DOCTORATE OF HEALTH SCIENCE
EXEGESIS & PORTFOLIO

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

VOLUME 1 - EXEGESIS

Submitted By:
Lysa Legault Kingstone
MApPSc (Ultrasound), RDMS, RVT, CRGS, CRVT, R.T. (MR).

Student Number:
11387045

Submitted to the Faculty of Science in fulfillment of the requirements for the degree of Doctorate of Health Science At Charles Sturt University

Ottawa, Ontario, Canada
May 25, 2014
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
ACKNOWLEDGEMENTS

At this point, I would like to express my sincere gratitude to some of the many people who have had to patiently endure my presence for so many years:

• First and foremost, I would like to thank my supervisor Dr. Geoffrey Currie whose guidance, patience and mentorship over the years has enabled me to achieve levels of success that I never imagined possible. I am forever in your debt (well, at least until I graduate).

• This Doctorate would not have been possible without Dr. Wael Shabana for his outstanding support, guidance and friendship. Most importantly, for coming in with a fluttering red cape and shaping the coursework and research component for the Doctorate.

• I owe my deepest gratitude to the Ottawa Hospital, Research Institute and specifically Dr. Andrew Hill, Kim Boles of the Vascular Surgery Department and Dr. John Sinclair and Dr. Howard Lesiuk from the Neurosurgery Department, for generously providing me the largest part of the work conducted during this Doctorate. Your support and help was invaluable.

• A special thank you for Dr. Carlos Torres for his friendship and for providing me with the opportunity to experiment with the excitement of technological advancement.
• To past and present colleagues who have made many years here more enjoyable: Dr. Santana Chakraborty, Dr. Thahn Nguyen, Dr. Rebecca Thornhill, Alain Berthiaume, Robert Chatelain and Megan White. I am very grateful for your guidance, patience and constructive criticism, which in turn made me a better researcher.

• To the late Joanna Lam, who collaborated her first clinical research experience for this Doctorate. Your enthusiasm re-ignited the spark, when I was running out of fuel. Thank you for making such a special scientific contribution and making this work an exceptional memory.

• A special thanks to my husband, Dr. Michael Kingstone for both his patience and understanding and for helping me overcome the numerous “obstacles” that surfaced during this important journey. I now understand why you chose to not do research. You never gave up on me, always believed in me and always supported me. I love you very much and more everyday.

• Most importantly, to my children Avelyn and Reve for allowing me to balance books and breastfeeding! You inspired me to try, rather than not have the chance at all. You define unconditional love and are the source of my happiness. Grace a vous, je veut etre meilleure tous les jours.
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.

<table>
<thead>
<tr>
<th>CITATION</th>
<th>ROLE</th>
<th>OTHER AUTHORS ROLES</th>
</tr>
</thead>
<tbody>
<tr>
<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>
<td>Second author's main contribution was assistance with data collection. Third and fourth authors are supervisors for this doctoral work and main contribution represented manuscript editing;</td>
</tr>
<tr>
<td>Kingstone L, Shabana W, White M, Lam J &amp; Currie G 2013, Comparison and accuracy of carotid plaque analysis between two- and three-dimensional ultrasound imaging: Journal of diagnostic medical sonography; 36(3), 123-130.</td>
<td>80%</td>
<td>Second author's represented assistance with phantom data collection. The third and fourth authors' contributions represented assistance with data collection and manuscript editing. The fifth author's is a supervisor for this doctoral work.</td>
</tr>
<tr>
<td>Kingstone, L., Shabana, W., Chakraborty, S., Kingstone, M., Nguyen, T., Thorhnill, R., Berthiaume, A., Chatelain, R. &amp; Currie, G. (2014). Vulnerable carotid artery plaque evaluation: detection agreement between advanced ultrasound, computed tomography and magnetic resonance imaging. A phantom study. <em>Journal medical radiation science, 46</em>(1), in press March 2015.</td>
<td>80%</td>
<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>
</tr>
<tr>
<td>Kingstone, L. &amp; Currie, G. (2014). The utility of three-dimensional (3D) plaque imaging in carotid stenosis. Under review: <em>Journal of Medical Ultrasound.</em></td>
<td>90%</td>
<td>Second author is a supervisor for this doctoral work.</td>
</tr>
</tbody>
</table>
# Table of Contents

STATEMENT OF AUTHENTICITY ii
ACKNOWLEDGMENTS iii
PREFACE v
EXECUTIVE SUMMARY xi
LIST OF FIGURES xvii
LIST OF TABLES xix
LIST OF ABBREVIATIONS AND ACRONYMS xx

1.0 BACKGROUND 1

1.1 Introduction 2

1.2 Carotid artery disease 6

1.2.1 Epidemiology of carotid artery disease 6

1.2.2 Risk factors of carotid artery disease 8

1.2.3 Pathophysiology of carotid artery disease 10

1.2.4 Pathophysiology of cerebrovascular events 13

1.3 Diagnostic imaging studies 16

1.3.1 Background 16

1.3.2 Current modalities for carotid artery imaging 17

1.3.3 Principles of carotid plaque morphology imaging 21

1.4 Summary 22
2.0 ENHANCED US PLAQUE IMAGING

2.1 Introduction

2.2 US principles of carotid plaque morphology

2.2.1 2-dimensional (2D) US principles in plaque morphology

2.2.2 3-dimensional (3D) US principles in plaque morphology

2.2.3 Advantages

2.2.4 Disadvantages

2.2.5 Acquisition parameters

2.2.6 3D data reconstruction

2.3. Quantification of combine plaque US imaging

2.3.1 Validation of advanced methodology

2.3.2 Data interpretation

2.3.3. Classification

2.4 Enhanced US imaging principles

2.5 Summary

3.0 CLINICAL CONSIDERATION AND APPLICABILITY FOR ENHANCED US

3.1 Current clinical availability for in vivo carotid plaque imaging

3.1.1. CT imaging acquisition and protocol

3.1.2. MRI imaging acquisition and protocol
3.1.3. US imaging acquisition and protocol 72
3.2 Clinical diagnostic performance of enhanced US 74
3.2.1 Overall agreement and accuracy amongst US and other clinically available modalities 76
3.2.2. Clinical reporting accuracy for US 85
3.3 Summary 87

4.0 DISCUSSION 88
4.1 DISCUSSION 89
4.2 LIMITATIONS 104
4.3 RECOMMENDATIONS 105
4.4 CONCLUSION 107

5.0 REFERENCES 108
EXECUTIVE SUMMARY

REFEREED JOURNAL ARTICLES:


JOURNAL ARTICLES UNDER REVIEW:


CONFERENCE PRESENTATION:


REFERENCES (for flow diagram on previous page):


LIST OF FIGURES

FIGURE 1.1: Carotid artery atherosclerosis plaque formation schematically represented (Rodríguez, Orbe & Paramo, 2007, page 121).  

FIGURE 1.2: The accumulation of cholesterol in the wall of the internal carotid artery is shown after surgical removal of the atheromatous plaque by CEA. Photograph courtesy of Dr. J. P. Veinot, the Ottawa Hospital, Department of Pathology, Ottawa, Canada.  

FIGURE 1.3: Illustration of different types of vulnerable plaques (Naim et al., 2012, page 3).  

FIGURE 1.4: Demonstrates multplanar reconstructed images using MRI TOF and CE imaging of the extracranial vessels, with emphasis on the ICA segment for CAS detection on a 3-Tesla (T) and 1.5-Tesla (T) magnet.  

FIGURE 1.5: Multiplanar image three-dimensional reformatted computed tomography of a severe internal carotid artery stenosis.  

FIGURE 1.6: US of an ICA stenosis detected with color and spectral Doppler.  

FIGURE 2.1: Gray-scale US images identified a heterogeneous plaque with mixed internal high to low-level echoes and a homogenous plaque consisting of internal low-level echoes.  

FIGURE 2.2: US image demonstrating an echolucent area within a heterogeneous plaque. This type of plaque has an increased-fold risk of CVA events.  

FIGURE 2.3: US image demonstrating an ICA heterogeneous plaque with evidence of ulceration.  

FIGURE 2.4: Volumetric, broadband linear array US transducer.  

FIGURE 2.5: Post-processing reconstruction of a volumetric 3D US image acquisition using built-in automated software with X, Y and Z planes for re-orientation of acquired slab.  

FIGURE 2.6: Schematic overview of sonographic morphological appearances in vulnerable carotid atherosclerotic plaques.
FIGURE 2.7: Myriad technique for US morphological plaque assessment.

FIGURE 3.1: A. CT image of an internal carotid artery using standard, clinically available imaging protocols identifying an ulcerated component of plaque: and B. Internal area of hemorrhage within plaque.

FIGURE 3.2: High-resolution, cross-sectional MRI of the right internal carotid artery. (A) On T1W acquisition, the plaque appears heterogeneous reflecting fibro calcific tissue. (B) T2W showing hyper intense area in medial internal carotid artery, while likely representing loose matrix fibrous tissue.

FIGURE 3.3: Internal area of lucency seen on axial 2D US images: longitudinal T1W MRI imaging and axial CT image.

FIGURE 3.4: Irregular plaque surface on longitudinal high-resolution 2D US; axial CT; and axial T2W MRI images.

FIGURE 3.5: Reformatted 3D US; axial CT; and axial T2W MRI images of ulcerated simulated plaque comparison.

FIGURE 3.6: In vivo ulcer identification on 3D US and CT.

FIGURE 3.7: Surgical pathological specimen in correlation with above US and CT findings identifying the ulceration.

FIGURE 3.8: US demonstrating area of hemorrhage with Rad-Path correlation.
LIST OF TABLES

TABLE 1.1. Illustrates the proportion (%) of Canadian population at risk of having a stroke due to the presence of specific risk factors (Public Health Agency of Canada, 2011). 9

TABLE 2.1 Clinical trials conducted on correlation between evaluation of plaque morphology on US and histological composition. 35

TABLE 2.2. Graphs the technical cost of US versus other current imaging modalities for cerebrovascular imaging (Ontario Health Insurance Schedule of Benefits and Fees, n.d., para 3). 44

TABLE 2.3: Schematic overview of 2D and 3D US acquisition methodology for plaque Imaging. 52

TABLE 3.1. Summary of studies comparing current cross-sectional modalities to specific, vulnerable morphological features. 79

TABLE 3.2. Overall agreement among the three modalities regarding each morphological characteristic. 85

TABLE 3.3. Accuracy of each modality for each morphological characteristics. 86
LIST OF ABBREVIATIONS AND ACRONYMS

CAS- Carotid atherosclerosis
CE- Contrast Enhanced
CEA- Carotid Endarterectomy
CNR- Contrast to Noise Ratio
CT- Computed Tomography
CTA- Computed Tomography Angiography
CVA- Cerebrovascular accident
dB- decibel
DFOV- Distance Field of View
DSA- Digital Subtraction Angiography
ECST- European Carotid Surgery Trial
Fo- Frequency
FOV- Field of View
ICA- Internal Carotid Artery
ICC- Intra-class correlation
kV- Kilovolt
mA- milliamperes
mm- millimetres
MHz- Megahertz
MRI- Magnetic Resonance Imaging
NPV- Negative predictive value
NASCET- North American Carotid Endarterectomy Trial
PPV- Positive predictive value
Rad-Path – Radiological-pathologic
SFOV- Scan Field of View
SNR- Signal to noise Ratio
3D- Three-dimensional
T- Tesla
T1W- T1-weighted images
T2W- T2-weighted images
TIA- Transient Ischemic Attack
TGC- Time Gained Compensation
ul- microletre
2D- Two-dimensional
VIBE- Volumetric interpolated brain examination
WHO- World Health Organization
US – Ultrasound
1.1 Introduction

1.2 Carotid artery disease
   1.2.1 Epidemiology of carotid artery disease
   1.2.2 Risk factors of carotid artery disease
   1.2.3 Pathophysiology of carotid artery disease
   1.2.4 Pathophysiology of cerebrovascular events

1.3 Diagnostic imaging studies
   1.3.1 Background
   1.3.2 Current modalities for carotid artery imaging
   1.3.3 Principles of carotid plaque morphology imaging

1.4 Summary

Publications of the candidate cited in this chapter

1.1 INTRODUCTION

In industrialized countries, cerebrovascular events are the third leading cause of mortality (Chien, Furtado, Su-Chun, Lam, Schaeffer, Chun & Wintermark, 2013; Naim, Douziech, Therasse, Robillard, Giroux, Arsenault, Clouthier & Soulez, 2013). The leading cause of CVA is atherosclerosis of the carotid artery, which instigates ischemic or infarction of the cerebrum (Mazighi, Labreuche, Gongora-Rivera, Duyckaerts, Hauw, Amarenco, 2008). Currently, the current primary descriptor used to characterize carotid atherosclerotic disease is internal carotid artery (ICA) luminal stenosis severity grading, which is based on the North American Symptomatic Carotid Endarterectomy (NASCET) (North American Symptomatic Carotid Endarterectomy trial collaboration, 1991) and the European Carotid Surgery trials (ECST) (MRC European Carotid Surgery Trial, 1991). In the past, ICA luminal stenosis severity grading of >70%, which is the cutoff number required for possible surgical assessment, resulted in significant reduction in stroke risk after surgical management by carotid endarterectomy (CEA). Conversely, Halliday et al., 2010 determined that stenosis severity is a poor predictor of cerebrovascular events in asymptomatic patients, with a 2% annual risk from a >60% stenosis (17.9% at 10 years), indicating the CEA offers little risk reduction of stroke.

Recently, the focus of research in carotid atherosclerosis (CAS) disease has shifted from relying solely on luminal stenotic grading towards incorporating atheromatous plaque imaging, to further identify unstable plaques prone to rupture. Vulnerable and lesion stability appears to be dependent on biological alterations that lead to thrombosis, embolism and plaque rupture causing
luminal obstruction responsible for strokes. Plaque morphology in atheromatous formations generating less than 70% or in the absence of a hemodynamically significant stenosis play an important role in the future of CVAs, causing intracranial thromboembolisms (Naghavi et al., 2003) and further examining carotid atherosclerosis morphology can only help predict clinical behavior and improve medical or preventative therapy (Eesa et al., 2010; Li, Zheng, Li & Sun, 2010). Current cross-sectional imaging techniques are the new tomographic imaging methods used to stratify cerebrovascular risk by identifying unstable plaques seen with specific morphological features or characteristics. Conventional imaging modalities such as Magnetic Resonance Imaging (MRI), Computed-Tomography (CT) and Ultrasound (US) can provide key elements to a successful diagnostic examination for carotid plaque assessment.

Of these conventional modalities, US has emerged as the key noninvasive imaging technique to evaluate and characterize carotid atherosclerotic plaques (Wantanabe et al., 2008). US-based plaque characterization imaging has been developed as an accurate and cost-effective quantifying tool for carotid atherosclerosis (Chiu, Shamdasani, Entrekin, Yuan & Kerwin, 2012). US can identify internal tissue components and the overall arterial structure of specific plaque characteristics, which are all-important biological contributory factors responsible for causing a stroke. Advanced approaches to carotid atheroma imaging with US are now possible due to a number of developments in imaging technology, including:
• The introduction of increased operating frequency (fo) and efficiency in linear array transducers for high-resolution two-dimensional (2D) imaging (Kremkau, 2010, p. 101).

• Increased detail resolution (axial and lateral) in the evaluation of plaque echotexture, resulting from higher-operating transducer imaging, allowing finer detailed imaging of internal echostructure via distinctive imaging (axial) and enhancing soft-tissue contents by separate reflectors (lateral) (Kremkau, 2010, p. 101).

• Technological developments responsible for the addition of volumetric, three-dimensional (3D) probe technology for imaging, which in turn increases diagnostic integrity by maximizing structural anatomical information and directly evaluating the atheromatous plaques’ development and/or progression and detection of atheromas (Chiu et al., 2013; Ludwig, Zielinski, Schremmer & Stumpe, 2008; Kremkau, 2010, p.101).

• Image-plane orientation, impossible to obtain with conventional 2D, achieved from newer units with 3D and/or reformatting imaging capabilities, allocating serial slice presentations, plaque volume and surface rendering (Kremkau, 2010, p. 101).

These advances are the leading innovations investigated in recent US imaging clinical trials. When combined with a detailed plaque imaging methodology, the structural quantification of echomorphology and interpretation of carotid arterial US studies can be used to pre-determine the risk of carotid...
atheromas, assess their progression, and ascertain future risk of CVAs. In theory, the development of a noninvasive imaging technique that integrates these advances in US imaging analysis as an adjunct to stenotic grading on routine carotid US imaging, can lead to a better understanding of the pathophysiology of atherosclerotic carotid disease. The benefits of adding the evaluation of plaque echomorphology using enhanced imaging techniques for carotid imaging studies (Kingstone, Currie, Torres, 2012) include:

- increase potential risk stratification
- improved diagnostic accuracy,
- increased quality of examination,
- enhanced therapeutic intervention.

It should be noted that there remain a number of fundamental clinical limitations of these US advances including but not limited to; restricted visibility due to inaccessible vessels, inexperience with plaque echomorphology, analysis and/or interpretation difficulties, lack of access to 3D technology, and inter-observer inaccuracies amongst operators and during reporting. These factors combined potentially limit assessment and analysis of US plaque echomorphology in the clinical environment. Nevertheless, a critical mass has emerged of those performing enhanced US echomorphology plaque imaging, as an adjunct to routine carotid Doppler examinations. Significantly, this technique as an adjunct to current best practice does slightly

---

increase the clinical cost and has minimal additional to time or inconvenience.

**1.2 CAROTID ARTERY DISEASE**

Cerebrovascular disease is a pressing health problem. Worldwide CVAs are the second leading cause of death; and the third leading cause of death in Westernised countries (Naim et al., 2012; Ozturk et al., 2010). WHO (2004) estimates that CVAs account for 8.4% of proportional mortality worldwide. Eighty-seven percent of strokes are ischemic in nature, followed by intracerebral and subarachnoid hemorrhage(s) (Yazdani, Vorpahl, Ladich & Virmani, 2010). CAS is the principal underlying cause of CVA by pathological process either by diminishing luminal stream or occluding distal cerebrovascular flow from the propagation of a tromboembolic material sourced off a carotid atheroma from the plaque itself (Feussner & Matchar, 1988; Oikawa et al., 2009; Singh, O'Donnell, Gillespie & Goff, 2010), which in turn instigates an ischemic or infarction of the cerebrum.

**1.2.1 EPIDEMIOLOGY OF CAROTID ARTERY DISEASE**

In Canada, CVAs are the leading cause of death and disability (Public Health Agency of Canada, 2012), and there is a daily estimated occurrence of a stroke every minute. In 2009, 315,000 (1.1%) of Canadians reported suffering from a CVA event (Statistics Canada, 2012). In 2007, 11,276 deaths were attributed to strokes, 10.3% of those occurred in people under the age of 65 (Vital Statistics Database, Statistics Canada). These numbers are most likely higher, as the true number of strokes, including untreated strokes or deaths...
that occur prior to victims reaching health care facilities, are either underreported or unreported. In 2006, CVAs were recorded as the main reason for 38,341 Canadian hospitalizations (Hospital Morbidity Database, Canadian Institute for Health Information). The direct and indirect cost of CVAs are estimated to be $3.6 billion per year for Canadian health care and $51 billion per year in the USA (Thom et al, 2006; The Heart and Stroke Foundation of Canada, 2003). This damage is considerable, as the loss of productivity due to premature death and long-term disability are not inclusive in the above figures (“Ontario Health Insurance Schedule of Benefits and Fees”, n.d.). Thanks to successful preventative measures, organized patient care and early intervention, morbidity and mortality rates for cerebrovascular disease have decreased significantly. Earlier and improved diagnostic imaging capabilities contribute significantly to this development, by increasing the rate of detection for pathological source at a much earlier stage thus, directly impacting the rate of treatment and hospitalization. In spite of the declining mortality rates, CVAs are still a pressing problem as the incidence of strokes is still escalating. In Canada, the number of people suffering strokes is rising at an alarming rate, affecting the population in their fifties by 24% and 13% for those in their sixties (Public Health Agency of Canada, 2012). Furthermore, CVAs are being reported in younger patient populations (24-64 years average) and is expected to double in the coming fifteen years (Public Health Agency of Canada, 2012). This, in turn will create a snowball effect and pose a significant challenge to our health-care system and predicted rate of strokes.
will likely climb to difficult-to-sustain levels (Public Health Agency of Canada, 2012).

1.2.2. **Risk Factors of Carotid Artery Disease**

Multiple etiologies have been implicated in CAD including traditional risk factors such as: hypertension, hyperlipidemia, smoking, diabetes, decreased physical activity, obesity, poor dietary habits and particular infectious agent (Kingstone et al., 2012; Ozturk et al., 2010; Singh et al., 2010). Other related risk factors include aneurysms, arteritis, dissections, fibro muscular dysplasia, radiation exposure and vasospasms (Kingstone et al., 2012; Singh et al., 2010). Less-traditional risk factors may include inflammatory molecules, cytokines, and homocysteine (Ozturk et al., 2010), as well as exposure to infectious agents, immune and inflammatory components disrupts reversible vascular wall changes, creating a plaque formation (Ozturk et al., 2010). Interestingly, 80% of Canadians are at risk of having a stroke due to the presence of at least one of these risk factors (Statistics Canada, 2012). The alarming rise in predisposing risk factors such as obesity, smoking, diabetes and cholesterol directly result the rise of CVAs incidence.

---

Table 1.1. Illustrates the proportion (%) of Canadian population at risk of having a stroke due to the presence of specific risk factors (Public Health Agency of Canada, 2011).

<table>
<thead>
<tr>
<th>Risk behaviours</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking (current daily)</td>
<td>14.1</td>
</tr>
<tr>
<td>Physical inactivity (0s total daily expenditure ≤ 1.5 kcal/kg/day)</td>
<td>47.8</td>
</tr>
<tr>
<td>Not enough vegetables and fruit (&lt; 5 servings daily)</td>
<td>54.9</td>
</tr>
<tr>
<td>Salt consumption:</td>
<td></td>
</tr>
<tr>
<td>Does not avoid certain foods because of salt content</td>
<td>43.1</td>
</tr>
<tr>
<td>Adds salt to food (excluding cooking) (always or often)</td>
<td>23.2</td>
</tr>
<tr>
<td>Adds salt during cooking or preparation (always or often)</td>
<td>41.0</td>
</tr>
<tr>
<td>Life stress (quite a bit or extremely)</td>
<td>24.1</td>
</tr>
<tr>
<td>Regular alcohol consumption</td>
<td>65.1</td>
</tr>
</tbody>
</table>

Underlying health conditions

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression (≥ 2 weeks)</td>
<td>11.4</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>22.7</td>
</tr>
<tr>
<td>Overweight (25-30 kg/m²)</td>
<td>37.3</td>
</tr>
<tr>
<td>Obese (≥ 30 kg/m²)</td>
<td>24.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8.0</td>
</tr>
<tr>
<td>High total blood cholesterol (≥ 6.2 mmol/L)</td>
<td>13.1</td>
</tr>
<tr>
<td>Higher risk ApoA/ApoB ratio</td>
<td></td>
</tr>
<tr>
<td>Women (≥ 0.8)</td>
<td>16.3</td>
</tr>
<tr>
<td>Men (≥ 0.9)</td>
<td>15.6</td>
</tr>
<tr>
<td>Heart disease</td>
<td>5.1</td>
</tr>
<tr>
<td>Suffers from the effects of a stroke</td>
<td>1.2</td>
</tr>
</tbody>
</table>
Identifying patients at increased risk for CAS can be a challenging for clinicians in the prevention of strokes due to the lack of risk factors and symptoms. Traditional risk factors and biomarkers have limited value in the prediction of strokes. To some degree, the risk of stroke can be greatly reduced by reducing modifiable risk factors such as smoking, physical inactivity, poor nutrition and excess weight (Public Health Agency of Canada, 2011). Furthermore, medically controlling certain underlying health non-modifiable risks for disease such as diabetes, obesity, depression, hypertension, and hyperlipidemia can significantly reduce the risk of CVAs (Statistics Canada, 2012).

1.2.3. Pathophysiology of Carotid Artery Disease

Carotid atherosclerosis is a chronic, progressive and diffuse inflammatory degenerative disease of the wall of the arteries, where certain arterial segments are susceptible to plaque formation due to the accumulation of lipids and fibrous elements (Naim et al., 2013). The formation of atherosclerotic disease and mechanism is complex; the initial damage of the endothelial layer is a result of shear stress, inflammation, neovascularization, and/or thrombosis (Naim et al., 2013). Risk factors are directly responsible for physiological conditions that disrupt endothelial functions, increasing cholesterol depositions or connective tissue, proliferating smooth-muscle cells, and extravasation inflammatory cells (Hanke, Lenz & Finking, 2001; Shi, Varghese, Dempsey, Salamat & Zagzebski, 2008; Ross, Faggiotto, Bowen-Pope & Raines, 1984; Naim et al., 2013). Early atheromatous lesions consist of the
infiltration of monocytes, resulting in thickening of the intima-media arterial layers, which in turn form into a xanthoma (Hanke et al., 2001; Yazdani et al., 2010). Extracellular lipid pols, degenerating foam cells and evidence of extracellular matrix such as proteoglycans and collagen, form these fatty streaks (Yazdani et al., 2010). The confluence of these molecular alterations proliferate and progress the pathologic thickening of the intima-medial arterial layers, marking the transition from early to advanced fibroatheromas, typically exhibiting monocyte infiltration, macrophages and/or extracellular lipids (Naim et al., 2013; Hanke et al., 2001; Yazani et al., 2010). Figure 1.1 demonstrates the schematic representation of a carotid artery atherosclerotic plaque formation. These alterations modify the structural and mechanical properties of the intima media, leading to formation an atheroma, most commonly on the lateral walls (Yazdani et al., 2010) and in regions of high shear stress, such as at the branch levels, bends and carotid bifurcation (Li, Zheng, Li & Sun, 2010). Figure 1.2 displays a surgical pathological sample of a disease carotid artery segment with the accumulation of cholesterol in the wall.
Figure 1.1: Carotid artery atherosclerosis plaque formation schematically represented (Rodriguez, Orbe & Paramo, 2007, page 121).

Figure 1.2: The accumulation of cholesterol in the wall of the internal carotid artery is shown (arrow) after surgical removal of the atheromatous plaque by CEA. Photograph courtesy of Dr. J. P. Veinot, the Ottawa Hospital, Department of Pathology, Ottawa, Canada.
1.2.4 Pathophysiology of Cerebrovascular Events

Cerebral circulation is essential to deliver oxygenated blood, glucose and several other important nutrients to the brain (Osborn, 1998). Although the human brain comprises only 2% of total body weight, it receives 15-20% of the body’s blood supply and consumes the same proportion of oxygen, a reflection of the importance of aerobic metabolism (Osborn, 1998). The cerebral flow is vulnerable and any failure can result in a state of hypoxic brain deprivation, with a potentially fatal outcome (Osborn, 1998). The cerebrovascular blood supply is dependent on normal uniform, continuous, laminar flow dynamics throughout its major bilateral carotid arteries with no alternations (Kremkau, 2010). During a fibroatheromatous pathological process, the materialized atheroma disrupts this steady flow by either causing a significant carotid artery stenosis or forming a thrombus within the plaque, which is at risk of emboli, causing a distal occlusion. The loss of demand of blood flow caused by narrowing of the blood vessel is of significance when atheromatous lesions cause a hemodynamically significant stenosis, typically when the luminal area reduction is greater than 50% according to North American Symptomatic Carotid Endarterectomy Trial (NASCET) (North American symptomatic carotid endarterectomy trial collaboration, 1991) and European Carotid Surgery Trail (ESCT) (MRC European carotid surgery trial, 1991). Likewise, it is also thought that with certain atheromas’ resultant molecular disruption, specific alterations or morphological changes result in future embolic states associated with neurological events (AbuRahma, Kyer, Robinson & Hannay, 1998; Carr, Farb, Pearce, Virmani & Yao, 1996; Spagnoli et al., 2004; Dahl, Dumont, Allen, Miller & Trahey, 2009; Yazdani et al., 2010).
which may be responsible for thromboemboli or fragments that propagate into the cerebral circulation (Davies, Richardson, Woolf, Katz & Mann, 1993). Both of these elements transpire to decrease, disrupt or inhibit the ability of the arterial blood flow to deliver this critical oxygenated blood to the cerebral tissue (Kingstone et al., 2012). 

Plaque features, retrospectively identified in histopathology studies of culprit coronary plaques, have similar characteristics to those found in carotid atheroma (Redgrave, Gallagher, Lovett, & Rothwell, 2008). Redgrave et al.’s findings further support that the risk of CVAs are completely dependent upon plaque composition. Specific atheroma morphological alterations or vulnerable plaque characteristics/features (Figure 1.3) purported as susceptible to rupture, thrombosis, which subsequently cause a CVA include (Alsheikh-Ali, Kitsios, Balk, Lau & Ip, 2010; Carr et al., 1996; Spagnoli et al., 2004; Shi et al., 2008; Tureyen, Vemuganti, Salamat & Dempsey, 2006; Yazdani et al., 2010):

- plaque surface ulcerations,
- active inflammation,
- microvascular formation,
- fissured plaque,
- the presence of a thin or fissured fibrous capsule <200-um thick (Redgrave et al., 2008),
- large lipid core(s) defined as a cross-sectional plaque area of at least 25% (Redgrave et al., 2008).

---

• intra-plaque hemorrhage(s),
• severe stenosis,
• superficial calcified nodule or,

a combination of these findings.

Figure 1.3. Illustrates the different types of vulnerable plaques in a disease carotid arterial segment (Naim et al., 2012, page 3).
1.3 DIAGNOSTIC IMAGING STUDIES

1.3.1 BACKGROUND

Conventional risk factors only aid in the prediction of 60-65% of cerebrovascular events (Kingstone et al., 2012\(^4\); Ray, Tamsma, Hovens, Roodt & Huisman, 2009). Unfortunately, the presence of a clinical symptoms has little to no value in the prediction of strokes, as they usually present once the plaque has caused a major stenosis, thrombosed or embolized distally resulting in clinically significant decrease in perfusion of the vascular territory in the cerebrovascular segment (Kingstone et al., 2012\(^5\); Singh et al., 2010). The ongoing challenge in health care and research of this pathological process is the lack of early markers or identification therein to properly detect and monitor progression of the disease. To date, no single imaging modality has been validated to accurately characterize all of these plaque features. Thus, a reliable diagnostic imaging modality technique to image the plaque has yet to be established. Current diagnostic imaging examinations still employ the measurement and severity of the luminal diameter stenosis as a standard; however, emerging diagnostic technology, with its enhanced imaging quality and greater anatomic definition, has improved investigation capabilities and expanded the role of this technology in identifying early changes for carotid atherosclerosis. This emerging diagnostic technology can now image specific morphology, recognized as key features responsible for a patients' cerebrovascular prognosis.


\(^5\)
1.3.2 Current Approach for Carotid Artery Imaging

Current imaging modalities apply global luminal narrowing criterion for imaging based on the NASCET and ECST trials and apply them as a reference guidelines. Both of these studies determined that the positive findings amongst symptomatic patients with a hemodynamically significant ICA stenosis greater than 70% stenotic lesions were at higher risk of stroke and benefited from therapeutic surgical intervention (Kingstone et al., 2012). The clinical imaging modalities used for the screening and assessment of carotid artery disease include:

- Digital subtraction angiography (DSA).
- Magnetic resonance imaging (MRI).
- Computed tomography (CT).
- Ultrasound (US).

Historically, DSA was considered the gold standard in the evaluation and extension of ICA stenosis and luminal diameter narrowing criterion. Thus, DSA was the basis for referencing in pertinent pivotal trials such as NASCET and ECST. Presently, invasive testing such as DSA is performed infrequently, being commonly reserved only for confirmation of noninvasive findings or problem-solving situations (Kingstone et al.,

---

MRI has replaced DSA as one of the primary, noninvasive imaging methods for CAS (Kingstone et al., 2012). MRI has widely become the global, clinical modality of choice as it offers non-radiated, high-resolution anatomical imaging with an overall high sensitivity of 91.2%, specificity of 88.3% for time-of-flight (TOF) and a sensitivity of 94.6%, specificity of 91.9% (Debrey et al., 2008) for contrast-enhanced (CE) angiographic imaging (Figure 1.4). While valuable, MRI is expensive, not globally accessible, and time sensitive, making it prohibitive in the clinical environment (Kingstone et al., 2012). Other shortcomings of MRI can include poor image quality, mainly due to motion artifacts, which can occur in as much of 30% of the patient population during examination (Naim et al., 2013).

Figure 1.4: Demonstrates multiplanar reconstructed images using MRI TOF and CE imaging of the extracranial vessels, with emphasis on the ICA segment for CAS detection (arrow) on a 3-Tesla (T) (left) and 1.5-Tesla (T) (right) magnet.

---


CT is currently the most common primary imaging modality used to assess ischemic strokes. It is considered the optimal imaging modality in luminal assessment for carotid artery disease (Josephson et al., 2004; Kingstone et al., 2012). With the latest multi-detector, high-speed scanners, CT enables optimal anatomic evaluation of the carotid vasculature with a very high negative predictive value (100% for 70% stenosis, 99% for 50% stenosis) and a high sensitivity (100% for 70% stenosis and 86% for 50% stenosis) (Josephson et al., 2004). In addition, CT’s 3D reformatting capabilities can provide multiple viewing planes and multi-planar surface rendering allowing unprecedented quantification of the lumen. Figure 1.5. demonstrates a CT image of a severe internal carotid artery stenosis on a reformatted three-dimensional image. CT does have associated variability and limitations such as certain sectional viewing restrictions due to overlapping Hounsfield densities, in addition to high costs, while exposing patients to ionizing radiation (Kingstone et al., 2012).

Ultrasound has proven to be an accurate, cost effective, and noninvasive means of evaluating the extracranial carotid artery circulation (Grant et al., 2003; Kingstone et al., 2012). B-mode, color Doppler in conjunction with spectral Doppler is now an integral part of the duplex extracranial US examination (Figure 1.6), enabling synchronized assessment of the vascular flow in the vessels and measurement of velocity parameters in the detection and/or quantification of arterial stenosis. US ICA stenotic detection has become the first-line examination requested for carotid artery luminal grading.

---

exhibiting an overall sensitivity of 85% and specificity of 90%, respectively (Feussner & Matchar, 1988). US can be limiting by anatomical impedance and is subjected to high inter-operator variability (Kingstone et al., 2012).13

Figure 1.6. US of an ICA stenosis detected with color (top) and spectral (bottom) Doppler.

1.3.3 Principles of Carotid Plaque Morphology Imaging

Extensive studies have been performed that identify plaque composition and characteristics associated with an increased risk for CVAs (Hellings et al., 2010; Li et al., 2010; Oikawa et al., 2009; Rudd et al., 2009). Of these studies, there is increasing evidence to support the theory of CVA risk stands

completely dependent upon plaque composition. With emerging diagnostic imaging technology and enhance imaging quality, greater anatomic detail of carotid atheroma is possible, including the critical identification of certain early morphological features of vulnerable carotid plaques (Kingstone et al., 2012). With these newer developments in carotid atherosclerotic imaging, clinical noninvasive modalities are being explored to assess plaque morphology, with the objective of identifying specific plaque characteristics associated with neurological events, which in turn are critical to early detection and to patients’ cerebrovascular prognosis. The principles of carotid plaque morphology imaging for each current clinical modality with be further discussed in subsequent chapters of this exegesis.

1.4 SUMMARY

This chapter has explored the pathogenesis, current clinical analysis and diagnostic imaging methodology of carotid artery disease. The introduction of carotid plaque morphology imaging and characterization to identify early predisposition is now possible with the application of higher-resolution anatomical, and soft-tissue imaging of the atheromas, validating the concept for risk prediction of CVAs. The use of noninvasive imaging applications, specifically aimed at US, will be explored in the remainder of this exegesis.

2. ENHANCED US PLAQUE IMAGING

2.1 Introduction

2.2 US principles of carotid plaque morphology
   2.2.1 2-dimensional (2D) US principles in plaque morphology
   2.2.2 3-dimensional (3D) US principles in plaque morphology
   2.2.3 Advantages
   2.2.4 Disadvantages
   2.2.5 Acquisition parameters
   2.2.6 3D data reconstruction

2.3 Quantification of combine plaque US imaging
   2.3.1 Validation of advanced methodology
   2.3.2 Data interpretation
   2.3.3 Classification

2.4 Enhanced US imaging principles

2.5 Summary
Publications of the candidate cited in this chapter


2.1 INTRODUCTION

While the mechanism of CVAs is not completely understood, ultrasound in carotid artery disease allows the clinical risk management of the patients, especially those at increased risk for rupture or major cerebrovascular event. US is a widely available, low-cost, low-risk tool used to evaluate atherosclerotic carotid disease (Kingstone et al., 2012\(^{15}\)). It is not uncommon that US be used as the only diagnostic imaging modality prior to surgical intervention (Naim et al., 2013). For the carotid artery, US has provided a reproducible, noninvasive, prognostic clinical imaging capability, within an accurate diagnostic strategy to investigate carotid artery luminal flow dynamics and quantify significant plaque structural features in clinically significant lesions (Kingstone, Torres & Currie, 2013\(^{16}\)). Despite the emergence of this new imaging procedure, the value of US in plaque assessment and characterization remains under-researched. The principles of US plaque imaging methodology and current imaging data are discussed in this fragment of the exegesis.

2.2 US PRINCIPLES OF CAROTID PLAQUE MORPHOLOGY

The ability to identify early morphology features and characteristics of vulnerable carotid plaque has opened new possibilities in the discipline of US carotid artery imaging for stroke prevention. The characterization of carotid


atherosclerotic plaque morphology by US incorporates (Kingstone et al., 2013):)

- early diagnosis of carotid artery disease,
- more diagnostic information than traditionally gathered by routine Doppler examinations (Kingstone, Shabana, White, Lam & Currie, 2014),
- improved detection and assessment of carotid artery disease,
- prognosis and risk stratification of atheromatous lesions,
- sourcing of neuro-embolic ischemic events.

Clinicopathologic studies (Beroncini A, Filho A, Ramos S, Martins A & Murta L, 2007; Saba et al., 2009; Verhoven, B et al., 2005) have demonstrated that US can effectively evaluate plaque morphology by identifying the structure and internal components of specific plaque appearances found in patients with carotid ischemic neurological disease. Specific sonographic features constitute the basis of US plaque morphology imaging, and are known to have increased vulnerability. These include:

- Specific echotextural and echogenicity variations
- Intraplaque echolucency, representing recent hemorrhage or lipid core
- Presence of surface ulceration

---


• Irregular, thinning or discontinuity of the plaque surface or contour (Kingstone et al., 2013\textsuperscript{19})

Current US plaque categorization currently only consists of two basic types: heterogeneous, which displays various mixtures of echogenic to echolucent material (Figure 2.1, left); and homogenous, which demonstrates uniformly dense material (Figure 2.1, right) (Geroulakos, Ramaswami, Nicolaides, 1993; Gray-Weale, Graham, Burnett, Byrne & Lusby, 1988; Kingstone et al., 2013\textsuperscript{20}, Szatjzel, 2005). Compared to homogenous plaques, heterogeneous plaques carry a higher risk of CVA (Kingstone et al., 2013\textsuperscript{21}, Szatjzel, 2005). For sonographic purposes, tissue characteristics are not based on the presence or absence of calcifications, and the analysis is based on non-calcified tissue only.


US plaque characteristics can be further defined by echogenicity classification according to the overall distribution of grey-scale tones on B-mode or 2-dimensional (2D) imaging, with a variance from predominantly anechoic to a mixed form of hyperechoic (Szatjel, 2005). Echogenicity is standardized compared to three main parameters for referencing (Debrey et al., 2008; Sztajzel 2005): intraluminal flowing blood for anechoic; the sternocleidomastoid muscle for isoechoic; and the transverse apophysis of the cervical vertebrae for hyperechoic. Li et al. (2010) identified that hyperechoic-appearing plaques containing mainly fibrous tissue consistency, were considered hard plaques and demonstrated more stability. The most significant US morphological feature is the presence of a predominant echolucent plaque, those with a hypo- to iso- pattern.
or with or without focal echolucency (Figure 1.2). These types of plaques contain more lipids or intra-plaque hemorrhage(s), undoubtedly a sonographic representation of loss of texture, focal lipid regions or hemorrhages (Carra, et al. 2003; Kingstone et al., 2013; Mathieson, Bonaa & Joakimse, 2001). These sonographic plaque features are suggestive for plaque instability and propensity for rupture, form a thrombus or embolize (Langsfield, Gray-Waele & Lusby, 1989; Li et al. 2010; O’Holleran, Kennelly, McClurken & Johnson, 1987) and have a greater incidence of neurovascular events, presenting with an increased-fold risk of ipsilateral ischemic strokes (Aldoori, Baird, Al-Sam, Cole, Mera & Davies, 1987; Gronholdt, Nordestgaard, Schroeer, Vorstrup & Sillesen, 2001; Mathieson, Kaare & Joakimsen, 2001). Consequently, 2D US cannot reliably determine whether an echolucent area represents one or another (Kingstone et al., 2013).

---

Carotid plaque surface characteristics evident on US that demonstrate irregularity and ulceration are contributing factors to the risk of CVAs; therefore, US quantification is important. Fibrous cap thinning as a result of infiltration of inflammatory cells leads to plaque surface erosion, ulceration, or rupture, which in turn causes the thrombogenic segment or loose necrotic layers of the plaque to embolize (Kingstone et al., 201324,25; Seabra, Pedro, Femades & Sanches, 2009). US surface characterization is categorized as smooth/regular, irregular with contour variations between 0.4-2mm, or ulcerated (Kingstone et al., 201325; Sztajzel, 2005). US evidence of ulceration corresponds to a minimum 2mm irregular break in the

surface (Figure 2.3), seen on two different planes on 2D imaging with the presence of reversal flow by color Doppler (Sztajzel, 2005).

![Image of US image demonstrating an ICA heterogeneous plaque with evidence of ulceration (arrow).](image.png)

Figure 2.3: US image demonstrating an ICA heterogeneous plaque with evidence of ulceration (arrow).

The diagnostic accuracy in characterizing the surface morphology has increased with the development of 3-dimensional (3D) US imaging, especially in the detection of ulcerations (Chiu, Shamdasani, Entrekin, Yuan & Kerwin, 2012; Kingstone et al., 2013). Table 2.1 demonstrates the most relevant studies conducted that correlated US-evaluated plaque morphology and the corresponding histological composition. For the purpose of this table, we included all relevant studies conducted to measure the applicability, diagnostic

---

accuracy or performance of US-evaluated carotid plaque carotid morphology assessment with corresponding histological composition in human clinical trials. We limited our search strategy to published, English articles that assessed these specific morphological characteristics: Echogenicity/echotexture, internal lucency (hemorrhage or lipid) and surface alterations, including ulcerations. We excluded articles that were: (1) not focused on plaque vulnerability or characterization; (2) included plaque assessment for the purpose of treatment or progression in plaque assessment; (3) and used non-commercially available software for the analysis or assessment of plaque.

Table 2.1 Clinical trials conducted on correlation between evaluation of plaque morphology on US and histological composition.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Morphology characteristic(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AbuRahma AF</td>
<td>1998</td>
<td>135</td>
<td>Hemorrhage</td>
</tr>
<tr>
<td>Aldoori MI</td>
<td>1987</td>
<td>27</td>
<td>Hemorrhage/Fibrous</td>
</tr>
<tr>
<td>Geroulakos G</td>
<td>1993</td>
<td>72</td>
<td>Echogenicity/Echotexture</td>
</tr>
<tr>
<td>Goes E</td>
<td>1990</td>
<td>54</td>
<td>Echogenicity/Capsule</td>
</tr>
<tr>
<td>Gray-Waele AC</td>
<td>1998</td>
<td>220</td>
<td>Hemorrhage/Lipid</td>
</tr>
<tr>
<td>Grogan JK</td>
<td>2005</td>
<td>48</td>
<td>Hemorrhage/Lipid, Echogenicity</td>
</tr>
<tr>
<td>Gronholdt MLM</td>
<td>1997</td>
<td>78</td>
<td>Lipids</td>
</tr>
<tr>
<td>Heliopoulos J</td>
<td>2009</td>
<td>284</td>
<td>Ulceration</td>
</tr>
<tr>
<td>Kardoulas DG</td>
<td>1996</td>
<td>36</td>
<td>Ulceration/Hemorrhage</td>
</tr>
<tr>
<td>Mathieson EB</td>
<td>2010</td>
<td>223</td>
<td>Hemorrhage/Lipids</td>
</tr>
<tr>
<td>Reilly LM</td>
<td>1983</td>
<td>54</td>
<td>Hemorrhage</td>
</tr>
<tr>
<td>Saba L</td>
<td>2007</td>
<td>237</td>
<td>Ulceration</td>
</tr>
<tr>
<td>Spagnoli LG</td>
<td>1988</td>
<td>43</td>
<td>Hemorrhage/Lipids</td>
</tr>
<tr>
<td>Wantanabe Y</td>
<td>2008</td>
<td>54</td>
<td>Echotexture/Soft plaque</td>
</tr>
</tbody>
</table>
Diagnostically, US imaging in early to late carotid atheromatous plaque lesions is clinically significant as it has the capabilities to detect and evaluate the overall risk of cerebrovascular events. This is valuable in identifying patients with a high potential for CVA, as any atheromatous lesion may depict vulnerability.

### 2.2.1 2-DIMENSIONAL (2D) US PRINCIPLES IN PLAQUE MORPHOLOGY

Existing US plaque assessment includes B-mode or grey-scale, otherwise known as 2D imaging. 2D imaging has gained wide-reaching acceptance as an accurate method for atheroma tissue assessment using high-resolution US imaging (Lorenz, Kegler, Steinmetz, Markus & Sitzer, 2006; Yamagishi et al., 2009). With the development of premium, high-performance, high-resolution US transducers, the quality of US examinations have improved significantly in recognition of improved technology, equipment and resolution (Kingstone et al., 2014\(^\text{27}\)). Enhanced probe technology, such as broadband linear higher-frequency array transducers (>12 MHz), offers higher frequencies with shorter pulse length, providing ultra-fine 2D imaging that significantly improves spatial and axial resolution. This enhanced resolution provides higher detail of the plaque echomorphology and is used to assess intimal alterations, surface alterations or internal echotextural variations such as smaller hemorrhage(s) (Kingstone et al. 2014\(^\text{28}\)). These enhanced transducers also improve the ability


to characterize echotextural details, which are often veiled due various regional acoustic interfaces that have relatively large differences in acoustic impedance.

High-resolution 2D US capabilities can distinguishing sonographic patterns and evaluate the entire plaque composition configuration collected by two imaging planes. Plaque surface alterations are optimal when the sound beam is at 90 degrees to the fibrous cap. Required US apparatus parameters include distinct grey-scale and high instrumental gain settings, which are necessary to enhance low amplitude and prevent loss of low-level echoes. This enables the accurate distinction between echotextural and echogenicity patterns, by defining the demarcations of internal echoes. 2D US for plaque characterization composition has excellent sensitivity, with an accuracy of 82% of finding intra-plaque hemorrhage in homogenous plaques and 65% in heterogeneous plaques (Reilly et al. 1983).

2.2.2 3-DIMENSIONAL (3D) US PRINCIPLES IN PLAQUE MORPHOLOGY

Although 2D US is widely accessible and is standard imaging technique for plaque morphology imaging, the traditional freehand 2D US imaging technique currently used has a significant limitation as atherosclerotic plaques develops asymmetrically and are not limited to one single direction for
changes. 2D US, based on a single scan projection, does not entirely represent the true plaques development, composition or morphology. Planar reconstructed imaging is required to accurately analyze the true circumferential development of plaque. Comprehensive imaging of the anatomic atheromatous progression and structure is now possible with the addition of volumetric 3D US imaging, in all three dimensions of morphological plaque progression, once limited by the single-direction limitations of 2D plane structures (Kingstone et al., 2014\textsuperscript{29}; Kingstone et al., 2014\textsuperscript{30}; Kingstone et al., 2014\textsuperscript{31}; Ludwig, Zielinski, Schremmer & Stumpe, 2008; Heliopoulos, Vadikolia, Piperdou & Mitsias, 2009). Most existing clinical US systems have volume acquisition capabilities using a 2D linear-array transducer, which acquires the 3D dataset (Kremkau, 2010). Alternatively, the introduction of volumetric, broadband linear array US transducers (Figure 2.4) with 3D capability allows rapid analysis of data from a volume of interest. These transducers further enhance tissue imaging with extended operating, high frequency range (13-15 MHz) amid applying high-resolution technology (lateral resolution, –20 dB, axial resolution, –20 dB) for US carotid artery

imaging (Kingstone et al., 2014; Kingstone et al., 2014; Kingstone et al., 2014).

Figure 2.4: Volumetric, broadband linear array US transducer.


In general, the 192 element-3D volumetric transducer platform is capable of scanning the anatomic area by producing a stacked set resulting in multi-planar, multi-format or surface-rendered 3D volumetric images. Reformatting of the anatomical segment is allocated by manipulation and precision slicing of the volumetric acquisition by post-processing applications on the US system’s equipment software. Studies by Heliopoulos et al. (2009) and Landry, Spence & Fenster (2004) established that 3D US improves the quality, visualization, and quantification of internal composition of the atheroma, thus enhancing plaque quality for assessment, visualization and quantification of carotid plaque morphology. In addition, surface-rendering capabilities provide highly detailed imaging for alterations with accuracy (Kingstone, Castonguay & Currie, 201335; Kingstone et al., 201336). While 3D US of the carotid vessels is valuable to further quantify plaque morphology, it has yet to be adopted in clinical practice due to its inauguration into the US imaging applicability.

2.2.3 ADVANTAGES

The application of US imaging studies to assess plaque morphology has a number of advantages, including:

---


• simultaneous capabilities of identifying vascular segment hemodynamics and carotid atheromatous plaque internal tissue or structural components,

• highly detailed surface representation of the atheromatous structure,

• improved anatomic detail and definition of vascular territory, including extent of disease, as a result of enhanced technology (Kingstone et al. 2013\(^{37}\); Kingstone et al. 2013\(^{38}\); Landry et al., 2005),

• ability to improve lesion detectability and surface defect locations as a result of increasing axial and/or lateral resolution or contrast by high detailed US imaging (Kingstone et al., 2013\(^{39}\); Kingstone et al., 2013\(^{40}\); Kingstone et al., 2014\(^{41}\)).

• Enhanced anatomical display of atheroma progression and imaging in multiple dimensions using 3D US, important for imaging intimal surface

---


details and plaque borders (Kingstone et al., 2013; Kingstone et al., 2014; Kingstone et al., 2013; Kingstone et al., 2014; Heliopoulos et al. 2009)

• Procedural 2D imaging mechanism and 3D stacked raw data for streamlining are widely available

• Clinically validated high inter-observer reliability and reproducibility (Kingstone et al., 2014; Ludwig et al., 2008)

• Increased certainty by reporting physicians (Kingstone et al. 2014; Kingstone et al., 2014) demonstrated that there was a high inter-reader reliability when using standard imaging and reporting for US of the plaque

---


The major advantage of US carotid plaque imaging over other modalities and standard luminography is its noninvasive nature, while providing good mean results and accuracy in assessing the echomorphology of carotid plaque (Kingstone et al., 2013⁴⁹; Kingstone et al., 2014⁵⁰). In addition, US imaging costs significantly less compared to other clinical diagnostic radiological modalities (Ministry of Health and Long Term Care). Table 2.2 demonstrates the cost of US imaging versus other current imaging modalities for cerebrovascular imaging.


Table 2.2. Graphs the technical cost of US versus other current imaging modalities for cerebrovascular imaging (“Ontario Health Insurance Schedule of Benefits and Fees”, n.d., para 3).

![Graph](image-url)

Unit of cost
The addition of US plaque interpretation using 2D alone does not increase costs and adds minimal acquisition time—approximately 2-5 minutes (Kingstone et al., 2014^51; Kingstone et al., 2014^52; Kingstone et al., 2014^53).

Using 3D US in addition to 2D also adds minimal time: less than a minute for acquisition and 5 minutes for reformatting purposes (Kingstone et al. 2014^54).

### 2.2.4 Disadvantages

While US plaque imaging has significant benefits it also has a number of limitations, mostly beyond the operator or equipment capabilities. Interference in the uniformity and/or visualization of the internal contents of the plaque is caused by heavy calcifications, high anatomical bifurcation of the common carotid artery, tortuous vessel segments, tracheostomy tubes, surgical sutures, bandages, central lines or an uncooperative patient—all of which can make this area inaccessible for sonographic evaluation, thereby limiting examination. Moreover, the conventional 2D US imaging technique may also be prove unsatisfactory as it has imaging planes, which may be difficult to reproduce. Imaging planes can be minized by applying 3D US;


however, since 3D US technology is not available in all hospitals and clinics, and because 3D US imaging requires additional storage space, there can be increased costs. While these costs are not prohibitive, they can be a deterrent.

The newest US units have built-in 3D technology and single-slice stacking capabilities, which is becoming the normalized standard for sonographic imaging. Furthermore, to save processing time and storage space for 3D imaging, only the raw data and/or reformatted still 3D images can be saved (Kingstone et al., 201455). A major shortcoming of current 3D US probe technology is the use of freehand manual manipulation for imaging, which can cause considerable variations in the angular relationship with skin surface or sweep speed, thereby increasing the inter-observation variability (Kingstone et al., 201356; Kingstone et al., 201457; Landry et al., 2004; Ludwig, et al., 2008). Using a mechanical sweep to enhance performance and reproducibility can minimize this diagnostic issue. Ludwig et al. (2008) further indicate that using standardized central US scanning along and reading protocol along with strict quality control procedures can achieve reliable, reproducible 3D US imaging.

In summary, current 3D US has unproven diagnostic capabilities because it is

so new. Of those systems studied, planar artifacts such as sound beam attenuation, and side or grading lobe artifacts that appear pronounced on the 3D US imaging, make plaque boundaries less than optimal (Heliopoulos et al., 2009). Ludwig et al. (2008) recommend the use of Sono-CT to minimize this effect.

Although Ludwig et al. (2008) reported that calcified plaques were not measurable due to attenuation, Kingstone et al. (2014)\textsuperscript{58} identified internal calcifications with high accuracy using minimal slice reformatting techniques to review the plaques’ internal contents. Kingstone et al. (2014)\textsuperscript{59} further observed that plaque assessment was improved by using an increased number of slices and reducing the sweep angle to maximize information gained, especially when imaging smaller plaques (<40 ul). Diagnostic diagnostic US is a highly operator-dependent modality and a device-dependent technique, which may result in complex image acquisitions and significant fluctuation in inter-operator variability. Kingstone et al. (2014)\textsuperscript{60} investigated and reported reduced inter-observation variability and increased reproducibility by employing a robust, reproducible US imaging protocol for the morphological assessment and analysis of carotid atheroma. Findings from this study revealed that the conformity further increased with the application of 3D versus 2S US.

alone, as 3D capabilities enabled reformatting and rotational manipulation, which improved visualization in the evaluation of vulnerable plaque characteristics of the atheromatous lesion. Kingstone et al.’s (2014)\textsuperscript{61} sonographic plaque imaging method provides a reproducible and reliable diagnostic method for assessing characteristics morphological changes in carotid plaque atheroma, with excellent inter-rater variability. This method will be supported in the next segment of the exegesis.

\textbf{2.2.5 Acquisition parameters}

Current US applications do not include comprehensive plaque morphological details in their reporting; rather, most rely solely on luminal grading for carotid artery disease imaging. Although some institutions have incorporated some plaque imaging features in their routine practice, there is an urgent need to develop imaging standardization and establish a more robust method to properly identify echomorphology for specific vulnerable plaque appearances with the use of clinically available enhancing US technologies. Plaque morphology evaluation using US is generally performed supine, with images acquired when the patient faces towards the operator when examining the left carotid vessels, and away from the operators when examining the right carotid vessels. An alternative and more ergonomically sound approach would

be to have the patient’s head at 90 degrees to the scanning limb. Based on previously published recommendations (Kingstone et al., 2013; Nicolaides et al. 2003), Kingstone et al. (2014) developed a US plaque imaging protocol to standardize the practice of US imaging of plaque using the following technical US settings to ensure optimal image quality for plaque morphology and texture analysis, using a high-resolution, high-frequency (minimum 12MHz) linear array transducer for 2D imaging:

1- The initial assessment begins with a systematic overview of the carotid bulb and internal carotid artery and/or specimen.

2- Static image acquisitions with two longitudinal and two transverse images of the intimal or atheroma along the proximal ICA segment to isolate echomorphology via grey-level analysis for echotexture and echogenicity. Any focal internal area must provide measurement calipers to provide size assessment.

3- US technical parameters must include a maximum dynamic range to ensure the greatest display of grey-scale value and persistence setting set on low and frame rate on high to ensure good temporal scale values.

4- The following scanning parameters are adjusted to the patient’s body habitus to give optimum image quality: power, overall gain and compensation, focus zoom and image depth; however, the time gain

---


compensation curve (TGC) must be placed vertically through the lumen of the vessel, to ensure similar brightness of the adventitia of the anterior and posterior wall (Nicolaides et al., 2003). Overall gains must be adjusted to minimize but not eliminate noise and depth must be set at a minimum to ensure the plaque occupies the larger part of the image.

Subsequent 3D imaging repeats the 2D process, using a linear array transducer with 3D capabilities or, if available, a volumetric broadband transducer (VL13 MHz). Kingstone et al. (2014) established and reported the following precise method for 3D US plaque morphology imaging:

1. In order to attain 3D echo volumes, the transducer is placed through the long axis of the vessel and is positioned for the center slice of the volume located at the plaque specimen.

2. 3D mechanical sweep must be employed at a 15-degree angle for volumetric acquisitions.

3. Frame rate should be constant, in the 10-second range, with final 25-slice volume data set, at a minimum.

---


4. Comparable to 2D parameters, scanning settings such as power, gain compensation, focus zoom and image depth are optimized for the anatomical area in mind.

5. 3D raw data format is saved to minimize storage space.

If 3D probe technology is unavailable, it can undoubtedly be removed from the analysis as high-resolution 2D has been proven to demonstrate the compulsory features alone (Kingstone et al., 2014) however, an alternative and more worthwhile approach is clinically available by obtaining 3D manual sweeps of the atheromatous segments with the use of any high-resolution linear, high-frequency transducer and reformatting the acquisition in the US unit’s built-in quantification software for post-processing manipulation. This will enable the acquired data to be reviewed in an accurate, offline reading setting. Table 2.3 Illustrates the schematic overview of a standardized, US acquisition for 2D and 3D US plaque imaging.

Table 2.3: Schematic overview of 2D and 3D US acquisition methodology for plaque imaging.

<table>
<thead>
<tr>
<th>2D USING HIGH-RESOLUTION, HIGH-FREQUENCY (MINIMUM 12MHZ) LINEAR ARRAY TRANSDUCER</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYSTEMATIC OVERVIEW OF INTERNAL CAROTID ARTERY</td>
</tr>
<tr>
<td>PROXIMAL ICA STATIC IMAGE ACQUISITIONS: TWO LONGITUDINAL AND TWO TRANSVERSE IMAGES FOR ECHOTEXTURE AND ECCHONEOGENICITY</td>
</tr>
<tr>
<td>ECHOMORPHOLOGICAL, GREY LEVEL ANALYSIS ANY FOCAL INTERNAL AREA(S) ALTERATIONS MEASURED</td>
</tr>
<tr>
<td>MAXIMUM DYNAMIC RANGE LOW PERSISTENCE AND HIGH FRAME RATE SETTINGS</td>
</tr>
<tr>
<td>OPTIMIZE POWER OVERALL GAIN, COMPENSATION, FOCUS ZOOM, IMAGE DEPTH, ETGC AND OVERALL GAINS FOR ANATOMICAL AREA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3D USING A LINEAR ARRAY TRANSDUCER WITH 3D CAPABILITIES OR VOLUMETRIC BROADBAND TRANSDUCER (VL13 MHZ).</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRANSDUCER PLANE IN LONG AXIS AND CENTER SLICE OF VOLUME LOCATED AT MID PLAQUE SPECIMEN</td>
</tr>
<tr>
<td>3D MECHANICAL SWEEP AT 15 DEGREE ANGLE</td>
</tr>
<tr>
<td>FRAME RATE IN THE 10 SECOND RANGE WITH MINIMAL FINAL 25 SLICE VOLUME DATA SET</td>
</tr>
<tr>
<td>POWER GAIN COMPENSATION, FOCUS ZOOM AND IMAGE DEPTH ARE OPTIMIZED FOR THE ANATOMICAL AREA</td>
</tr>
<tr>
<td>3D RAW DATA FORMAT SAVED</td>
</tr>
</tbody>
</table>
2.2.6. **3D DATA RECONSTRUCTION**

2D ultrasound imaging comprises of X and Y picture elements, by grey-scale pixel analysis (Kremkau, 2010). 3D reconstruction imaging further extends this concept by allowing multi-planar manipulation, applying X, Y and Z sequential volume rendered imaging planes (Figure 2.5) processed by the following (Kremkau, 2010; Philips, Netherland):

1. Stacking a series of 2D acquired images creates the depth or z-plane dimension.
2. These stacked 2D images are further interpolated to create a volume element.
3. This acquired voxel is stored digitally as the 3D raw data.
4. Post-processing analysis and evaluation of the plaque segment is achievable by built-in automated software, though rotating capabilities in the X, Y and Z planes to re-orient the view of the acquired slab.
5. Alternative views can be directed using the volumetric slice section technique. This method enables the selection of a single volumetric slices throughout the plaque segment, which can further be manipulated to assist in the internal quantification of plaque components of the atheromatous lesion.
6. It is important to note that the raw data processed should take into account 3D imaging artifacts and errors caused by patient motion, vessel pulsatility and attenuation artifacts, which in turn may undermine the integrity of imaging.

Figure 2.5: Post-processing reconstruction of a volumetric 3D US image acquisition using built-in automated software with X (red), Y (green) and Z (blue) planes for re-orientation of acquired slab.

2.3. QUANTIFICATION OF COMBINE PLAQUE US IMAGING

The increased interest of using US to image plaque morphology present as a paradigm for finding a relationship between morphological characteristics and additional risk factors, identifying atherosclerotic plaques at higher risk for cerebrovascular events, thus improving stroke prevention. During this last decade, US has greatly improved in image standardization and in the assessment of carotid plaque characterization. High-resolution 2D US and 3D volumetric imaging are now able to identify potential characteristics of atherosclerotic plaque that is prone to rupture, leading to possible
thromboembolic events. Acquiring additional, combined plaque imaging and analysis of the carotid arteries provides additional knowledge of possible causative conditions in the carotid arteries and is a more effective method to identify abnormal carotid atheromatous structures, capable of identifying significant plaque characteristics responsible for strokes.

### 2.3.1 Validation of Enhanced Methodology

As stated in an earlier fragment of the exegesis, one of the foremost limitations of enhanced US plaque imaging, is the influence of imaging conditions, which in turn impacts reproducibility. In addition, US as an imaging modality, can present with high inter-equipment variation and is entirely favorable for operator dependency. The reproduction quality, inter-observation reliability, and variability are integral to the assessment of carotid plaque imaging. The quality control study by Nicolaide et al. (2003) identified scanning specifics and provided guidance for a standard in plaque imaging characterization. Specifically, the authors identified that applying prerequisites, such as instrumentation settings, image standardization, scanning and personnel training are essential to add credibility to the examination results. Kingstone et al. (2014) applied these recommended prerequisites when measuring inter-observation in their combined 2D and 3D analysis for plaque

---

morphology; they observed that the areas requiring agreement were attributed from the lack of understanding and training, specifically in US plaque characterization. Although high-resolution 2D US can correctly identify most vulnerable plaque characteristics, enhanced volumetric 3D US imaging, specifically the raw 3D data, enhances the plaque’s characteristics and further aids in the quantification of plaque morphology (Kingstone et al., 2014; Kingstone et al., 2014; Kingstone et al., 2014). The application of this enhanced US technique increases accurate recognition of the pathological segments regardless of the sonographers’ plaque morphology experience or equipment variations. Kingstone et al. (2014) reported a significant reduced inter-rater variability when exercising post-processing 3D reformatted applications with volumetric slice selection for internal plaque quantification, used as an adjunct to high-resolution 2D US applications. Kingstone et al.'s findings strengthen the concept of combining 2D and 3D US in

plaque assessment reduces inter-rater variability, which in turn increases the sensitivity and specificity of each plaque specimen.

2.3.2 Data Interpretation

Although the practice of carotid plaque US imaging is in its infancy, the most important component is adequate visual reporting, analysis, and documentation of internal plaque characteristics and surface details. Current guidelines vary between professional bodies or clinical practice and specific plaque interpretation guidelines are not clinically applied worldwide. Of the guidelines reported, nearly all (Gray-Weale et al., 1988; Geroullakos et al., 1993; Reilly et al., 1983; Szatajzel, 2005) evaluate the basis of echogenicity and echotexture using a single B-mode imaging analysis or apply complex, commercialized software to extract specific plaque features, unavailable to most imaging centers or laboratories (Kingstone et al., 2013). It is imperative that radiologists involved in the interpretation and assessment of carotid plaque US recognize other sonographic features, including internal plaque matter and surface alterations, to properly characterize the plaque. Image standardization, classification criteria, and thresholds should be employed to aid in the interpretation of quantitative grading; several plaque echomorphology features should be used inclusively to increase the potential

---

risk of stratification. Kingstone et al. (2013)\textsuperscript{77} integrated these characteristics to establish an imaging based criterion, based on the literature (Kingstone et al., 2013)\textsuperscript{78} and clinical experimentation (Kingstone et al. 2014\textsuperscript{79}, Kingstone et al., 2014\textsuperscript{80}, Kingstone et al., 2014\textsuperscript{81}). There are a number of morphology US characteristics that should be considered when evaluating, interpreting and reporting US imaging analysis (Figure 2.6). Firstly, the simple characterization between homogenous or heterogeneous plaques should be used to reliably predict the soft tissue content and plaque uniformity or consistency. Homogenous plaques, presenting as uniformly echogenic internal echotexture, contain high collagen and fibrotic components whereas heterogeneous plaques, present with mixed echoes, contain lower calcium content but larger amount of intraplaque hemorrhage or lipid (Mathieson et al., 2001;Langsfield et al.,

Homogenous plaques have a lower incidence rate of clinical neurological events than the unstable heterogeneous plaques (Langsfield et al. 1989; AbuRhama et al., 1989; Carr et al., 1996). Secondly, the overall echo plaque density, distinguished by specific echogenicity of the plaque, should be documented. Overall brightness of the plaque should be based on the reference structures and reported accordingly. Hypoechoic plaques predict a higher risk of ipsilateral ischemic strokes over echorich plaques (Gronholdt et al., 2001; Carra et al., 2003, Sterpetti, Mathieson et al. 2001; Kingstone et al., 2013). Thirdly, internal presence of US echolucency is described when a focal predominant hypoechoic/echolucent area is identified within the internal structure representing a lipid region, hemorrhage, or thrombi (Carra et al., 2003; Kingstone et al., 2013; Mathieson et al., 2001), are associated with a higher incidence of CV disease (Geroulakos et al. 1994; Langsfeld et al. 1989; Sterpetti et al. 1988). Distinguishing between a lipid, hemorrhage, or thrombus is not possible by interpretation, as B-mode US imaging cannot reliably determine the particular pathophysiological characteristic. Finally, surface irregularity such as fissures, alterations, cap thinning and ulcerations must be recognized. The specimen plaque is considered regular or no abnormality detected, when no variations in the plaque surface larger than 0.3mm on the contour of the plaque, and/or no

---

alterations in the internal echotexture or echogenicity are noted. Irregular surface is observed if surface contour exceeds 0.3mm (Sztajzel, 2005). Ulcerations are considered when the specimen contains a focal, circumferential irregularity or break in the surface of the plaque, with a minimum depth of 3mm and fissures are identified when there was evidence of a linear break in the surface (Sztajzel, 2005). Any of these surface irregularities significantly increases the risk of CVA (Carra et al. 2003; Kingstone et al. 2013\textsuperscript{85}).

Figure 2.6 Schematic overview of sonographic morphological appearances in vulnerable carotid atherosclerotic plaques.

At a minimum, all evaluations of plaque characteristics must be reviewed using still, high-resolution 2D images; if using raw data, it should be of a 3D reformatted section. If 3D probe technology is unavailable, stacked imaging

using sequential 2D acquisition is obligatory to enable the reporting radiologist to review the raw slice data from the anatomical segment. For interpretation purposes, radiologists do not need to have manipulation capabilities of reformatted stacks or 3D images however, sufficient still images must be captured to cover all aspects of the plaques (Kingstone et al., 2014\textsuperscript{86}).

2.3.3 Classification

Several sonographic reporting classification systems have been published; however, most are outdated, apply expensive software, or do not incorporate newer technology for high-resolution imaging to their grading systems (Kingstone et al., 2013\textsuperscript{87}). Standardized plaque analysis, characterization, and reporting are lacking, with no existing global classification system for reporting. In order to improve US's eminence and bring light to possible pathophysiological sources of stroke, incorporating newer US techniques and newly discovered morphological features in existing categorical mechanisms is necessary. Kingstone et al. (2013\textsuperscript{88}) developed a classification scheme to accurately stratify the risk of stroke in relation to plaque feature(s) based on a collection of published guidelines and studies with histological validation and

\begin{thebibliography}{9}
\end{thebibliography}
reported high accuracy (Kingstone et al. 2014⁸⁹; Kingstone et al. 2014⁹⁰) when applied in clinical trials. Based on these analyses, each plaque is divided into one of three possible categorical groups according to risk assessment:

- **Type A** (no to low risk for vulnerability): a carotid plaque exhibited no US characteristics that suggested vulnerability, regardless of the existence of borderline or vulnerable US features.
- **Type B** (moderate risk for vulnerability): a carotid plaque exhibited one US characteristic for vulnerability regardless of the existence of additional borderline or vulnerable US features.
- **Type C** (high risk for vulnerability): a carotid plaque exhibit two or more US characteristics that suggest a vulnerable lesion with no borderline features.

The reporting physician can apply these classification criteria for the final analysis and risk assessment of the plaque.

### 2.4. ENHANCED US IMAGING PRINCIPLES

To maximize the information gathered by US and exhaust all of the clinically available imaging capabilities to accurately identify echomorphological features

---


and specific characteristics with US, the sonographic acquisition must encompass three attributes:

1. The combined use of additional, advanced US technologies, such as high-resolution imaging and the extraction of volumetric 3D or reformatted imaging to further characterize plaque morphology (Table 2.3).

2. A simple sonographic appearance guideline to identify specific vulnerable plaque appearance, creating uniform assessment in plaque US imaging (Figure 2.4).

3. Inclusive assessment of carotid plaque morphological features using a myriad technique for plaque analysis and imaging (Figure 2.7).

Figure 2.7 Myriad technique for US morphological plaque assessment.
Kingstone et al. (2013)\textsuperscript{91} developed and applied this enhanced US imaging protocol, which lead to many advantages; improved assessment of plaque, increased resolution, and expanded overall proficiency for US plaque characteristic imaging (Kingstone et al 2014\textsuperscript{92}; Kingstone et al. 2014\textsuperscript{93}; Kingstone et al. 2014\textsuperscript{94}). This comprehensive methodology will be discussed in detail in the next fragment of the exegesis, upon discussing the clinical consideration and applicability of plaque US imaging.

\textbf{2.5 SUMMARY}

Increasingly, US carotid plaque characterization and morphology is being applied in everyday clinical applications of carotid imaging. Currently, it is the best noninvasive, and most accessible, cost effective and accurate imaging modality to study carotid atherosclerosis for stroke prevention. US is a reliable and reproducible diagnostic method for assessing characteristic morphologic changes in carotid plaque atheroma, with excellent inter-rater variability. The use of enhancing advanced US methods such as 2D and 3D


sonographic imaging for carotid atheromatous plaque morphology amplifies the detection and evaluation of plaque progression and development, and can maximize carotid plaque information. This method, in combination with a uniform reporting mechanism, signals a paradigm shift in the standard protocol for carotid duplex US imaging.
3.

CLINICAL CONSIDERATION
AND APPLICABILITY FOR
ENHANCED US PLAQUE
IMAGING

3.1 Current clinical availability for in vivo carotid plaque imaging
   3.1.1. CT imaging acquisition and protocol
   3.1.2. MRI imaging acquisition and protocol
   3.1.3. US imaging acquisition and protocol

3.2 Clinical diagnostic performance of enhanced US
   3.2.1 Overall agreement and accuracy amongst US and other clinically available modalities
   3.2.2. Clinical reporting accuracy for US

3.3 Summary
Publications of the candidate cited in this chapter


3.1 CURRENT CLINICAL AVAILABILITY FOR IN VIVO CAROTID PLAQUE IMAGING

The focus of research has been shifting from imaging the degree of luminal narrowing towards incorporating plaque morphological imaging, even in the absence of stenosis (Chien et al., 2013). A growing body of literature (Chien et al., 2013; Naim et al., 2013; Wintermark et al., 2008) suggests that the evaluation of carotid plaque morphology provides a superior means of predicting future CVA. These significant clinical findings have led to the concept of vulnerable plaque imaging in diagnostic radiology. Although the development of carotid plaque imaging with the use of cross-sectional imaging techniques such as CT, MRI and US can properly visualize the internal contents and surface structure of the plaques, current clinical imaging applications do not include specific parameters or protocols for carotid atheromatous morphological applicability. Diagnostic imagers and reporting radiologists involved in cerebrovascular disease must be attentive of the pathophysiology source and take into consideration current developments of imaging techniques for CAS to improve risk stratification and provide appropriate preventative therapy in the clinical setting. The practical consideration of including plaque morphology in everyday clinical imaging is a cornerstone for stroke prevention, by identifying specific relationships of quantifiable plaque features and associating them to risk factors. This fragment of the exegesis will detail the prospective and currently clinical available imaging applications, and the benefits and drawbacks of noninvasive imaging techniques for carotid artery plaque imaging.
3.1.1. CT IMAGING AND ACQUISITION PROTOCOL

CT is widely available and routinely used as part of the standard of care in the evaluation of patients with cerebrovascular disease (Magge et al. 2008) and stroke protocol imaging (Chien et al., 2013). With the advent of multi-slice helical 64-slice CT scanners, enhanced near-isotropic, high-resolution imaging to quantitatively and accurately assess in vivo histologic carotid plaque composition and characteristics have resulted in considerable improvement in carotid artery imaging (Kingstone et al., 2012; Naim et al., 2013; Wintermark et al. 2008). CT is capable of imaging minimal sectional thickness, enabling sub-millimeter datasets and rapid acquisition for minimal motion artifact adept to adherent plaque tissue characterization (Kingstone et al., 2012). Wintermark et al. (2008) found 72.6% agreement between CT plaque characteristics and histology, perfecting the concordance for ulcerated surface pathologies. Similarly, Naim et al. (2013) disclosed internal hemorrhage detection of 100% sensitivity and 64.7% specificity, and ulceration detection of 95% sensitivity and 98% specificity in median dense plaques. The present evidence serves to strengthen the hypothesis that CT interpretation should include clinical assessment of the characteristics of the carotid atheroma to examine the association between vascular risk factors in everyday imaging, especially when questioning a stroke diagnosis (Figure 3.1). We believe this assessment can be undoubtedly be performed without coupling it with complex algorithms.

reformatting or contrast-enhancement by using the following non-contrast CT protocol for in vivo plaque imaging acquisition (Kingstone et al., 2014; Santos, 2013):

- Studies must obtained through the multiplanar capabilities of a 64-slice multidetector CT scanner to enable anatomical and structural details and internal architecture of plaque.
- Helical 0.5 sec rotation, 120 kV, 250mA, collimation of 20mm, acquisition 0.625mm, and a pitch of 0.969:1 with a table feed of 19.37mm per rotation.
- Reconstructed data result in 1.25mm axial images with a 512 x 512 pixels matrix.
- The data is acquired in a scan field of view (SFOV) of 32cm and displayed in a 22cm field of view (DFOV).
- Scan acquisition ascends in a cranio-caudal direction, starting from the vertex of the head and proceeds as low as the aortic arch.

Although the use of contrast-enhanced angiographic acquisitions (computed tomography angiography-CTA) has demonstrated great agreement in identifying ulcerations, lipid cores or hemorrhages and specific fibrous cap thickness changes (Chien et al., 2013; Eesa, Hill & Al-Khathaami, 2010; Wintermark et al., 2008) the associations between these clinical plaque features visualized with by CTA studies still lacks specificity (Chien et al., 2013). Furthermore, the use of CTA for imaging is not always inclusive for routine standard of care and stroke assessment, therefore unfeasible for everyday clinical imaging.
3.1.2. MRI Imaging and Acquisition Protocol

Studies with histologic validation (Chiu et al., 2009; Demarco & Huston, 2014; Hatsukami, Ross, Polissar & Yuan, 2000) have determined that multi-contrast MRI can accurately characterize carotid plaque morphology, making it the lead noninvasive modality for imaging (Figure 3.2). MRI’s increasing field-strength units and improving quality and high-resolution imaging with multi-contrast capabilities promise to provide diverse atheromatous tissue weighing to quantify plaque morphology (Kingstone et al., 2012). MRI has demonstrated a 93% sensitivity and 96% specificity (Cappendijk et al., 2005) for internal plaque lipid-rich core(s) or hemorrhages(s) and 81% sensitivity and 90% specificity in identifying thin or ruptures cap (Mitsumori et al., 2003) pathologies. To visualize atherosclerotic plaque components, a combination of three to four minute carotid plaques sequences provides all the information necessary to fully characterize the plaque using clinically available applications. It is important to note that plaque imaging should always be performed, minimally on a 3.0T magnet MRI scanner (Kingstone et al., 2014; Naim et al., 2013) over a 1.5T to improve signal-to-noise (SNR) and contrast-to-noise.


(CNR) ratio. The following scanning parameters (Kingstone et al., 2014) are utilized based on using a phased-array 32-channel head coil or dedicated, 4-channel phased array neurovascular carotid receive only coil:

- Multiple contrast weighing sequence, high-resolution imaging.
- T1-weighted (T1W) repetition time/echo time 500ms/12.4ms.
- T2-weighted (T2W) 3500ms/62ms.
- 3-dimension volume interpolated sequence for reconstruction capabilities echo time 2.9ms with a flip angle, 15 degrees.
- All sequence imaging obtained with a field of view (FOV) of 14.0 x 14.0cm, matrix size 256 x 256.
- High-resolution spatial resolution by applying a slice thickness of 2mm and inter-slice gap of 2mm in T1W and T2W and 1mm in volumetric interpolated imaging.
- Scan coverage must be 3.2cm (32 slices) in T1W and T2W and 1mm in volumetric interpolated weightings.
- Scan acquisition includes area from the mandible to the base of the neck at the clavicular level.

Figure 3.2. High-resolution, cross-sectional MRI of the right internal carotid artery. (A) On T1W acquisition, the plaque appears heterogeneous reflecting fibro calcific tissue. (B) T2W showing hyper intense area in medial internal carotid artery, while likely representing loose matrix fibrous tissue.

Additional techniques such as pulse sequences, including black- or bright-blood imaging to suppress flowing blood signals and the use of natural gadolinium chelate contrast agent can be applied to improve or complement the conventional information of plaque morphology. Currently, these parameters are not inclusive of clinical recommendations for MRI plaque imaging (Chien et al., 2013; Naim et al., 2014) and have yet to be proven to be associated with CVA (Oikawa et al., 2009). Compared to other imaging modalities, MRI plaque imaging continues to be the modality of choice for sensitivity and specificity in carotid atheromatous plaque morphology and is
the subject of numerous clinical studies (Kingstone et al., 2013\textsuperscript{101}). Two significant drawbacks of MRI are that it is prohibitive for widespread clinical use and is not suitable for screening purposes (Naim et al., 2013; Kingstone et al., 2013\textsuperscript{102}).

### 3.1.3. US Imaging and Acquisition Protocol

As previously discussed in this exegesis, US is a renowned imaging modality and the preferred noninvasive method to evaluate carotid artery plaque for the purpose of identifying internal textural alterations, and the structural appearance of vulnerable features. In the remainder of this exegesis, a justifiable criterion for its clinical application will be established to transition the science of enhanced US plaque imaging to everyday clinical practice.

To accurately identify echomorphological features and specific characteristics with enhanced US, four attributes must be incorporated in the sonographic acquisition and interpretation (Kingstone et al. 2014\textsuperscript{103}; Kingstone et al., 2014\textsuperscript{104}; Kingstone et al., 2014\textsuperscript{105}):


1. The combined use of additional enhanced US technologies, including high-resolution imaging and the extraction of volumetric 3D or reformatted imaging to further characterize plaque morphology.

2. The majority of US plaque-imaging paradigms are focused on the development of a single US morphological trait; therefore, collective or combined US echomorphological imaging is essential to accurately assess the overall risk.

3. A simple, sonographic parameter or imaging guideline should be applied to identify specific vulnerable plaque appearance and create a uniform assessment or result.

4. A specific morphological characterization reporting and classification system to properly analyze the correct type of plaque according to risk stratification.


Kingstone et al.’s (2014) solution for this dearth of clinical guidelines was to coalesce the above critical information and establish an imaging approach, based on several prosperous models, for clinical implementation and determine the efficacy of this approach into clinical practice. The following section of the exegesis will outline the validation of this US method, in comparison to other clinically available modalities and in in vivo imaging.

3.2 CLINICAL DIAGNOSTIC PERFORMANCE OF ENHANCED US

Multiple clinical imaging modalities evaluating morphological characteristics of carotid artery plaque for stroke prevention have been developed; however, the best application with the use of a noninvasive imaging modality has yet to come.

Although multiple investigations have assessed the agreement between US and other currently available, cross-sectional diagnostic tools such as MRI and CT in the evaluation of carotid vulnerable plaques, not a single study used an


all-encompassing, enhanced imaging US approach for plaque morphological diagnostic efficacy. Furthermore, most studies have not operated everyday clinical imaging applications. Table 3.1 summarizes the published studies comparing current cross-sectional modalities to plaque morphological features.

Table 3.1. Summary of studies comparing current cross-sectional modalities to specific, vulnerable morphological features.

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>YEAR</th>
<th>MODALITY</th>
<th>FEATURE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heliopoulos J</td>
<td>2009</td>
<td>US (3D)</td>
<td>Ulceration</td>
</tr>
<tr>
<td>Saba L</td>
<td>2009</td>
<td>CT</td>
<td>Fissured Surface/Capsule</td>
</tr>
<tr>
<td>Geroulakos G</td>
<td>1993</td>
<td>US</td>
<td>Internal alterations</td>
</tr>
<tr>
<td>Chu B</td>
<td>2009</td>
<td>US (3D)</td>
<td>Surface Irregularities</td>
</tr>
<tr>
<td>Takaya N</td>
<td>2010</td>
<td>MRI</td>
<td>Hemorrhage</td>
</tr>
<tr>
<td>Seabra JC</td>
<td>2009</td>
<td>US (3D)</td>
<td>Surface/Internal alterations</td>
</tr>
<tr>
<td>ECPSG</td>
<td>1995</td>
<td>US</td>
<td>Internal alterations</td>
</tr>
<tr>
<td>Nighoghossian N</td>
<td>2005</td>
<td>MRI/US</td>
<td>Surface/Internal alterations</td>
</tr>
<tr>
<td>Oikawa M</td>
<td>2009</td>
<td>MRI</td>
<td>Surface/Internal alterations</td>
</tr>
<tr>
<td>Naim C</td>
<td>2013</td>
<td>US/CT/MRI</td>
<td>Surface/Internal alterations</td>
</tr>
<tr>
<td>Belcaro G</td>
<td>1993</td>
<td>US</td>
<td>Internal alterations</td>
</tr>
<tr>
<td>Santos F</td>
<td>2012</td>
<td>CT</td>
<td>Surface/Internal alterations</td>
</tr>
<tr>
<td>Kingstone LL</td>
<td>2013</td>
<td>US (3D)</td>
<td>Surface/Internal alterations</td>
</tr>
<tr>
<td>Soloperto G</td>
<td>2010</td>
<td>MRI</td>
<td>Surface/Internal alterations</td>
</tr>
<tr>
<td>Gray-Waele AC</td>
<td>1998</td>
<td>US</td>
<td>Hemorrhage/Lipid</td>
</tr>
<tr>
<td>Mathieso EB</td>
<td>2010</td>
<td>US</td>
<td>Hemorrhage/Lipids</td>
</tr>
<tr>
<td>DeMarco JK</td>
<td>2014</td>
<td>MRI</td>
<td>Surface/Internal alterations</td>
</tr>
<tr>
<td>Saba L</td>
<td>2007</td>
<td>US/CT</td>
<td>Internal alterations</td>
</tr>
<tr>
<td>Arora S</td>
<td>2013</td>
<td>CT</td>
<td>Surface/Internal alterations</td>
</tr>
<tr>
<td>Gronholdt MLM</td>
<td>1997</td>
<td>US</td>
<td>Lipids</td>
</tr>
<tr>
<td>Magge R</td>
<td>2008</td>
<td>CT</td>
<td>Internal alterations</td>
</tr>
<tr>
<td>Esposito-Bauer L</td>
<td>2013</td>
<td>MRI</td>
<td>Surface/Internal alterations</td>
</tr>
<tr>
<td>Reilly LM</td>
<td>1983</td>
<td>US</td>
<td>Hemorrhage</td>
</tr>
<tr>
<td>Chiu B</td>
<td>2012</td>
<td>US/MRI</td>
<td>Surface/Internal alterations</td>
</tr>
<tr>
<td>Chien JD</td>
<td>2012</td>
<td>CT</td>
<td>Surface/Internal alterations</td>
</tr>
<tr>
<td>Kardoulas DG</td>
<td>1996</td>
<td>US</td>
<td>Ulceration/Hemorrhage</td>
</tr>
<tr>
<td>Hatsukami TS</td>
<td>2000</td>
<td>MRI</td>
<td>Surface alterations</td>
</tr>
<tr>
<td>Goes E</td>
<td>1990</td>
<td>US</td>
<td>Surface/Internal alterations</td>
</tr>
<tr>
<td>Kingstone LL</td>
<td>2014</td>
<td>US</td>
<td>Hemorrhage/Surface alterations</td>
</tr>
<tr>
<td>Nicolaides A</td>
<td>2010</td>
<td>US</td>
<td>Surface/Internal alterations</td>
</tr>
<tr>
<td>Grogan JK</td>
<td>2005</td>
<td>US</td>
<td>Hemorrhage/Lipid</td>
</tr>
</tbody>
</table>
In clinical practice, US remains the first line of defense in carotid arterial imaging because of its accessibility, noninvasive nature, and low cost, for establishing final diagnosis and treatment prognosis for patients with CAS (Kingstone et al., 2014\(^{109}\)). CT or MRI is generally used only after an US analysis underlined a pathological condition (Saba et al., 2009) due to their cost, bio-effects and nature of risks. Conversely, patients seen whose clinical events are not explained by the severity of the stenosis need further work-up to identify potential embolic sources, such as evaluating the plaque matter components. US, CT, and MRI all have the capabilities of detecting most morphological features at increased risk for vulnerability using everyday clinical imaging parameters (Kingstone et al., 2014\(^{110}\)) and although many different studies have demonstrated the potential of each respective cross-sectional

---


imaging modality for plaque imaging, none define the correct imaging tool applicable for the commonplace clinical techniques. The accuracy of each modality in identifying CAS morphological features is of great importance to re-direct clinicians to the appropriate modality. This theory was evaluated by both a clinical phantom and in vivo methodology (Kingstone et al., 2014111; Kingstone et al., 2014112). The phantom results (Kingstone et al., 2014113) demonstrated that when applying a myriad technique (Table 2.3, Figure 2.7) (Kingstone et al., 2013114; Kingstone et al. 2014115) to analyze the plaque and applying both enhanced 2D, and 3D US imaging for plaque analysis and characterization, US imaging had the highest overall accuracy (range of 88-100% accuracy) over other clinically available modalities such as CT (range 83-97%) and MRI (range 67-95%). These considerations were advocated when surveying specific morphological features of plaque and US yield the most accuracy (95%) in the internal plaque quantification, including alterations.

such as lipid cores or hemorrhages over CT (87%) and MRI (67%) (Kingstone et al., 2014[116]) (Figure 3.3).

![Figure 3.3. Internal area of lucency (arrows) seen on axial 2D US images (left); longitudinal T1W MRI imaging (middle); and axial CT image (right).](image)

This is foreseeable considering both CT and MRI are limited in their ability to distinguish internal matter due to lack of resolution to quantify internal cores, with the use of contrast-enhancement, dedicated coils, or detailed reformatting, leaving enhanced US as the appropriate clinical frontrunner (Kingstone et al., 2014[117]) for quantification of the plaque’s soft tissue.

---

contents. Subsequently, US also had the highest accuracy (90%) in visualizing parenchymal wall tissue and identifying plaque surface irregularities identifying plaque surface irregularities (Figure 3.4) over CT (87%) or MRI (78%), despite reports of CT (Eesa et al., 2010) and MRI (Hatsukami et al., 2000) holding the lead in surface imaging. This outcome is due to ultrasound’s 3D circumferential and reformatting capabilities to correctly identify any surface alterations.

![Figure 3.4. Irregular plaque surface (arrows) on longitudinal high-resolution 2D US (left); axial CT (middle); and axial T2W MRI images (right).](image)

This was further evident when assessing for specific surface defects such as ulcerations (Figure 3.5), where US had no significant difference in accuracy with CT ($p=0.58$) but was significantly more accurate (88% accuracy) over MRI ($p=0.04$) (Kingstone et al., 2014\textsuperscript{118}).

Figure 3.5. Reformatted 3D US (left); axial CT (middle); and axial T2W MRI images (right) of ulcerated (arrows) simulated plaque comparison.

Table 3.2 and 3.3 demonstrates the overall agreement and accuracy among the three clinical modalities for each morphological characteristics (Kingstone et al., 2014). It should be noted that multiple factors involved were in the consistency with the use of the same hardware, techniques, operators, and data standardization, and therefore, any of these parameter alterations will result in minimal modifications.

Table 3.2. Overall agreement among the three modalities regarding each morphological characteristic. Note: NAD = No abnormality detected.

<table>
<thead>
<tr>
<th>Assessment Criterion</th>
<th>Inter-rater agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Agreement</td>
</tr>
<tr>
<td>NAD</td>
<td></td>
</tr>
<tr>
<td>US vs. CT</td>
<td>Substantial</td>
</tr>
<tr>
<td>US vs. MRI</td>
<td>Substantial</td>
</tr>
<tr>
<td>Lucency</td>
<td></td>
</tr>
<tr>
<td>US vs. CT</td>
<td>Substantial</td>
</tr>
<tr>
<td>US vs. MRI</td>
<td>Fair</td>
</tr>
<tr>
<td>Ulceration</td>
<td></td>
</tr>
<tr>
<td>US vs. CT</td>
<td>Moderate</td>
</tr>
<tr>
<td>US vs. MRI</td>
<td>Moderate</td>
</tr>
<tr>
<td>Fissure</td>
<td></td>
</tr>
<tr>
<td>US vs. CT</td>
<td>Substantial</td>
</tr>
<tr>
<td>US vs. MRI</td>
<td>Moderate</td>
</tr>
<tr>
<td>Irregular Surface</td>
<td></td>
</tr>
<tr>
<td>US vs. CT</td>
<td>Very good</td>
</tr>
<tr>
<td>US vs. MRI</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Table 3.3. Accuracy of each modality for each morphological characteristics. Note: TP=True positive, FN= False negative, TN= True negative, FP= False positive, Se=Sensitivity, Sp= Specificity

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>CT</th>
<th>MRI</th>
<th>US</th>
<th>CT</th>
<th>MRI</th>
<th>US</th>
<th>CT</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#TP</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>24</td>
<td>22</td>
<td>8</td>
<td>15</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>#FN</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>19</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>#TN</td>
<td>56</td>
<td>54</td>
<td>54</td>
<td>33</td>
<td>30</td>
<td>32</td>
<td>38</td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td>#FP</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Se</td>
<td>100</td>
<td>100</td>
<td>75</td>
<td>89</td>
<td>81</td>
<td>30</td>
<td>83</td>
<td>67</td>
<td>50</td>
</tr>
<tr>
<td>Sp</td>
<td>100</td>
<td>96</td>
<td>98</td>
<td>100</td>
<td>91</td>
<td>97</td>
<td>90</td>
<td>90</td>
<td>88</td>
</tr>
<tr>
<td>Accuracy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lucency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#TP</td>
<td>20</td>
<td>17</td>
<td>21</td>
<td>14</td>
<td>13</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#FN</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#TN</td>
<td>37</td>
<td>33</td>
<td>27</td>
<td>40</td>
<td>39</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#FP</td>
<td>1</td>
<td>5</td>
<td>11</td>
<td>4</td>
<td>5</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Se</td>
<td>91</td>
<td>77</td>
<td>95</td>
<td>88</td>
<td>81</td>
<td>69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sp</td>
<td>97</td>
<td>87</td>
<td>71</td>
<td>91</td>
<td>89</td>
<td>82</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>95</td>
<td>83</td>
<td>80</td>
<td>90</td>
<td>87</td>
<td>78</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In the prospective, radiographic pathology (Rad-Path) clinical study, it was noted that the US method (Kingstone et al. 2013\textsuperscript{120}; Kingstone et al., 2014\textsuperscript{121}; Kingstone et al., 2014\textsuperscript{122}) and CT has 100% accuracy in identifying plaque surface ulceration (Figure 3.6 and 3.7).

Figure 3.6. In vivo ulcer identification (arrow) on 3D US (left) and CT (right).


Figure 3.7. Surgical pathological specimen in correlation with above US and CT findings identifying the ulceration (arrows).

With respect to the identification of a lipid or hemorrhagic core(s), CT was unable to identify any of the two true positives, leading to a 0% sensitivity (100% specificity and 33% accuracy), whereas US successfully identified the core components in all cases (100% accuracy, sensitivity, and specificity (Kingstone et al., 2014). More importantly, US outperform CT in identifying these potential risk indicators in a greater part of categorical components, as CT does not identify any features not detected on US (Figure 3.8).

Figure 3.8. US demonstrating area of hemorrhage (arrow) with Rad-Path correlation (arrows). CT image of this patient not identifying any internal alterations.

The results of the clinical study demonstrate that a high-resolution 2D imaging of the carotid plaque with a high-frequency linear array transducer in conjunction with 3D US assessment via volumetric broadband imaging in patients with carotid artery disease shows significant observations in identifying characteristics of plaque vulnerability with high correlation rate, sensitivity, and specificity and superior to CT for certain categorical components (Kingstone et al., 2014). It is important to note that 3D US imaging is prone to artifacts, particularly those caused by physiological motion.

from carotid vessel pulsations. This artifact causes distortion and mis-registration 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 (Kingstone et al., 2014). Results from this clinical study took several attempts to obtain suitable volume without artifact (Kingstone et al., 2014). The empirical evidence supports the intuitive notion that enhanced US imaging provides a reproducible, and reliable diagnostic clinical imaging method that is globally available, for assessing morphological changes in carotid plaque, optimal over routine CT or MRI imaging.

### 3.2.2. CLINICAL REPORTING ACCURACY FOR US

The visual US imaging analysis, including standardized quantification and reporting criterion for carotid atheroma, is quintessential for the accurate detection, clinical management, and therapeutic consideration in CAS.

---

(Kingstone et al., 2014\(^{127}\)). In the phantom and clinical trials (Kingstone et al. 2014\(^{128}\); Kingstone et al., 2014\(^{129}\)), an imaged based criterion (Table 2.3) was used with high accuracy (80-85%) when assessing plaque morphology characteristics with US to improve the reproducibility of the visual manifestation for reporting mechanisms. When using this criterion, there was widespread agreement among radiologists (ICC=0.61, 95% CI 0.46-0.74), when reporting plaque morphological characteristics (Kingstone et al., 2014\(^{130}\)). Radiologists implemented a quality assurance tool for plaque classification criteria, without the using complex or expensive software, by categorizing plaque into three categorical groups, defined according to risk validated the uniformity and accuracy (\(p=0.75\)) in terms of their assessment of plaque subtypes (Kingstone et al., 2014\(^{131}\)). The findings from these clinical studies corroborates the inevitability of global, standardized analysis and reporting to improve accuracy and reporting of plaque characterization assessment in a clinical setting. It is noteworthy that in these clinical trials, despite only a small percentage of reporting neuroradiologists, indicated that the acquired volumetric 3D imaging component assisted their assessment (ICC=0.01, 95% CI 0.06-0.12, \(p<0.001\)), all agreed that the raw sequential,

---

3D data images helped their plaque assessment and attested that 3D US data should be inclusive of US imaging (Kingstone et al., 2014). 

### 3.3 SUMMARY

Ultrasound remains the first line of defense in carotid arterial imaging because of its accessibility, risk-free nature and low cost. Results from prospective clinical trials fill the void created by an ongoing paradigm shift in diagnosing early atherosclerotic vascular disease by assessing beyond the lumen to provide significant clinical information of the atheroma. Enhanced US method for plaque imaging is a reproducible, reliable, and clinically available diagnostic method for the quantification and assessment of morphological characteristics in carotid plaque that is optimal to routine CT and MRI imaging. Proper identification of specific US morphologic features and plaque categorization can unify the language between the radiologist and referring physicians to promote standardized US classification analysis for reporting carotid atherosclerotic lesions, thereby improving the patient’s management and care. One should note that the information derived should be critically compared and validated with other clinical diagnostic techniques in human atheroma, suggestive of a long-term clinical trial.

---

.4. DISCUSSION

4.1 DISCUSSION

4.2 RECOMMENDATIONS

4.3 CONCLUSION

Publications of the candidate cited in this chapter


4.1 DISCUSSION

The early identification of morphological 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. A review of the role, accuracy, and cogency of ultrasound for CAS disease imaging found that characterizing plaque using B-mode, or 2D and 3D US scans in real time can accurately distinguish specific, distinctive findings. These findings are evidenced to be morphological indicators in rupture-vulnerable plaques (Kingstone et al., 2013\textsuperscript{133}). The outcome of these analyses indicate the necessity of incorporating plaque imaging and/or characterization as a comprehensive examination in CAS imaging, in addition to luminal grading. This evolved approach of carotid plaque US imaging technique is universally accessible, and can easily be performed in any department. Despite its development, this method is not applied widely in clinical practice as an adjunct to current standard imaging. In addition, it fulfills the requirement for a universal, low-cost screening and imaging technique for CAS, to extend risk assessment and succeed in prophylactic treatment strategies.

Ultrasound is an accurate imaging modality with high sensitivity and specificity for carotid plaque characterization (Kingstone et al., 2013\textsuperscript{134}). With theoretical

advancements in US technology, higher detailed imaging is now clinically achievable to improve imaging quality. High-resolution 2D and 3D volumetric imaging is obligatory, either alone or in a collective approach, to amplify the diagnostic evaluation of plaque morphology in standard imaging practice. Correspondingly, the inclusion of several, if not all, vulnerable echomorphology features in the evaluation and characterization of plaques, using a myriad technique (Kingstone et al. 2013; Kingstone et al., 2014; Kingstone et al., 2014; Kingstone et al., 2014; Kingstone et al., 2014) increases the potential to stratify risk. The current clinical significance of enhanced US imaging was evident by corroborating the recognized information on plaque imaging and contrasting its clinical applicability with existing clinical imaging modalities and/or surgical specimens (Kingstone et al., 2014; Kingstone et al., 2014; Kingstone et al., 2014). While there is a wide spectrum regarding the types of plaque

classifications published, there is little agreement (Kingstone et al., 2013\textsuperscript{(14)}) on key procedural issues between categorizations; one might conclude that a guideline incorporating all new aspects of imaging are not inclusive, and that those already published are outdated. In order to provide methodological considerations and interpreted reporting, to transmit information evenly from one clinical center to another, researchers and clinicians studying US plaque morphology must apply standardization of plaque description, guidelines, and protocols thus improving patient care.

Based on current US studies (Kingstone et al., 2014\textsuperscript{(14)})\textsuperscript{2}, the extensive analysis of US applications, as well as the assessment of their accuracy and validity in present clinical imaging practice provided the groundwork to design a methodical and practical approach to image vulnerable plaque morphology imaging. This new concept of US carotid plaque imaging is intended to improve existing practices by identifying vulnerable plaque features to facilitate earlier pathological diagnosis and optimize treatment strategies to decrease the rate of future cerebrovascular events.

Treatment strategies, such as preventative benefits of carotid endarterectomy (CEA) have been acknowledged for symptomatic patients with


hemodynamically significant stenosis (North American Symptomatic Carotid Endarterectomy trial collaboration, 1991; MRC European Carotid Surgery Trial, 1991; Yazdani, Vorpahl, Ladich & Virmani, 2010); however, the benefit of CEA remains equivocal. In asymptomatic patients, stenosis severity is a poor predictor of non-fatal or fatal CVA, with only a 2% annual risk with a >60% stenosis (17.9% at 10 years) (Halliday et al., 2004). Thus, better stratification is needed for patients with lesser-degree stenosis in terms of their risk, as without intervention or better treatment decisions in this population, these plaques have potential for harmful outcome. Emerging knowledge of plaque biology and pathological process has established a definitive relationship between plaque morphological characteristics and the development of neurological events; these plaques are also independent to luminal stenotic degree (Spagnoli et al, 2004). Therefore, the composition of atherosclerotic plaques holds a significant predictive value for cerebrovascular outcomes (Carra et al., 2003; Hellings et al., 2010; Spagnoli et al., 2004; Verhoven et al., 2005; Yazdani, Vorpahl, Ladich & Virmani, 2010). Despite reports of increased risk in these subgroups of patients, the benefit from prophylactic treatment is still being investigated in lower graded lesions (Carra et al., 2003).

The early detection of asymptomatic or new lesions requires diagnostic screening in order to image and identify early vulnerable plaque features, which is imperative for the prevention or vascular intervention of future cerebrovascular events. Presently, there is no single, gold standard reference or clinical imaging method applied to quantify and investigate plaque
morphology. Furthermore, the cost effectiveness of noninvasive screening for CAS is a subject of existing considerations. Duplex US remains the first-line imaging modality of choice in the evaluation of CAS imaging because it is accessible, inexpensive, and noninvasive. According to the Ministry of Health and Long-term Care of Canada, the cost of an US examination less than half that of other current cross-sectional imaging modalities, such as CT and MRI, making it the most appropriate diagnostic strategy clinically available, based on cost-analysis (Ontario Health Insurance Schedule of Benefits and Fees, n.d., para 3). Additionally, US has an exceptional imaging reputation to delineate CAS plaque tissue progression and development, with excellent histologic correlation (Reilly et al., 2007; Saba, Caddeo, Sanfilippo, Montisci & Mallarini, 2006; Verhoven et al., 2005).

Despite these facts, present-day plaque imaging modalities is not sufficiently in current clinical practice and Canadian National Practice Guidelines (“Canadian Association of Radiologists guideline”, n.d., para 3) have no recommendations or inclusions for US plaque imaging. Unremarkably, there is a high concordance amongst experienced carotid artery imaging researchers and clinicians to incorporate plaque imaging and assessment with traditional carotid imaging techniques in standard practice; this could broaden the atherosclerosis or stroke risk assessment, elucidate the possible pathophysiology of stroke and lead to a better stroke prevention practice. The inclusion of sonographic plaque imaging is important for several reasons: (1) Any atheromatous lesions may contain unstable plaques at higher risk for
rupture or exposing the highly thrombogenic core to the bloodstream, causing a distal embolus, resulting in a cerebral infarct (Kingstone et al., 2013\textsuperscript{13}); (2) Ultrasound of the plaque echomorphology will provide additional information of the patient’s potential disease (Kingstone et al., 2014\textsuperscript{14}; Kingstone et al., 2014\textsuperscript{15}; Kingstone et al., 2014\textsuperscript{16}); (3) Additional US plaque imaging is readily available at minimal cost and acquisition time (Kingstone et al., 2013\textsuperscript{17}); (4) Supplementary elements from the US echomorphology analysis are essential for clinical decisions and a crucial measurement for prophylactic neurological treatment and/or interventions.

Improving US’s eminence in plaque imaging is key to improving information acquisition and elucidate the possible pathophysiology sources of stroke. A significant effort has been made to accurately and statistically characterize the morphology and texture of carotid plaques in US imaging with report of great potentialities (Carr, Farb, Pearce, Virmani & Yao, 1996; Goes, Janssens, Maillet, \textit{\textsuperscript{13}}


Freson, Steyaert, & Osteaux, 1990; Gray-Waele, Graham, Burnette, Byrne & Lusby, 1988; Reilly et al., 2007; Mathieson, Bonaa & Joakimsen, 2001); however, imaging has significantly improved since these publications, as most were performed with outmoded US scanner equipment. Enhanced transducer technology leads to an enriched US-based plaque characterization approach, with reports of higher accuracy than traditional linear-array frequency imaging (Seabra, 2009). It is crucial to acknowledge that B-mode or 2D US imaging for plaque morphology must be scanned using the highest frequency, broadband linear array transducer (>12MHz) possible, in order to maximize the axial or lateral resolution to properly distinguish internal plaque material and enhance delineation of surface alterations (Kingstone et al., 2014). Furthermore, to minimize single-plane projection perceived by high-resolution 2D US, the application of 3D US magnifies this information and reliably improves the quality of characterization of plaque (Heliopoulos, Vadikolia, Piperidou & Mitsia, 2009; Kingstone et al., 2013). When both sonographic techniques are applied simultaneously, high-resolution 2D correctly identifies the majority of vulnerable plaque characteristics; however, the conformity further increased with the application of volumetric 3D imaging (Kingstone et al., 2014). The reformatting 3D capabilities further

---


improves the enumeration or visual capabilities of the distribution and shape of the atheromatous plaque structures by the rotation abilities of the true plaque circumferential asymmetrical development (Kingstone et al., 2014). This, in turn, improves the capabilities to further quantify additional vulnerable carotid plaque features, mainly due to the improved capabilities of 3D US to visualize parenchymal wall tissue and true plaque circumference of surface development in vivo (Kingstone et al., 2014). While the 3D US probe accessibility, which has yet to be adopted in clinical practice, hinders use for most medical facilities, an insightful finding by Kingstone et al. (2014) reported that interpreting neuroradiologists found stacked raw 3D data to be the most useful in morphological diagnosis, over the reformatted volumetric images. This is of particular importance for practicable applicability as most Canadian facilities employ commercially available, modern US equipment, all of which have 3D capabilities using linear high-frequency transducers to manually generate a sweep stack acquisition to create a raw,

---


3D data series similar to that sourced from volumetric 3D probe acquisitions (Philips, Botell, WA). Likewise, this data is capable of volumetric or slice image reformatting, using an internal post-processing quantitative software mechanism, to further improve plaque characterization and identify new risk indicators within a plaque volume.

With respect to the most appropriate strategy for US plaque imaging, currently there are no established recommendations or guidelines. The role of US in plaque imaging must exhaust all capabilities to image specific plaque morphological features by advocating a methodological systematic imaging guideline and integrating the practice of 2D and 3D US in conjunction with the analysis. This inclusive assessment of a carotid atheroma results in improving overall recognition of specific plaque features, thus increasing clinical imaging proficiencies for plaque morphological analysis and assessment by broadening the US method in finding the relationship between morphological characteristics and vascular risk factors in all types of atheromatous lesions (Kingstone et al. (2014). Multiple factors are involved in the plaque morphologic pathophysiology mechanism for patients at increased risk. While the accuracy of US in quantifying vulnerable plaques has been revealed to be excellent by several investigators, most evaluated a single morphological feature (AbuRhama, Kyer, Robinson & Hannay,

\[156\] Kingstone, L, Shabana, W, White, M, Lam, J & Currie, G. (2013). Comparison and accuracy of carotid plaque analysis between two- and three-
Enhanced Plaque Ultrasonography

1998; Mathieson, Bonaa & Joakimsen, 2001; Nicolaide et al., 2003; Saba, Caddeo, Sanfilippo, Montisci, & Mallarini, 2006; Verhoven et al., 2005). In practice, it is imperative a comprehensive evaluation of the plaque segment should collectively encompass all of the main parameters that constitute the basis of plaque echomorphology characterization to increase potential risk stratification and serve as a paradigm to understand the evolution of CAS lesions (Szatjzel, 2005; Yazdani, Vorpahl, Ladich & Virmani, 2010). These US parameters include plaque: (1) echogenicity; (2) texture; (3) surface alterations, including fissured, irregular contoured or ulcerated. This all-encompassing, myriad US imaging technique improves diagnostic performance in the identification and recognition of several morphological features to properly analyze atherosclerotic plaques (Kingstone et al. (2014)157,158159). This, in turn leads to an increased source for CVA in radiologic pathologic specimens (Kingstone et al., 2014160).

The use of US, over other clinical available imaging modalities in current atherosclerotic carotid evaluation attests as a reliable, reproducible, and commonly, the only diagnostic imaging modality used prior to therapeutic CEA (Naim et al., 2013). Noninvasive modalities such as US, MRI and CT US’s are increasingly being studied as potential leading modalities in the early identification of plaque formation, changes and/or stability; however, these imaging techniques are all at a development stage and have yet to be used in clinical practice (Naim et al., 2013). CT has an increased advantage by its availability, advent of multi-slice helical and rapid ability to measure tissue density to quantify plaque material with good accuracy. CT is leading in imaging fibrous cap and detection of surface alterations, with a 98% sensitivity and 98% specificity for ulceration (Saba, Caddeo, Sanfilippo, Montisci, & Mallarini, 2006) and plaque density analysis with CT enables detection of internal area of hemorrhage with 100% sensitivity and 64.7% specificity in plaques with median density below 31 Hounsfield units (Adjuk et al., 2009). Despite these advantages, CT has significant drawbacks, including beam hardening due to calcifications, exposure to ionizing radiation and nephrotoxic iodine-based contrast agents, all of which can contribute to inaccurate or inaccessible everyday clinical plaque characterization imaging. By contrast, MRI offers significant promise in distinguishing morphological plaque components and has been researched extensively as a potential modality with such success that the American Heart Association has supported an imaging criteria for MRI plaque characterization (Demarco & Huston, 2014). Histologic validation
determined that MRI, with appropriate sequences and coils, offers unmatched internal plaque tissue contrast and characterization such as lipid-rich necrotic core(s) and hemorrhage(s), with 93% sensitivity, 96% specificity (Moody et al., 2003) and a 81% sensitivity, 90% specificity in recognizing fibrous cap alterations (Saam et al., 2009). Although MRI appears promising compared to other imaging modalities, it has considerable drawbacks preventing it from being easily introduced into clinical practice, namely: the high-cost, contraindications, limited availability, lengthy examination times, and lack of designated coils, thus making it unsuitable for screening purposes. In addition, MRI can be susceptible to poor image quality, mainly due to patient motion, which can reach >30% of examinations (Arora & Soares, 2008).

Not surprisingly, in terms of operational cost and accessibility, US is the leading diagnostic imaging modalities for CAS imaging (Chien et al., 2013). This assumption was validated by applying the enhanced US imaging method and yielding the highest correlation rate, sensitivity, and specificity over CT and MRI, in identifying specific morphological features in a greater proportion of categorical components by implementing every day imaging instruments (US 88-100%, CT 83-97%, MRI 67-95% accuracy) (Kingstone et al., 2014).\textsuperscript{161}

Although CT is known to be highly sensitive in detecting carotid atheromatous surface alterations (Saba et al., 2009) and MRI with respect to internal alterations (Chien et al., 2013), enhanced sonographic imaging and analysis can accurately identify surface and internal textural focal or lucent changes, validating its accuracy over MRI and CT (Kingstone et al., 2014). This ratifies that an enhanced US, clinical imaging approach has sufficient precision to identify critical vulnerable markers in plaque, susceptible in generating a CVA; further, ultrasound is optimal to radiating CT, and outdoes MRI in identifying potential risk indicators.

While US has been shown to accurately image specific plaque morphology features, there are two important considerations. Firstly, US diagnostic integrity relies on a high degree of technical expertise and a device dependent technique, which may result in complex image acquisitions, significant fluctuations in inter-operator variability, reproduction quality and inter-observation unevenness (Thomson, Woods, Iannos & Sage, 2001). Acknowledging that the quality and consistency of examination is an important aspect in assessing the potential for imaging technique as the diagnostic performance, quality control and operator dependency has a significant impact on many areas of clinical application. By employing a reliable,

---

collective diagnostic imaging technique, with the use of 2D and 3D US imaging, superior inter-observation reproducibility is acquired with excellent inter-rater variability (Kingstone et al., 2014). While 2D is reliable in correctly identifying the types of plaque pathology, 3D imaging quantifies plaque morphology further, increasing proper recognition of pathological types, especially in surface alterations and/or ulcerations (Heliopoulos, Vadikolia, Pironidou & Mitsaia, 2009) and irrespective of the operator’s technical application or experience for characterization (Kingstone et al., 2014). Rendered 3D imaging and volumetric slices selection compliments high-resolution 2D imaging, whilst reducing inter-rater variability (Kingstone et al., 2014). Secondly, the most important component of carotid US echomorphology assessment is adequate visual reporting, analysis, and documentation of internal plaque characteristics and surface details.

Current guidelines vary between professional bodies in different countries and clinical practice worldwide, and although several classifications (Geroulakos et al., 1994; Gray-Wael, Grahann, Burnett, Byrne & Lusby, 1988; Reilly, 2007; Szatajzel, 2005) have previously been reported, they generally direct

single B-mode imaging analysis or apply complex, commercialized software to extract specific plaque features. There are currently no established recommendations or pragmatic guidelines with respect to the most appropriate strategy for US imaging of carotid plaque echomorphology. A standardized, central imaging protocol for carotid plaque imaging produces a highly reliable US analysis visual interpretation data for morphological assessment, with excellent inter-observation (Kingstone et al. 2013166; 2014167).

To enhance quality assurance and globalize plaque categorical reporting mechanism by way of delivering substantial agreement among reporting neuroradiologists in the assessment of subtypes, the implementation of a classification system, according to risk improves the accuracy of plaque characterization assessment and reporting (Kingstone et al., 2013168; 2014169).

This developed US imaging algorithm based on multiple parameters and classification trees enables proper plaque characterization interpretation and

displays potential for assessment of plaque vulnerability risks (Kingstone et al., 2014).

4.2 LIMITATIONS

Our research should be interpreted in the context of the following limitations:

We acknowledge a fragment our investigation were performed on phantom specimens, in association with human trail series. One objection that could be moved to our investigation, is the basis of our phantom pseudo-soft-plaque, which does not accurately represent complex atheromas. A second objection is the lack of clinical reference standard. Multiple factors are involved in the plaque morphological 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.

Results from our in vivo investigation represent pilot findings, all of which require further development. This would especially be of interest in the applicability for patients with lower grade stenosis or earlier plaque formation.

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 study analysis was reduced. This is not feasible in everyday, clinical applications, and would be of interest to evaluate this as a separate trial. Lastly, we acknowledge that certain findings may be related to the inherent nature of the CT and MRI scanner technology or protocol used, directly having an effect on the data, especially since we applied routine neurological parameters for imaging, not taking in that special coils or sequences could optimize imaging features in both modalities, enabling proper identifying of internal hemorrhage/cores or small surface ulcerations.

4.3 RECOMMENDATIONS

Plaque imaging is required as a standard for risk prediction as multiple factors are involved in the plaque morphological pathophysiology mechanism for patients at increased risk. The absence of a global unanimous imaging technique or guidelines, supported by the validation of US as an accurate, cost effective, and first-line acquisition imaging method to detect morphological markers, the body of work included in this exegesis and the supportive analyses based on empirical evidence within the associated portfolio provide the opportunity to make the following recommendations:

1. Include all sonographic features of plaque echomorphology, using a myriad technique to increase risk stratification.

2. Include 2D and 3D US as a collective imaging technique.

3. Direct US as the first-line, lead investigative, noninvasive imaging technique for CAS imaging.

4. Employ a rigid, standardized clinical US imaging protocol.
5. Strict measure in US imaging standard reporting and classification criteria must be used to aid in the interpretation and quantitative grading of CAS plaques.

The research exhibited in this exegesis and portfolio demonstrate that our enhanced US imaging’s methodological application has a high correlation rate, sensitivity, and specificity that is optimal to CT and MRI, in the identification of early vulnerable markers (Kingstone et al., 2014\(^\text{171}\)). 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 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 plaque to correctly define these points. The proposal of using contralateral carotid artery as controls may be use of age-matched category in lower-graded disease. This method may develop an appreciation of who among the population is most likely at risk to have future cerebrovascular events. A separate subset of data should be included to evaluate high-resolution 2D and volumetric 3D US independently, in vivo. Although the information derived from our research is currently clinically applicable, it should be critically

compared and validated with other diagnostic techniques in human atheromas, suggestive of a long-term trial.

4.4 CONCLUSION

Ultrasound remains the first line of defense in carotid arterial imaging due to its accessibility and low cost. Although the standard tool for US is currently directed at luminal grading, research and clinical practice have shown that it alone is a poor predictor of stroke and any atheromatous plaque could be vulnerable to rupture. We observed that proper identification of plaque characterization with the use of our enhanced US method provides a reproducible and reliable diagnostic method for assessing these specific morphological features. This enhanced method has been demonstrated optimal in the quantification and assessment of vulnerable features of plaques over current CT and MRI imaging methods. Our results could fill the void created by an ongoing paradigm shift by assessing beyond the lumen, in hopes of providing additional clinical information of the vulnerable atheroma; however, our findings suggest that the information derived should be critically compared and validated in larger prospective human trials and with other diagnostic techniques to fully assess the potential of this imaging approach.
REFERENCES


