3D image. The 3D probe swept the region of interest of the phantom mechanically with a fixed frame rate of approximately 10 per second, resulting in a final 25-slice volume set. At the end of the scan, the acquired 3D sequential volume-rend ered images were stored digitally for further analysis by 3D automated software that was routinely available on the system. Each sonographer evaluated the phantom by rotating the x, y, and z axes in the 3D volume view as needed. To further evaluate the internal echotexture(s), the sonographers could also select precise slices of the volumetric data set. Constructed 3D plaque images were assessed independently and evaluated using the same morphologic features as for the 2D images, and the findings were reported on the worksheet.

Based on a previously published literature review of carotid plaque characterization and earlier experimentation with the phantom model, specific imaging criteria were adopted to quantify the pathology of each specimen. The phantom was considered to have NAD or regular when no variations in the phantom’s surface contour larger than 0.3 mm were observed and/or no alterations in the internal echotexture or echogenicity were noted. Internal echoluency was identified as a focal hypoechoic or echolucent internal area within the plaque structure (Figures 3a and 3b). An irregular surface contour was defined as an observed variation greater than 0.3 mm (Figures 4a and 4b). Surface ulceration in the phantom was defined by a focal irregularity or break in the surface of the phantom of greater than or equal to a depth of 3 mm (Figures 5a and 5b). A fissure was considered to be present when there was evidence of a linear break in the surface of the specimen (Figures 6a and 6b). Regions of focal, echogenic foci with the presence of acoustic shadowing were defined as calcifications (Figures 7a and 7b).

**Statistical Analysis**

The degree of agreement among the three sonographers was measured by assessing the concordance or inter-rater agreement between each sonographer’s specific findings. Inter-rater reliability was determined by a joint probability of agreement using the intraclass correlation coefficient (ICC) and Cohen’s kappa (κ) coefficient. Inter-rater agreement or reliability was rated on the following scale: an ICC or κ value of 0 to 0.20 indicated poor agreement; 0.20 to 0.40, fair agreement; 0.40 to 0.60, moderate agreement; 0.60 to 0.80, substantial agreement; and 0.80 to 1.00, very good agreement. Inter-rater agreement was evaluated for each of the six morphologic features (NAD,
echolucency, surface irregularity, ulceration, fissure, and calcification) for all levels of experience for both 2D and 3D techniques, followed by subanalyses across levels of sonographer experience (senior, experienced, and novice) and technique (2D versus 3D). In addition, overall sensitivity, specificity, and accuracy were assessed for each morphologic feature and for each technique and level of sonographer experience, using the phantom’s simulated pathology as a reference standard. Statistical analyses were performed using MedCalc Professional statistics software version 12.1.1 (MedCalc Software, Mariakerke, Belgium).

Results
All 60 samples included for the study were evaluated and included in the analysis. All sample data were used to calculate the agreement between 2D and 3D sonography and among the three levels of sonographer experience. Figure 8 shows the agreement (ICC scores) for 2D and 3D scans for specific simulated plaque morphologies, and Table 1 shows the agreement for overall sensitivity, specificity, and accuracy for each technique and level of sonographer experience.
shows the overall strength of agreement among sonographers for the simulated plaque characteristics.

In the regular or NAD specimens, the agreement between the 2D and 3D methods was perfect for the novice sonographer ($\kappa = 1.00$, 95% CI 1.00-1.00) but was substantially lower for the senior and experienced sonographers ($\kappa = 0.65$, 95% CI 0.20-1.00, respectively) compared with the experienced sonographer ($\kappa = 0.83$, 95% CI 0.69-0.97).

Overall agreement in the identification of internal echolucency was very good across all levels of sonographer experience ($ICC = 0.81$, 95% CI 0.74-0.86); however, the agreement increased when sonographers applied 3D sonography ($ICC = 0.89$, 95% CI 0.83-0.93) compared with 2D alone ($ICC = 0.80$, 95% CI 0.71-0.87). In this subcategory, the senior sonographer had the best agreement ($\kappa = 0.83$, 95% CI 0.69-0.97) compared with the experienced and novice sonographers ($\kappa = 0.76$, 95% CI 0.60-0.95).

Observed agreement in the identification of fissures between 2D and 3D was at the lower end of substantial ($ICC = 0.64$, 95% CI 0.54-0.73) across all sonographers. The level of agreement was increased for 3D alone ($ICC = 0.74$, 95% CI 0.63-0.82) versus moderate for 2D alone ($ICC = 0.59$, 95% CI 0.45-0.71). The concordance was highest for the experienced sonographer ($\kappa = 0.83$, 95% CI 0.72-0.9) and lowest for the novice ($\kappa = 0.45$, 95% CI 0.19-0.67).

Plaque surface irregularity agreement was just in the substantial range ($ICC = 0.61$, 95% CI 0.50-0.71) across all levels of experience. There was improved agreement with the application of 3D sonography ($ICC = 0.66$, 95% CI 0.54-0.77) compared with only moderate agreement for 2D alone ($ICC = 0.49$, 95% CI 0.34-0.64). The senior and novice sonographer yielded very good agreement ($\kappa = 0.88$, 95% CI 0.74-1.00, respectively) compared with the experienced sonographer ($\kappa = 0.53$, 95% CI 0.29-0.77).

The observed agreement for calcifications was substantial ($ICC = 0.69$, 95% CI 0.60-0.78), and agreement was substantial among sonographers for each 2D and 3D technique independently ($ICC = 0.78$, 95% CI 0.68-0.85; $ICC = 0.70$, 95% CI 0.59-0.80, respectively). The senior sonographer had the highest agreement ($\kappa = 0.83$, 95% CI 0.69-0.97) compared with the experienced ($\kappa = 0.65$, 95% CI 0.45-0.84) and novice ($\kappa = 0.60$, 95% CI 0.40-0.81) sonographers.

For phantoms depicting plaque ulceration, agreement across all levels of experience was found to be borderline between moderate and substantial ($ICC = 0.60$, 95% CI 0.49-0.70). The 3D sonography had substantial agreement for ulceration ($ICC = 0.67$, 95% CI 0.55-0.77) compared with moderate agreement for 2D sonography ($ICC = 0.53$, 95% CI 0.38-0.66). The senior sonographer had the highest agreement ($\kappa = 0.89$, 95% CI 0.76-1.00) regarding ulceration between 2D and 3D scans compared with the experienced ($\kappa = 0.54$, 95% CI 0.31-0.77) and novice ($\kappa = 0.63$, 95% CI 0.42-0.84) sonographers.

Discussion

Cerebral thromboembolisms are increasingly being recognized as the source of ischemic strokes, as the emboli typically originate from a carotid atheromatous plaque or from a thrombus originating from the site of plaque rupture. Emerging data suggest that the severity of carotid plaque morphology can significantly affect cerebrovascular prognosis. Specific plaque characteristics are associated with neurologic events including a thin or fissured capsule, large lipid core(s), active inflammation, severe stenosis, or a combination of these findings. The identification of early morphologic features and characteristics of vulnerable carotid plaque have opened up new possibilities in the discipline of carotid artery imaging for stroke prevention. Imaging modalities that offer potential identification of
Figure 8. Level of agreement (intraclass correlation coefficient) for two-dimensional (2D) and three-dimensional (3D) imaging techniques in the identification of simulated pathologic features of atherosclerotic plaque.

### Table 1. Overall Inter-rater Agreement Scores (Cohen’s $k$ Coefficient) for No Atheromatous Disease (NAD) and for Each of the Five Types of Simulated Atherosclerotic Plaque Pathology

<table>
<thead>
<tr>
<th>Assessment Criterion</th>
<th>Agreement</th>
<th>Cohen’s $k$</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcification</td>
<td>Substantial</td>
<td>0.69</td>
<td>0.60-0.78</td>
</tr>
<tr>
<td>NAD</td>
<td>Very good</td>
<td>0.85</td>
<td>0.80-0.90</td>
</tr>
<tr>
<td>Echogenicity</td>
<td>Very good</td>
<td>0.81</td>
<td>0.74-0.86</td>
</tr>
<tr>
<td>Uteration</td>
<td>Moderate/substantial</td>
<td>0.60</td>
<td>0.49-0.70</td>
</tr>
<tr>
<td>Fissure</td>
<td>Substantial</td>
<td>0.64</td>
<td>0.54-0.73</td>
</tr>
<tr>
<td>Irregular surface</td>
<td>Substantial</td>
<td>0.61</td>
<td>0.53-0.71</td>
</tr>
</tbody>
</table>

Table 1. Overall Inter-rater Agreement Scores (Cohen’s $k$ Coefficient) for No Atheromatous Disease (NAD) and for Each of the Five Types of Simulated Atherosclerotic Plaque Pathology.

These features include magnetic resonance imaging, computed tomography, and sonography. Sonography is commonly the first-line imaging modality for the initial evaluation of asymptomatic patients at risk for stroke, transient ischemic attacks, or stroke symptoms. Traditionally, carotid duplex imaging is limited to grading specific severities of stenosis of lesions within the carotid artery. With the advancement of high-resolution transducers and 3D imaging capabilities, sonographic plaque characterization investigators present a new tomographic imaging method in the evaluation of plaque morphology by identifying internal components and the structure of specific plaque appearances and possibly stratifying the risk. Specific markers of possible clinical significance seen with sonography include echotexture, the presence of echolucency, and surface alterations or ulcerations. Besides traditional 2D imaging, the use of 3D sonography imaging techniques may provide additional information in the evaluation and risk stratification of vulnerable carotid plaque.

The purpose of this study was to analyze the ability to recognize morphologic features in simulated carotid artery atherosclerotic plaques using high-resolution 2D and 3D sonography and to demonstrate whether 3D imaging improved the visualization of these characteristics. In addition, the inter-rater reliabilities of the morphologic assessment were assessed using both 2D and 3D sonography. Sixty tissue-like carotid phantoms simulating various pathologic plaque features were created, which provided good sonographic representation of a carotid artery segment. The two minor limitations were noted in creating these phantoms. The first was the occasional damage to the specimen when reversing the glove prior to filling with mineral oil. The second resulting simulated vessel diameter was slightly larger (average 1.2 cm) than a standard carotid artery, which could create trial increased resolution in imaging. The phantoms were noted otherwise to be good replicas of carotid atherosclerotic lesions and were easily used for measuring inter-rater variability. Given that the phantoms were used for validity and inter-rater agreement only, we did not measure the speed of sound in the embedding media, scattering coefficients, or attenuation coefficients to determine how closely they truly mimicked soft tissue.
All phantoms were scanned within 3 days of creation; however, based on previous experience with these samples, phantoms can last for several weeks when properly refrigerated.

The senior sonographer’s results yielded the highest inter-rater reliability when all six ratings were considered simultaneously; reliability decreased with fewer years of experience with characterizing plaque morphology. The areas lacking agreement may be due to the lack of understanding and training, specifically in sonographic plaque characterization; it would be of interest to repeat this study after standardized training of sonographers. Based on the type of plaque pathology simulated by the phantoms, the use of 2D imaging alone was not reliably high in identifying each specific pathology. In each case, 3D demonstrated a higher reliability, and consistency was substantially higher in the agreement and type of plaque pathology, irrespective of the sonographer’s experience in characterizing plaque morphology. The identification of surface irregularity and ulceration showed the weakest reliability; however, substantial agreement increased with the application of 3D sonography for both parameters. This remained a consistent finding with the other factors as well when comparing 3D sonography versus 2D sonography alone. While high-resolution 2D sonography was able to identify correctly most vulnerable plaque characteristics, volumetric 3D imaging quantified plaque morphology further, increasing the proper recognition of the pathological type. In addition, the combined use of rendered 3D imaging and postprocessing volumetric slice selection used as a complement to high-resolution 2D sonography reduced the inter-rater variability, which in turn increased the sensitivity and specificity for each plaque pathology type. Using a combination of 2D and 3D sonography, the identification of internal echolucency had the highest reliability (0.81) while ulceration had the poorest (0.60). The 3D inter-rater reliabilities were significantly higher when using 3D alone versus 2D alone. This was especially evident in the presence of fissures, irregular surfaces, and ulcerations. The 3D method was not as sensitive in identifying calcifications; however, the precision slicing of volumetric display may augment the imaging and diagnostic assessment of the internal content or echotexture of the plaque. The above data indicate that a combination of both 2D and 3D would provide the best results in identifying vulnerable plaque characteristics.

The novel findings from this study are as follows: (1) 3D sonography improves recognition of a plaque’s echographic parameters and may help improve assessment of the vascular risk in all types of atheromas; thus possibly improving stroke prevention; (2) the use of high-resolution 2D and 3D sonography for advanced imaging of simulated carotid plaque pathology provides a reproducible and reliable method for the analysis and morphologic assessment of disease with excellent inter-rater reliabilities; and (3) we hypothesize that combining the severity of stenosis with specific plaque morphology using high-resolution 2D and 3D imaging may help increase the assessment of total risk based on plaque vulnerability and could possibly be of use as a basis for predicting future ischemic events.

These results showed that combined 2D and 3D sonographic imaging can demonstrate high accuracy in plaque morphology assessment; however, this must be further investigated for true atheromatous lesions in human subjects and in all types of plaques. Inter-rater manipulation was not assessed, which is an important variable in the operator dependency of sonography; thus, we cannot make any definitive conclusions about the inter-rater variability and consistency. Further studies are required to evaluate these findings.

Conclusion
Advanced 2D and 3D sonographic imaging of simulated plaque morphology provides a reproducible and reliable diagnostic method for assessing characteristic morphologic changes in carotid plaque atheromas, with excellent inter-rater variability. This prospective phantom study suggests a paradigm shift in the standard protocol in carotid duplex sonographic imaging; however, larger prospective human studies are indicated to corroborate these findings.

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This article is dedicated to the late Joanna Lam (September 2013), who made a special scientific contribution to the work in this article. We are grateful for Joanna’s guidance, patience, and constructive criticism, which in turn made us better researchers.

Declaration of Conflicting Interests
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Enhanced Plaque Ultrasonography


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Abstract

Objectives: Imaging carotid plaque morphology with the use of ultrasound (US) may improve stroke risk management by identifying alterations in atherosclerosis at increased risk for cerebrovascular events. Limited reports on advanced US plaque imaging have identified the potential for evaluation and risk stratification of vulnerable carotid plaques. The purpose of this series was to evaluate the usefulness of integrating an advanced US plaque imaging method to characterize atherosclerosis and to measure the agreement with multidetector computed tomography (CT) and radiographic pathology.

Methods: Three patients with known high-grade symptomatic carotid artery disease confirmed on CT and scheduled for endarterectomy were recruited for this study. Before surgery, we prospectively assessed carotid arteries for high-risk morphological characteristics using our advanced US plaque imaging method. The plaque characteristics considered included the presence of ulceration, internal lipid or hemorrhagic core(s), calcification(s), and/or thin/dense fibrous plaque caps. US plaque features were correlated with previous CT imaging and postendarterectomy histologic studies.

Results: There was substantial agreement in the detection of morphologic characteristics. Our advanced US method yielded 100% sensitivity, specificity, and accuracy in the identification of ulceration, lipid/hemorrhagic core(s), and calcification(s), leading over 100% sensitivity, specificity, and accuracy in the identification of ultrasound plaque features. The plaque characteristics considered included the presence of ulceration, internal lipid or hemorrhagic core(s), calcification(s), and/or thin/dense fibrous plaque caps. US plaque features were correlated with previous CT imaging and postendarterectomy histologic studies.

Conclusions: Advanced US plaque imaging to further identify significant plaque abnormalities responsible for strokes can reliably identify vulnerable plaque characteristics on both two-dimensional and three-dimensional US. Our results suggest that the type of abnormality identified with our advanced US imaging method surpassed information gathered on CT. Our advanced imaging protocol shows potential for early noninvasive prediction of plaque vulnerability, thus improving preventive management of atherosclerosis.

Conclusion

L'imagerie de la morphologie de la plaque carotidienne par échographie peut permettre d’améliorer la gestion du risque d’AVC par la recension des altérations de l’athérome présentant un risque accru d’événements cérebrovasculaires. Des renseignements limités provenant d’une étude américaine d’imagerie avancée de la plaque montrent un potentiel d’évaluation et de stratification des risques des plaques carotidières vulnérables. Cette étude avait pour but d’évaluer l’utilité d’utiliser une méthode américaine avancée d’imagerie de la plaque dans la caractérisation des athéromes et de mesurer le degré d’accord avec une tomodensitométrie (CT) à rayons multiples de détecteurs et la pathologie radiographique (Rad-Path). Méthodologie : Trois patients présentaient une pathologie carotidienne de haut niveau reconnaître et confirmée par CT, et pour lesquels une endartérectomie était prévue ont été recrutés pour cette étude. Avant le chirurgie, nous avons procédé à une évaluation prospective de l’athérome carotidien afin d’en déterminer les caractéristiques morphologiques présenter un risque élevé à l’aide de notre mécanisme échographique d’imagerie de la plaque. Les caractéristiques
Introduction
Carotid atherosclerosis is the leading cause of cerebrovascular accidents (CVAs) by instigating ischemia or infarction of the cerebral vasculature. This pathologic event is critical for risk prediction of a cerebrovascular event, particularly against conventional metrics like arterial luminal narrowing. Thus, the lack of accurate, noninvasive tools for the assessment of vulnerable plaques. Traditionally, grading of the carotid artery stenosis degree was the accepted method in identifying risk for cerebrovascular events; however, recent developments in morphologic plaque composition as a risk for vulnerability and the valuation of certain unstable molecules leaves ultrasound (US) as the least costly method for triage, diagnosing, and monitoring carotid atheromatous disease, and nuclear medicine hamper its application. This, in turn, leaves ultrasound (US) as the least costly method for staging, diagnosing, and monitoring carotid atheromatous disease. Furthermore, US offers an increased advantage because it is capable of assessing structural anatomic details and vessel flow information concurrently, combining conventional and morphologic imaging of the atheromatous plaque in real-time imaging.

We assessed the diagnostic performance of an advanced US evaluation technique seeking to improve visualization and characterization of several morphologic features of plaques that would lead to increasing potential risk stratification and improve plaque characterization. The plaque characteristics assessed with the advanced US evaluation included the presence of ulceration(s), internal areas of lipid or hemorrhagic core(s), calcification(s), and evidence of thin or dense fibrous caps. Using this technique, plaque analysis was performed correlating our US findings with previous CT imaging and final pathology using radiologic pathology specimens.

Methods
A prospective, randomized clinical series was piloted to evaluate our US protocol in human atherosclerotic carotid plaques. The research protocol and approval of this sonographic series were obtained by the local institutional review board, the Research Ethics Committee of the Ottawa Hospital, and Charles Sturt University Human Research Ethics Committee. Written informed consent was obtained from all patients.

Selection of Study Participants
Between April 2012 and August 2013, three patients were prospectively enrolled for this study. Inclusion criteria consisted of males and females, patients >18 years of age, and patients referred from the Department of Neurosurgery at The Ottawa Hospital with known symptomatic carotid artery disease (>70% carotid stenosis) confirmed by recent CT and formerly scheduled for endarterectomy. The study group was composed of 2 men and 1 woman (age range, 67–81 years; mean age, 74.6 years). All patients were symptomatic with respect to their carotid disease before enrollment and had a history of amaurosis fugax, transient
ischemic attack, or CVA in the territory of the ipsilateral carotid artery within the previous 3 months. All patients showed evidence of bilateral disease ranging from mild to severe and subsequently underwent carotid endarterectomy (CEA) within 3 months (mean, 33 days) for the symptomatic side. Research participants excluded from this study included patients who were pregnant, obese, had a prior history of carotid artery surgery, or were unable to provide consent to the study and/or answer the medical questionnaire because of a disability preventing the full understanding of what was being consented to; no patients were excluded from the study.

**Ultrasound Imaging Acquisition**

All sonographic imaging examinations for this series were performed using an identical US technical protocol. Human carotid atheromatous plaque examinations were performed on an IU22 ultrasound system (Philips Healthcare, Bothell, WA) equipped with a high-resolution, linear small parts probe (L-12 MHz) for high-resolution two-dimensional (2D) imaging and a volumetric, high-mechanical linear-array transducer (VL-13 MHz) for three-dimensional (3D) imaging. Each patient was assessed and imaged for certain US morphologic features such as internal echolucency, the presence of surface ulceration(s), plaque cap alterations, and internal calcification(s). The sonographer was blinded to the patient’s clinical information, including previous CT results. Our US imaging protocol started with a systematic anatomic overview of the affected internal carotid artery using a high-resolution, small parts probe for 2D imaging. US parameters (ie, depth, focus, resolution, and gain curve) on the unit were preset for the protocol and remained consistent among patients. Time gain compensation was adjusted manually to optimize image quality and analyze each specimen. Subsequently, the imaging process was repeated using the volumetric transducer for 3D imaging. Upon switching to the 3D volumetric imaging mode and before acquisition, scanning parameters such as power, gain compensation, and focus zoom were present in the unit. Three-dimensional acquisitions were performed by using a 15-degree angle mechanical sweep along the long axis of the vessel and positioned for the center volumetric slice to be located midplaque. The frame rate was consistent among patients, with a final 25-slice volume data set averaging approximately 10 seconds. Acquired 3D US volumetric-rendered images were analyzed using the built-in iLAB software to rotate in the x-, y-, and z-axis volumetric slice and quantitate internal contents of the plaques using iSlice (Philips Healthcare).

**Previous CT Imaging Acquisition**

Each participant had previous, clinically indicated CT imaging of the head and neck within 3 months of the US. All carotid plaques of atheroma were imaged with an identical CT imaging protocol performed using a multidetector 64-channel CT scanner (HD 750 Discovery; GE Healthcare, Milwaukee, WI). Routine CT technical parameters were as follows: a 0.5-second helical rotation, 100 kV, 250 mA, collimation of 20 mm, acquisition of 0.625 mm, and a pitch of 0.969:1 with a table feed of 19.37 mm per rotation. Data was acquired using a scan field of view of 32 cm and displayed in a 22-cm field of view. Reconstructed data was performed at 1.25-mm axial images with a 512 x 512 matrix. The course of the CT scan was cranio-caudally and started from the top of the head and proceeded as far down the neck as possible, always including the base of the skull or common carotid artery.

**Plaque Excision**

An experienced cardiovascular pathologist (IPV) examined all carotid specimens macroscopically immediately after the CEA at the time of the operative exposure. The proximal portion of the plaque was identified with a single suture marked by the neurosurgeon to facilitate pathology marking and photographed in the fresh state before being subjected to decalcification and subsequent histologic examination. The plaques were serially sectioned in 3- to 4-mm increments from the proximal common branch to the distal internal and external branches. Sections were prepared and stained with hematoxylin-eosin and Movat pentachrome elastic stain. Plaque ulceration was defined as a plaque surface irregularity, and the presence of thrombus was noted. Plaque hemorrhage was noted by looking for evidence of blood or hemosiderin within the plaque itself. The core was assessed and characterized into areas of lipid (cholesterol crystals or lipid-laden macrophage foam cells), necrotic debris, inflammation, and calcium (granular or plate-like with or without ossification). The plaque cap was examined for intactness and whether this was a thin cap atheroma or not. All slides were photographed and mapped using Snagit. The pathologist annotated each image, mapping the plaque morphology at each level, and described the specific morphologic characteristics identified. At the time of the CEA and pathology review, the pathologist was blinded to the US and CT findings.

**Data Collection and Image Analysis**

All data were collected prospectively, compiled, and processed by accessing institutional patient medical records and reviewing them for outcome information, demographics, and relevant imaging findings when available using an open architecture clinical information system (vOasis; Dinmar, Atlanta, GA) and/or picture archiving and communication system. An experienced neuroradiologist (MK, 12.5 years) reviewed the US and CT images independently on high-resolution, flat screens at the same workstation. Window parameters were not preset. The reader reviewed high-resolution 2D, raw US data, 3D reformatted sectional imaging, and still US images. For CT reporting, the reviewing mechanism allowed radiologists to measure Hounsfield units by sampling an elliptical region of interest in the area of plaque, thus allowing density assessment. At the time of reporting, the neuroradiologist was blinded to the macroscopic findings and the pathologist’s report of the histologic morphology of...
the endarterectomy specimens. US and CT imaging findings were independently declared on the standard report work sheet. Two-dimensional and 3D US data were reported separately. Based on a previously published literature review [5], we used four variables in order to quantify and report plaque abnormalities using our advanced US imaging protocol. Our prospective classification criteria included the following: (1) internal lucency, described when a focal, predominant internal hypoechoic/echolucent (US) or lucency area (CT) was seen within the atheroma; (2) internal region density on CT or echogenic foci with evidence of shadowing on US-confirmed calcification(s); (3) ulceration(s) were considered to be present in the specimen if we identified a focal, circumferential irregularity or break in the surface of the plaque, with a minimum depth of 3 mm; and (4) plaque cap alterations were identified in the presence of increased echogenicity or when a structural breach was evident. A final data sheet using binary codes was created to associate the variables between the independent 2D, 3D US and CT imaging findings by the neuroradiologist and compared it to the histologic pathology results, as the gold standard.

Statistical Analysis

The diagnostic accuracy of each technique for the assessment of each plaque characteristic was assessed by constructing 2 × 2 contingency tables with specimen histopathology as the gold standard. Statistical analysis was performed using MedCalc Professional statistics software version 12.1.1 (MedCalc Software, Mariakerke, Belgium).

Results

During the 15-month investigative period, 3 patients who underwent CEA were included for this series. No patients were excluded. Of these 3 patients, 2 had right hemispheric symptoms, and 1 had left hemispheric symptoms. The ipsilateral carotid arteries served as cases (n = 3), and all arteries contained a high-degree (>70%) stenosis that was confirmed on previously performed CT imaging of the carotid arteries (Figure 1). The mean follow-up time from US to surgery was 33 days. Histopathology of the surgical specimens revealed that all three specimens were complicated plaques. Sixty-six percent intraplaque hemorrhage or significant lipid cores identified as well-organized, large, and deeply situated in predominantly fibrous plaques (Figure 2). All plaques had thin or fibrous caps and evidence of internal calcifications (Figure 3). Ulceration (Figure 4) was observed in two subjects/specimens. When compared with pathology, both US and CT identified plaque ulceration with 100% accuracy (Figure 5). With respect to the identification of a lipid or hemorrhagic core(s), CT was unable to identify either of the two true positives, leading to 0% sensitivity (100% specificity and 33% accuracy), whereas US successfully identified the core components in both cases (100% accuracy, sensitivity, and specificity, Figure 6). In the identification of a thin/dense fibrous cap, CT yielded 0% sensitivity versus 33% on US (Figure 7). Both CT and US successfully identified the presence of calcification in all three cases (100% sensitivity for each, Figure 8). We did observe that US identified two
Discussion

In the past, it was assumed that the primary source of cerebral infarction was caused by stenotic segments that reduced hemodynamic flow within the blood vessel, impeding distal vascular perfusion. Recent discoveries have challenged this concept and identified that certain types of plaques contain areas potential for rupture. These plaques are known to be at increased “vulnerability” for thromboemboli or fragmentation, which can propagate into cerebrovascular circulation, occluding distal cerebral circulation and causing an infarct. The morphologic composition of the vulnerable plaque has a high probability of causing thrombotic complications, which can significantly affect cerebrovascular prognosis. In addition, these specific morphologic factors, aside from luminal stenotic determination, may predict clinical outcomes. Plaque formation with these specific morphologic features could cause a luminal narrowing less than 70% but still be a major contributor to future cerebrovascular events. Vulnerable morphologic plaque characteristics associated with a neurologic event include the presence of thin or fissured fibrous caps, surface irregularities, and/or ulcerations and the presence of large lipid core(s) or hemorrhage(s), active inflammation, severe stenosis, or a combination of these findings.

Diagnostic neuroimaging plays a vital role in the diagnosis, workup, and follow-up of cerebrovascular atherosclerosis analysis by assisting clinicians in accurately triaging patients, expediting clinical decisions, and planning optimal preventative treatment to improve patient outcome. Multiple imaging techniques and analysis should be considered by imaging specialists when assessing carotid arteries of patients with/without symptoms of stroke in order to guide clinicians to better treatments and improve clinical management. Quantitative assessment in plaque composition and/or morphology in the early identification of plaque change can possibly pinpoint the etiology of strokes and is made possible with the use of the latest diagnostic imaging methods. US remains the first line of defense in carotid arterial imaging because of its accessibility, noninvasive nature, and low cost, offering promising results in this innovative examination in plaque imaging. Although the standard tool for US is currently directed at luminal grading, it is agreed that it alone is a poor predictor of stroke and any atheromatous plaque could be vulnerable to rupture. Over the past decade, considerable gains have been made in the quality of US examinations because the technology, equipment, and resolution have improved significantly.

Enhanced probe technology, such as broadband linear array transducers, offers higher frequencies with shorter pulse length, providing ultrasonic imaging that significantly improves spatial and axial resolution for superficial vascular imaging such as imaging the carotid arteries. These high-resolution transducers can now enable B-mode or 2D US to accurately measure and image the carotid intima media, detecting any preintrusive thickening of the artery wall and/or higher detail of the echomorphology such as surface alterations or internal echotextural variations. Moreover, the introduction of volumetric, broadband linear array US transducers with 3D capabilities has allowed data analysis from a volume of interest, allowing monitoring and imaging in all three dimensions of morphologic plaque progression once limited by the one single-direction limitations of 2D plane structures. The application of high-resolution 2D and 3D US imaging used as an adjuvant imaging technique may provide additional information in vulnerable plaques. Findings from our research highlight the importance of improving care by using advanced carotid plaque imaging in routine carotid US assessment.
Based on this research, we promoted the development of noninvasive imaging parameters for patients at risk of stroke because advanced plaque imaging is necessary for optimal and complete carotid US imaging and assessment. This research series generated information about the promising and vital use of US in the evaluation of specific morphologic features, known to be key features for at-risk plaques, with the use of an advanced US imaging analysis. This study’s intent was to address and explore the possible applications of our advanced US carotid plaque imaging to identify critical morphologic features with the hope of predicting clinical outcome. The novel findings from our series yielded three separate results as follows. The first result we obtained was high correlation and accuracy between our US imaging technique, CT, and radiographic pathology specimen in specific morphologic characteristics such as ulceration (sensitivity 100%, specificity 100%, and accuracy 100%). Our second observation showed that US yielded a higher sensitivity in identifying internal hemorrhagic or lipid cores (sensitivity: 100% for US and 33% for CT). This is most likely caused by the superior capabilities of US over CT in identifying soft tissue alterations in vulnerable plaques. Our last results validated that 3D imaging further quantified additional vulnerable carotid plaque features for each variable. This may be caused by the improved capability of 3D US to visualize parenchymal wall tissue and correctly image the true plaque circumference of surface development. This notion may also be the reasoning behind the higher sensitivity of US in identifying thin/dense fibrous capsule over CT (sensitivity: 33% for US and 0% for CT). Our findings ascertained that supplementary application of 3D US improves the quality of characterization for plaque morphology, especially when assessing surface alterations. US remains the first-line imaging modality of choice for extracranial cerebrovascular assessment because of its noninvasive nature, low cost, and real-time capabilities. Duplex scanning has the ability to not only assess luminal patency but also show plaque abnormalities, which reflect their critical importance of composition. Improved technology and transducer performance now enable enhanced assessment of plaque morphology. Our series indicates that high-resolution 2D imaging of the carotid plaque with a high-frequency linear transducer in conjunction with 3D US assessment via volumetric broadband imaging in patients with carotid artery disease shows a significant improvement in identifying characteristics.
of plaque vulnerability with a high correlation rate, sensitivity, and specificity. This method may develop an appreciation of who among the population is most likely at risk to have a future cerebrovascular event, including those who are asymptomatic and those with high-risk plaques other than high-degree stenosis. In addition, our series showed that our method was superior compared with CT in identifying certain categorical components in potential risk indicators. The framework shown in our research allows for justification for a large-scale, multicenter trial probing the capabilities of our US imaging technique as a screening tool for identifying patients with high stroke risk, particularly those who have not

Figure 7. The identification of a dense thin capsule on 2D US correlating with the surgical specimen.

Figure 8. Agreement in the identification of calcification for US and CT with the surgical specimen.
reached high-risk, high-degree stenosis. Our methodology applied a mechanical, 3D transducer for volumetric acquisitions because it has been shown to reduce inter-rater variability [5]. An alternate 3D technique, such as frehand 3D US scanning and/or equipment to create volume data, may be applied. Our series should be interpreted in the context of the following limitations. We acknowledge our investigation lacked clinical reference standard. Multiple factors are involved in the plaque morphologic pathophysiology mechanism for patients at increased risk, and features should be assessed in all grading/types of plaques to foster the applicability of imaging method for cerebrovascular risk assessment. We limited our series data to high-grade stenosis, and it would be of benefit to investigate lower-grade stenosis to possibly identify morphologic changes beforehand. The proposal of using the contralateral carotid artery as controls may be of use for age-matched category in lower-graded disease. Our research included multiple factors involved in the consistency with the use of the same hardware, techniques, operators, and data standardization so that the variability in the series analysis was reduced. Three-dimensional US is prone to artifacts, particularly those caused by physiological motion from the carotid vessel pulsations. This artifact may cause distorted images and misregistration of the region of interest, inaccurately representing the structures. Although this artifact may be difficult to eliminate, it can be minimized by reducing the mechanical sweeping angle to cover only the carotid plaque and maintaining a short acquisition time. It may take several attempts to obtain a suitable volume without artifact. The CT scanner technology applied could be optimized using special sequences or reformatting capabilities to properly identify internal contents or surface alterations. This is not feasible in everyday applications and it would be of interest to evaluate this as a separate trial. Lastly, we acknowledge that our series was too small to support a multivariate analysis, to promote universal, standardized, and global US classification analysis for reporting carotid atherosclerotic lesions, thereby improving the patient’s management and care. Our advanced US plaque imaging using combined high-resolution 2D and 3D imaging provides a reproducible and reliable diagnostic method for assessing morphologic changes in carotid plaque that is optimal over routine CT imaging. Larger prospective human studies are intended to corroborate these findings and fully assess the potential of this imaging system.

Conclusion

US remains the first line of defense in carotid arteriographic imaging because of its accessibility and low cost. Our results may fill the void created by an ongoing paradigm shift in diagnosing early atherosclerotic carotid vascular disease by assessing beyond the lumen and providing significant clinical information of the atheroma. Proper identification of specific US morphologic features and plaque categorization can unify the language between the radiologist and referring physicians to promote universal, standardized, and global US classification analysis for reporting carotid atherosclerotic lesions.

References


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ABSTRACT

Purpose: Imaging plaque morphology, in addition to luminal grading, may improve stroke risk management by identifying structural atherosclerotic plaques alterations responsible for cerebrovascular events. The purpose of this study was to evaluate the agreement between our enhanced ultrasound (US) imaging method and high-resolution cross-sectional imaging modalities, such as multidetector-row computed tomography (CT) and magnetic resonance imaging (MRI), in the characterization of vulnerable plaques.

Methods: Sixty tissue-like phantoms were created to simulate various types of diseased plaque segments. We prospectively assessed each sample with US, CT, and MRI. Plaque characteristics considered included surface irregularity, ulceration, fissure, and presence of internal fluid content. We evaluated the agreement between and among the three modalities, as well as the accuracy of each compared with the true pathology.

Results: There was moderate to substantial agreement among the three modalities in the detection of morphologic characteristics. There was no significant difference in accuracy between US and CT in the presence of ulceration(s) (P = .23), necrotic (P = .23), or fissures (P = .07); however, US was significantly more accurate than MRI for each of these characteristics (P = .001, P = .001, P = .03, respectively). None of the three modalities did display any significant difference in accuracy in the identification of irregular surface. There was substantial agreement among the three radiologists (intraclass correlation coefficient, 0.61; 95% confidence interval, 0.46-0.74) in their assessment of plaque subtype, ranging from 80%-85% accuracy in identifying the plaque subtypes for each classification.

Conclusions: Enhanced plaque imaging can identify potentially significant plaque characteristics and provide insight into early causative conditions of carotid atherosclerosis. Our results suggest that the type of plaque pathologies derived from our US method showed good agreement with CT and surpass information gathered on MRI. This imaging protocol could potentially shift the paradigm in early carotid plaque imaging likely to predict the onset of vulnerable plaques, thus improving preventive management of atherosclerosis.

RÉSUMÉ

Objectif : L’imagerie de la morphologie de la plaque, en plus du classement luminal, peut améliorer la gestion du risque d’AVC en déterminant les modifications des plaques d’athérosclérose structurales responsables des accidents cérébrovasculaires. La présente étude a pour but d’évaluer la concordance entre notre méthode d’imagerie par échochographie perfectionnée (US) et les modalités d’imagerie transversale haute résolution, comme la tomodensitométrie par ordinateur à plusieurs détecteurs et l’imagerie par résonance magnétique (IRM) dans la caractérisation des plaques vulnérables.

Méthodes : Soixante structures en tissu ont été créées afin de simuler divers types de segments de plaques atheroscléreuses. Nous avons procédé à une évaluation prospective de chaque échantillon selon les trois modalités (US, CT et IRM). Les caractéristiques examinées comprenaient l’irrégularité de la surface, les ulcérations, les fissures...
et la présence de noyaux fluides. Nous avons évalué l'accord entre les trois modalités ainsi que l'exactitude de chacune en comparaison de la pathologie réelle.

**Results** : Les auteurs ont constaté un degré modéré à substantiel d'accord entre les trois modalités dans la détection des caractéristiques morphologiques. Il n’y avait pas de différences de précision significatives entre les modalités US et CT en présence d’ultrasons (p = 0.23), d’espaces clairs (p = 0.23) ou de fissures (p = 0.07), respectivement. La CT est notablement plus précise que l’IRM pour chacune de ces caractéristiques (p < 0.001, p = 0.001, p = 0.02, respectivement). Aucune des trois modalités n’a présenté de différence de précision significative dans l’identification des surfaces irrégulières. Il y avait accord substantiel entre les trois radiologues (ICC=0.61, 95 % CI 0.46-0.74) dans leur évaluation des sous-types de plaque, le degré d’exactitude dans l’identification des sous-types de plaque variant entre 80 et 85 % pour chaque classification.

**Conclusion** : Les techniques avancées d’imagerie avancées peuvent permettre l’identification de caractéristiques potentiellement significatives de la plaque et donner un aperçu des conditions causales avancées de l’athérosclérose carotidienne. Nos résultats donnent à penser que les types de pathologies de la plaque dérivées de nos méthodes d’échographie avancée (US) affichent une bonne correspondance avec la CT et surpassent l’information obtenue par l’IRM. Ce protocole d’imagerie avancée pourrait potentiellement modifier le paradigme de l’imagerie préopératoire de la plaque carotidienne susceptible de permettre la prédiction de l’apparition de plaques vulnérables, ce qui permettrait d’améliorer la gestion préventive de l’athérosclérose.

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**Introduction**

In 2000, cerebrovascular events (CVA) accounted for the death of 15,409 Canadians [1], which represents 7% of all mortalities. Eighty percent of Canadians have at least one of the clinical risk factors for cerebrovascular disease [1]. The alarming rise in predisposing risk factors such as obesity, smoking, diabetes, and cholesterol may be contributing to a recent increase in stroke among younger patients. Additionally, earlier detection of carotid disease with improved diagnostic imaging could further contribute to this development, as detection of pathologic source is being recognized at a much earlier stage. Regardless, CVAs can be debilitating and potentially life-threatening.

One of the key challenges presented by this pathology is the lack of early noninvasive imaging markers for monitoring or measuring disease progression and identification to properly quantify disease progression and monitoring. Given that plaque composition and morphology have been proposed as markers for “vulnerable plaque”, the valuation of certain unstable molecules within the plaques is of great interest in the research domain [2]. The next step is to validate these concepts for risk prediction of CVA, including prospective comparisons with conventional diagnostic reporting of arterial luminal narrowing.

Current clinical imaging applications for the assessment of carotid plaque morphology and characterization include magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound (US). Of the noninvasive modalities, MRI has widely become the modality of choice as it offers nonradiated, high-resolution anatomic imaging. MRI has recently gained positive reception in research for the assessment of specific plaque morphologic characteristics because of its increasing field strength units joined with dedicated phased-array surface coils designed specifically for carotid artery imaging. The use of a natural gadolinium chelate contrast agent can further distinguish and emphasize morphologic intraplaque composition (Figure 1). Nonetheless, MRI is not without its limitations, as the cost can be prohibitive for widespread use and it is not always available globally.

With the latest multi-detector high-speed scanners, CT enables optimal anatomic evaluation of the carotid vasculature with a high sensitivity, 100% for 70% stenosis and 80% for 50% stenosis [3]. Recent CT units are now using a near-isotropic spatial resolution with minimal sectoral thickness slices as small as 0.75 mm. This enables submillimeter data sets and provides the ability to evaluate both the carotid wall and adherent plates involvement within the internal carotid artery segment (Figure 2). In addition, CT’s three-dimensional (3D) reformatting capabilities can provide multiple viewing planes and multi-planar surface rendering, allowing unprecedented quantifications. Contrast-enhanced CT angiography has demonstrated great detection [4] in identification of ulcerations, intraplaque lipid cores or hemorrhages, and specific fibrous cap thickness alterations, all of which are biological features assumed to be associated with plaque vulnerability [5]. Although promising, CT does have associated variability and limitations—such as certain sectional viewing restrictions due to overlapping Hounsfield densities, making it challenging to identify smaller lipid-rich necrotic cores or hemorrhages—in addition to high costs, and exposure to ionizing radiation.

Carotid Doppler US is the most common imaging examination requested worldwide to help diagnose carotid artery disease and is an accurate, cost-effective, and noninvasive means of evaluating the extra cranial carotid artery circulation. With recent advances such as premium performance and design of US transducers, newer imaging methods have been introduced that improve the quality for vascular US imaging. Enhanced probe technology offers higher frequencies, providing ultrafine imaging that significantly improves spatial and axial resolution for carotid intima-media imaging to detect any prestenous thickening (Figure 3) of the artery wall and/or higher detail of the echomorphology, such as surface alterations or internal echo textural variations. In addition, the introduction of volumetric transducers with 3D capabilities and extended operating high-frequency range (13–15 MHz) have allowed rapid analysis of data from a volume of interest, allowing monitoring and imaging in all three dimensions of morphologic plaque progression once limited

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by the one single direction limitations of two-dimensional (2D) plane structures. US can offer an advantage over other modalities in carotid artery assessment because it is capable of optimally assessing anatomic details and vessel flow information concurrently, combining conventional and morphologic imaging of the atherosclerotic plaque in real-time imaging. Although appearing promising, US is both operator dependent and limited to extracranial imaging only.

Early identification and imaging of at-risk plaque underscore the importance of conducting imaging research in this population. The focus of this study was to assess the diagnostic performance of applying an enhanced-US plaque imaging technique and measuring the agreement between our method, CT, and MRI in the evaluation and characterization of several morphologic features of plaque in hopes of increasing the potential risk stratification and improving diagnosis.

Material and Methods

Phantom Experiments

Sixty carotid-specimen phantoms containing segments of meat proteins to mimic a variety of plaque compositions [6] were used. Based on previously published phantom experimentation [6], it was established that internal coagulated milk casein was the optimal substance for mimicking internal plaque hardness. Sculpting a section of the protein enabled simulation of various surface irregularities, ulcerations, and fissures (Figure 4). Creating the represented vessel involved a powder-free nitrile examination glove with the specimen held in place inside the small finger of the glove using adhesive gel. Once dissected, the glove was reversed inside out, filled with the mineral oil, and the upper-end of the fingers knotted, creating a representable-sized (1.0–1.3 cm) carotid segment with an internal atheroma. The vessel segment was submerged in a liquid concoction acquired from previously published formulas [6–9] and refrigerated at specific intervals to entrap the inclusion (Figure 5).

Imaging Technique

CT image acquisitions (Figure 9) for this investigation were imaged with a multidetector 64 channel CT scanner.
Figure 4. Sagittal view of animal test specimen to mimic plaque surface alterations.

(HD 750 Discovery; GE Healthcare, Milwaukee, WI). CT technical parameters were as follows: helical 0.5 seconds rotation, 100 kV, 250 mA, collimation of 20 mm, acquisition 0.625 mm, and a pitch of 0.96:1 with a table feed of 19.37 mm/rotation. Data were reconstructed at 1.25 mm axial images with a 512 × 512 matrix. The data were acquired in a scan field of view (FOV) of 32 cm and displayed in a 22 cm FOV. The scan direction was craniocaudal and started from the top of the phantom and proceeded as far as possible to include the base of the phantom.

All MRI examinations were performed on a 3.0 T Magnetom Trio MRI scanner (Siemens, Germany), using a phased-array 16-channel head coil. The following three MRI-contrast weightings were obtained to establish optimal plaque characterization: T1-weighted (T1W), T2-weighted (T2W), and a three-dimensional volume interpolated breath-hold exam (VIBE) for reconstruction capabilities. Scan protocols were as follows: for T1W, repetition time/echo time, 500 ms/12.4 ms and for T2W, 3500 ms/62 ms, both being tube spin-echo-based and for VIBE, repetition time 5.53 echo time 2.9 ms with a flip angle, 15°. All 2D images were obtained with a FOV of 14.0 × 14.0 cm, matrix size of 256 × 256, and slice thickness of 2 mm. Inter-slice gaps were 0 mm in T1W and T2W and in VIBE images. Scan coverage was 96 mm with 120 slices in VIBE-weighting, yielding an isotropic voxel of 0.8 mm. Scan coverage included the top of the phantom to the base. Figure 7 illustrates an axial MRI-T2W image of the phantom.

US imaging for this investigation was performed on an IU22 US system, Philips Medical System (Philips Healthcare, The Netherlands) with an initial systematic overview of the specimen using the high-resolution, linear small parts probe (L-12 MHz) for 2D imaging and analysis. For each specimen, US parameters on the unit were preset (depth, focus, resolution, gain-curve) to remain consistent among phantoms; however, time-gained compensation was adjusted manually. Subsequent imaging for 3D imaging repeated the 2D process.

Figure 5. Concolodi mixture with five entrapped tubular structures, creating our phantom.

Figure 6. Longitudinal CT imaging of a phantom with five simulated carotid artery segments with luminal plaque components. CT, computed tomography.

Figure 7. Axial MRI imaging of a phantom on a T2W sequence with representation of internal plaque times. MRI, magnetic resonance imaging; T2W; T2-weighted.
using a volumetric, mechanical, high-resolution linear-array
transducer (volumetric linear-13 MHz). 3D scanning param-
eters such as power, gain, focus, and depth were preset to sus-
tain consistency and each acquisition retained the same frame
rate, sweeping at a rate of 10 seconds with a final volume data
set of 25-slice. The center slice was placed in the mid long-
axis of the specimen and mechanically swept at a 15-degree
angle to capture 3D echo volumes. Volumetric rendered
images were stored digitally in the unit’s built-in software
QLAB software (Philips Healthcare, The Netherlands).
Sequential volume images were evaluated by rotating X, Y,
and Z 3D volume views and internal contents of the plaques
were reviewed using iSlice (Philips Healthcare, The
Netherlands). Figure 8 illustrates a 2D and a reformatted
3D US image of the phantom specimen.

Each sample was imaged and evaluated for the following
morphologic features: no abnormality detected (NAD), inter-
ternal lumen lucentcy, presence of fissure(s) or surface ulcer-
tion(s), and irregular surface alterations.

Image Analysis

A criterion was established for imaging criteria for quanti-
fying and reporting carotid atheroma based on previous phan-
tom experimentation [6] and a published literature review [10].
Prospective morphologic criteria were as follows: (1) the spec-
imen was considered regular or NAD when variations were
<0.3 mm on the contour of surface, and no alterations were
noted in the internal texture; (2) surface variations >0.3 mm
were considered irregular; (3) internal lucent areas were
described when the identification of an internal focal alterations
in echogenicity or density was observed; (4) specimens were
considered ulcerated if a circumferential focal break or
irregularity of the surface of the plaque with a minimum
depth/width of 3 mm was identified; and (5) evidence of a linear
break in the surface was considered a fissure. The initial con-
sideration for calcification was omitted from the analysis because
after imaging the phantoms with each individual modality, it
was determined that the material used in the phantom displayed
excellent representation on US imaging (Figure 3A), but was un-
acceptable for an accurate representation on CT or MRI
(Figure 9B, C, respectively).

Three experienced neuroradiologists, blinded to the spec-
imen pathology and other imaging data, performed indepen-
dent CT, MRI, and US reporting and analysis. Phantoms
were assigned a designated number and series for referencing.
All imaging was reviewed on high-resolution flat screen pic-
ture archiving communication systems. Images were analyzed
with a varying magnification from 120%−400% in compari-
sion to the acquisition and window parameters (width and
level), which were not preset. The reviewing mechanism for
CT reporting allowed radiologists to sample the mean or me-
dian Hounsfield unit by placing a circular or elliptical region of
interest cursor in the predominant area of plaque. For
MRI, multi-contrast capabilities and resolution provided pla-
ques composition features according to signal intensities and
weightings of the plaque. The US evaluation of the plaque
characteristics was analyzed reviewing, high-resolution 2D
images, raw data 3D reformatted section, and 3D reformatted
images. Radiologists did not have the capabilities to manipu-
late 3D images however, sufficient still images were captured
to cover all aspects of the plaques. Furthermore, constructed
3D plaque images were assessed independently.

Radiologists reported their individual findings on work-
sheets for each modality. For US imaging, the types of plaques

Figure 8: A, US imaging of a phantom using longitudinal acquisition 2D and B, 3D reformed imaging, 2D, two-dimensional; 3D, three-dimensional; US, ultrasound.
were further classified, using a novel classification system, dividing each plaque into one of three possible categories: (1) type A (no to low risk for vulnerability), a carotid plaque exhibiting no US characteristics that suggested vulnerability, regardless of the existence of borderline or vulnerable features; (2) type B (moderate risk for vulnerability), a plaque exhibiting one US characteristic for vulnerability; and (3) type C (high risk for vulnerability), a carotid plaque exhibiting two or more US characteristics.

Statistical Analysis

The agreement between and among the imaging modalities was assessed via Cohen’s kappa or intraclass correlation coefficients (ICC), as appropriate (i.e., Cohen’s kappa when evaluating categorical data and ICC when the data were ordinal). A kappa or an ICC value of 0–20 indicates poor agreement; 20–40 fair agreement; 40–60 moderate agreement; 60–80 substantial agreement; and 80–100 very good agreement. The agreement among radiologists was assessed regarding the added value (or not) of applying additional 3D US technique (six ratings), using ICC statistics. The sensitivity, specificity, and accuracy was assessed for each variable or morphologic factor (NAD, lumen, ulceration, fissure, and irregular surface) for all modalities using the specimen pathology as a reference standard. The final data set assessed categorical agreement, using our own classification system, among three independent radiologists on specific plaque types using Cochran Q test by measuring the overall agreement with phantom specimen pathology for referencing. Statistical analysis was performed using MedCalc professional statistics software version 12.1.1 (MedCalc Software, Mariakerke, Belgium).

Results

Tissue-like phantoms were created to simulate various types of diseased plaque segments. None of the samples were excluded from the analysis. Tables 1 and 2 demonstrate the overall agreement and accuracy among three modalities for each morphologic characteristic.

In the regular or NAD specimens, when all three modalities were considered simultaneously there was substantial agreement among the three modalities (ICC = 0.71; 95% confidence interval [CI], 0.60-0.81). There was substantial agreement between US and CT (kappa = 0.78; 95% CI, 0.49-1.00) and between US and MRI (kappa = 0.64; 95% CI, 0.26-1.00) regarding the assessment of NAD. There was no significant difference in accuracy between US and CT (P = .50) or MRI (P = .25) for identifying a segment as NAD.

Agreement in the identification of lumen was moderate (ICC = 0.61; 95% CI, 0.25-0.75) among the three modalities. There was substantial agreement (kappa = 0.62; 95% CI, 0.26-0.82) between US and CT and fair agreement (kappa = 0.26; 95% CI, 0.05-0.48) between US and MRI (Figure 10). There was no significant difference in accuracy
Table 1

<table>
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<tr>
<th>Assessment Criteria</th>
<th>Inter-Observer Agreement</th>
<th>Cohens Kappa</th>
<th>95% Confidence Interval</th>
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<td>NAD</td>
<td>Substantial</td>
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<td>0.49-1.00</td>
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<td>US vs. CT</td>
<td>Substantial</td>
<td>0.64</td>
<td>0.26-1.00</td>
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<td>US vs. MRI</td>
<td>Substantial</td>
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<td>0.42-0.82</td>
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<td>US vs. MRI</td>
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<td>Lesion</td>
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<td>US vs. CT</td>
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<td>US vs. CT</td>
<td>Substantial</td>
<td>0.60</td>
<td>0.39-0.81</td>
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<tr>
<td>US vs. MRI</td>
<td>Moderate</td>
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<td>0.38-0.77</td>
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<td>Irregular Surface</td>
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<td>US vs. MRI</td>
<td>Substantial</td>
<td>0.41</td>
<td>0.17-0.66</td>
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</tbody>
</table>

CT, computed tomography; MRI, magnetic resonance imaging; NAD, no abnormality detected; US, ultrasound.

between US and CT (P = 0.23), however, US was significantly more accurate than MRI (P = 0.001).

In the ulcerated specimen, moderate agreement (ICC = 0.51; 95% CI, 0.36-0.65) was observed. There was moderate agreement between US and CT (kappa = 0.48: 95% CI, 0.24-0.72) and US and MRI (kappa = 0.51, 95% CI, 0.27-0.75). There was no significant difference in accuracy between US and CT (P = 0.50); however, US was significantly more accurate than MRI (P = 0.04) with respect to the assessment of ulceration (Figure 1).

Observed agreement in the identification of fissures was moderate (ICC = 0.55; 95% CI, 0.41-0.68) among the three modalities when considered simultaneously. There was substantial agreement (kappa = 0.60; 95% CI, 0.39-0.81) between US and CT and moderate agreement (kappa = 0.58; 95% CI, 0.38-0.77) between US and MRI regarding the identification of fissures (Figure 12). US was more accurate than CT; however, this difference was not significant (P = 0.07). US was significantly more accurate than MRI (P = 0.02).

The agreement in the identification of irregular plaque surface across all levels of modalities yielded substantial agreement (ICC = 0.61; 95% CI, 0.48-0.73; Figure 13). There was very good agreement (kappa = 0.84; 95% CI, 0.69-0.99) between US and CT vs. moderate agreement (kappa = 0.41; 95% CI, 0.17-0.66) between US and MRI with respect to detecting irregular surfaces. There was no significant difference in accuracy between US and CT (P = 0.63) or US and MRI (P = 0.12).

Three independent radiologists further quantified the plaque using our predefined classifications system. There was substantial agreement (ICC = 0.61; 95% CI, 0.46-0.74) among the three radiologists in their assessment of plaque subtype, ranging from 80-85% accuracy in identifying the subtypes in each classification. Cochran's Q test identified no significant difference in accuracy among the three radiologists (P = 0.75) in terms of their assessment of plaque subtypes.

Good agreement was established with the conventional 2D method; however, there was poor agreement among the three radiologists in terms of their assessment of whether the 3D component helped the assessment (ICC = 0.01; 95% CI, 0.06-0.12). Our results indicated that there was a significant difference between the first radiologist and the others with respect to whether the 3D US data provided additional diagnostic value. The first radiologist was much more likely to have indicated that the 3D component assisted their assessment in 88% of samples vs. 34% and 22% for the other two readers, respectively; P < .001.

Discussion

The purpose of this investigation was to evaluate the imaging applicability of an enhanced US method in identifying and quantifying vulnerable carotid atheromas and demonstrate whether our method improved the visualization of specific characteristics. To verify US's role as one of the leading diagnostic imaging modalities, we validated this assumption by developing a US imaging protocol based on the under-researched US imaging applicability of examining multiple plaque characteristics as a myriad technique and including a combined imaging theory of 2D and 3D application. We evaluated the agreement of our method in contrast with other, currently clinically available modalities such as CT and MRI and corroborated with the true plaque pathology. The novel findings from our research are as follows: (1) our enhanced US imaging method provides an excellent method for the analysis and morphologic assessment of a plaque and surpasses other current imaging method such as CT.

Table 2

<table>
<thead>
<tr>
<th>NAD</th>
<th>CT</th>
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CT, computed tomography; FN, false negative; FP, false positive; MRI, magnetic resonance imaging; NAD, no abnormality detected; Se, sensitivity; Sp, specificity; TN, true negative; TP, true positive; US, ultrasound.
and MRI; (2) US has proven to improve the morphologic reporting parameters of atheromatous lesions, improving imaging quantification; and (3) we resolve that combining the traditional stenotic degree quantification and specific plaque morphologic analysis using advanced high-resolution US imaging would help increase the assessment of total plaque risk vulnerability and could possibly be of use as a base for predicting future ischemic events.

CVAs and the associated thromboembolic complications in carotid atherosclerosis continue to be the second leading cause of death globally and the leading cause of death in North America [11], with numbers on the rise. The disease mechanism of carotid atherosclerosis initially starts with alterations in the structural and mechanical properties in the endothelial layer of the vessel [12], eventually causing an atheroma, resulting in progressive narrowing or thrombosis of the specific vascular segment. The fact that atherosclerosis of the carotid arteries is a source of ischemic strokes is unquestioned; cerebral embolism typically originates from a thrombus at the site of the carotid atheromatous plaque [13-15]. The morphologic composition in vulnerable plaques has a high probability of causing thrombotic complications, which can significantly affect cerebrovascular prognosis. Vulnerable morphologic plaque characteristics associated with neurologic event include: presence of thin or fissured fibrous capsule, surface irregularities and/or ulcerations, internal presence of large lipid core(s) or hemorrhage(s), active inflammation, severe stenosis, or a combination of these findings [16-18]. Plaque formations with these specific morphologic factors could cause a luminal narrowing <75% but be a major contributor to future CVA. Therefore, specific morphologic detection, aside from luminal stenosis determination, could possibly predict clinical outcomes.

The early identification of morphologic features and characteristics in vulnerable carotid plaques has opened up new possibilities in the discipline of carotid artery imaging for stroke detection, progression, and prevention. Diagnostic imaging modalities are increasingly being studied as potential modalities to identify early plaque formation, changes, and/or stability in carotid atheromatous plaques. MRI has increasingly become one of the most valuable tools in distinguishing carotid plaque compositions, as newer, higher field strengths, and designated carotid imaging coils are emerging and currently used for research. MRI has an extra advantage as it is noninvasive in nature and produces increased spatial resolution for tissue weighting capacity, and is thus able to examine the fibrous cap status including its neovascularity. Although MRI appears promising, it is currently in its infancy in terms of plaque imaging development for clinical applicability. Its high operational cost and limited accessibility as a primary imaging role in the quantification of atheromas is currently restrictive. The advancement of CT multidetector-row scanners and delivery of angiographic protocols, such as CT angiography, is currently the gold standard in quantifying carotid stenotic degree. CT has the capacity to image optimal segmental imaging due to its submillimeter capabilities and...
can easily distinguish internal components of selected complicated plaques, especially in the diagnosis of surface ulcerations. Although CT appears quite promising, trials investigating the sensitivity of CT in plaque morphologic imaging and analysis are current and research is ongoing. US, being the first-line imaging modality for transient ischemic attacks or stroke-related symptoms, has an important and emerging role in carotid morphologic imaging. With the advancement of high-resolution transducers and 3D capabilities, US plaque characterization investigation is the new noninvasive imaging method of choice to evaluate the internal textural alterations and structure of specific plaque appearances; however, US does have a high variability and technological application in echomorphology in its infancy.

We created carotid phantoms with excellent replicas of diseased atheromas for multi-modality imaging to obtain several outcomes. The first result we obtained was the observation agreement between US and CT and US and MRI. Substantial agreement was the highest among all modalities in normal specimens and irregular surfaces, but only moderately in the remaining. The kappas between the correlation of US and CT over MRI were higher, especially in the identification of irregular surface (kappa = 0.84 CT, 0.41 MRI). This may be due to the fact that US and CT are optimal in distinguishing smaller submillimeter slice, and MRI is currently lacking this resolution. US agreement with MRI for the presence of lucency had the lowest kappa values (0.26), which was unexpected considering MRI is currently the contender in internal plaque tissue weightings/classification.

Our second observation demonstrated the accuracy in correctly identifying specific plaque morphologic features among modalities. US observed the highest accuracy in identifying all parameters (range, 88%–100% accuracy), with CT second (range, 83%–97% accuracy), and MRI last (range, 67%–95% accuracy), keeping in mind that all three modalities had high accuracy in normal segments. Intraplaque haemorrhages or large lipid cores have long been recognized as a complication of atherosclerotic plaque and carry an increased risk of subsequent ischemic CVA, as this type of plaque is often soft and friable. Although most imaging approaches cannot reliably distinguish hemorrhage(s) from lipid core(s), our study found that US was the most accurate method to detect the presence of an internal focal and lucent area with 95% accuracy over CT (87%) and MRI (67%). This outcome proved that our US method had excellent capabilities over both modalities in identifying internal alterations in vulnerable plaques. Surface irregularities, commonly representing a thinned or ruptured fibrous capsule, indicate as an important vulnerable morphologic characteristic in atherosclerotic plaque. Surface imaging demonstrated that US had the highest accuracy (90%) over CT (87%) or MRI (78%). This is more likely due to US’s capability of visualizing the parenchymal wall tissue and surface appropriately; however, the presence of surface fissures changed these limitations, as US was more accurate than CT ($P = .07$) and significantly more accurate than
MRI ($P = .02$) in identifying fissured plaques. Historically, CT has been known to be highly sensitive in the detection of surface ulcerations [19]. Although marginal, our result contradicts this notion, as our US imaging method was the most accurate (88% accuracy) in detecting ulcerations, CT being second (85% accuracy) with no statistically significant difference in accuracy between the modalities ($P = .58$). US was significantly more accurate than MRI with respect to the assessment of ulceration ($P = .04$).

Given the phantom was used for measuring US method accuracy and detection agreement only, we did not measure the speed of sound in the mediums, scatter or attenuation coefficients, or density units for the purpose of our research. Our research included multiple factors involved in the consistency with the use of the same hardware, techniques, operators, and data standardization so that the variability in study analysis was reduced. This is not feasible in everyday applications and would be of interest to evaluate this as a separate trial. We also acknowledge that certain findings may be related to the inherent nature of the CT and MRI scanner technology used directly having an effect on the data, especially because we applied routine neurologic parameters for imaging not taking in that special coils or software could optimize imaging features in both modalities, enabling proper identification of internal hemorrhage in small surface ulcerations. All phantoms were scanned within three days of creation; however, based on previous experience [10] with these samples, phantoms can last for several weeks when properly refrigerated.

US remains the first-line imaging and modality of choice for CVA imaging to image soft-tissue contents such as atheromatous plaques because of its easy accessibility, low-cost, and its noninvasiveness. Newer US techniques are showing great potential to maximize the information gathered by traditional 2D and to enhance morphology imaging. Although 2D had its limitations because of its single-plane projection, it does offer excellent high-resolution imaging that can identify several important plaque characteristics alone and with high accuracy. This started the deliberations to design and implement an imaging protocol that is inclusive and comprehensive for the US detection of vulnerable carotid atheromas plaques. Our investigations permitted us to explore a broad coverage of US applicability, including a combined enhanced 2D and 3D imaging method to improve the quality of characterization for plaque surface morphology.

In an effort to globalize image and reporting standardization, we created and implemented a quality assurance tool for plaque classification criteria without the use of complex or expensive software using three categorical groups defined according to risk and applied it in our reporting mechanism for our research. Our classification system yielded substantial agreement among radiologists in the assessment of subtypes, thus improving the accuracy of plaque characterization assessment and reporting.
This study demonstrated that our advanced US plaque imaging methodological application had a high correlation rate, sensitivity, and specificity between US, CT, and the true pathologic findings. In addition, it appeared this US method was a touch optimal to CT and outdled MRI in identifying these potential risk indicators in a greater part of categorical components. These results demonstrate that our US imaging approach may be a sensitive tool in the identification of early vulnerable markers. The framework shown in this research allows for justification for a large-scale multicenter trial probing the capabilities of our US imaging technique as a screening tool for identifying patients with high stroke risk, particularly those who have not reached a high-risk and high-degree stenosis. This philosophy must be further investigated in prospective, randomized human trials and include all types or grading of plaques to correctly define these points. Lastly, a separate subset of data should be included to evaluate 2D and 3D US independently.

Conclusions

A good agreement was observed between US, CT, and the true pathology in the evaluation of a representable carotid plaque atheroma. Poor agreement was found between US and MRI. Our enhanced US method exhibited dominance over other evolving imaging modalities in the quantification and assessment of specific morphologic characteristics considered vulnerable for strokes. Our findings suggest that the information derived should be critically compared and validated with other diagnostic techniques in human atheromas, suggestive in a long-term clinical trial.

References


JOURNAL ARTICLES UNDER REVIEW


THE UTILITY OF THREE-DIMENSIONAL (3D) PLAQUE IMAGING IN CAROTID STENOSIS

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Abstract

Objective: Emerging data suggests that carotid plaque morphology and severity can significantly affect cerebrovascular prognosis. Recent studies have reported that three-dimensional ultrasound (3DUS) used as an adjuvant imaging technique may provide additional information in the evaluation and risk stratification of vulnerable carotid plaque. The focus of this study was to evaluate the utility of 3DUS in characterizing plaque from various degrees of stenosis.

Methods: In a cohort of symptomatic patients referred from neurosurgery, 3DUS of the carotid arteries was conducted using a vascular ultrasound system (IU22, Philips Medical System) equipped with a volumetric, mechanical, high-resolution linear-array transducer for 3D imaging. We employed a 3DUS imaging method to allow high-detailed studies in mild, moderate and severe stenotic plaques. Constructed 3D plaque images were quantified using internal plaque echotexture, volume and surface morphology, and evaluated by an independent observer using our own classification protocol. Results: Results indicate that 3DUS for plaque characterization was significantly better in mild to moderate imaging, possibly due to the fluid-filled lumen acting as a substantial acoustic transmission for optimal plaque visualization. Higher-grade stenoses (>70%) was difficult to assess; however, proximal and edge surface imaging was diagnostic. These results indicate that our 3D approach may be a sensitive tool in the identification of early vulnerable markers in lower-graded stenoses, possibly identifying early prediction of stroke. Conclusion: 3DUS shows a high sensitivity and negative predictive value of carotid plaque 3DUS in mild to moderate stenosis, and can reliably characterize surface, volume and ulcerations. The sensitivity decreased with the severity of stenoses. 3DUS carotid plaque quantification may serve as an important additional clinical screening tool in early onset of
significant carotid disease, for high-risk patients, and for those without known significant

carotid disease.

Keywords: 3D; ultrasound; carotid; plaque; vulnerable

Introduction

Carotid plaque morphology is increasingly being studied and imaged, as a potential hopeful

prospect to identify patients’ cerebrovascular prognosis. Better methods are being presented
to identify potential markers of high risk plaques, in hopes to identify specific imaging
parameters to help describe the vascular risk. One of modalities is the use of high definition
ultrasound (US) to further image the plaque.

With the recent addition of volumetric 3 dimensional ultrasound (3DUS) probes and imaging
capabilities, studies have reported that (3DUS) used as an adjuvant imaging technique may
provide additional information in the evaluation and risk stratification of vulnerable carotid
plaque in addition to 2-dimensional (2D) US imaging.

The aim of this investigation was to evaluate the utility of 3DUS in characterizing plaque from
various degrees of stenosis.

Materials and Methods

The pilot study protocol and use of this sonographic method was approved by the Research
Ethics Committee of the xxxxxx. Written informed consent was obtained from all patients.

Patients

The final population consisted of three patients exhibiting various degrees of stenosis. All
patients were symptomatic. Two were experiencing transient ischemic attacks (TIAs) and the
other had non-specific neurological symptoms. All patients had underwent computed
tomography (CT) or magnetic resonance imaging (MRI) in the radiology department, referred
from the neurosurgery or neurology department, to investigate neurological symptoms, prior
to the ultrasound (US). US imaging was performed after-hours, at the patient’s bedside.
Research participants excluded from this study included patients who were pregnant, obese,
had prior history of carotid artery surgery and unable to provide consent to the study or answer
the medical questionnaire due to a disability that prevented the full understanding of what was
being consented to. We did not encounter any excluded patients therefore, did not track any
list of exclusions.

Sonographic examination and analysis
A research sonographer, who had additional specialization and training in 3DUS imaging,
performed a detailed carotid plaque examination using a vascular ultrasound system IU22,
Philips Medical System (Philips Healthcare, Netherlands) equipped with a volumetric,
mechanical, high-resolution linear-array transducer for 3D imaging. The sonographer was blind
to the CT or MRI results however, was provided the affected side for reference. Patients were
scanned in a supine position, with the neck slightly rotated away from the transducer. The
examination began with a systematic overview of the carotid artery, using a 9 MHz linear
transducer. The plaque was imaged using 2-Dimensional (2D) B-mode imaging and assessed for
specific morphological features such as homogeneity, internal echotexture, ulceration, surface
irregularities, intraplaque haemorrhage/lipid core and calcification. 3DUS imaging method was
followed to allow high-detailed, volumetric imaging of the plaques. Constructed 3D plaque
images were quantified using internal plaque echotexture, volume and surface morphology,
Both 2D and 3D images were reviewed by a single observer, and systematized using our own classification protocol (Table 1) and compared to the previous CT or MRI findings. Institutional patient medical records were reviewed for outcome information, when available.

Statistical Analysis

The utility of 3DUS in carotid plaque imaging and analysis with regard to the presence or absence of specific morphological features was evaluated by calculating the sensitivity, specificity, positive and negative predictive values together with 95% confidence intervals. Accuracy and degree of concordance was measured between the sonographic classification of disease and disease classification based on the additional the imaging findings. We did not combine history, gender, prospective sonographic diagnosis, segment of carotid affected, diffuse disease, ancillary findings or clinical diagnosis as categorical explanatory variables. A logistic regression analysis model was created to measure our data and allow us to assess the significance of the association between the carotid plaque sonographic examination and the probability of carotid disease. This analysis was also used to estimate the rate of false-positive and false-negative diagnoses.

Results

Of the 3 patients identified, all 3 were included in the final analysis for this pilot study. The cohort of the 3 patients had a mean age of 61 years (range, 37-72 years). The group was composed of one male (30%) and 2 females (60%). The dedicated 3DUS plaque imaging took between three and ten minutes to complete.

All three (100%) patients included in the study had prior cross-sectional imaging, CT or MRI (CT, n=2, MRI, n=1). In all cases where positive plaque sonography findings present, all were
confirmed with another imaging modality, the location and classification of disease type
correlated. Using additional cross-section imaging as the gold standard, the dedicated 3DUS
plaque imaging yielded a sensitivity of 91.6% and a specificity of 92.8% using a 95% confidence
interval with a total width of the 30%. The positive predictive value (PPV) was 91.6% and the
negative predictive value (NPV) was 92.8%.

Sonographic Findings and Plaque Type

Results indicate that 3DUS for plaque characterization was significantly better in mild (Figure 1)
to moderate (Figure 2) imaging, possibly due to the fluid-filled lumen acting as a substantial
acoustic transmission for optimal plaque visualization. Higher-grade stenoses (>70%) was
difficult to assess (Figure 3); however, proximal and edge surface imaging was diagnostic. In the
patient with >70% stenotic atheroma, ulceration was seen on the 3DUS but not on the 2D US
imaging. However, calcification in the high-grade stenosis impeded the acoustic sound waves,
causing significant dropout in the mid portion of the plaque. In the moderate graded stenotic
plaque, the plaque was visualize very well as a whole and 3D manipulation allowed the
reviewer to evaluate the plaque at multiple angles, allowing proper identification of surface
irregularities, ulcerations or the identification of abnormal variables within the plaque. Lumen
assessment was also unremarkable, compared to 2D imaging due to the post-data processing
and manipulation capabilities. The moderate plaque did not exhibit as much calcification as the
severe however, where present no acoustic artifact or shadowing occurred, allowing for full
visualization of the plaque and lumen. The plaque’s irregular surface was also optimally
visualized using the 3DUS tool and was well depicted in this stenotic grading. The normal
segment did not demonstrate any discrepancy from the 2D US however, the analysis of the
intima layer was improved due to the high-resolution capabilities of the 3D US.
These results indicate that our 3D approach may be a sensitive tool in the identification of early
vulnerable markers in lower-graded stenoses, possibly identifying early prediction of stroke in
both symptomatic and asymptomatic population.

Discussion

Ischemic strokes are associated with cerebral embolisms originating from a carotid
atheromatous plaque or from a thrombus originating from the site of the rupture. The
vulnerability of the carotid plaque is dictated by its morphological composition, which plays an
important role in the risk of embolization or stroke. Studies have demonstrated that specific
plaque characteristics are often associated with neurological event. Postulated
morphological criteria of vulnerable plaque include a thin or fissured capsule, large lipid core(s),
active inflammation, severe stenosis or a combination of these findings. Emerging approaches in identifying early morphological features and characteristics of
vulnerable carotid plaque have opened up new avenues in the field of carotid artery imaging
for stroke. Imaging modalities that offer possible identification of these features include MRI,
CT and US. Sonography is currently the most common imaging study used as the first-line
imaging tool in the initial evaluation of transient ischemic attacks (TIAs) or stroke symptoms,
especially in the current era of radiation safety concerns. Until recently, US carotid imaging was
limited to grading specific stenotic lesions within the carotid plaque segment: however, US has
good mean results in the evaluation of plaque morphology by identifying internal components
and the structure of specific plaque appearance and any carotid lesion should include a detailed plaque assessment to complete the evaluation.

In recent years, the US assessment of atheromatous lesions using high-frequency and high-definition transducers has allowed further visualisation of the carotid plaque segment, many of which may contain unstable plaques that may rupture, exposing the highly thrombogenic necrotic core to the blood stream and causing a distal embolus, resulting in cerebral infarct. Specific markers include echotexture, the presence of echolucency and surface alterations or ulcerations. Recent studies have reported that 3DUS used as an adjuvant imaging technique may provide additional information in the evaluation and risk stratification of vulnerable carotid plaque.

The novel findings from this study are as follows: (1) 3DUS has proven to improve some of the plaque's echographic parameters and help describe the vascular risk in all types and grade of atheromatous lesions; (2) Although its use in high-grade stenotic lesions were limited by calcification and lack of acoustic window by the tight lumen, 3DUS still provided additional information over conventional 2DUS, matching the findings to the previous CT imaging and surgical sample results; (3) We hypothesized that combining the stenotic degree and specific plaque morphology including surface irregularity or ulceration, echolucency and texture would help increase the assessment of total plaque risk vulnerability and use it as a base for predicting future ischemic events; (4) 3DUS was useful in identifying parameters in atherosclerotic plaques at higher risk for cerebrovascular events, thus improving stroke prevention.

Our results showed that additional 3DUS imaging demonstrated high-accuracy in plaque morphology assessment however, we acknowledge several limitations of our study.
Interobservation manipulation was not assessed which is an important variable in US’s operator dependency. Thus, we cannot make any definitive conclusions about the inter-operator variability, consistency. Furthermore, we limited our findings to a single sample from each stenotic grading criteria, preventive global assessment in various types of plaques. The study would benefit having a larger scale study, with proper surgical radiographic-pathologic correlation.

In conclusion, results from this prospective pilot study suggest that the utility of 3DUS adjunct to conventional 2D carotid plaque assessment has the potential to be a valuable method for evaluating various morphological changes of atheroma, some of which are critical markers in the early indication of stroke prevention. This small prospective study may be the impetus for a paradigm shift in the usual protocol in carotid US imaging, however larger prospective studies are indicated to corroborate these findings.

References


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<td>• a carotid plaque exhibit two or more US characteristics that suggest a vulnerable lesion with no borderline features.</td>
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Table 1. Classification protocol for carotid plaque assessment and reporting.
Figure 1. 3DUS of a mild stenosis (arrows).

220x149mm (72 x 72 DPI)
Figure 2. 3DUS of a moderate stenosis (arrows). Imaging was optimal, most likely due to fluid-filled lumen acting as substantial acoustic transmission for optimal plaque visualization.

334x173mm (72 x 72 DPI)
Figure 3. 3DUS of a severe, higher-grade stenoses (>70%) (arrows). This type of stenosis was difficult to assess due to acoustic impedance.

32x199mm (72 x 72 DPI)
CAROTID PLAQUE CLASSIFICATION SYSTEM: A NEW STANDARD

DIAGNOSTIC CRITERION

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Keywords: Carotid; Classification; Plaque; Ultrasound
Abstract

Objective: Ultrasound (US) carotid plaque imaging can provide valuable information on the morphology of the atherosclerotic plaque. Particular sonographic features of the plaque have been recognized as the foundation for stroke. Carotid plaque imaging is increasingly recognized as being as important as stenotic grading; however, various methods of echographic image standardization have been described with a number of these systems using complex, expensive or unavailable software. Standard plaque analysis and characterization is lacking and, to our knowledge, no global classification system or form of image standardization exists. Our objective was to develop a standardized US characterization method and reporting data system of carotid atherosclerotic lesions for clinical management: the Carotid Plaque Imaging Reporting and Data System (CPIRADS).

Methods: We designed this prospective study based on the concept of the BIRADS and TIRADS from the American College of Radiology. We reviewed randomized, controlled human clinical trials that validated the applicability, diagnostic accuracy and classification of US carotid plaque characterization. Based on these findings, we created and implemented a quality assurance tool for plaque classification criteria in an effort to globalize image and reporting standardization without the use of complex or expensive software. We subjectively graded US images using a standardized classification report form that combines specific echographic image features. Three categorical groups were defined according to
risk: Type A (no to low risk for vulnerability), Type B (moderate risk for vulnerability) and Type C (high risk for vulnerability).

**Results:** The CPIRADS classification was evaluated in each categorical classification (no to low risk: 1, moderate risk: 1 and high-risk: 1). Results indicate that the inter-observer and inter-reader reliabilities were high and that plaque neuroradologist’s report were 96% sensitive and 97% specific respectively, using our classification system.

**Conclusion:** The CPIRADS standardized classification system has allowed us to improve the consistency and accuracy of plaque characterization imaging and assessment without of the use of computed or automated methodologies. This plaque analysis criterion may help promote the use of a standard, global US classification analysis and uniform reporting for carotid atherosclerotic lesions. Large-scale prospective studies are required to fully assess the potential of this grading system.
Introduction:

Cerebrovascular (CVA) accidents are the second leading cause of death globally [1] and the leading cause of death in North America[2], with an estimated one stroke in every ten minutes occurring daily in Canada[3]. Ischemic strokes are associated with cerebral embolisms originating from a carotid atheromatous plaque or from a thrombus originating from the site of rupture[4]. The vulnerability of the carotid plaque is dictated by its morphological composition, which plays an important role in the risk for embolization or stroke. Studies have demonstrated that specific plaque morphological characteristics are often associated with neurological events [5-8] and thus any atheromatous lesions should be assessed as they may contain unstable plaques that can rupture, exposing the highly thrombogenic necrotic core to the blood stream and causing a distal embolus, resulting in a cerebral infarct.

Emerging approaches in the identification of these morphological features in carotid plaques have opened up new avenues in the field of carotid artery imaging for stroke. One of the primary, non-invasive imaging modalities that offer possible identification of these features include the use of duplex, high-resolution US. Until recently, US carotid imaging was limited to grading specific stenotic lesions within the carotid plaque segment; however, newer and emerging technology now provides enhanced image quality and greater anatomic definition, thereby allowing earlier imaging and detection of carotid atheromas maximizing the information traditionally gathered with spectral Doppler examinations. US has good mean results in the evaluation of plaque morphology by directly visualizing the plaque and
quantify features such as the internal components or echotexture, surface morphology, ulcerations, volume and the overall structure of the specific plaque. However, many studies report variability in the diagnostic accuracy or have considerable overlap in the appearance for distinction between mild, moderate and severe lesions, regardless of their sonographic appearances.

A few prospective studies report the diagnostic accuracy of carotid plaque classification and various methods of echographic image standardization have been described; however, most use a complex, costly, computer software unavailable to most imaging centers or laboratories. One of the most referred system using basic B-mode was described by Grey-Waele et al.[5], who proposed a 4-step classification system for carotid atheromas; however, US morphological features have since emerged due to higher resolution imaging and newer, current data or technological changes have not been applied to this grading system. Standard plaque analysis and characterization is lacking and to our knowledge, no global classification system or form of image standardization using prospective real-time US classification for carotid atheromas exists.

The American College of Radiology developed the Breast Imaging Reporting and Data System (BIRADS)[9] to characterize in a standardized fashion, both mammographic and US breast lesions and their correlation with malignancy and is currently the world-wide accepted clinical categorical reference. A similar reporting system based on the BIRADS using the concept to differentiate categorical thyroid nodules is further being developed called Thyroid Imaging Reporting and Data System (TIRADS)[10].

We decided to study the feasibility of applying this concept to the US evaluation of carotid lesions and develop a classification criteria to aid in the evaluation and interpretation of quantitative grading for carotid atheromatous lesions and call it Carotid Plaque Imaging Reporting And Data System (CPIRADS), taking the BIRADS and TIRADS as models. Our goal was to (1) categorize carotid atheromatous lesions of different risks for vulnerability based on previous literature; and apply a imaging based standardization, with associated classification system to better stratify their potential risk; and (3) create a methodological, systematic guideline for US use in the assessment of plaque, adjunct to stenotic grading.

Materials and Methods:

During the course of three consecutive years, the prospective evaluation and literature review of US plaque morphology was assessed[11]. We reviewed randomized, controlled human clinical trials that validated the applicability, diagnostic accuracy and classification of US carotid plaque characterization; however, we restricted to articles published in peer-reviewed medical journals, as we believe that this evidence carries the most weight. Based on these findings, we created and implemented a quality assurance tool for plaque classification criteria in an effort to globalize image and reporting standardization without the use of complex or expensive software. We designed a US carotid plaque classification system, based on the BIRADS and TIRADS concept from the American College of Radiology[9, 10].

Carotid Plaque US

To further evaluate our findings, we evaluated each types of plaque
to institutional review board-approved prospective studies[12, 13] and applied our CPIRADS classification system. A total of 3 in vivo plaques and 60 simulated plaques, performed by a sonographer with advanced carotid plaque training, were evaluated for the purpose of this study. US plaques were imaged using a linear 7-12MHz transducer on a Philips IU22 unit (Philips Healthcare, Netherlands). Plaque was assessed for specific plaque imaging analysis in identifying specific morphological features such as homogeneity, internal echotexture, ulceration, surface irregularities and intraplaque haemorrhage/lipid core. A list of standardized images were documented and specific US unit settings were applied to globalized imaging parameters.

Inclusion criteria for the US characteristics of vulnerability identified sonographic features of carotid atheromas were as follows: Marked homogeneity, irregular surface/capsule, presence of ulceration and internal areas of echolucency. Marked homogeneity was defined as an area of predominantly smooth or uniformly hypoechoic in the lesion; an irregular surface was defined as having the presence of irregular or spiculated margin on the surface of the plaque with a loss of a smooth or thin echogenic cap; ulceration was defined as a >2 mm divid into the surface with presence of color Doppler; internal echolucency was defined by a remarkable hypoechoic or anechoic area within the plaque.

Lesion Classification

US images were subjectively graded using a standardized classification report that combines echographic image features and three categorical groups were created and defined according to risk including the following: if a carotid plaque exhibited no US characteristics that suggested vulnerability in the carotid internal artery (ICA), regardless of the existence...
of borderline or vulnerable US features, it was considered low-risk, or Type-A; if a carotid plaque exhibited one US characteristic for vulnerability regardless of the existence of additional borderline or vulnerable US features, it was considered as being moderately at risk for vulnerability, or Type-B; if a carotid plaque exhibit two or more US characteristics that suggest a vulnerable lesion with no borderline features, it was considered as being high-risk for vulnerability or Type-C. All carotid atheromas were assessed by a single neuroradiologist using high-resolution images.

Reference Standard

All 3 patients (M:F = 1:2; mean age 59 [12.4] years) imaged underwent CT imaging prior to the US scan, as they were symptomatic for stroke related symptoms. Simulated phantoms also had CT imaging, as well as true pathology identified at time of creation. Accuracy of the method was determined by measuring the agreement of plaque characterization using standardized US images and previous CT images. In addition, in vivo plaques incorporated Radpath correlation.

Statistical Analysis

The utility of our classification system for carotid plaque atheromas and analysis with regard to the presence or absence of specific morphological features was evaluated by calculating the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) values together with 95% confidence intervals for each CIRAD groups. Accuracy was definitively using additional cross-section imaging (CT) as well as additional secondary analysis was provided for high-risk plaque, using surgical specimen as the gold standard. We did not combine history, gender, prospective sonographic diagnosis, segment of carotid
affected, diffuse disease, ancillary findings or clinical diagnosis as categorical explanatory
variables. Degree of concordance was measured between the sonographic classification of
disease and disease classification based on the previous imaging findings.

Results:
The CPRADS classification was evaluated in one sample of each categorical classification.
One neuroradiologist evaluated the US plaque high-resolution images and categorized each
plaque accordingly, using a standard report form while applying our classification system. All
patients and simulated phantoms were confirmed with prior CT imaging and high-risk
plaque was confirmed at the time of endarterectomy.

Although not included are the classification parameters, it was noted that high-risk plaques
were significantly larger than moderate-risk plaques (mean size, 20.7 mm ± 11.4 vs 15.5
mm ± 7.5 respectively; p < 0.001). Patients with normal carotid were younger than those
with moderate or high-risk plaques (mean age, 59 ± 12.4 vs 47.5 ± 13.7, years
respectively; p= .001). There were no statistically significant relationship between the risk of
vulnerability and sex.

At univariate analysis, the following US features showed a significant association with
vulnerability: homogeneity, ulceration, surface irregularities and intraplaque
haemorrhage/lipid core. Multivariate analysis showed that the risk of vulnerability increased
as the number of suspicious US features increased. As the number of suspicious US
features increased, the probability of vulnerability increased. With these findings, we created
CPRADS Type A (no risk for vulnerability), Type B (moderate risk for vulnerability) and
Type C (high risk for vulnerability), using the BIRADS and TIRADS categorization as a model.

The utility of high-resolution 2D US imaging yielded the following reliability was significantly high in identifying each specific pathology and categorical classification. In each case, high reliability was identified in plaque echotexture, surface alterations and specific plaque types. The largest area of weakness identified was in the sub-categorical plaque classification of surface irregularity. We strongly suspect this may be due to the ambiguous or vague definition of this morphological appearance in US, and it would be of interest to repeat this study post-training.

Discussion:

High-resolution carotid plaque US imaging is the most useful, non-invasive diagnostic tool for evaluating carotid atheromas. The widespread use of imaging US technique has generated an overwhelming increase in the identification and recognition of several US characteristics that have been identified as potential predictors of stroke vulnerability, thus there is a need to establish a global US imaging criteria to possibly identify lesions at risk for stroke to minimize costs and maximize benefits. There is considerable overlap or complex reports of current diagnostic classification systems, unusable to global everyday US imaging applications. 2D US currently is the best tool to identify vulnerable plaque characteristics and morphology, with the use of newer, high-resolution linear transducers.

Selecting and identifying at risk plaques, especially through early atherosclerotic changes, is a future necessity in the prevention of strokes. Current US classifications are using complex,
expensive software to expand plaque data, whereas the CPIRADS classification is useful in the description of all types of plaques and uses everyday, global carotid applications such as 2D US in routinely used equipment. To our knowledge, there are no studies identifying the use of different US diagnostic system according to 2D classification to grade plaque morphological assessment in addition to stenotic grading. There is a desperate need for better guidelines to facilitate US reports and scanning parameters in order to communicate with and reduce confusion among physicians, patients and sonographers.

We attempted to determine the diagnostic accuracy of a US grading and reporting system using a 3-categorical classification system to improve US characterization of carotid atheromas by establishing a risk guideline in carotid imaging. The American College of Radiology has successfully used this type of system for breast lesions (BI-RADS) as well as a similar approach is being described for thyroid lesions (TI-RADS). Our classification system is modeled off the BI-RADS and TI-RADS, based on both fitted the probability and risk of lesions, using specific US features as a guideline for classification. Upon reviewing previously published articles on vulnerable US characteristics, we were able to categorize 3 groups of patterns that encompass all types of carotid lesions and their risk for vulnerability.

Compared to the previously published B-mode classification system described by Grey-Waerle et al. \(^1\), the diagnostic accuracy of vulnerability in carotid atheroma is greater in the present study; however, our sample size is much smaller. Other limitations to consider for this study were performance and interpretation by a single sonographer and radiologist, by as single radiologist. To validate our preliminary findings, a full, large-scaled multi-center, prospective study is required.
The use of the CPIRADS criteria has allowed us to properly quantify identifiable plaques and has proven to be an effective tool for selecting patients at risk of vulnerability for emboli. According to our definition of risk groups, patients with CPIRADS type B (moderate risk for vulnerability) may require follow up to follow the plaque for risk. Patients with CPIRADS Type C (severe risk for vulnerability) were operated and clinically warranted due to the high risk of vulnerability. We would like to stress that the CPIRADS classification is a pilot assessment for carotid atheromatous lesions and further investigation is required to validate this valuable study.

Conclusion

The CPIRADS standardized classification system has allowed us to improve the consistency and accuracy of plaque characterization imaging and assessment without of complex, computed or automated methodologies. The proper identification of specific US morphological features and categorization can unify the language between radiologist and referring physicians to promote universal, standard and global US classification analysis for reporting carotid atherosclerotic lesions, improving the patient’s management and care. The risk stratification of carotid atheromas according to the number of specific plaque US morphology features allows for a practical and convenient CPIRADS classification however, large-scale studies are required to fully assess the potential of this grading system.

Reference:


**CD-ROM CONTENTS**

**POWERPOINT PRESENTATIONS**


Kingstone, L, Torres, C & Currie, G. (2013). Advanced ultrasound evaluation of carotid plaque: can a combined 2D and 3D ultrasound analysis provide additional information and identify significant plaque characteristics responsible for strokes?, The American Institute of Ultrasound in Medicine (AIUM) Annual Convention, New York, USA.

**COURSEWORK**

HSC700 – Research Critique and Publication

HSC701 – Reflective Practice in Health Sciences

HSC702 – Proposal for Applied Research/Investigation

HSC703 – Research Project and Report
CONFERENCE PRESENTATION ABSTRACTS


Kingstone, L, Torres, C & Currie, G. (2013). Advanced ultrasound evaluation of carotid plaque: can a combined 2D and 3D ultrasound analysis provide additional information and identify significant plaque characteristics responsible for strokes?, The American Institute of Ultrasound in Medicine (AIUM) Annual Convention, New York, USA.
CAROTID ARTERY DISEASE IMAGE RECONSTRUCTION: A HOME-PRODUCED PHANTOM FOR 3D-ULTRASOUND SIMULATION

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Objective: Ultrasound (US) plaque characterization has emerged as the predominant approach in the evaluation and progression of carotid atherosclerosis. 3-dimensional ultrasound (3DUS) plaque imaging has revealed great potential to maximize the information traditionally gathered with B-mode, by demonstrating the ability to directly visualize plaque and to quantify better features such as surface morphology, geometry as well as volume and echotexture. One of the major pitfalls of carotid imaging, is the use of freehand manual manipulation. 3D application of angling, steering, as well as variability in the technical parameters, can increase the interobservation inconsistency. A limited number of commercial phantoms are available to teach this advanced technique but come at a high cost. We developed a home-produced phantom model to practice and teach carotid atherosclerotic disease imaging. We also investigated interobservation variability using two-dimensional (2D) characterization and 3D mechanical planimetry. This study presents a recipe to create an ultrasonic phantom that simulates a diseased carotid artery segment and how it can be used in identifying the 2D and 3D US interobservation variability.
Method: We created five tissue-like phantoms to simulate various types of diseased plaque segments. Each mold contained dissimilar types of mimicked-plaque including a soft-plaque, fissured, ulcerated, irregular surfaced and calcified segment. Soft tissue was mimicked using a mixture of gelatin and Metamucil, previously published. The carotid atheroma was created using a nitrile examination glove, mineral oil, adhesive gel and a piece of animal protein to mimic the diseased vessel. Preparation included interval refrigeration of the concoction of the mold. Trained sonographers imaged the plaque using a linear small parts probe for 2D and mechanical-3D probe for 3DUS. Two neuroradiologists assessed the corresponding images and reported their findings including the internal plaque contents, volume, and geometry. Analysis was performed on the inter-observation and inter-reading variability.

Results: Interobserver and inter-reader reliabilities were high, and plaque volume measurement variability decreased with increasing plaque volume. There was increased sensitivity and specificity for each plaque phantom with the use of 3D versus 2D alone. Neuroradiologist’s reports were 96% sensitive and 97% specific, respectively, when they used combined 2D and 3D US.

Conclusion: We created a 2D and 3D vascular US carotid phantom and implemented a standardized, central US scanning protocol using strict quality control procedures for reading plaque US imaging to achieve optimal imaging. This phantom is an excellent educational tool to simulate various degrees of
diseased carotid segments, which is easily made, inexpensive.; moreover and reusable. Additional studies are required to address the phantom’s longevity and whether or not it can improve the sonographer’s skills.
EVALUATION OF CAROTID ARTERY PLAQUE

MORPHOLOGY AND CHARACTERIZATION WITH ULTRASONOGRAPHY

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Although ultrasound (US) evaluation of the carotid artery for stenosis is the accepted method for identifying risk factors for cerebrovascular (CV) events, patients with specific plaque morphology may be at increased risk. US plaque characterization is a potentially useful adjunct to stenotic grading for identifying vulnerable carotid disease. Postulated morphological criteria of vulnerable plaque include a thin or fissured capsule, large lipid core(s), active inflammation, severe stenosis or a combination of these findings.

Emerging approaches in identifying early morphological features and characteristics of vulnerable carotid plaque using US have opened up new avenues in the field of carotid artery imaging for stroke. Duplex, high-resolution US imaging is currently the most common noninvasive imaging study performed to diagnose carotid artery disease. Until recently, US carotid imaging was limited to grading specific stenotic lesions within the carotid plaque segment; however, any atheromatous lesions may contain unstable plaques that can rupture, exposing the highly thrombogenic necrotic core to the blood stream and causing a distal embolus, resulting in a cerebral infarct.
US has good mean results in the evaluation of plaque morphology by identifying internal components and the structure of specific plaque appearance. Specific markers include echotexture, the presence of echolucency, surface alterations or ulcerations and volume assessment using 3-dimensional US (3D US). The collected evidence shows that US is effectively able to detect specific carotid plaque characteristics related to high-risk plaques, vulnerable for CV events. The increased interest in using US to image plaque morphology may present a paradigm for finding a relationship between morphological characteristics and additional risk factors and identifying atherosclerotic plaques at higher risk for cerebrovascular events, thus improving stroke prevention.
Cerebrovascular (CVA) accidents are the second leading cause of death worldwide and their numbers are increasing. Strokes can arise from several causes: extracranial carotid artery atherosclerosis (CAS) is one of the leading causes. CAS causes these strokes either by diminishing blood flow distal to the diseased stenotic segment of the artery or, as more recently discovered, by a thromboembolic event of material from the plaque site itself. The specific etiology of CAS is unknown, but causative factors in the formation of atherosclerotic plaque of the carotid arteries have been linked to specific morphological areas within the plaque that may be vulnerable to rupture, leading to thromboembolic into the cerebrovascular circulation.

The current means for imaging and reporting CAS is through the measurement of the severity of luminal diameter stenosis caused by atherosclerotic disease. Recent developments in medical imaging techniques have expanded the role of early imaging and detection of CAS. Although current practice uses luminal narrowing as the surrogate marker to assess CAS, it has been recently discovered that plaque morphology and composition may help predict the clinical behavior of CAS and better
determine the necessary medical intervention or risk of stroke. Although a single optimized imaging modality for standard CAS imaging has not been established or agreed on, various modalities can provide key elements to a successful exam. This review poster will review the most commonly used imaging methods for CAS imaging along with the new and upcoming uses, advantages, and limitations for advanced CAS imaging.
THE UTILITY OF THREE-DIMENSIONAL (3D) PLAQUE IMAGING IN CAROTID STENOSIS

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Dr. Geoffrey Currie, MMedRadSc, MAppMngt, MBA, PhD
Faculty of Science – Dentistry and Health Sciences, Charles Sturt University, Wagga Wagga, Australia

Objective: Emerging data suggests that carotid plaque morphology and severity can significantly affect cerebrovascular prognosis. Recent studies have reported that three-dimensional ultrasound (3DUS) used as an adjuvant imaging technique may provide additional information in the evaluation and risk stratification of vulnerable carotid plaque. The aim of this study was to evaluate the utility of 3DUS in characterizing plaque from various degrees of stenosis.

Methods: In a cohort of symptomatic patients referred from neurosurgery, 3DUS of the carotid arteries was conducted using a vascular ultrasound system (iu22, Philips Medical System) equipped with a volumetric, mechanical, high-resolution linear-array transducer for 3D imaging. We employed a 3DUS imaging method to allow high-detailed studies in mild, moderate and severe stenotic plaques. Constructed 3D plaque images were quantified using internal plaque echotexture, volume and surface morphology, and evaluated by two independent observers using our own classification protocol.
**Results:** Results indicate that 3D US for plaque characterization was significantly better in mild to moderate imaging, possibly due to the fluid-filled lumen acting as a substantial acoustic transmission for optimal plaque visualization. Higher-grade stenosis (>70%) was difficult to assess; however, proximal and edge surface imaging was diagnostic. These results indicate that our 3D approach may be a sensitive tool in the identification of early vulnerable markers in lower-graded stenosis, possibly identifying early prediction of stroke.

**Conclusion:** 3DUS shows a high sensitivity and negative predictive value of carotid plaque 3DUS in mild to moderate stenosis, and can reliably characterize surface, volume and ulcerations. The sensitivity decreased with the severity of stenosis. 3DUS carotid plaque quantification may serve as an important clinical screening tool in early onset of significant carotid disease, for high-risk patients, and for those without known significant carotid disease.
CAROTID PLAQUE CLASSIFICATION SYSTEM: A NEW STANDARD DIAGNOSTIC CRITERION

Lysa Legault Kingstone, MApSc., R.T. (MR), RDMS, RVT, CRGS, CRVT and Dr. Carlos Torres, MD
The Ottawa Hospital, Ottawa, Ontario, Canada

Dr. Geoffrey Currie, MMedRadSc, MApMngt, MBA, PhD
Faculty of Science – Dentistry and Health Sciences, Charles Sturt University, Wagga Wagga, Australia

Objective: Ultrasound (US) carotid plaque imaging can provide valuable information on the morphology of the atherosclerotic plaque. Particular sonographic features of the plaque have been recognized as the foundation for stroke. Carotid plaque imaging is increasingly recognized as being as important as stenotic grading; however, various methods of echographic image standardization have been described with a number of these systems using complex, expensive or unavailable software. Standard plaque analysis and characterization is lacking and, to our knowledge, no global classification system or form of image standardization exists. Our objective was to develop a standardized US characterization method and reporting data system of carotid atherosclerotic lesions for clinical management: the Carotid Plaque Imaging Reporting and Data System (CPIRADS). We based this prospective study using previously published concepts of the American College of Radiology using the Breast Imaging Reporting Data System (BIRADS) and the Thyroid Imaging Reporting and Data System (TIRADS).
Method: We designed this prospective study based on the concept of the BIRADS and TIRADS from the American College of Radiology. We reviewed randomized, controlled human clinical trials that validated the applicability, diagnostic accuracy and classification of US carotid plaque characterization. Based on these findings, we created and implemented a quality assurance tool for plaque classification criteria in an effort to globalize image and reporting standardization without the use of complex or expensive software. We subjectively graded US images using a standardized classification report form that combines specific echographic image features. Three categorical groups were defined according to risk: Type A (no to low risk for vulnerability), Type B (moderate risk for vulnerability) and Type C (high risk for vulnerability).

Results: The CPIRADS classification was evaluated in each categorical classification (no to low risk: 1, moderate risk: 1 and high-risk: 1). Results indicate that the inter-observer and inter-reader reliabilities were high and that plaque neuroradiologist’s report were 96% sensitive and 97% specific respectively, using our classification system.

Conclusion: The CPIRADS standardized classification system has allowed us to improve the consistency and accuracy of plaque characterization imaging and assessment without of the use of computed or automated methodologies. This plaque analysis criterion may help promote the use of a standard, global US classification analysis and uniform reporting for carotid
atherosclerotic lesions. Large-scale prospective studies are required to fully assess the potential of this grading system.
Advanced Ultrasound Evaluation of Carotid Plaque: Can a Combined 2D and 3D Ultrasound Analysis Provide Additional Information and Identify Significant Plaque Characteristics Responsible for Strokes?

Lysa Legault Kingstone, MAppSc., R.T. (MR.), RDMS, RVT, CRGS, CRVT and Dr. Carlos Torres, MD
The Ottawa Hospital, Ottawa, Ontario, Canada

Dr. Geoffrey Currie, MMedRadSc, MAppMngt, MBA, PhD
Faculty of Science – Dentistry and Health Sciences, Charles Sturt University, Wagga Wagga, Australia

Objective: Imaging carotid plaque morphology with the use of ultrasound (US) may improve stroke risk management by identifying alterations in atheroma at increased risk for cerebrovascular events. Limited reports on advanced US plaque imaging have identified the potential for evaluation and risk stratification of vulnerable carotid plaques. The purpose of this series was to evaluate the usefulness of integrating an advanced US plaque imaging method to characterize atheromas and to measure the agreement with multidetector row computed tomography (CT) and radiographic pathology.

Methods: Three patients with known high-grade symptomatic carotid artery disease confirmed on CT and scheduled for endarterectomy were recruited for this study. Before surgery, we prospectively assessed carotid arteries for high-risk morphological characteristics using our advanced US plaque imaging mechanism. The plaque characteristics considered included the presence of ulceration, internal lipid or hemorrhagic core(s), calcification(s), and/or thin/dense fibrous plaque caps. US plaque features were correlated with previous CT imaging and post-endarterectomy histologic studies.
Results: There was substantial agreement in the detection of morphologic characteristics. Our advanced US method yielded 100% sensitivity, specificity, and accuracy in the identification of ulceration, lipid/hemorrhagic core(s) and calcification(s), leading over CT. In the identification of a thin/dense fibrous plaque cap, CT yielded 0% sensitivity versus 33% on US.

Conclusion: Advanced US plaque imaging to further identify significant plaque abnormalities responsible for strokes can reliably identify vulnerable plaque characteristics on both two-dimensional and three-dimensional US. Our results suggest that the type of abnormality identified with our advanced US imaging method surpassed information gathered on CT. Our advanced imaging protocol shows potential for early noninvasive prediction of plaque vulnerability, thus improving preventive management of atherosclerosis.
COURSEWORK

HSC700 PREFACE

The final version of HSC700 submission is enclosed in this portfolio. Critical analysis of the literature for HSC700 was reported based on information in evidence based practice and randomized controlled trials, in order to pursue the industry survey and explore current imaging applications in carotid artery imaging. Modifications were made from the original submission to Charles Sturt University, to improve consistency and establish better command of the research area. The final versions provided a more focused, critical evaluation of previously completed research in the area and formed a discussion, clearly demarcating the known applicability and information of current imaging, and its impact on current clinical practice. The final work of HSC700 was valuable tool to demonstrate the validity, enhanced by numerical support, to our findings, and it was published in a high-impact peer-reviewed journal, as well as presented in an international and distinguished conference.
HSC701 PREFACE

The final version of HSC701 submission is enclosed in this portfolio. This critical analysis of the literature related to US plaque morphology helped identifying the gaps in the knowledge and limitations of evolving clinical practices, and was the key for the research idea aimed for the doctoral work. Minor amendments were made to the original submission to Charles Sturt University, mainly completing a Jadad scale and scoring for the examined literature. The final version was published in a peer-reviewed journal. This review and analysis was resourceful as we conducted a small investigation, to help illuminate our key research project and establish our projected methodology. This investigation was presented at an international, renowned conference and published in a peer-reviewed journal.
HSC702 PREFACE

The enclosed copy of HSC702 refined our original research questions by acquiring a detailed research proposal. No alterations were made for original submission, and equivalent copies were accepted for ethical approval to both Charles Sturt University and The Ottawa Hospital.
HSC703 PREFACE

The final HSC703 submission answered our research questions by undertaking investigations and exploring several projects. The results from our studies provided strong evidence and solutions to our queries, however it influenced several others. All research studies for HSC703 were published in high-impact peer-reviewed journals, as well as presented at international and highly distinguished conferences.
DOCUMENTATIONS

Charles Sturt University Human Research Ethical Approval

The Ottawa Hospital Human Research Ethical Approval
Ms Lysa Kingstone
514 Denbury Ave
Ottawa, Ontario, Canada
K2A 2N7

Dear Ms Kingstone,

The School of Dentistry and Health Sciences Ethics Committee has approved your proposal entitled “Carotid ultrasound plaque imaging: Can an ultrasound multimodality plaque-imaging analysis system provide additional information and identify significant plaque characteristics responsible for strokes?” for a twelve month period from 15th November 2011 to 15th November 2012.

The protocol number issued with respect to this project is 414/2011/09. Please be sure to quote this number when responding to any request made by the Committee.

Please note that the Committee requires that all consent forms and information sheets are to be printed on Dentistry and Health Sciences School letterhead. Students should liaise with their Supervisor to arrange to have these documents printed.

You must notify the Committee immediately should your research differ in any way from that proposed.

You are also required to complete a Progress Report form, which can be downloaded from www.csu.edu.au/research/forms/ehrc_annrep.doc, and return it on completion of your research project or by 31st October 2012 if your research has not been completed by that date.

The Committee wishes you well in your research and please do not hesitate to contact Jessica Guthrie on telephone 02 6933 2874 or email jguthrie@csu.edu.au if you have any enquiries.

Yours sincerely,
Jessica Guthrie
School of Dentistry and Health Sciences Ethics Committee
Direct Telephone: 02 6933 2874
Email: jguthrie@csu.edu.au

www.csu.edu.au
CRICOS Provider Numbers for Charles Sturt University are 00006F (NSW), 01947G (VIC) and 00900E (ACT). ABN: 83 878 708 551
March 2, 2012

Dr. Carlos Torres
Ottawa Hospital - Civic Campus
Radiology Research office - Intern's Residence Building
602-751 Parkdale Avenue
Ottawa, ON
K1Y 1J7

Dear Dr. Torres,

Re: Protocol # 2011736-01H Carolus Ultrasound Plaque Imaging: Can an Ultrasound Multimodality Plaque Imaging Analysis System Provide Additional Information and Identify Significant Plaque Characteristics Responsible for Strokes?

Protocol approval valid until - May 2, 2012

This protocol was reviewed by the full Board of the Ottawa Hospital Research Ethics Board (OHREB) at the meeting held on November 1, 2011 and re-submitted to the full Board of the Ottawa Hospital Research Ethics Board at the meeting held on January 10, 2012. You have met the requirements of the OHREB and your protocol has been granted approval by the OHREB for two months to start recruiting English-speaking participants. No changes, amendments or addenda may be made to this protocol or the consent form without the OHREB's review and approval.

Approval is for the following documentation:
- Protocol received February 1, 2012
- English Information and Consent Form dated February 20, 2012

Upon receipt and review of the French consent form, the protocol may be extended to January 9, 2013 (one year from the last meeting date), and the recruitment of French-speaking participants may commence. When submitting the French documentation to the OHREB, confirm that it has been translated by an external translator or approved by an internal translator.

The validation date should be indicated on the bottom of all consent forms and information sheets (see copy attached).

The Ottawa Hospital Research Ethics Board is constituted in accordance with, and operates in compliance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; Health Canada Good Clinical Practice Consolidated Guidelines Part C Division 5 of the Food and Drug Regulations of Health Canada, and the provisions of the Ontario Health Information Protection Act 2004 and its applicable Regulations.

Yours sincerely,

Raphael Segmura, M.D.
Chairman
Ottawa Hospital Research Ethics Board

End.

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