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Optimal Cutoff Threshold for Calcium Quantification in Isotropic CT Calcium Scans by Validating Against Registered Intravascular Ultrasound with Radiofrequency Backscatter

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Abstract— **3D Computed Tomography (CT) provides non-invasive, low-radiation method of coronary artery calcium (CAC) measurement. Conventional CAC images are acquired on multidetector-row CT scanners without contrast, and reconstructed with 3 mm slice thickness. The calcium volume is quantified by registering voxels with attenuation values greater than or equal to 130 Hounsfield Unit (HU). In isotropic CAC images with 0.5 mm slice thickness obtained from 320-detector row CT, the optimal value of attenuation cutoff threshold is unknown. In this paper we find the optimal cutoff threshold for calcium quantification in isotropic CT calcium scans by validating against registered intravascular ultrasound with radiofrequency backscatter (IVUS/VH). From the statistical analysis of calcium data obtained from the images of 9 patients we found a range of optimal thresholds and the conventional threshold of 130 HU was in the range. Further, the optimal values were different for individual patients.**

I. INTRODUCTION

Atherosclerosis is a common disease that is responsible for a vast majority of cardiac events such as angina and heart attack. Computed tomography (CT)-based measurement of coronary artery calcium (CAC) introduced by Agatston et al. [1] is a noninvasive, low-radiation method to assess the overall coronary arterial atherosclerotic burden, by quantifying calcium in the coronary vasculature. Due to a vast body of research data supporting and validating the clinical utility of CAC, it is becoming a mainstream routined clinical procedure [2]. One such study done in 25,253 asymptomatic individuals demonstrated CAC to be an independent predictor of mortality [3]. Conventional CAC images are acquired on multidetector-row CT scanners without contrast, and reconstructed with 3 mm slice thickness. Calcium in CAC is quantified by calculating the volumes of the voxels with attenuation values greater than or equal to 130 Housfield unit (HU). Although, the 130 HU cutoff threshold is somewhat arbitrary, it has become a conventional value for identifying calcium after Agatston et al. [1] first used it.

CAC images can be acquired in a volumetric mode on the 320-detector row CT system, and reconstructed using 0.5 mm slice thickness to achieve 0.5 mm isotropic resolution with no increase in radiation dose. Compared to conventional CAC images reconstructed at 3 mm slice thickness, the 0.5 mm isotropic reconstruction achieves higher spatial resolution and potentially reduces the partial volume effect. However, the accuracy of calcium quantification using 0.5 mm isotropic resolution and the effect of different HU thresholds have not been studied.

Intravascular Ultrasound with radiofrequency backscatter (IVUS/VH) is clinically established method of atherosclerosis characterization which can classify a pixel as one of the four major components: fibrous tissue, fibrofatty tissue, necrotic core, and dense calcification. The IVUS-VH has been shown to detect different composition both in vivo [4] and ex vivo [5] with very high predictive accuracies.

In this paper we study the accuracy of calcium quantification on 0.5 mm isotropic CAC scans by comparing against the spatially registered IVUS/VH on a very detailed slice-by-slice basis, and study the effect of varying the cutoff thresholds on the correlation of the calcium quantified by the two modalities. IVUS and CAC are two very different imaging modalities. In IVUS, a catheter travels through the artery and acquires a stack of 2D cross-sectional images along the artery that lacks the knowledge of the 3D Cartesian coordinates, while CAC is a 3D volumetric data set that includes all the anatomical structures in the thoracic area. Furthermore, CAC is based on non-contrast-enhanced CT scans in which coronary arteries are difficult to be automatically detected. Therefore, we have developed software tools to manually extract a desired vessel from CAC image and register it with IVUS/VH based image by using salient landmark and fine tuning by panning and scaling the calcium score curves sideways. Calcium scores obtained from different HU thresholds were analyzed by correlation as well as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) to find an optimal threshold range. Based on the statistical analysis on a population of 9 patients a range from 123 to 148 HU yielded best correlation with high sensitivity and specificity. The statistics of individual patients revealed patient specific optimal thresholds.

II. METHOD

In order to compare the CT-based CAC images with IVUS/VH, we need to extract the corresponding coronary artery from the CT images. Since it is difficult to extract coronary artery automatically from the non-contrast-enhanced CT scans, we have developed a proprietary software to manually extract the vessel centerline from the CT images, and transform the vessel to a straight-vessel view. We also developed a software tool to align and register the CAC images with the IVUS/VH, so that the calcium quantification

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in CAC and IVUS/VH can be compared on a very detailed slice-by-slice basis in each of the cross-sectional slice that is perpendicular to the vessel centerline.

A. Centerline Extraction in CAC Images

Our software allowed the users to browse through the 3D image set and manually annotate the centerpoints of the vessel of interest which gave a set of 3D coordinates representing the actual path of the vessel. The set of 3D points were then interpolated and made smooth by using the SNAKE deformable model [6] which is an energy-minimizing spline normally used for segmentation of desired object in an image. The SNAKE starts by an initial set of points close from the desired image object and is iteratively smoothed by the internal forces and guided towards the image features such as edges, lines etc. by a set of external forces. In order to smooth our 3D set of points we started with a curve obtained by cubic interpolation of the initial set of 3D points. These set of points obtained manually acted as the salient feature in 3D space which pulled the curve towards them in each iteration bringing it sufficiently close from them and meanwhile smoothing it to approximate a vessel centerline.

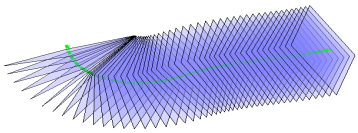


Fig. 1. 2D cross-sectional slices are sampled along the vessel centerline in the CAC image.

In order to compare the CAC volume with the set of 2D IVUS/VH images, appropriate images from the 3D CAC data had to be extracted and lined up as in IVUS/VH image set. As shown in Fig. 1, we extracted the images perpendicular to the centerline and equally spaced from each other in order to emulate the images taken by IVUS catheter inside the vessel. In order to achieve more reliable registration and to emulate the volume quantified by conventional 3 mm slice thickness reconstruction, we set the slice-to-slice spacing to be 3 mm, which resulted in a total of 178 slices in both the modalities.

B. Calcium Quantification in CAC Images

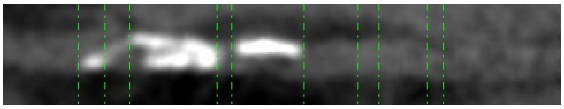
The smoothed vessel centerline in CAC images was densely re-sampled and dilated in 3D using the morphological dilation operation [7] with a spherical structural element of radius of 7 voxels. The choice of 7 voxels was determined experimentally which was enough to cover all the possible calcified voxels in the selected vessels without including any non-arterial calcification. All the voxels in the dilated vessel were then perpendicularly projected into the vessel centerline to derive their distance values to the vessel ostium along the vessel centerline. Initially, we implemented the conventional calcium attenuation cutoff threshold of 130 HU to derive the calcified volume in the CAC image, i.e., if the Hounsfield unit (HU) of a voxel was equal to or greater than 130 HU, it was reported as a unit of calcium.

A voxel in the dilated CAC vessel was assigned to the 2D slice closest to the voxel's projection in the centerline. The calcium volume in each cross-sectional slice along the centerline in the CAC images was calculated by multiplying the volume of a voxel with the total number of voxels whose attenuation values are equal to or greater than 130 HU, and belongs to that slice. In Fig. 3(a), the calcium volume quantified along a vessel centerline in a CAC image set is shown. The initial threshold of 130 HU was used only for the registration of CT CAC with IVUS/VH.

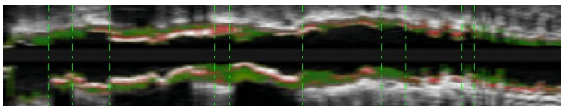
C. CAC and IVUS Registration

Previous studies in Computed Tomography Angiography (CTA) and IVUS registration were done by using contrast agent which is generally iodine based liquid injected intravenously to enhance the contrast of the vessel in the CT scan. Leber et al. for example, registered CT vessel with IVUS by visual comparison by looking at landmarks such as side branches in order to study the accuracy of 64-slice CT in classifying and quantifying plaque volume [8]. Marquering et al. matched IVUS and CTA data manually along the longitudinal views, and semi-automatically registering segmented vessel contours in 2D cross-sectional views [9]. More recently, Qian et al. registered CTA images obtained from 64-slice CT with IVUS/VH by simulating the CTA image from IVUS/VH, and by using mutual information based registration algorithm [10]. All of these works used contrast enhanced CT images. Different from the previous works, we use the 320-detector-row CT without any contrast agent. Since it is difficult to segment the non-contrast-enhanced CT automatically, we chose to manually register it by using the software tools we developed.

Vessel straight view of the IVUS/VH was reconstructed by stacking the 2D IVUS/VH slices together and forming a longitudinal view. The registration between the straight views of IVUS/VH and CAC was done by manually selecting a set of landmark points in the straight views of both IVUS/VH and CAC by looking at different salient features, such as vessel branches and calcium deposits, at different regions along the vessel. Fig 2 (a) and (b) show the vessel straight views of aligned CT and IVUS/VH respectively. The green dotted lines were the manually selected landmarks.



(a) CT



(b) IVUS/VH

Fig. 2. Manual alignment of the (a) CAC and (b) IVUS/VH images by visually comparing the vessel straight views. Salient image features, such as vessel branches and calcium deposits, were utilized in the manual alignment. Calcium deposits can be seen as white patches in CT and as white linings within the color-encoded vessel wall in IVUS/VH.

Visual alignment of the straight views gave a rough registration between IVUS/VH and CAC. However, it was not accurate enough for a slice-by-slice comparison. In order

to fine-tune the registration, we introduced a calcium volume curve alignment step by manually panning and scaling the curves sideways in the calcium curves obtained from both the modalities. The calcium volume along the centerline of the IVUS/VH scan was interpolated and calculated using the same sampling intervals as in the CAC images. Fig 3 shows an example of the curve alignment of the (a) CAC and (b) IVUS/VH derived calcium volume. Curves in between the manually aligned landmarks were realigned by linear interpolation.

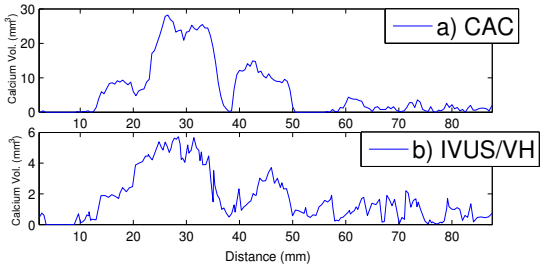


Fig. 3. Manual aligned calcium volume curves that are derived from (a) CAC and (b) IVUS/VH.

D. Calcium Quantification in CAC images using different cutoff threshold

For the 0.5 mm isotropic CAC images it is unknown if the 130 HU threshold is optimal. Therefore, we quantified the CAC volumes by using different cutoff thresholds starting from 50 HU to 400 HU and obtained a group of calcium volume quantification values corresponding to each threshold. The group of calcium volume values were then compared to IVUS/VH calcium values on a slice-by-slice basis by using the registration coordinates obtained from the previous mentioned alignment of IVUS/VH with the CAC curve.

E. Statistical analysis

We calculated the correlation coefficient of calcium volumes in IVUS/VH with CAC obtained with different thresholds. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) assessment were done to find the optimal attenuation threshold for individual as well as the population of patients studied. In our case, the true positive (tp) is the total number of calcium lesions in CAC images that are also present in corresponding IVUS/VH images, the true negative (tn) is the total number of slices without calcium lesions in both the modalities, false positive (fp) is the total number of lesions present in the CAC images but not in the IVUS/VH images, and false negative (fn) is the total number of calcium lesions in IVUS/VH images but not in CAC images. Then, $Sensitivity = tp/(tp + fn)$, $Specificity = tn/(tn + fp)$, $PPV = tp/(tp + fp)$, and $NPV = tn/(tn + fn)$. In addition, we conducted linear regression and Bland-Altman analysis to study the accuracy of calcium quantification obtained from the CT CAC with optimal threshold by comparing to the calcium volume from IVUS/VH.

III. Experiments

The study was approved by IRB of Piedmont Heart Institute. Nine patients undergoing 0.5 mm isotropic CAC and IVUS/VH were enrolled. Patient demographic information and CAC scores are listed in Table 1. Isotropic CAC was obtained using the conventional CAC imaging protocol with no increase in radiation dose. Imaging parameters included: prospective volumetric mode with a tube voltage of 120 kV, tube current of 100 - 550 mA, and 0.5 mm detector width. CAC images were reconstructed using 0.5 mm slice thickness. IVUS/VH was conducted in selected vessels with intermediate to severe disease. The isotropic CAC and IVUS/VH were co-registered using the aforementioned registration method, and the calcium quantification corresponding to different thresholds in CAC were compared with the registered IVUS/VH by quantifying 3D volume curves from both the modalities.

TABLE I
Patient demographics and CAC Agatston / volume scores

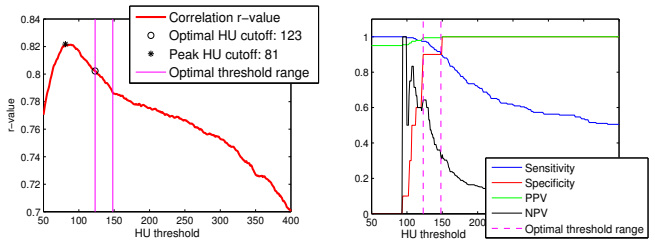
Total Patient Number	9
Gender	Male: 6; Female: 3
Age	63.55 $\pm$ 5.547
Agatston Score	542 $\pm$ 444
Volume Score	473 $\pm$ 353

IV. Results

While the linear correlation r value quantifies the linear relationship of the calcium quantified by CAC with that of IVUS/VH, it does not consider the accuracy of detecting calcific lesions. The sensitivity analysis gives the probability of accurately detecting actual calcium lesions in a CAC image; and specificity analysis gives the ability to correctly identify the absence of calcium lesions in the slices. The PPV finds the true proportion of positive values among all positives classified by the CAC and the NVP identifies the true proportion of negative values. A high value from all the statistical measures was desired.

Fig. 4(a) shows that the correlation changed with different attenuation thresholds used in the quantification of CT CAC. In a population of 9 patients with demographic shown in Table 1, we found 81 HU corresponded to the peak correlation of $0.82, p < 0.0001$. However, by choosing the thresholds for which the sensitivity and specificity were $\geq$90% ,we obtained a range of optimal values from 123 to 148 HU shown between the pink vertical lines in Fig. 4(b) and in Fig. 4(a). The sensitivity in the range varied from 90% to 97%, a specificity remained constant at 90%, NPV varied from 32% to 64% and PPV remained constant at 99%. The conventional threshold of 130 HU was still in the range of optimal thresholds obtained from our experiment and the CAC measured with 130 HU was found to be significantly correlated ($r = 0.80, p < 0.0001$) with the calcium volume in IVUS/VH. Since 123 HU had the highest r value in the optimal range, 123 HU was selected to be the optimal threshold.

From the linear regression analysis (Fig. 5(a)), Bland-Altman analysis (Fig. 5(b)) and correlation figures, we found that the isotropic CAC scan was able to detect calcified



(a) (b)

Fig. 4. Correlation between CAC and IVUS-VH (a) and Sensitivity, Specificity, PPV and NPV analysis of CAC (b) of 9 patients at different thresholds.

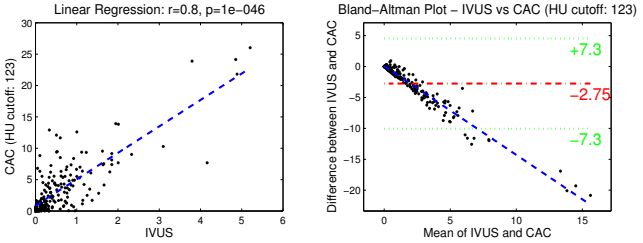
lesions equal to or larger than 11 mm^3 (by 95% prediction level) in each studied slice in IVUS/VH, but over-estimated the calcified volume by a factor of 4.0 at 130 HU and 4.2 at 123 HU, which might be explained by partial volume effects resulting in calcium blooming.

In case of individual patients the optimal threshold differed with a mean of 125 and standard deviation of 16. The result is shown in Table 2.

TABLE II

OPTIMAL THRESHOLD AND CORRESPONDING LINEAR CORRELATION VALUE FOR INDIVIDUAL PATIENTS

Correlation	Optimal Threshold (HU)
0.91	123
0.73	128
0.72	129
0.88	113
0.79	144
0.88	131
0.81	111
0.70	150
0.84	97
mean = 0.81, std = 0.08	mean = 125, std = 16



(a) (b)

Fig. 5. Linear Regression Analysis (a) and Bland-Altman analysis (b) of IVUS/VH against CT CAC for a population of 9 patients.

In a previous validation study of calcium quantification accuracy by contrast-enhanced CT angiography against IVUS/VH [11], the correlation coefficient r = 0.43 in the slice-by-slice comparison, and the over-estimation factor by CTA is 4.4. Compared to this previous study, the calcium volume quantification using isotropic CAC imaging technique achieved higher correlation level and lower over-estimation level.

V. DISCUSSION AND CONCLUSION

In this paper we have studied the calcium quantification accuracy of non-contrast-enhanced 0.5 mm isotropic CAC using different attenuation thresholds by comparing it against the IVUS/VH-derived calcium volume on a slice-by-slice basis. We developed software tools to extract the coronary vessels and register them manually with the IVUS/VH images so that the comparison could be done on a slice-by-slice basis in the two modalities. The CT CAC quantified by using different thresholds differed in correlation with the IVUS/VH. We derived the optimal HU threshold on a comprehensive basis that produced high correlation coefficient, sensitivity, and specificity values. From the statistical analysis we found that 0.5 mm CT CAC significantly correlates with IVUS/VH on a slice-by-slice basis. Furthermore, patients had different optimal thresholds which suggests patient specific attenuation threshold for better calcium quantification. Patient specific differences in threshold may be explained by partial volume effect which is caused by classifying a voxel with two or more tissue types solely as a calcium. The probability of finding high proportion of calcium in a voxel has been noted to be different for different HU thresholds [12]. Differences in chest lateral width, image noise level etc. might be other factors responsible for the difference in threshold. Finding patient specific optimal threshold based on these factors can be an avenue for future research. Comparison of 0.5 mm isotropic and 3.0 mm conventional CAC quantification with respect to different factors such as correlation coefficient with IVUS-VH calcium quantification, over-estimation of calcium volume and the influence of cutoff thresholds in these factors can also be of future interest.

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