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Computer-aided quantification of contrast agent spatial distribution within atherosclerotic plaque in contrast-enhanced ultrasound image sequences

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ABSTRACT

Recent studies have revealed that the contrast-enhanced ultrasound (CEUS) correlates to the presence and degree of intraplaque neovascularization as determined histologically. However, most studies used a qualitative system to visually grade CEUS images. A computer-aided method is proposed for objective and convenient quantification of contrast agent spatial distribution within plaques in CEUS image sequences. It consists of three algorithms including cardiac cycle retrieval and sub-sequence selection, temporal mean image segmentation, and texture feature extraction. The first algorithm automatically retrieves and selects cardiac cycles from CEUS frames without electrocardiogram gating. The second is composed of three steps, i.e., temporal averaging, interactive plaque delineation, and automatic neovascularization segmentation. The third extracts eight texture features from the grayscale temporal mean images and the binary segmented images. The capability of the quantitative features in discriminating between qualitative grades is examined via the *t*-tests, analysis of variance (ANOVA), Fisher criterion of inter-intra class variance ratio and logistic regression classification with leave-one-out cross-validation. Experimental results on 33 carotid plaques demonstrated that the optimal feature, namely the combined area ratio, exhibited significant difference among three qualitative grades ($P < 0.001$, ANOVA). When distinguishing between low-grade and high-grade plaques, the features improved the area under the receiver operating characteristic curve, sensitivity and specificity by 36.4%, 16.7%, and 11.1%, respectively, contrasted with a classic feature, the traditional area ratio. These results demonstrate the usefulness and advantage of the proposed method in quantifying the spatial distribution of contrast agents in CEUS.

1. Introduction

Contrast-enhanced ultrasound (CEUS) is a noninvasive imaging modality, applying microbubble-based contrast agents to traditional medical ultrasound to increase the backscatter of the ultrasound signal [1]. It enables detailed visualization of blood flow and perfusion and thus covers broad medical application.

In recent years, the use of CEUS continues to grow in the assessment of carotid atherosclerotic plaques [2–6]. Vulnerable plaques, also known as "rupture-prone plaques," have a high probability of undergoing rapid progression and rupture, causing local thrombosis and embolism, and thus leading to stroke, one of the major causes of death worldwide [7]. Recent evidence has linked elevated plaque vulnerability with plaque angiogenesis and has demonstrated feasibility of CEUS as a noninvasive way for evaluation of intraplaque neovascularization (IPN) [5]. Therefore, CEUS could be of importance to assess plaque vulnerability and identify vascularized, "high-risk" lesions before rupture [8].

For assessment of plaque vulnerability, it is valuable to measure the presence and degree of IPN in CEUS images. The IPN is traditionally measured by applying a qualitative visual approach, usually by using a discrete grading system. Coli et al. [9] categorized the echogenicity as low if no bubbles were detected within plaques and as high if extensive contrast enhancement was depicted. Staub et al. [10] categorized the degree of IPN at CEUS as absent (grade 1), moderate (grade 2), or extensive (grade 3). However, these

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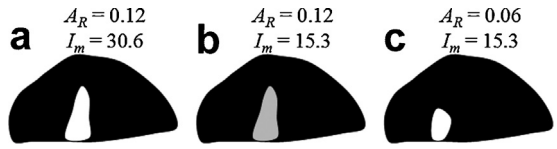

Fig. 1. An example for illustration of the difference between the area ratio (A_R) and the mean intensity (I_m). The neovascularization invades 12% area of the plaque in both (a) and (b) ($A_R = 0.12$) and 6% in (c) ($A_R = 0.06$). But because the intensity of contrast agents in (b) is half of the intensities in (a) and (c), the I_m-value inside the plaque in (b) is only half of that in (a) and equal to that in (c).

qualitative methods are subjective and affected by inter-observer and intra-observer variability [11,12]. Thus, it is required to develop computer-aided methods for objective quantification of IPN.

There are two categories of computer-aided methods. One is intensity based, and the other is area based. Papaioannou et al. [13] measured the mean and median intensities of pixels in the plaque before and after injection of microbubbles. Huang et al. [14] and Xiong et al. [15] calculated average intensities in the plaque, including the baseline intensity, peak intensity, and enhanced intensity equaling to the peak intensity subtracting the baseline intensity. Furthermore, Xiong et al. [15] calculated the ratio of enhanced intensity in the plaque to that in the lumen. Slightly differently, Moguillansky et al. [3] used the ratio of peak intensity in the adventitia to that in the lumen. However, in all these intensity based studies, the intensity is averaged as the mean or median gray levels of pixels in a region of interest (ROI), so that the information of spatial distribution of contrast agents is neglected. Hoogi et al. [4] proposed an area based method by calculating the ratio of the IPN area to the total plaque area. This area ratio measures the relative extent of contrast agents inside a plaque, with a larger value representing more extensive spatial distribution of contrast agents. It is different from the intensity based quantities, as illustrated with an example in Fig. 1. The area ratio is proved to be correlated well with histopathologic results, demonstrating the great value of incorporating the information of spatial distribution in quantification of IPN on CEUS [4].

For the calculation of this area ratio, named the traditional area ratio ($A_{R,H}$), CEUS images of a plaque are segmented offline frame by frame in a video sequence that is previously acquired in real time during patient examination. The image segmentation is used to detect IPN regions in each frame, and then an accumulation process is performed by integrating these regions from all frames to obtain the total area of IPN. However, there arise four questions.

First, CEUS images are corrupted by speckle noise, which makes robust image segmentation a difficult task [16]. It is complicated, cumbersome and time-consuming to segment a CEUS sequence frame by frame. When the accumulation of the segmented frames is conducted to derive the total IPN area, the segmentation error in all frames might also be accumulated. How can we determine the IPN area in a more accurate and efficient way?

Second, a CEUS sequence acquired from pre-injection of contrast agents to post-injection usually consists of hundreds and thousands of frames, so that a sub-sequence containing several cardiac cycles needs to be selected from the long sequence to simplify the computing [4,17]. But for an effective and objective analysis, which portion of the long sequence should be selected?

Third, it needs electrocardiogram (ECG) gating for the selection of sub-sequence [4,13]. In clinical CEUS examinations, we may not always record ECGs; even if we do, the recorded ECGs may not be synchronized with CEUS. In that case, can we retrieve cardiac cycles from the CEUS data themselves?

Finally and most importantly, there is detailed information of contrast agent spatial distribution that both the intensity and area based methods have ignored. Coli et al. [9] stated that the neovascularization should derive mainly from the adventitial vasa vasorum network and, therefore, progressively grow from the external layers toward the plaque core. In addition to the area ratio, the uniformity or nonuniformity of the contrast agents may also reflect the distribution characteristics of contrast agents [18]. Therefore, the degree of neovascularization invading to the plaque core and the uniformity of the contrast agents within the plaque appear to be promising features describing the spatial distribution of contrast agents. From the viewpoint of image processing, these features can be regarded as measures of texture within the plaque [19]. Now the question is: how can we quantify them?

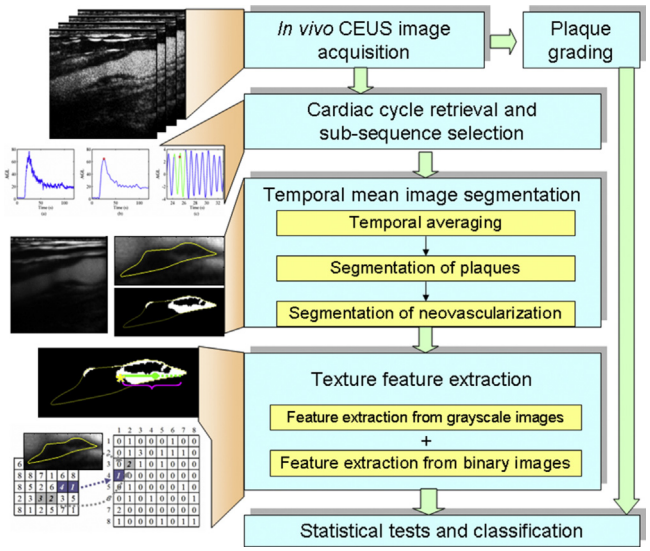

Fig. 2. The flowchart of the proposed methods. CEUS image sequences of plaques were acquired and plaques were qualitatively graded. From each image sequence, cardiac cycles were automatically retrieved and a sub-sequence was selected for further computerized image analysis including image segmentation followed by feature extraction. The image segmentation consisted of temporal averaging, interactive delineation of plaques, and automatic segmentation of intraplaque neovascularization. The feature extraction produced two categories of texture features including features from grayscale images and binary images.

The contribution of the paper is twofold. First, aiming at answering the aforesaid first three questions, we propose a computer-aided method for more objective and convenient detection of IPN. Second, in order to answer the last question, we propose extracting texture features to quantify the spatial distribution of contrast agents at IPN areas, including texture features based on grayscale images and binary images.

2. Materials and methods

An overview of the methods is summarized in Fig. 2 and the details are described in this section. All algorithms were implemented by MATLAB R2007a (The MathWorks, Natick, MA, USA).

2.1. *In vivo CEUS image acquisition and plaque grading*

The in vivo CEUS images were acquired at the Department of Ultrasound, Zhongshan Hospital, Fudan University, Shanghai, China. The study protocol was approved by a local institutional review board and informed consents were obtained from each patient. CEUS examination was performed with the Philips iU22 system (Philips, Bothell, WA, USA) using a convex-array transducer (C5-2). The mechanical index was set at 0.07, and the focal zone was positioned below the area of interest. The contrast agent SonoVue (Bracco, Milan, Italy) was injected intravenously at a dose of 2 mL as a bolus, followed by an immediate flush of 5 mL of