MAPPING SPATIAL AND TEMPORAL CHANGES IN CAROTIDATHEROSCLEROSIS FROM THREE-DIMENSIONAL ULTRASOUND IMAGES

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Abstract—This study was designed to evaluate changes in carotid atherosclerosis using plaque and wall thickness maps derived from three-dimensional ultrasound (3DUS) images. Five subjects with carotid stenosis were scanned at baseline and 3 mo as part of a placebo-controlled intensive statin treatment study and three subjects with moderate atherosclerosis were scanned at baseline and again within 14 ± 2 d. 3DUS-derived vessel wall volume (VWV) was measured using manual segmentation to provide segmentation contours that were used to generate scan and rescan carotid atherosclerosis thickness maps and thickness difference maps. There was no significant difference in VWV between scan and rescan for the three subjects scanned twice in 2 wk or the single subject treated with placebo. There was a significant difference between scan and rescan VWV for carotid stenosis subjects treated with atorvastatin (p < 0.001). Carotid atherosclerosis thickness difference maps showed visual qualitative evidence of thickness changes in vessel wall and plaque thickness in the common carotid artery for all statin-treated subjects and no change in a placebo-treated subject and subjects scanned twice in 2 wk. Carotid atherosclerosis thickness difference maps generated from 3DUS images provide evidence of vessel wall and plaque thickness changes for all subjects assessed. (E-mail: gep@imaging.robarts.ca) © 2007 World Federation for Ultrasound in Medicine & Biology.

Key Words: Atherosclerosis, 3D Ultrasound, Thickness maps, Vessel wall volume, Carotid plaque, Stenosis.

INTRODUCTION

Despite our improved understanding of the mechanisms of atherosclerosis, it is still difficult to evaluate and confirm the positive clinical effects and outcomes associated with lipid lowering therapies by visually inspecting the coronary and carotid vessels (Brown et al. 1990, 2001). The discordance between clinical and angiographic findings (Tardif 2000) has been attributed to a number of factors, including the fact that in some cases, arterial wall and plaque changes cannot be detected using angiography due to the limitations imposed by the representation of three-dimensional (3D) vessels with single or even multiple two-dimensional (2D) images. In addition, it has been postulated that specific changes resulting from lipid lowering and other therapies do not result in wall or bulk plaque changes that are readily measured using standard clinical imaging equipment. In other words, such potential plaque or wall-specific changes resulting from lipid lowering therapy comprise atherosclerotic phenotypes that may not have been, as of yet, visualized, identified or quantified.

While early evidence for atherosclerosis regression came from animal (Armstrong et al. 1970; Fritz et al. 1976; Vesselinovitch et al. 1974; Wagner and Clarkson 1977) and postmortem studies (Crawford et al. 1977), regression has been difficult to prove in vivo in clinical studies (Newby 2006). Recent results from carotid ultrasound (Ashrafian et al. 2007; Mercuri et al. 1996; Nolting et al. 2003; Smilde et al. 2001; Taylor et al. 2002), intravascular ultrasound (Jensen et al. 2004; Nissen et al. 2003, 2004, 2006; Takagi et al. 1997) and magnetic
resonance imaging (MRI) studies (Corti et al. 2002; Fayad and Fuster 2001; Lima et al. 2004; Saam et al. 2006; Yuan et al. 2006; Corti 2006) suggest that bulk plaque regression can be measured in one, two and three dimensions. For example, statin therapy has been shown to reduce inflammation and the lipid content of preexisting lesions in patients (Crisby et al. 2001) and promote increased collagen synthesis and decreased matrix metalloproteinase (MMP) activity in rabbits (Aikawa et al. 1998). It has also been shown that lipid lowering was strongly correlated with plaque regression and vascular remodeling (Lima et al. 2004) and significant regression in plaque volume following 6 mo of statin treatment (Lima et al. 2004). Significant changes in plaque volume after 3 mo of treatment have also been reported using three-dimensional ultrasound (3DUS) in the study of subjects with significantly advanced atherosclerosis (Ainsworth et al. 2005). Despite the indication provided by this previous work that atherosclerotic plaque may change over relatively short periods of time, there has been no evidence provided for spatial or topological plaque changes, challenging us to explain the mechanisms and dynamics of potential plaque regression processes.

The analysis of 3D images of atherosclerosis-mediated plaque and vessel wall changes has the potential to provide both quantitative and dynamic measures of the volumetric and spatial changes. To directly examine and evaluate potential spatial changes coincident with bulk volumetric changes in atherosclerosis, we developed a method that analyzes successive carotid artery wall and lumen segmentation outlines from 3D images and displays these as spatial maps of vessel thickness. We provide our first qualitative results of this approach utilizing vessel wall and lumen segmentations from scan and rescan 3DUS images of: (1) five subjects with carotid stenosis treated in a placebo-controlled intensive statin study for 3 mo and, (2) three subjects with moderate atherosclerosis scanned twice within a 2-wk period who were undergoing standard lipid lowering therapy for moderate carotid atherosclerosis. The carotid atherosclerosis thickness and thickness difference maps presented here provide qualitative evidence of plaque and carotid vessel wall changes that occur over short periods of time in subjects.

MATERIALS AND METHODS

Study subjects

Eight subjects were evaluated. Three subjects with carotid plaque area greater than 0.5 cm² were scanned twice within 14 ± 2 d and five subjects with carotid stenosis (>60% stenosis defined by carotid Doppler flow velocities) were assessed as part of their enrollment in a randomized placebo-controlled study of intensive statin treatment as previously described (Ainsworth et al. 2005). All subjects were recruited from The Premature Atherosclerosis Clinic and The Stroke Prevention Clinic at University Hospital (London Health Sciences Centre, London, Canada) and provided written informed consent to the study protocol approved by The University of Western Ontario Standing Board of Human Research Ethics. The study was performed according to local institutional guidelines and in accordance with local guidelines for subject privacy and confidentiality. The eight subjects were evaluated in two subgroups as follows: (1) three subjects with carotid plaque area greater than 0.5 cm² (moderate atherosclerosis subjects) were scanned twice in 2 wk to assess the variability of the ultrasound measurements due to image variability, scanning parameter changes, sonographer changes and observer variability and, (2) five subjects with carotid stenosis (carotid stenosis subjects) were scanned twice, once at baseline and once after 12 wk of statin or placebo therapy with three subjects having received 80 mg atorvastatin daily and two subjects receiving placebo treatment.

Three-dimensional ultrasound image acquisition and analysis

3DUS images were acquired by translating the ultrasound transducer (L12–5, 50 mm, Philips, Bothel, WA, USA) along the neck of the subject an approximate distance of 4.0 cm while video frames from an US machine (ATL HDI 5000, Philips, Bothel, WA, USA) were digitized and saved to a computer workstation. The orientation and speed of the transducer were adjusted so that the resulting transverse 2D images were parallel to each other with a spatial interval of 0.15 mm. The acquired 2D images were reconstructed immediately into a 3DUS volume and displayed using 3D Quantify Software as previously described (Landry and Fenster 2002).

Manual planimetry was used in the analysis of 3DUS images and vessel wall volume (VWV) measurements were quantified using 3D Quantify previously developed in our laboratory and described (Landry and Fenster 2002). To reduce inter-scan measurement variability, the carotid bifurcation was used as point of reference (Ainsworth et al. 2005) and was first identified and marked within the ultrasound volume so that all measurements could be initialized on the same 2D image slice. A 30 mm axis was placed parallel to the longitudinal axis of the common carotid artery and centred on the coordinates of the carotid bifurcation with segmentation through the image volume using an inter-slice distance (ISD) of 1 mm to minimize measurement variability (Landry et al. 2004). The common carotid artery was segmented proximally a distance of 15 mm and the
internal and external carotid branches were each segmented distally a distance of 10 mm from the bifurcation. The average area enclosed by two sequential contours was multiplied by the ISD to give the volume between adjacent slices and the inter-slice volumes were summed to determine the total volume of each contour. Vessel wall volume was calculated by subtracting the volume enclosed by the lumen contours from the volume enclosed by the vessel contours.

**Carotid atherosclerosis thickness map generation**

As previously described (Chiu et al. 2006a, 2006b), VWV segmentation allows for the generation of plaque thickness maps. Briefly, as shown in Fig. 1, mean vessel wall and lumen surfaces (shown in Fig. 1A) are reconstructed from the five repeated segmentations of each carotid image (Egger et al. 2007). The 3D carotid thickness map shown in Fig. 1B is generated by establishing corresponding points on the vessel wall and lumen surfaces with the resultant thickness of the vessel wall and plaque considered to be the distance between each pair of corresponding points (Chiu et al. 2006a). To map the 3D wall and plaque thickness maps shown in Fig. 1B onto a 2D plane (Chiu et al. 2006b), the 3D carotid map is bisected (as shown in Fig. 1C) to generate a flattened 2D thickness map (Fig. 1D). The flattened thickness map shown in Fig. 1D shows the spatial distribution of wall and plaque thickness within the artery and provides a continuous wall and plaque surface (Chiu et al. 2006a, 2006b) to facilitate the visualization and qualitative assessment of carotid artery wall and plaque thickness distribution.

In addition to creating thickness maps, thickness difference maps may also be generated by subtracting the thickness map at baseline (scan) from the thickness map at re-scan. The resultant thickness difference map provides a continuous surface in which to examine location-specific differences in wall and plaque thickness (Chiu et al. 2006a; Chiu et al. 2006b).

**Statistical methods**

SPSS version 14.0 (SPSS Inc., Chicago, IL, USA) was used to determine intra-class correlation coefficients (ICC) for repeated measurements of VWV. The standard deviations (SD) of VWV were divided by the corresponding means to calculate scan and re-scan coefficients of variation (CV). Inter-scan CV was calculated

<table>
<thead>
<tr>
<th>Table 1. Subject demographic baseline characteristics</th>
<th>Moderate atherosclerosis subjects</th>
<th>Carotid stenosis subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n)</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Male sex (n)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Diabetes (n)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Smoking (n)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Treated hypertension (n)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Treated hyperlipidemia (n)</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Age ± SD (Y)</td>
<td>69 ± 12</td>
<td>71 ± 7</td>
</tr>
<tr>
<td>Weight ± SD (kg)</td>
<td>73 ± 9</td>
<td>ND</td>
</tr>
<tr>
<td>Intima media thickness (mm)</td>
<td>0.82 ± 0.03</td>
<td>ND</td>
</tr>
<tr>
<td>Total plaque area (mm²)</td>
<td>ND</td>
<td>3.38 ± 1.00</td>
</tr>
<tr>
<td>3DUS total plaque volume (mm³)</td>
<td>850 ± 80</td>
<td>490 ± 320</td>
</tr>
<tr>
<td>3DUS vessel wall volume (mm³)</td>
<td>620 ± 30</td>
<td>1030 ± 310</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>ND</td>
<td>4.39 ± 0.65</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>ND</td>
<td>1.15 ± 0.20</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>ND</td>
<td>2.60 ± 0.71</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>ND</td>
<td>1.25 ± 0.25</td>
</tr>
</tbody>
</table>

TPV is expressed as the sum of both left and right carotids ± standard deviation. IMT is expressed as the mean of the individual left and right carotids ± standard deviation. 3DUS VWV is expressed as the mean of one carotid side (left or right) measurement.
using the SD of the difference between scan and re-scan measurements and the corresponding inter-scan mean (Egger et al. 2007).

RESULTS

Table 1 shows the baseline demographic characteristics of the eight subjects analyzed for vessel wall volume (VWV). Mean age and baseline plaque measurements were significantly higher in the carotid stenosis subject subgroup.

Vessel wall and lumen segmentation results for a cross-sectional slice of a number of 3DUS carotid images are shown (Fig. 2) for a single carotid stenosis subject treated with atorvastatin at scan and 12-wk...
rescan (Fig. 2A), a single carotid stenosis subject treated with placebo at scan and 12-wk rescan (Fig. 2B) as well as scan and rescan images for a moderate atherosclerosis subject who was scanned twice in 2 wk (Fig. 2C).

Absolute values of VWV for all eight subjects at scan and rescan as well as the change in VWV measured over the scan-rescan period are provided in Table 2. Intra-observer COV and the intraclass correlation coefficient (ICC) are also provided based on the five repeated measures of VWV (Egger et al. 2007). There was no significant difference between scan and rescan VWV for all three moderate atherosclerosis subjects scanned twice in 2 wk nor for the two carotid stenosis subjects treated with placebo. There was a significant difference between scan and rescan VWV for all three carotid stenosis subjects treated with atorvastatin (for each subject \( p < 0.001 \)) and for the subject subgroup, \( p < 0.001 \).

Table 2. Vessel wall volume measurements at scan and rescan

<table>
<thead>
<tr>
<th>Subject</th>
<th>Baseline scan</th>
<th>Rescan</th>
<th>Difference (rescan-scan)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VWV (mm(^3) ± SD)</td>
<td>CV %</td>
<td>VWV (mm(^3) ± SD)</td>
</tr>
<tr>
<td>P1</td>
<td>940 ± 30</td>
<td>3.4</td>
<td>880 ± 40</td>
</tr>
<tr>
<td>P2</td>
<td>890 ± 30</td>
<td>3.5</td>
<td>860 ± 40</td>
</tr>
<tr>
<td>Mean P</td>
<td>910 ± 30</td>
<td>3.4</td>
<td>870 ± 40</td>
</tr>
<tr>
<td>A1</td>
<td>990 ± 40</td>
<td>4.5</td>
<td>710 ± 50</td>
</tr>
<tr>
<td>A2</td>
<td>770 ± 40</td>
<td>5.0</td>
<td>670 ± 20</td>
</tr>
<tr>
<td>A3</td>
<td>1570 ± 90</td>
<td>6.0</td>
<td>1120 ± 40</td>
</tr>
<tr>
<td>Mean A</td>
<td>1110 ± 60</td>
<td>5.7</td>
<td>840 ± 40</td>
</tr>
</tbody>
</table>

VWV measurements expressed as a mean of five measurement repetitions ± standard deviation.

* Significant difference between rescan and scan volumes.

Scan and rescan flattened vessel wall plus plaque thickness maps are shown for a single carotid stenosis subject treated with atorvastatin at scan and 12-wk rescan (Fig. 3A), a single carotid stenosis subject treated with placebo at scan and 12-wk rescan (Fig. 3B), as well as scan and rescan images for a moderate atherosclerosis subject (Fig. 3C) who was scanned twice in 2 wk. Plaque and wall thickness is represented in color as shown by thickness color gradients alongside each set of scan and rescan maps.

Scan-rescan topology difference maps are provided in Fig. 4 for six subjects as follows: (1) two moderate atherosclerosis subjects (Fig. 4A and B), and (2) three carotid atherosclerosis subjects treated with atorvastatin (Fig. 4D and F) and (3) a single carotid atherosclerosis subject treated with placebo (Fig. 4C). These six carotid thickness difference maps allow for a qualitative examination of plaque and wall changes in these subjects over the different scan-rescan periods. Plaque and wall thickness differences between scan and rescan are color-coded with the color scale provided alongside all six topology difference maps and the color scale is normalized according to the range of thickness changes observed for statin-treated subject A1 (shown in Fig. 4E and Table 2 with a change in VWV at rescan of 280 ± 60 mm\(^3\) VWV in 12 wk). Carotid topology difference maps for a single carotid stenosis subject (P1) scanned after 12 wk of treatment with placebo and for two moderate atherosclerosis subjects scanned twice within 2 wk indicate no change (green = 0 mm thickness difference). However, thickness difference maps for all three carotid stenosis subjects treated with atorvastatin do show plaque and wall thickness changes in the common carotid artery with plaque and wall thickness changes ranging from -4.5 mm to +2.5 mm.

**DISCUSSION**

A central challenge in our understanding of atherosclerosis progression and regression is an appreciation of how specific changes in plasma lipid levels alter macroscopic atherosclerotic lesions in vivo. Recent advances in understanding the vascular biology of atherosclerosis and the development of reproducible 3D imaging techniques that afford longitudinal determinations of plaque volume and morphology provide us with an opportunity to begin to understand the temporal and spatial dynamics of both atherosclerosis progression and regression. Up until now, significant lesion regression has been difficult to demonstrate. Although the lowering of LDL cholesterol levels reduces the incidence of vascular outcomes, these clinical benefits are rarely accompanied by...
reduced luminal stenosis (Brown et al. 2001). One hypothesis that may account for this discrepancy is the stabilization of vulnerable plaques through statin therapy (Dansky and Fisher 1999). Adaptive vascular remodeling and outward expansion of the artery wall allows for the growth and development of lesions without encroaching upon the lumen, making it difficult to properly characterize disease through angiographic measurements of luminal stenosis (Genest and Pedersen 2003). Our current understanding is that plaque regression may occur through a reduction in the lipid, connective tissue or smooth muscle components of a lesion (Brown 1993). Regression may also be observed as a reduction in luminal stenosis (Brown 1993) but it is important to note that apparent plaque regression may occur through other processes as well. For example, occlusive thrombi may experience lysis or fissuring, disrupted plaques may undergo favorable remodeling and adaptive enlargement of the artery may result in decreased luminal stenosis despite there being no change in the size of the lesion (Brown 1993). Some have also postulated that vascular changes and remodeling are due to the artery wall shrinking (Tardif et al. 2006).

To assess the spatial and temporal changes in carotid atherosclerosis, we devised a method to analyze successive segmentation contours of carotid lumen and vessel walls from 3DUS images and that generates carotid vessel wall and plaque thickness maps as well as thickness difference maps, displaying changes in plaque and vessel wall thickness throughout the carotid artery and over time. We applied this approach to carotid stenosis subjects undergoing intensive statin or placebo therapy over a 12-wk treatment period as well as subjects with moderate atherosclerosis scanned over a 2-wk period to provide qualitative evidence of the resultant spatio-temporal changes in atherosclerotic lesions in the carotid artery. Here we provide an evaluation of this method and show: (1) significant VWV changes in three subjects with carotid stenosis measured over a 12-wk scan-rescan period from 3DUS images, (2) no VWV change in three subjects with moderate atherosclerosis measured over a 2-wk period from 3DUS images, or two

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**Fig. 3. Carotid vessel wall and plaque topology maps at scan and rescan.** (A) Carotid stenosis subject baseline scan (i) and 12-wk rescan (ii) treated with atorvastatin. (B) Carotid stenosis subject baseline scan (i) and 12-wk rescan (ii) treated with placebo. (C) Moderate atherosclerosis subject scan baseline scan (i) and 2-wk rescan (ii).
subjects with carotid stenosis treated with placebo over 3 mo, (3) 2D carotid topology maps at scan and rescan showing plaque and vessel wall thickness measurements in two-dimensions and, (4) 2D carotid topology difference maps that qualitatively display plaque and carotid vessel wall thickness differences over two different scan-rescan periods.

VWV baseline scan and rescan measurements for all subjects showed no change for the two placebo treated carotid stenosis subjects, and no change for the three subjects with moderate atherosclerosis scanned twice in 2 wk. Measurements were performed five times with COV and ICC indicating excellent intra-observer variability and, which allows for a quantitative assessment of the differences measured between scan and rescan. For the three carotid stenosis subjects assessed, there was a significant decrease in VWV observed \( (p < 0.001) \) after 12-wk treatment with atorvastatin, which is similar to previously reported results for TPV (Ainsworth et al. 2005) in these subjects. In tandem with the assessment of bulk volumetric changes, we utilized individual 3DUS segmentation boundaries to generate quantitative 2D thickness maps (Fig. 3) and from the subtraction of scan from rescan images, 2D thickness difference maps (Fig. 4). Such maps provide a 2D view of the location-specific wall and plaque thickness changes that can be measured from noninvasive 3DUS or any 3D image where successive segmentation contours can be measured (such as from magnetic resonance imaging or intravascular ultrasound). For subjects treated with atorvastatin, much of the bulk plaque and wall thickness changes were observed within the common carotid artery and for the other two subjects scanned twice in 2 wk or for a single subject treated with placebo for 12 wk, no such changes were observed. These results show qualitative evidence of spatial and temporal plaque changes in statin-treated subjects with the dark blue patches indicating decreased thickness and bright red spots indicating areas of increased thickness. The apparent simultaneous decrease in plaque and wall thickness in the common carotid with more modest increases in thickness adjacent to regions of large thickness decreases may be related to vascular wall remodeling, adjacent plaque remodeling or perhaps due to registration errors in the proximity of these large thickness changes that occurred over a relatively short period of time (12 wk). We continue to assess carotid stenosis subject disease progression with statin treatment to identify any trends in the types of changes observed and correlations between plaque type and plaque responses.

Limitations of this study include the small group of subjects in which we piloted this approach and the specific finding described here for eight subjects may not show broader clinical relevance in different types of subjects or studies. To address this specific limitation, we are currently undertaking the large scale analysis of a larger cohort of patients with moderate atherosclerosis as well as all subjects previously enrolled in a placebo-controlled statin treatment study to establish a more quantitative understanding of vessel wall and plaque changes over time. In addition this will provide both more and varied data to assess and pilot different analysis approaches of the resultant difference maps. The current approach involves manual VWV segmentation and, although robust with good reproducibility, this is laborious, time-consuming and inter-observer variability.
is too high to allow for the use of multiple observers, which limits the translation of the method to large scale cohort studies and clinical trials. We propose that a semiautomated 3DUS segmentation approach currently under development may adequately address these shortcomings. Our study is also limited by the fact that we were only able to assess segmentation contours from 3DUS images. One of the major advantages of our approach is that it can potentially be used to assess MR and intravascular ultrasound images (IVUS). A prospective study where 3DUS, IVUS and MRI images are acquired and analyzed would provide an important data set to validate this approach.

During progressive atherosclerotic disease, it is believed that adaptive vascular remodeling and outward expansion of the artery wall occur followed by further lesion development with calcification (Glagov et al. 1987). Until recently, regression of carotid atherosclerosis was considered to be theoretically possible but the mechanisms by which plaque regression occurred however were not and, still, are not well understood (Newby 2006). A number of studies using MRI and IVUS have identified both an attenuation of plaque progression and bulk plaque regression in response to statin therapy (Corti et al. 2001; Schartl et al. 2004; Nissen et al. 2003; Jensen et al. 2004; Tardif et al. 2003; Von Birgelen et al. 2004). Nevertheless, the absolute change measured in most studies does not reflect the magnitude of the clinical outcome and risk improvement observed. This apparent discordance (Tardif 2000) may be due to plaque responses that are not directly related to volumetric lesion changes. Arterial wall contraction in response to plaque regression, plaque compositional changes, endothelial changes and lesion stabilization may all play a role in the response of the carotid artery to lipid lowering therapy (Klein 2007). The method evaluated in this study may provide a means of tracking both vessel wall and atherosclerotic plaque lesions over time, which could allow for a better visualization and understanding of the spatial and temporal changes occurring due to disease progression and concomitant with novel treatments. Moreover, the method described may allow for the tracking of different plaque types and their response to therapy which should provide a more precise understanding of the links between treatment, time and the macroscopic topographical changes observed in plaque progression and regression.

**SUMMARY**

We report VWV measurements from 3DUS images as well as scan and rescan carotid atherosclerosis thickness maps and thickness difference maps for subjects with carotid stenosis and moderate atherosclerosis. Scan-rescan thickness difference maps showed visual qualitative evidence of changes in vessel wall and plaque thickness in the common carotid artery for statin-treated subjects and no change in a placebo-treated subject and subjects scanned twice in 2 wk.

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