

Relationship between Automated Coronary Calcium Volumes and a Set of Manual Coronary Lumen Volume, Vessel Volume and Atheroma Volume in Japanese Diabetic Cohort

SUMIT K. BANCHHOR¹, NARENDRA D. LONDHE², LUCA SABA³, PETIA RADEVA⁴, JOHN R. LAIRD⁵, JASJIT S. SURI⁶

ABSTRACT

Introduction: A high degree of correlation exists between Coronary Artery Diseases (CAD) and calcification of the vessel wall. For Percutaneous Coronary Interventional (PCI) planning, it is essential to have an exact understanding of the extent to which calcium volume is correlated to the lumen, vessel, and atheroma volume regions in the coronary artery, which is unclear in recent studies.

Aim: Four automated Coronary Calcium Volume (aCCV) measurement methods {threshold, Fuzzy c-Means (FCM), K-means, and Hidden Markov Random Field (HMRF)} and its correlation with three manual (experts) coronary parameters namely: Coronary Vessel Volume (mCVV), Coronary Lumen Volume (mCLV), and Coronary Atheroma Volume (mCAV), was determined in a Japanese diabetic cohort.

Materials and Methods: Intravascular Ultrasound (IVUS) image dataset from 19 patients (around 40,090 frames) was collected using 40 MHz IVUS catheter (Atlantis[®] SR Pro, Boston Scientific[®], pullback speed of 0.5 mm/sec). The methodology consisted of automatically computing the calcium volume in the entire IVUS coronary videos using FCM, K-means, and

HMRF based pixel classification and comparing it against the previously published threshold-based method. The Coefficient of Correlation (CC) was then established between the four aCCV and three manually (experts) coronary parameters: mCVV, mCLV, and mCAV computed using iMAP software Boston Scientific[®]. Statistical tests (Two-tailed paired Student t-test, Wilcoxon signed rank test, Mann-Whitney test, Chi-square test, and Kolmogorov-Smirnov KS-test) were performed to demonstrate consistency, reliability, and accuracy of the proposed work.

Results: Correlation coefficient of: (a) automated threshold-based volume; (b) automated FCM based volume; (c) automated K-means based volume; and (d) automated HMRF based volume and corresponding three manually (expert's) coronary parameters (mCLV, mCVV, mCAV) were: (0.51, 0.40, 0.48), (0.52, 0.38, 0.49), (0.56, 0.45, 0.52), and (0.57, 0.42, 0.56), respectively. The CC between age and haemoglobin was 0.50.

Conclusion: Automated coronary volume measurement using HMRF method is more accurate compared to threshold, FCM, and K-means-based method, since it is more strongly correlated with three expert's readings.

Keywords: Atherosclerosis, Correlation, Vessel wall

INTRODUCTION

Occlusive CAD produce enormous health and economic burdens worldwide [1,2]. Diabetic patients are at increased risk of atherosclerosis, particularly CAD [3]. Atherosclerosis usually advances silently and clinical symptoms arise late in the CAD [4]. Progression of atherosclerosis causes a blockage in the arteries (stenosis), limiting the flow of oxygen-rich blood to the heart leading to a myocardial infarction. Coronary calcium volume can be an early biomarker for the diagnosis of coronary artery stenosis [5-7]. The planning of the PCI procedures requires prior knowledge of the exact location, position, and volume of the calcified plaque in the coronary arteries [8]. Many segmentation techniques namely; iterative threshold-based [9,10], FCM, K-means [11,12], and HMRF and can be adapted to screen coronary artery stenosis [13]. Various imaging modalities such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Optical Coherence Tomography (OCT), and IVUS are used to quantify atherosclerotic walls of the coronary arteries [14,15]. Compared to other modalities, IVUS is less expensive, provides real-time data, and is less time-consuming [6,7,13,16].

Recent studies have shown that calcium deposition in the coronary arteries narrows the lumen area and is related to arterial stenosis [17-19]. It is important to note that in all the previous studies, the correlations are restricted to calcium area without taking the neighborhood frames into consideration. The current study utilizes a complementary idea by introducing the volume concept. Recently, Araki T et al., found a link between aCCV with automated carotid Intima-Media Thickness (IMT) from B-mode ultrasound in coronary artery disease population [5,6,7,13,20].

A high degree of correlation existed between CAD and calcification of the vessel wall [21]. Calcified plaque is only produced in the atheroma region which is between external elastic lamina (vessel region), and the internal elastic lamina (lumen region) in the coronary artery as shown in [Table/Fig-1]. In this study, we measured mCLV and mCVV by an experienced cardiologist, while mCAV was calculated by subtracting mCLV from mCVV. For PCI planning, it is essential to have an exact understanding of the extent to which calcium volume is correlated to the lumen, vessel, and atheroma volume regions in the coronary artery, which is unclear in above studies. In this work, we utilize the hypothesis that Coronary Calcium Volumes

(CCV) relate to: (i) coronary vessel volume; (ii) lumen volume; and (iii) atheroma volume. The block diagram of the proposed system is as shown in [Table/Fig-2]. This shows the extraction of CCV from the given IVUS videos and then developing the correlation with manual reading namely: mCVV, mCLV, and mCAV computed using iMAP software (Boston Scientific®).

MATERIALS AND METHODS

In this volumetric correlation study, nineteen patients IVUS data were taken from a single-center study [5] who underwent PCI between July 2009 and December 2010 with stable angina pectoris. Out of 19 patients, 17 were men and 3 women in the age group of 36 to 79 (average age of 66 years).

In this, nine patients had proximal lesion location, six at the middle and four at a distal location. Eleven patients had calcium present on the left anterior descending coronary artery, seven on the right coronary artery, two on the left circumflex coronary artery and two on the left main coronary artery.

The mean total cholesterol, LDL cholesterol, and HDL cholesterol were 169.47 mg/dl, 97.47 mg/dl, and 46.58 mg/dl, respectively and mean haemoglobin was 6.04 g/dl. Eleven patients from the pool of twenty-two, were smokers. Before performing coronary intervention procedure, a mixed dose of clopidogrel (75 mg/day) and aspirin (100 mg/day) were given to the patients. Prior to the procedure, intravenous unfractionated heparin was also given to obtain a partial thromboplastin in a time of fewer than 250 seconds.

This study undertook a full ethics review by the Institutional Review Board of our institution and written informed consent is provided by all the patients. [Table/Fig-3] shows a typical example of five frames taken from six patients and arranged in a 5x4 matrix. This is represented as I(1,1)–I(5,4). The calcified plaques are indicated by the arrows. A 40 MHz IVUS catheter (Atlantis® SR Pro, Boston Scientific®) were used for data acquisition and the computer program MATLAB® (Math Works, Inc., Natick, MA) was used for the image analysis. Target lesions imaging were performed during automatic pullback of the catheter at a speed of 0.5 mm/second.

Data Preparation

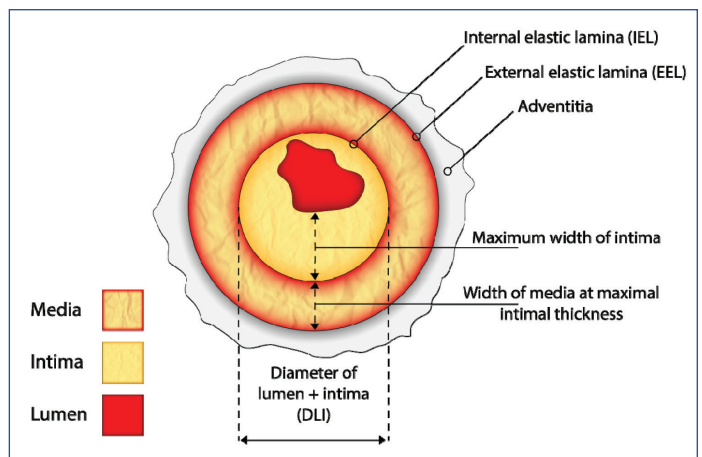
For extracting the vessel wall region, we have used the ImgTracer™ system (courtesy of AtheroPoint™, Roseville, CA, USA). The images were traced manually by two tracers; each traced about 20,045 frames, totaling 40,090 frames corresponding to 19 patients. The example of typical tracing is shown in [Table/Fig-4]. The inner yellow curve indicates the Internal Elastic Membrane (IEL) and outer yellow curve indicates the External Elastic Membrane (EEL) interface as shown in [Table/Fig-4a]. Now calcium can be extracted from the atherosclerotic area region as indicated in [Table/Fig-4b]. Equidistant spline fitting was used for smoothing the borders of the vessel wall region. Recently Araki T et al., [13] have used this software (ImgTracer™) to compute ground truth by manual tracing the lumen-intima interface or IEL and media-adventitia interface or EEL borders of coronary arteries.

Coronary Calcium Volume Measurements

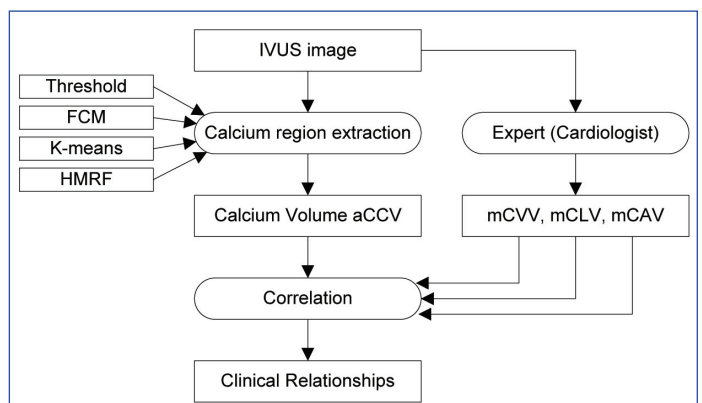
We have used a real-time automated system for the measurement of CCV given the borders of coronary vessel wall for all the frames of the intravascular ultrasound video. Four soft computing fuzzy classification techniques namely iterative thresholding (Santos), FCM, K-means, and HMRF were adopted. In this study, calcium volume is computed using conventional integration method which is like Simpson's rule proposed by Scott [22].

STATISTICAL ANALYSIS

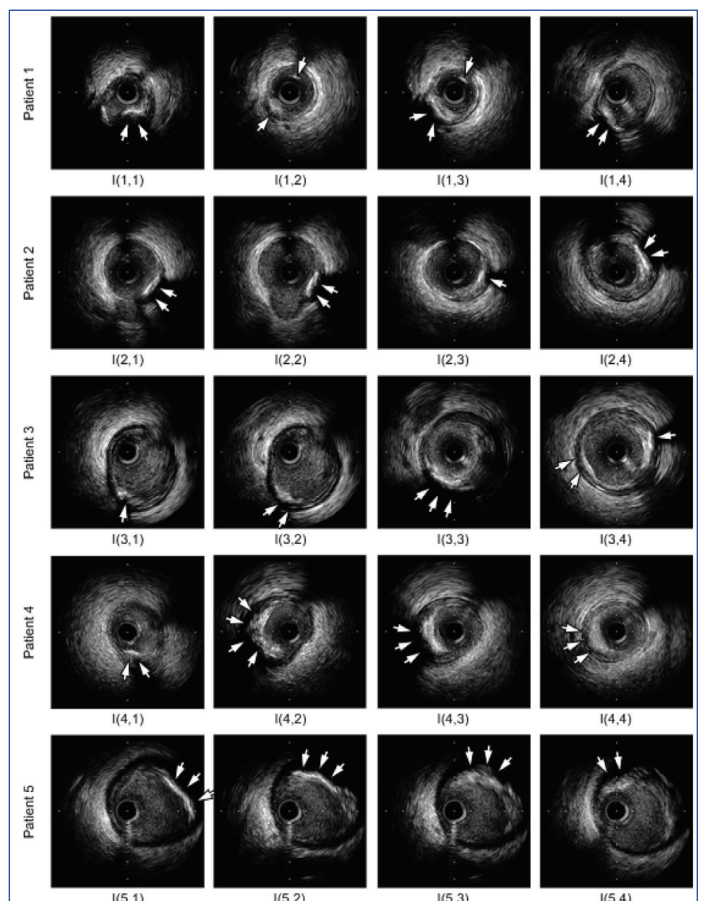
This paper examines the consistency, reliability, and accuracy of the system by performing the statistical tests (two-tailed paired Student's t-test, Wilcoxon signed rank test, Mann-Whitney test,



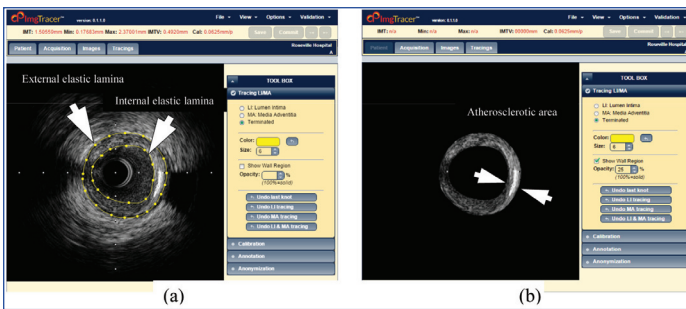
[Table/Fig-1]: IEL (Internal elastic membrane); EEL (External elastic membrane); (Courtesy of AtheroPoint™, Roseville, CA, USA).



[Table/Fig-2]: Block diagram of the overall system and its relationship to expert readings (iMAP software).



[Table/Fig-3]: Sample IVUS frames I(1, 1)–I(5,4) with a calcified plaque of five patients from the entire intravascular ultrasound (IVUS) videos.



[Table/Fig-4]: (a) manual tracings (yellow) of the vessel wall region showing (internal elastic lamina) and outer borders (external elastic lamina) of the vessel wall region using ImgTracer™; (b) greyscale atherosclerotic area region image obtained from the input image (a) (Courtesy of AtheroPoint™, Roseville, CA, USA).

Chi-square test, Kolmogorov-Smirnov (KS) test). In the current study, all the statistical analyses were performed using MedCalc 16.0 software (Ostend, Belgium). All p-values less than 0.05 were considered statistically significant. We performed two-tailed paired Student's t-test as we had less than 30 readings. The nonparametric Wilcoxon signed rank test subtracts the median of the values from the hypothetical population median. When the hypothetical population median is higher/lower, the result will be correspondingly positive/negative. Statistical significance between the results was further analysed using Mann-Whitney U test and Chi-square test. Lastly, the normality of each variable group was confirmed by Kolmogorov-Smirnov (KS) test.

RESULTS

Automated Calcium Lesions Volume Measurement

[Table/Fig-5] shows the mean and standard deviation of computed calcium lesion volume using automated detection per frame followed by volume measurement using threshold-based, FCM, K-means, and HMRF methods. In our recent study led by Araki T et al., we had validated our soft computing methods (threshold-based, FCM, K-means, and HMRF) against an expert, trained in radiology/ultrasound area [13]. This study clearly demonstrated an accuracy score of 92.08%, 89.24%, 92.80% and 82.4%, respectively for the above four soft computing methods. Based on this reliability and accuracy, the current study is focused on the relationship between these four soft computing calcium volume measurements against three manual coronary parameters namely: coronary vessel volume (mCVV), coronary lumen volume (mCLV), and coronary atheroma volume (mCAV) and the results are very encouraging.

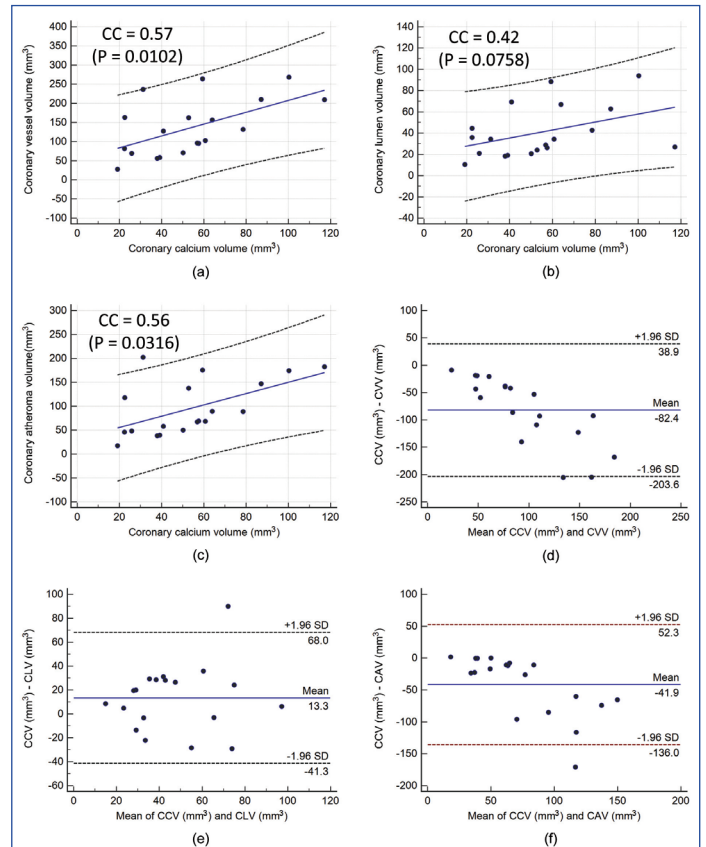
Correlation Between Manual and Automated Coronary Calcium Volumes

In this study, we have analysed CCV computed manually by an experienced cardiologist and automatically using four automated soft computing fuzzy segmentation techniques namely iterative thresholding (Santos), FCM, K-means, and HMRF.

We found a high correlation between mCVV, mCLV, and mCAV with aCCV. The correlations of aCCV with mCVV, mCLV, and mCAV for Santos calcium volume measurements were found: 0.51 ($p=0.0264$), 0.40 ($p=0.0929$), and 0.48 ($p=0.0378$) respectively. The correlations of aCCV with mCVV, mCLV, and mCAV for FCM calcium volume measurement technique were found: 0.52 ($p=0.0239$), 0.38 ($p=0.1062$), and 0.49 ($p=0.0312$), respectively. The correlations of aCCV with mCVV, mCLV, and mCAV for K-means calcium volume measurement technique were found: 0.56 ($p=0.0126$), 0.45 ($p=0.0543$), and 0.52 ($p=0.0213$), respectively. The correlations of aCCV with mCVV, mCLV, and mCAV for HMRF calcium volume measurement technique was found as 0.57 ($p=0.0102$), 0.42 ($p=0.0758$), and 0.56 ($p=0.0136$), respectively.

Segmentation Techniques	Mean Volume (mm ³)	Standard Deviation (mm ³)
Threshold-based	38.02	18.68
FCM	40.85	20.93
K-means	29.79	13.32
HMRF	53.84	27.10

[Table/Fig-5]: Automated calcium lesion volumes using proposed methods. FCM: Fuzzy c-Means; HMRF: Hidden Markov Random Field



[Table/Fig-6]: Scatter diagram showing a high correlation between: (a) coronary calcium volume and coronary vessel volume; (b) coronary calcium volume and coronary lumen volume; (c) coronary calcium volume and coronary atheroma volume. Bland-Altman plot of coronary calcium volume against three expert readings; (d) coronary vessel volume; (e) coronary lumen volume; (f) coronary atheroma volume.

It is observed that the correlation of aCCV with mCVV, mCLV, and mCAV for HMRF was higher compared to all the other three (Santos, FCM, and K-means) calcium volume measurement. For all the four calcium volume measurement techniques, correlation of aCCV with mCVV was higher. The scatter diagrams of aCCV vs. mCVV, mCLV, and mCAV using HMRF calcium volume measurement is shown in [Table/Fig-6a-c], respectively. The corresponding Bland-Altman plot of the above relationships is shown in [Table/Fig-6d-f]. Bland-Altman plots [23] exhibit the average of the differences of two CCV. It can be observed that the bias is higher in the negative difference direction which indicates that aCCV readings are slightly higher than the manual mCVV, mCLV, and mCAV readings.

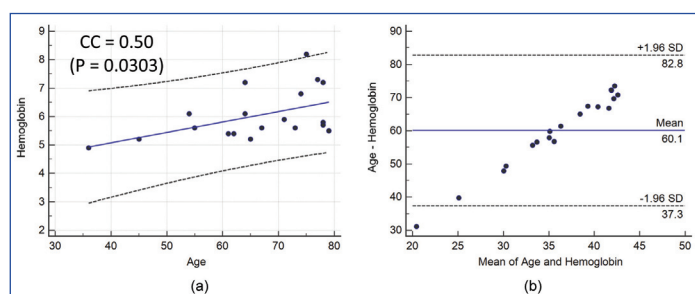
This paper examines the consistency, reliability, and accuracy of the system by performing the statistical test. The two-tailed paired Student's t-test, Wilcoxon signed rank test [24], Mann-Whitney test, and Chi-square test is performed and the statistical results are shown in [Table/Fig-7].

Correlation of Haemoglobin (HbA1c) with Age

In this study, we have also analysed the correlation of haemoglobin with age. The correlation coefficient of haemoglobin with respect to age was moderate: 0.50 ($p=0.0303$). The scatter diagram of age

Segmentation Techniques	Manual Reading using iMAP software	Two-tailed paired Student's t-test		Wilcoxon signed rank test	Mann-Whitney test	Chi-squared test	
		t	p	p	p	Contingency coefficient	p
Threshold-based	aCCV and mCV	6.502	<0.0001	<0.0001	<0.0001	0.973	=0.2356
	aCCV and mCLV	0.447	=0.6602	=0.9843	=0.9418	0.973	=0.2356
	aCCV and mCAV	4.908	=0.0001	<0.0001	=0.0002	0.973	=0.2356
FCM	aCCV and mCV	6.389	<0.0001	<0.0001	<0.0001	0.973	=0.2356
	aCCV and mCLV	-0.062	=0.9515	=0.9530	=0.8153	0.973	=0.2356
	aCCV and mCAV	4.733	=0.0002	<0.0001	=0.0008	0.973	=0.2356
K-means	aCCV and mCV	6.947	<0.0001	<0.0001	<0.0001	0.973	=0.2356
	aCCV and mCLV	2.126	=0.0476	=0.1447	=0.3000	0.973	=0.2356
	aCCV and mCAV	5.550	<0.0001	<0.0001	<0.0001	0.973	=0.2356
HMRF	aCCV and mCV	5.802	<0.0001	<0.0001	=0.0001	0.973	=0.2356
	aCCV and mCLV	-2.085	=0.0516	=0.0494	=0.1116	0.973	=0.2356
	aCCV and mCAV	3.797	=0.0013	<0.0001	=0.0173	0.973	=0.2356

[Table/Fig-7]: Statistical tests between automated coronary calcium volumes against manual readings.



[Table/Fig-8]: (a) Scatter diagram showing the positive correlation between haemoglobin and age; (b) Bland-Altman plot of haemoglobin and age.

with haemoglobin is shown in [Table/Fig-8a]. Bland-Altman plot of haemoglobin with age is given in [Table/Fig-8b] which shows the average bias, or the average of the differences of two quantities.

DISCUSSION

As the growth of calcified plaque in the coronary vessel wall is multifocal and irregular [22,25], it is required to process the entire frames all along the coronary artery for calcium volume estimation. In this study, we have used four fully automated techniques based on the threshold (Santos), FCM, K-means, and HMRF for calcium detection and volume computation [26]. Even though, the core segmentation methods and the concept of calcium volume estimation on entire coronary artery video is already published previously by Araki [13], the concept of establishing a relation between these four automated CCV and three manual reading namely: mCV, mCLV, and mCAV are innovative.

In our study, we found a high correlation between aCCV and manual coronary vessel, lumen, and atheroma volumes. While others have done only manual readings comparisons [17-19], our study has automatized the process by automatically computing the calcium volume in the entire coronary artery using IVUS videos.

A review of previous studies is summarized in [Table/Fig-9]. Mintz GS et al., worked on the relationship between IVUS calcium lesion

and lesion severity in X-ray coronary angiography [17]. The authors measured the lumen diameter in diastole before intervention using an automated edge detection method. The IVUS study was performed using the commercially available systems. They showed a moderate correlation between; cross-sectional narrowing in IVUS compared to the diameter narrowing in coronary angiography. Large cross-sectional narrowing in coronary arteries was observed due to a large calcium deposition, thereby increasing the atheroma area. We observed a similar relationship demonstrating an increase in coronary atheroma volume due to increase in CCV in our study.

Mintz GS et al., studied the effects of arterial remodeling on the coronary artery stenosis [18]. The authors analysed IVUS target lesion and proximal reference segment (i.e., a most normal-looking cross section within 10 mm proximal to the lesion but distal to any side branch). The coronary lesion-site/reference-site ratio was then related to lumen diameter obtained using angiography. This study examined 603 nonostial coronary artery stenosis with chronic stable angina. The authors also observed a high correlation between angiographic lumen diameter stenosis and the ratio of IVUS lesion/reference segments vessel areas. Angiographic lumen diameter stenosis is caused due to an increase in calcium deposition. Thus, we can assume that an increase in calcium has a high correlation with the increase in vessel area that supports our assumption.

A detailed histopathology study was performed by Sangiorgi G et al., [19], where the authors exploring the relationship between coronary calcification and atherosclerotic plaque burden. This study was conducted in 13 patients and calcium area was computed using microradiography images. They showed a high correlation between patient's age against coronary plaque area and coronary calcium area. The study consisted of the following analysis: (i) complete coronary artery; (ii) individual coronary artery (LAD, LCX, and RCA); and (iii) individual coronary segments. For individual coronary segments, the complete coronary artery was sectioned at 3 mm intervals. For all the three above mentioned methods, their study suggested a mild correlation $r=0.48$ between coronary lumen area

Authors	N	F/Video	Calcium Detection	Statistical analysis	Analysis done on video	Calcium volume computation
Mintz GS et al., [17]	1442	1043 frames	Semi-automated	CC, ANOVA	None	None
Sangiorgi G et al., [19]	13	723 frames	Manual	CC	None	None
Proposed	19	≈ 40,090 frames (≈ 2,110 frames per video)	Automated	CC, Bland-Altman, Student t-test, Wilcoxon test, Mann-Whitney test, and Chi-square test	Yes	Yes

[Table/Fig-9]: Survey on calcium detection techniques and volume measurements. N: Number of patients, F: Frames, CC: Correlation coefficient.

and coronary calcium area. Above results support our hypothesis of a moderate correlation between mCLV and aCCV measurements.

Our hypothesis of the high correlation of automated coronary calcium with the manual coronary vessel, lumen, and atheroma volume is also supported by the Glagov S et al., phenomenon [27]. The phenomenon suggests that in atherosclerotic human coronary arteries, lumen area remained constant until the percent stenosis exceeded 40% [28]. Saba L et al., evaluated the association of automated cIMT with HbA1c for CAD in a Japanese cohort [29]. An analysis was done on 370 patients and results clearly established a direct correlation ($p=0.0007$) between HbA1c and automated cIMT measurements. Hanafusa N et al., studied the relationship between HbA1c levels with mortality nonelderly populations experience poor prognosis with haemoglobin <10 g/dl, while elderly population only with haemoglobin <9 g/dl [30]. For both haemoglobin strata <9 , ≥ 9 , <10 g/dl, significant interactions were observed between age and haemoglobin. Results of our clinical relationship between age and haemoglobin are along the same lines as previous research.

The above relations can be used as a biomarker for detecting CAD and as a primary sign for recognizing patients with atherosclerotic plaques. The main strength of our techniques is the ability to automatically extract multi-focal calcium for volume measurement in the full coronary artery by utilizing the entire IVUS video. Second, we automatically computed the calcium lesion volume based on fuzzy pixel classification technique and benchmarking against the threshold-based method. Third, our results followed our assumptions and hypothesis.

LIMITATION

Even though, the number of patients utilized was not very large (19 patients), the numbers of frames used were 40,090, which is an equally large number to justify the strength of the system. Our future objective is to add more patients in the study to further validate our hypothesis in different sets of populations but the current results are truly encouraging.

CONCLUSION

We demonstrated four pixel classification methods for measuring the calcium volume and comparing against the three manual readings: mCVV, mCLV, and mCAV. A moderately higher CC was observed between HMRF and corresponding three manual methods and hence, aCCV measurement using HMRF method is more accurate. The relationship of aCCV with mCVV, mCLV, and mCAV can be used as a primary sign of CAD during atherosclerosis and can offer a means of recognizing patients at utmost risk for cardiovascular proceedings and in need of more severe treatments. We also observe a positive CC between age and haemoglobin which confirms higher risk of CVD with an increase in age.

Conflict of interest: Dr. Jasjit S. Suri has a relationship with AtheroPoint™, Roseville, CA, USA which is dedicated to Atherosclerosis Disease Management, including Cerebrovascular and Cardiovascular imaging.

ACKNOWLEDGEMENTS

We thank AtheroPoint™ for allowing NIT Raipur, India for using the lmgTracer™ software system for this study. We acknowledge our clinical collaborators for inputs during the design of the clinical study. We also acknowledge Toho Hospital, Japan for the ethics approved coronary image data set.

REFERENCES

- [1] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Executive summary: heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation*. 2016;133(2016):447-54.
- [2] Ulusoy FR, Yolcu M, Ipek E, Korkmaz AF, Gurler MY, Gulbaran M. Coronary artery disease risk factors, coronary artery calcification and coronary bypass surgery. *J Clin Diagn Res*. 2015;9(5):OC06-10.
- [3] Raggi P, Shaw LJ, Berman DS, Callister TQ. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. *J Am Coll Cardiol*. 2004;43(9):1663-69.
- [4] Rose G. ABC of vascular diseases. Epidemiology of atherosclerosis. *BMJ*. 1991;303(6816):1537-39.
- [5] Araki T, Nakamura M, Utsunomiya M, Sugi K. Visualization of coronary plaque in arterial remodeling using a new 40-MHz intravascular ultrasound imaging system. *Catheter Cardiovasc Interv*. 2013;81(3):471-80.
- [6] Araki T, Ikeda N, Molinari F, Dey N, Acharjee S, Saba L, et al. Link between automated coronary calcium volumes from intravascular ultrasound to automated carotid IMT from Bmode ultrasound in coronary artery disease population. *Int Angiol*. 2014;33(4):392-403.
- [7] Araki T, Ikeda N, Dey N, Acharjee S, Molinari F, Saba L, et al. Shape based approach for coronary calcium lesion volume measurement on intravascular ultrasound imaging and its association with carotid intima-media thickness. *J Ultrasound Med*. 2015;34(3):469-82.
- [8] Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Chuang YC, et al. Patterns of calcification in coronary artery disease. A statistical analysis of intravascular ultrasound and coronary angiography in 1155 lesions. *Circulation*. 1995;91(7):1959-65.
- [9] Otsu N. A threshold selection method from gray-level histograms. *Automatica*. 1975;11(285-296):23-27.
- [10] Santos Filho E, Saijo Y, Tanaka A, Yoshizawa M. Detection and quantification of calcifications in intravascular ultrasound images by automatic thresholding. *Ultrasound Med Biol*. 2008;34(1):160-65.
- [11] Hartigan JA, Wong MA. Algorithm AS 136: A k-means clustering algorithm. *Applied Statistics*. 1979;28(1):100-08.
- [12] Jain AK, Dubes RC. Algorithms for clustering data. Prentice-Hall, Inc., 1988.
- [13] Araki T, Banchhor SK, Londhe ND, Ikeda N, Radeva P, Shukla D, et al. Reliable and accurate calcium volume measurement in coronary artery using intravascular ultrasound videos. *J Med Syst*. 2016;40(3):1-20.
- [14] Ramani K, Judd RM, Holly TA, Parrish TB, Rigolin VH, Parker MA, et al. Contrast magnetic resonance imaging in the assessment of myocardial viability in patients with stable coronary artery disease and left ventricular dysfunction. *Circulation*. 1998;98(24):2687-94.
- [15] Coutts SB, Modi J, Shiel K, Patel SK, Demchuk AM, Goyal M, et al. CT/CT angiography and MRI findings predict recurrent stroke after transient ischemic attack and minor stroke results of the prospective catch study. *Stroke*. 2012;43(4):1013-17.
- [16] Schoenhagen P, Nissen S. Understanding coronary artery disease: tomographic imaging with intravascular ultrasound. *Heart*. 2002;88(1):91-96.
- [17] Mintz GS, Pichard AD, Popma JJ, Kent KM, Satler LF, Bucher TA, et al. Determinants and correlates of target lesion calcium in coronary artery disease: a clinical, angiographic and intravascular ultrasound study. *J Am Coll Cardiol*. 1997;29(2):268-74.
- [18] Mintz GS, Kent KM, Pichard AD, Satler LF, Popma JJ, Leon MB. Contribution of inadequate arterial remodeling to the development of focal coronary artery stenoses. An intravascular ultrasound study. *Circulation*. 1997;95(7):1791-98.
- [19] Sangiorgi G, Rumberger JA, Severson A, Edwards WD, Gregoire J, Fitzpatrick LA, et al. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. *J Am Coll Cardiol*. 1998;31(1):126-33.
- [20] Araki T, Ikeda N, Dey N, Chakraborty S, Saba L, Kumar D, et al. A comparative approach of four different image registration techniques for quantitative assessment of coronary artery calcium lesions using intravascular ultrasound. *Comput Methods Programs Biomed*. 2015;118(2):158-72.
- [21] Frink AJ, Achor RWP, Brown AL Jr, Kincaid OW, Branderburg RO. Significance of calcification of the coronary arteries. *Am J Cardiol*. 1970;26(3):241-47.
- [22] Scott DS, Arora UK, Farb A, Virmani R, Weissman NJ. Pathologic validation of a new method to quantify coronary calcific deposits in vivo using intravascular ultrasound. *Am J Cardiol*. 2000;85(1):37-40.
- [23] Bland JM, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;327(8476):307-10.
- [24] Altman D. Practical statistics for medical research. CRC Press, 1990.

- [25] Suri JS, Kathuria C, Molinari F. Atherosclerosis disease management. Springer Science & Business Media, 2010.
- [26] Pham DL, Xu C, Prince JL. Current methods in medical image segmentation. *Annu Rev Biomed Eng.* 2000;2(1):315-37.
- [27] Glagov S, Weisenberg E, Zarins CK, Stankunavicius K, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med.* 1987;316(22):1371-75.
- [28] Losordo DW, Rosenfield K, Kaufman J, Pieczek A, Isner JM. Focal compensatory enlargement of human arteries in response to progressive atherosclerosis: in vivo documentation using intravascular ultrasound. *Circulation.* 1994;89(6):2570-77.
- [29] Saba L, Ikeda N, Deidda M, Araki T, Molinari F, Meiburger KM, et al. Association of automated carotid IMT measurement and HbA1c in Japanese patients with coronary artery disease. *Diabetes Res Clin Pract.* 2013;100(3):348-53.
- [30] Hanafusa N, Nomura T, Hasegawa T, Nangaku M. Age and anemia management: relationship of haemoglobin levels with mortality might differ between elderly and nonelderly haemodialysis patients. *Nephrol Dial Transplant.* 2014;29(12):2316-26.

PARTICULARS OF CONTRIBUTORS:

1. Research Scholar, Department of Electrical Engineering, National Institute of Technology, Raipur, Chhattisgarh, India.
2. Assistant Professor, Department of Electrical Engineering, National Institute of Technology, Raipur, Chhattisgarh, India.
3. Neurologist, Department of Radiology, Azienda Ospedaliero Universitaria (A.O.U.), di Cagliari – Polo di Monserrato, Cagliari, Italy.
4. Associate Professor, Department of Applied Mathematics, University of Barcelona, Barcelona 08007, Spain.
5. Cardiologist, UC Davis Vascular Centre, University of California, Davis, CA, USA.
6. Professor, Fellow AIMBE, Monitoring and Diagnostic Division, AtheroPoint™, Roseville, CA, USA. Point-of-Care Devices, Global Biomedical Technologies, Inc., Roseville, CA, USA. Department of Electrical Engineering, University of Idaho (Aff.), ID, USA.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Jasjit S. Suri,
Professor, Monitoring and Diagnostic Division, AtheroPoint™, Roseville, CA, USA.
Point-of-Care Devices, Global Biomedical Technologies, Inc.,
E-mail: jasjit.suri@atheropoint.com

Date of Submission: **Dec 27, 2016**Date of Peer Review: **Mar 20, 2017**Date of Acceptance: **Mar 22, 2017**Date of Publishing: **Jun 01, 2017****FINANCIAL OR OTHER COMPETING INTERESTS:** As declared above.