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Accurate cloud-based smart IMT measurement, its validation and stroke risk stratification in carotid ultrasound: A web-based point-of-care tool for multicenter clinical trial

Luca Saba [a], Sumit K. Banchhor [b], Harman S. Suri [k], Narendra D. Londhe [b], Tadashi Araki [c], Nobutaka Ikeda [d], Klaudija Viskovic [e], Shoaib Shafique [f], John R. Laird [g], Ajay Gupta [h], Andrew Nicolaides [i,j], Jasjit S. Suri [k,l,m,*]

[a] Department of Radiology, University of Cagliari, Italy
[b] Department of Electrical Engineering, NIT Raipur, Chhattisgarh, India
[c] Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, Tokyo, Japan
[d] Cardiovascular Medicine, National Center for Global Health and Medicine, Tokyo, Japan
[e] Department of Radiology and Ultrasound, Zagreb, Croatia
[f] CorVasc Vascular Laboratory, 8433 Harcourt Rd #100, Indianapolis, IN, USA
[g] UC Davis Vascular Centre, University of California, Davis, CA, USA
[h] Brain and Mind Research Institute, Weill Cornell Medical College, NY, USA
[i] Vascular Screening and Diagnostic Centre, London, England
[j] Vascular Diagnostic Centre, University of Cyprus, Nicosia, Cyprus
[k] Monitoring and Diagnostic Division, AtheroPoint™, Roseville, CA, USA
[l] Point-of-Care Devices, Global Biomedical Technologies, Inc., Roseville, CA, USA
[m] Department of Electrical Engineering, University of Idaho (Affl.), ID, USA

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ABSTRACT

This study presents AtheroCloud™ - a novel cloud-based smart carotid intima-media thickness (cIMT) measurement tool using B-mode ultrasound for stroke/cardiovascular risk assessment and its stratification. This is an anytime–anywhere clinical tool for routine screening and multi-center clinical trials. In this pilot study, the physician can upload ultrasound scans in one of the following formats (DICOM, JPEG, BMP, PNG, GIF or TIFF) directly into the proprietary cloud of AtheroPoint from the local server of the physician's office. They can then run the intelligent and automated AtheroCloud™ cIMT measurements in point-of-care settings in less than five seconds per image, while saving the vascular reports in the cloud. We statistically benchmark AtheroCloud™ cIMT readings against sonographer (a registered vascular technologist) readings and manual measurements derived from the tracings of the radiologist.

One hundred patients (75 M/25 F, mean age: 68 ± 11 years), IRB approved, Toho University, Japan, consisted of Left/Right common carotid artery (CCA) artery (200 ultrasound scans), (Toshiba, Tokyo, Japan) were collected using a 7.5 MHz transducer. The measured cIMTs for L/R carotid were as follows (in mm): (i) AtheroCloud™ (0.87 ± 0.20, 0.77 ± 0.20); (ii) sonographer (0.97 ± 0.26, 0.89 ± 0.29) and (iii) manual (0.90 ± 0.20, 0.79 ± 0.20), respectively. The coefficient of correlation (CC) between sonographer and manual for L/R cIMT was **0.74** ($P < 0.0001$) and **0.65** ($P < 0.0001$), while, between AtheroCloud™ and manual was **0.96** ($P < 0.0001$) and **0.97** ($P < 0.0001$), respectively. We observed that **91.15%** of the population in AtheroCloud™ had a mean cIMT error less than 0.11 mm compared to sonographer's **68.31%**. The area under curve for receiving operating characteristics was **0.99** for AtheroCloud™ against **0.81** for sonographer. Our Framingham Risk Score stratified the population into three bins as follows: 39% in low-risk, 70.66% in medium-risk and 10.66% in high-risk bins. Statistical tests were performed to demonstrate consistency, reliability and accuracy of the results. The proposed AtheroCloud™ system is completely reliable, automated, fast (3-5 seconds depending upon the image size having an internet speed of 180 Mbps), accurate, and an intelligent, web-based clinical tool for multi-center clinical trials and routine telemedicine clinical care.

* Corresponding author at: Monitoring and Diagnostic Division, AtheroPoint™, Roseville, CA, USA.
E-mail address: Jasjit.Suri@atheropoint.com (J.S. Suri).

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1. Introduction

Cardiovascular diseases (CVDs) have been predicted as the main cause of morbidity globally. On an average, 7.4 million deaths were due to CVDs and 6.7 million were due to stroke [1]. It was found that over three quarters of CVD deaths take place in low and middle income countries. In particular, South-East Asia region shows a rapid increase of CVDs in the young and middle-aged group population. Between 2000 and 2030, it is estimated that about 35% of all CVD deaths in India will occur among the 35–64 year age group [2]. Coronary artery disease and carotid artery disease are two primary examples of diseases caused by the build-up of atherosclerotic plaque that fall under the broader category of CVDs [3].

Atherosclerosis is a progressive process that damages the endothelium due to the deposition of plaque in the arteries [4,5]. Atherosclerosis narrows the arteries, restricting the flow of oxygenated blood in the body [6]. As atherosclerosis progresses, the blockage can rupture, causing the clot to dislodge and travel downstream (Fig. 1) [7]. This results in myocardial infarction or stroke. People with cardiovascular disease or high cardiovascular risk may significantly benefit from early detection, monitoring and its management [8,9].

Carotid intima-media thickness (cIMT) is one of the most popular methods for monitoring CVD and predicting the occurrence of major adverse cardiovascular events [10–22]. Prediction of CVD has been tied to cIMT in the early studies in order to foresee cardiovascular events (CVE). Several studies have shown a relationship between threshold value of cIMT leading to CVD: (cIMT > 0.7 mm) [23], (cIMT > 0.85 mm) [24], (cIMT > 0.9 mm), [25,26] (cIMT > 1.0 mm) [27], and (cIMT > 1.26 mm) [28]. Recent studies have also revealed a strong relationship between cIMT values and the severity of coronary artery disease (CAD) [8,25,26,29]. The above studies have clearly shown that cIMT is risk biomarker for CVEs.

In spite of the strong relationship between cIMT and CAD, clinicians have not routinely benefitted from automated processing of carotid ultrasound scans. Several studies [17–20] emphasized the need for an automated system for cIMT computation. This is mainly because current manual [19] or semi-automated systems [30] used by sonographers are subjective and associated with operator or observer bias. Current systems are not fully automated [30] and lack advanced image-based features for risk assessment [31,32]. Often, these systems lack reliability, accuracy, reproducibility, and provide no comparative reference marker needed for monitoring. Furthermore, there is no standardization towards clinical trials [33]. The lack of reproducibility is due to the methodology in which they take the readings, such as: (i) caliper-based, and (ii) the readings are manually taken at a limited number of locations (positions) along the CCA [34]. We assume that a robust and validated automated system is more accurate and reliable as compared to sonographer's readings taken by registered vascular technologist (RVT) in vascular ultrasound laboratory. This assumption can be proven if the error between the automated AtheroCloud™ software-based cIMT readings and the gold standard (manual tracings taken by the radiologist) is lower compared to the error between sonographer's reading and the gold standard (manual).

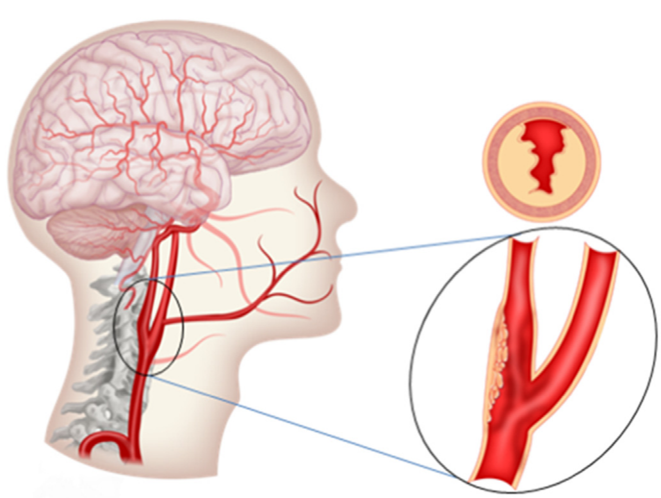

Fig. 1. Illustration of plaque formation in the carotid artery (Courtesy of AtheroPoint™, Roseville, CA, USA).

Through automated systems, the operator variability and subjectivity can be controlled, but still there are challenges in stroke/cardiovascular risk monitoring such as ability to serve in remote areas of the world. The current methods for cIMT measurement use a cart-based ultrasound machine or portable machines which are bulky to carry unlike pocket-sized machine [35] putting strain on mobile-based infrastructure. Patients and doctors are physically confined to a machine and a clinical protocol cannot be executed if the patient, for example, is in a rural area without access to a physician [36]. The concept of home-health care [37] is not prevalent and the traditional approach lacks an "anytime-anywhere" solution.

There are two major challenges in current cIMT system designs in cloud-based settings:

(i) Design of a two-pronged system, with a single (routine) mode and batch (pharmaceutical) mode, that can recognize the far wall of the carotid artery [38] and detect the lumen-intima and media-adventitia interfaces [39,40]; (ii) Design of a multicenter clinical tool which is completely automated (which can extract cIMT measurements over thousands of studies without interruption), which can handle the variability in image characteristics such as resolution, contrast, size, quality, formats, and be able to process images from different countries. A synopsis on previous techniques is presented in the discussion section.

The proposed patented system is "smart" in the sense that an intelligent cloud-computing is adapted for recognition of carotid anatomy in carotid scans (having multiple vascular beds) and computing the lumen-intima (LI)/media-adventitia (MA) (details discussed in next section) interfaces along with the cIMT measurements. The system is intelligent in the sense that, it is able to automatically recognize the far (posterior) wall of the carotid artery even in the presence of near and far walls of the jugular vein [41].

In a cloud-based approach, the physician can upload ultrasound scans in one of the following formats (DICOM, JPEG, BMP, PNG, GIF or TIFF) directly into the proprietary cloud of AtheroPoint from the local server of the physician's office, and then run the intelligent and automated AtheroCloud™ cIMT measurements in point-of-care settings in less than five seconds per image, while saving the vascular reports in the cloud. We then compare and validate AtheroCloud™ readings against a sonographer's measurements and manual (gold standard) readings by computing the precision of merit and coefficient of correlations between these methods. The performance of the AtheroCloud™ system is then analyzed by computing the area under the curve (AUC) of the receiver operating characteristics (ROC) [42]. We also compare Routine mode (single image at a time) against the Pharmaceutical trial mode (batch of images at a time without interruption) using AtheroCloud™ software system showing the reliability and reproducibility. Further, we benchmark AtheroCloud against the commercially available desktop-based systems such as AtheroEdge™ (AtheroPoint™, Roseville, CA, USA), that has been (i) previously benchmarked against OEM vendors like Siemens, [43] (ii) used for epidemiological study [44] and (iii) is 510(K) cleared medical device [45], establishing the standard for cIMT measurement [33] demonstrating the error difference which follow the criteria of acceptance under regulatory conditions.