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Concise biomarker for spatial–temporal change in three-dimensional ultrasound measurement of carotid vessel wall and plaque thickness based on a graph-based random walk framework: Towards sensitive evaluation of response to therapy

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ABSTRACT

Rapid progression in total plaque area and volume measured from ultrasound images has been shown to be associated with an elevated risk of cardiovascular events. Since atherosclerosis is focal and predominantly occurring at the bifurcation, biomarkers that are able to quantify the spatial distribution of vessel-wall-plus-plaque thickness (*VWT*) change may allow for more sensitive detection of treatment effect. The goal of this paper is to develop simple and sensitive biomarkers to quantify the responsiveness to therapies based on the spatial distribution of *VWT-Change* on the entire 2D carotid standardized map previously described. Point-wise *VWT-Changes* computed for each patient were reordered lexicographically to a high-dimensional data node in a graph. A graph-based random walk framework was applied with the novel Weighted Cosine (WCos) similarity function introduced, which was tailored for quantification of responsiveness to therapy. The converging probability of each data node to the *VWT* regression template in the random walk process served as a scalar descriptor for *VWT* responsiveness to treatment. The WCos-based biomarker was 14 times more sensitive than the mean *VWT-Change* in discriminating responsive and unresponsive subjects based on the *p*-values obtained in *T*-tests. The proposed framework was extended to quantify where *VWT-Change* occurred by including multiple *VWT-Change* distribution templates representing focal changes at different regions. Experimental results show that the framework was effective in classifying carotid arteries with focal *VWT-Change* at different locations and may facilitate future investigations to correlate risk of cardiovascular events with the location where focal *VWT-Change* occurs.

1. Introduction

Stroke is among the leading causes of death and disability worldwide, with a prevalence of 33 millions and 16.9 millions suffering a stroke in 2013 [1]. Over two-thirds of stroke deaths occurred in the developing countries [2]. China, as the most populous developing country, has an annual stroke mortality of 1.6 million [3], and the mortality rate is more than 7 times higher than in the United States [4]. As atherosclerosis is a complex disease that involves the interaction of many factors, such as genetic factors, cells of the arterial wall, blood chemistry and hemodynamics, rapid progression may occur despite intensive treatment of traditional risk factors [5]. The progression of plaque despite treatment are associated with higher stroke risk [6–8]. Therefore, these subjects should be identified early so that more intensive treatment strategies could be administered sooner. Objective identification of non-responders to treatments requires the development of sensitive quantitative biomarkers of carotid atherosclerosis.

Although ultrasound measurement of carotid intima-media thickness (IMT) (Fig. 1a) measured from 2D B-mode ultrasound has been widely used in clinical studies [9,10] and has been shown to correlate with the risk of cardiovascular events [11], the rate of change of IMT is typically small (0.01–0.03 mm/year) and large sample and long duration of observation are required to identify statistically significant changes [12].

Direct measurements of plaque have been developed to improve the sensitivity for detecting therapy response and stratify vascular risk. Patients with progression in total plaque area (TPA) (Fig. 1b) [6] were

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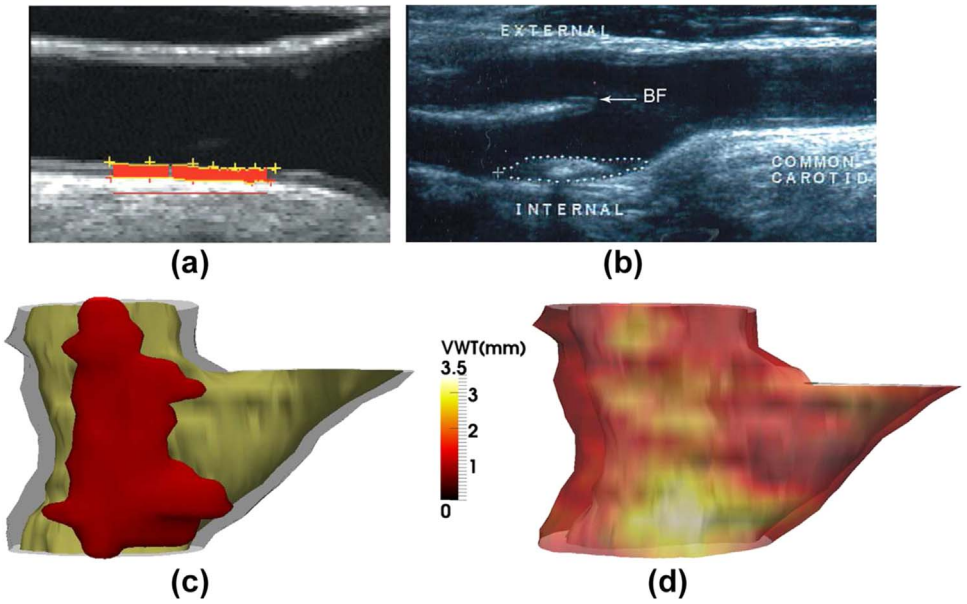

Fig. 1. Existing biomarkers of carotid atherosclerosis. (a) Intima-media thickness (IMT) measurement from a longitudinal B-mode ultrasound image. (b) Total plaque area (TPA) measurement from a longitudinal B-mode ultrasound image with plaque outlined by the dotted contour and bifurcation (BF) identified by an arrow. (c) Total plaque volume (TPV) measurement was made for the plaque surface (red) reconstructed from plaque segmentation on transverse images resliced from a 3D ultrasound image. Vessel wall volume (VWV) measurement was obtained by subtracting the volume of the semi-transparent outer wall surface from the volume of the lumen surface (yellow). (d) Vessel-wall-plus-plaque thickness (VWT) measurements were made on a point-by-point basis, color-coded and superimposed on the outer wall surface. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

found to have higher risk of vascular events compared to those with no change and regression in TPA. 2D B-mode ultrasound was used to quantify plaque textural features, which were able to discriminate symptomatic and asymptomatic patients [13,14]. However, 2D ultrasound images were difficult to reproduce due to the requirement to localize a 2D image plane in each scanning; for this reason, 2D ultrasound was not optimal in monitoring plaque changes in a longitudinal study. 3D carotid ultrasound has been developed to address this issue [15,16]. Wannarong et al. [8] reported that progression in total plaque volume (TPV) measured from 3D ultrasound (Fig. 1c) was more able to predict stroke than TPA. Egger et al. [17] introduced the use of vessel wall volume (VWV) to assess carotid atherosclerosis (Fig. 1c). VWV measurements incorporate both vessel wall and plaque without the need of isolating plaques from the vessel wall and were associated with higher intra-observer and inter-scan reproducibility than TPV. Although these biomarkers provide rich information regarding progression or regression on global plaque and vessel wall dimensions, the localized nature of carotid atherosclerosis suggests that biomarkers considering local change in plaque or vessel wall thickness may be more sensitive, thereby allowing more proof-of-principle studies to be conducted over a shorter duration that involves fewer subjects. To quantify the 3D distribution of vessel wall thickness change, our group measured vessel-wall-plus-plaque-thickness (*VWT*) (Fig. 1d) and *VWT* difference between baseline and follow-up scanning sessions [18] on a point-by-point basis and generated a 3D map that allows for the visualization and quantification of the *VWT-Change* distribution (Fig. 2c).

However, the shape and size of 3D *VWT-Change* maps constructed for different arteries are highly subject-specific, precluding quantitative comparisons between *VWT-Change* distributions of different arteries. We developed a technique to flatten 3D *VWT-Change* maps of different arteries onto a rectangular 2D standardized map [19] (Fig. 2d) to adjust for the inter-subject variability in carotid geometry. Since the *VWT-Change* distributions for all subjects could be mapped to a standardized 2D coordinate frame, the average *VWT-Change* maps for the atorvastatin and the placebo groups could be generated, thereby allowing group-wise comparison of *VWT-Change* distributions in these two treatment arms.

Although the 2D standardized *VWT-Change* maps adjust for the variability in arterial geometry and allow for quantitative comparison of local *VWT-Change* distributions, clinical conclusions are difficult to be drawn based on the complex distribution represented by thousands of *VWT-Change* data points per artery. In Chiu et al. [19], a biomarker was developed to quantify the effect of the atorvastatin treatment. The biomarker was developed based on a feature selection algorithm and was effective in identifying regions of interest (ROI) where the atorvastatin subjects experienced regression and the placebo subject experienced progression. Subject-based average *VWT-Change* computed over the ROI was more sensitive than that computed over the whole 2D map in identifying the effect of atorvastatin. However, the biomarker based on selected regions described above is less capable of identifying subjects with rapid focal progression despite treatment. In regions where atorvastatin subjects experienced rapid progression, the placebo subjects may also progress by various degrees. The difference in *VWT-Change* at these regions was not strong enough for them to be selected and included in the computation of the region-based biomarker. Moreover, the feature selection algorithm is a forward sequential searching algorithm that adds features one at a time without an objectively defined stopping criterion. To address this issue, we chose the size of the ROI selected by the algorithm to be the one that produces an average *VWT-Change* that discriminated the atorvastatin and placebo groups with greatest sensitivity within the searching range of 10–50% of the area of the entire 2D standardized map [19]. The rationale in choosing these upper and lower thresholds was to select regions that is large enough to detect “representative” patterns, while small enough so that we were still focusing on “local” instead of “global” patterns. Admittedly, the line between local and global patterns was hard to draw and the choices of these thresholds were based on empirical observation of the data. For these reasons, instead of considering selected ROI exclusively, a better biomarker would involve the whole distribution but be able to emphasize regional progression or regression. As subjects with rapid progression are exposed to higher stroke risk [6–8], there is a requirement of a metric that can identify subjects with rapid progression in an early stage so

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