Curr Atheroscler Rep (2014) 16:393
DOI 10.1007/s11883-013-0393-x

CORONARY HEART DISEASE (JA FARMER, SECTION EDITOR)

Ankle–Brachial Index and Its Link to Automated Carotid Ultrasound Measurement of Intima–Media Thickness Variability in 500 Japanese Coronary Artery Disease Patients

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Published online: 15 January 2014
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Abstract The purpose of this study was to evaluate whether the carotid intima–media thickness (cIMT) and intima–media thickness variability (IMTV) along the artery are correlated to the ankle–brachial index (ABI) in Japanese coronary artery disease patients. Five hundred consecutive patients (312 males; median age 69±11 years) who underwent carotid ultrasonography and first coronary angiography were prospectively analyzed. By using automated software (AtheroEdge™, AtheroPoint, Roseville, CA, USA), we obtained the cIMT and IMTV. Pearson correlation analysis was performed to calculate the association between ABI, automatically measured cIMT, automatically measured IMTV, and the

This article is part of the Topical Collection on *Coronary Heart Disease*

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SYNTAX score. The mean cIMT was 0.881±0.334 mm and the mean IMTV was 0.141±0.112. IMTV was negatively and significantly correlated to ABI (ρ=-0.147; p=0.001), whereas cIMT was not (ρ=-0.075; p=0.097). IMTV and cIMT had the same significant correlation with the SYNTAX score. When we considered patients with a higher risk factor (ABI ≤ 0.9), we found higher values of IMTV and the SYNTAX score, but not higher values of cIMT. Logistic regression analysis showed that IMTV was independently associated with the complexity of the coronary artery disease (as assessed by the SYNTAX score). In conclusion, we show that IMTV automatically measured using AtheroEdge™ was correlated with ABI, whereas cIMT was not. IMTV could be integrated with cIMT measurement to improve the assessment of cardiovascular disease.

Keywords Ultrasonography · Intima–media thickness · Intima–media thickness variability · Carotid · Ankle–brachial index · Automated measurement · Plaque score · SYNTAX score

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide and accounts for nearly one third of all global deaths [1]. It is estimated that by 2030 more than 23 million people will die of CVD annually [1]. The World Health Organization also estimated that about 80 % of CVD deaths occur in low- and middle-income countries [1]. Therefore, accurate and early markers of CVD onset are required in order to provide the populations with suitable screening and prevention protocols.

Particular attention has been dedicated to the estimation of the individual cardiovascular risk score, namely, the Framingham score [2, 3]. Large multicentric and epidemiological studies recommended the use of different markers and indicators to assess the CVD risk factor. For example, in 2010, the American College of Cardiology Foundation/American Heart Association guidelines recommended the use of the coronary artery calcium score (measured by computer tomography) [4], the carotid intima–media thickness (cIMT) measured 1 cm from the bulb [5], carotid plaque burden [6], and the ankle–brachial index (ABI) [7]. Another widely used indicator of CVD is given by the radiological measurement of the overall plaque complexity, namely, the SYNTAX score [8•].

Despite the large number of studies related to the individuation of CVD predictors, their usefulness is still limited [9]. Lauer [10] reported that a considerable number of myocardial infarctions and strokes occurred in subjects diagnosed with a medium or low risk factor. On these patients, the effect of lipid-lowering drugs showed more modest results than originally theorized [11••]. Hence, there is need for more accurate and specific predictors of CVD, particularly in subjects with mild or low risk factors.

The cIMT is a validated surrogate marker of early atherosclerosis and is associated with coronary atherosclerosis [12] and with the risk of future vascular events [13]. Because it can be measured relatively simply and noninvasively, it is well suited for use in large-scale population studies. Increased cIMT is associated with vascular risk factors and the presence of more advanced atherosclerosis [14], which includes coronary artery disease (CAD). Recently, Saba et al. [15••] proposed the intima–media thickness variability (IMTV) as a new marker of CVD and showed that it was associated with the presence of cardiovascular or cerebrovascular symptoms in a cohort of the Italian population. The proposal of the IMTV was justified by the observation that the cIMT variation along the carotid artery wall had a stronger correlation with atherosclerosis than did the cIMT itself [16•]. In fact, IMTV is an estimation of the wall irregularity [16•], which is a risk condition for plaque buildup.

In the past, the cIMT was calculated by the sonographers who performed the examination by tracing a line between the lumen–intima (LI) and media–adventitia (MA) interfaces [17]. In recent years, thanks to the rapid growth of hardware and algorithm analysis [18••], it became possible to automatically calculate the cIMT [15••, 19, 20], avoiding one of the most important limits of the manual analysis of the cIMT: the poor interobserver\intraobserver agreement [2, 21]. Another advantage of computer-based measurement of the cIMT is the possibility of measuring the IMTV with high accuracy and in an automated fashion.

The ABI is computed as the ratio between the systolic pressure in the ankle (measured at the dorsalis pedis or the posterior tibial artery, whichever has the higher pressure) and the systolic pressure in the arm (measured in either the left or the right arm, whichever has the higher pressure) [22]. The lower of the two values obtained (left side and right side) is the patient's ABI. Healthy subjects have ABI greater than 1.0 [22]. Previous studies have demonstrated that subjects with low ABI have a considerably higher prevalence of CVD than those with normal ABI [23]. A value below 0.91 indicates significant peripheral artery disease, and a value lower than 0.40 at rest generally indicates severe disease.

Like cIMT, the ABI is a widely used index that correlates with the presence of CAD [24•]. Measurement of the ABI is noninvasive, inexpensive, and quick. Also, more than half of patients with peripheral artery disease have CVD [24•].

In this study, we aimed to evaluate whether the IMTV identified by using automated software (AtheroEdge™ from AtheroPoint, Roseville, CA, USA), which can process a large set of ultrasound images automatically, was associated with ABI in a population affected by CAD.

Experimental Evidence of Association Between ABI and IMTV

Five hundred consecutive Japanese patients (218 males, 152 females; median age 69±11 years) admitted to Toho University Ohashi Medical Center from December 2008 to January 2011 who underwent carotid ultrasonography and first coronary angiography were prospectively analyzed. Coronary angiography was performed to evaluate patients for the presence of ischemic heart disease or cardiomyopathy and as the preoperative investigation for ischemic heart, aortic disease, or valvular disease. Our study complied with the Declaration of Helsinki, and written informed consent was obtained from all patients. Part of our population was used in recently published studies for a different set of applications [8•, 24•, 25]. Ultrasonographic examinations were performed with a scanner (Aplio XV, Aplio XG, Xario, Toshiba, Tokyo, Japan) equipped with a 7.5-MHz linear array transducer. All scans were performed by the same experienced sonographer (R. Fijisaki, with 10 years of experience). Subjects were examined in the supine position with the head tilted backwards. After the carotid arteries has been located by transverse scans, the probe was rotated 90° to acquire a longitudinal image of the anterior and posterior walls. The high-resolution images of the far wall were acquired according to recommendations of the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Moreover, high-resolution images of the internal carotid arteries and carotid bulbs (other than the common carotid arteries) were acquired.

The cIMT measurement was completely automated. Our strategy was based on the following three basic steps:

1. Step 1: automated image cropping
2. Step 2: automated carotid artery far wall recognition
3. Step 3: automated LI/MA far wall tracings

For an automated method, we need a correct region of interest, which consists only of tissue region. Therefore, in step 1, the goal is to automatically crop the region of interest (tissue region) in this ultrasound B-mode image. Since our images are in JPEG format, we adopt a gradient-based strategy, which removes all the image rows and columns that are black and do not contain intensity variations in the ultrasound image. The detailed procedure was previously reported by Molinari et al. [26]. Once the grayscale region of interest image has been obtained, step 2 consists of a multiresolution edge snapper coupled to a first-order Gaussian derivative filtering [27]. Once the far adventitia layer profile has been traced, step 3 consists of automated LI/MA tracings [27]. Figure 1a shows an original and already cropped B-mode image from our dataset. Figure 1b shows the automated tracing of the far adventitia layer, and Fig. 1c shows the final tracings of the LI/MA boundaries.

The cIMT was measured as the distance between the LI and the MA boundaries. We used the polyline distance method as a computation metric [28]. This metric computes the distance of the vertices of tracings from the segments of the other, and vice versa. The final cIMT is the average of all the distances of the vertices of the two tracings. Suri et al. [28] showed that this metric is robust and almost independent of the number of vertices in each tracing. Conceptually, the polyline distance method metric was used because it ensured a robust estimation of the actual distance between the LI and MA tracings even in

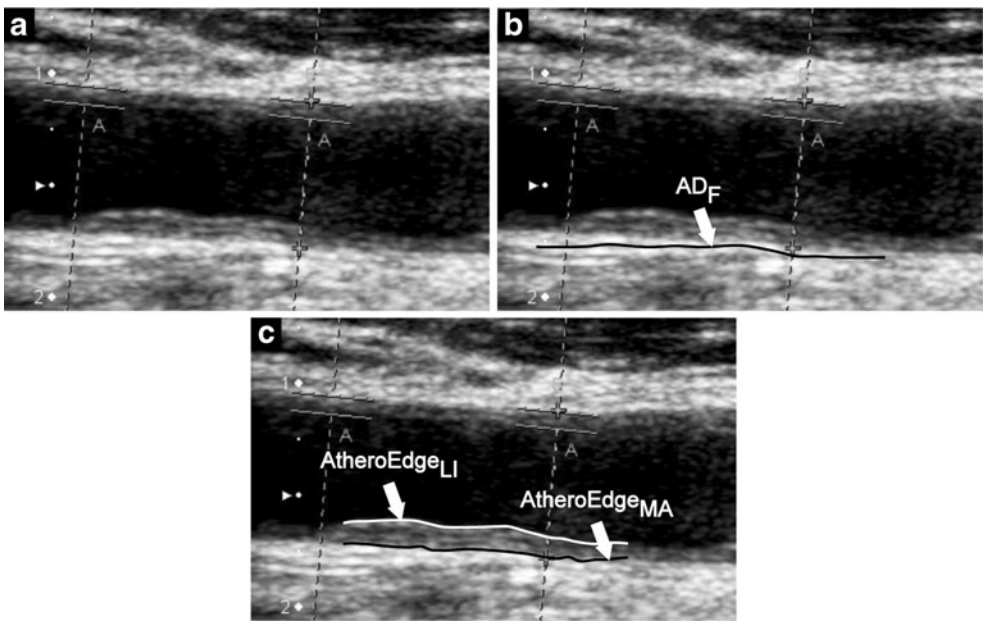

Fig. 1 Sample of automated image segmentation by AtheroEdge. **a** Original B-mode image. **b** Automated delineation of the far adventitia layer (AD_F). **c** Automated tracing of lumen–intima (*LI*)/media–adventitia (*MA*) boundaries

the presence of curved or inclined delineations (as might happen in carotid ultrasound images).

The IMTV is a measure of how variable the distance between the vertices of the LI tracing from the line segments of the MA tracing is, and vice versa. Hence, if we define σ_{LI} as the standard deviation of the distances of the vertices of the LI tracing to the line segments of the MA tracing, and σ_{MA} as the standard deviation of the vertices of the MA tracing to the line segments of the LI tracing, then

$$\mathrm{IMTV} = \sqrt{\frac{{\sigma_{LI}}^2 + {\sigma_{MA}}^2}{N_{LI} + N_{MA}}}, \quad (1)$$

where N_{LI} and N_{MA} are the number of vertices in the LI and MA tracings, respectively. The IMTV is a measure of irregularity in the LI interfaces due to plaque morphological variations in the carotid distal wall. Mathematically, it is quantified as a measure of the variability of the distance between the two LI and MA interfaces. For the purposes of this study, the maximum values of cIMT and IMTV for either side were considered for the patient.

Each patient rested for 5 min in the supine position. Then, the ABI was measured in the right and left limbs using a volume plethysmograph (FORM/ABI; Colin, Komaki, Japan) while the patient was asked to avoid any movement. All recordings were performed while the patients were receiving their regular medication. For the purpose of this analysis, the lowest ABI obtained for either side was taken as the ABI measurement for the patient.

The SYNTAX score [29] was measured as described by Ikeda et al. [8•]. The SYNTAX website reports the computation algorithm [29]. Each coronary lesion producing a stenosis equal to or greater than 50 % in vessels with a diameter greater than 1.5 mm was scored separately. The scores of the single lesions were summed to provide the overall patient's SYNTAX score. According to a previous study on the same cohort [8•], we defined the risk level on the basis of the SYNTAX score. We considered patients as having low risk if the SYNTAX score was lower than 22 (i.e., they belonged to the low-risk group), and we considered patients as having moderate to elevated risk if the SYNTAX score was higher than 22 (i.e., they belonged to the high-risk group). There were 80 patients in the high-risk group.

Correlation plots were constructed to assess the relationship between the various indexes (cIMT, IMTV, ABI, and SYNTAX score). Correlation was numerically measured by using the Pearson rho coefficient along with its 95 % confidence interval (CI). The statistical existence of correlation between the variables was measured by the correlation level of significance (correlation was considered significant if the p value was lower than 0.05). The normality of each continuous variable group was tested using the Kolmogorov–Smirnov Z test. Further, to assess the predictive value of the ABI, cIMT, and IMTV with respect to the severity of the risk (as measured by the SYNTAX score), we performed receiver operating characteristic (ROC) analysis and logistic regression. The severity of the risk was considered as the dependent variable. R (http://www.r-project.org) was used for the statistical analyses.

AtheroEdge™ was able to detect the cIMT in all patients from this population and its validation is yet to be published by our group (blinded for peer review). In detail, the average value of the cIMT evaluated at the level of the common carotid arteries was 0.881±0.334 mm. No significant differences were detected between the cIMT of men and women ($p > 0.1$). In a previous study (blinded for peer review), we showed that the cIMT measurement error we obtained when comparing the mesurements with an expert reader (sonographer with more than 10 years of experience in cIMT measurement) was 0.01±0.42 mm. The average IMTV was 0.141±0.112 mm.

Table 1 summarizes the demographics and the physical and clinical characteristics of the subjects studied. The SYNTAX score was 8.8±14.9, and the average ABI was 1.058±0.181.

Figure 2 shows the correlation plots between ABI and cIMT (Fig. 2a) and between ABI and IMTV (Fig. 2b). In both cases, there is a negative correlation. Table 2 reports the entire

Table 1 Demographics and clinical characteristics of the patients. The *rightmost column* reports the *p* value for the normality test (Kolmogorov–Smirnov)

Parameter	Value	Kolmogorov–Smirnov test
Male gender	62.3 %	–
Age	69±11 years	0.018
Patients with diabetes mellitus	17.4 %	–
Patients with hypertension	56.3 %	–
Albumin	4.14±0.37 g/dL	0.001[a]
Creatinine	1.58±2.09 mg/dL	0.001[a]
Hemoglobin A_{1c}	5.6±1.0 % (37±13 mmol/mol)	0.001[a]
Glucose	109±31 mg/dL	0.001[a]
Total cholesterol	182±38 mg/dL	0.604
Low-density lipoprotein cholesterol	105±34 mg/dL	0.556
High-density lipoprotein cholesterol	53±15 mg/dL	0.029
Triglyceride	122±70 mg/dL	0.001[a]
SYNTAX score	8.8±14.9	0.001[a]
ABI	1.058±0.181	0.004[a]
cIMT	0.881±0.334 mm	0.0001[a]
IMTV	0.141±0.112 mm	0.0002[a]

ABI ankle–brachial index, *cIMT* carotid intima–media thickness, *IMTV* intima–media thickness variability

[a] Statistically significant correlation

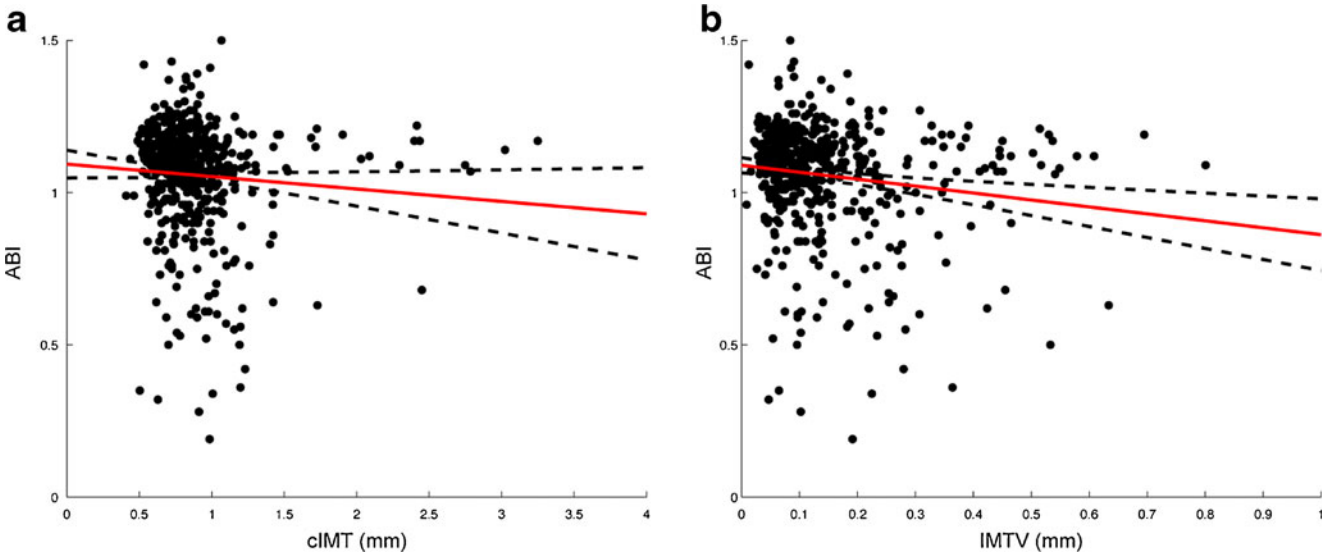

Fig. 2 **a** Correlation between ankle-brachial index (*ABI*) and carotid intima–media thickness (*cIMT*). **b** Correlation between ABI and intima–media thickness variability (*IMTV*). The correlation coefficient, the 95 % confidence interval, and the *p* value are reported in Table 2

set of correlation coefficients we computed for the data. The correlation coefficient between ABI and cIMT was −0.075 and was not statistically significant (p=0.0974). Conversely, the correlation coefficient between ABI and IMTV was −0.147 and was significant (p=0.001). Therefore, we found that IMTV was correlated with ABI, whereas cIMT was not.

As mentioned earlier, we computed the SYNTAX score for all the subjects. We also tested the correlation of cIMT and IMTV with the SYNTAX score. Figure 3a reports the correlation between the SYNTAX score and cIMT, whereas Fig. 3b reports the correlation between the SYNTAX score and IMTV. Correlation was positive and significant in both cases, but was higher for IMTV (ρ=0.230; p=0.00001) than for cIMT (ρ=0.225; p=0.0001).

Figure 4 reports the ROC graphs for the ABI, cIMT, and IMTV measurements as a function of the level of the patient's risk (as assessed on the basis of the SYNTAX score). The area under the ROC curve (AUC) for ABI was 0.6995 (95 % CI 0.6316–0.7673). The AUC for cIMT was 0.7089 (95 % CI 0.6466–0.7713), whereas that for IMTV was 0.7028 (95 % CI 0.6412–0.7644).

Table 3 reports the logistic regression results. The level of risk, assessed on the basis of the SYNTAX score, was considered as the dependent variable. The independent variables were ABI, cIMT, IMTV, diabetes mellitus, hypertension, and the levels of albumin and glucose. We found that ABI, cIMT, and IMTV were independently associated with the risk level and that IMTV had a higher coefficient (0.23795) with respect to cIMT (0.08511).

Table 2 Correlation coefficients between ABI, automatically measured cIMT (*Auto cIMT*), automatically measured IMTV (*Auto IMTV*), and SYNTAX score

	Correlation coefficient	*P*
ABI vs Auto cIMT	−0.075 (−0.161 to 0.014)	0.0974
ABI vs Auto IMTV	−0.147 (−0.232 to −0.060)	0.0010[b]
SYNTAX score vs Auto cIMT	0.225 (0.140–0.307)	0.00001[b]
SYNTAX score vs Auto IMTV	0.230 (0.145–0.311)	0.00001[b]

[a] The 95 % confidence interval is given in *parentheses*

[b] Statistically significant correlation

ABI and IMTV in the Prediction of CAD

CAD considerably overlaps with peripheral artery disease [6, 7]. Subjects with low ABI values have a considerably higher prevalence of CAD than those with normal ABI values. Fowkes et al. [7] showed that an ABI equal to or greater than 0.9 was associated with approximately twice the 10-year total mortality, cardiovascular mortality, and major coronary event rate compared with the overall rate in each Framingham risk score category. Ikeda et al. [24•] studied the relationship between ABI and the complexity of CAD. They showed that ABI is correlated to the SYNTAX score and that the combination of cIMT and ABI could be useful to predict the presence of CAD.

The main finding of this study was that IMTV was negatively correlated to ABI in a cohort of patients with CAD, but cIMT was not correlated in same population. This unprecedented observation might indicate that IMTV could be used as a complementary marker of CVD. Also, we showed that the performance of IMTV as an independent variable in predicting the severity of CAD (as measured by the SYNTAX score) is

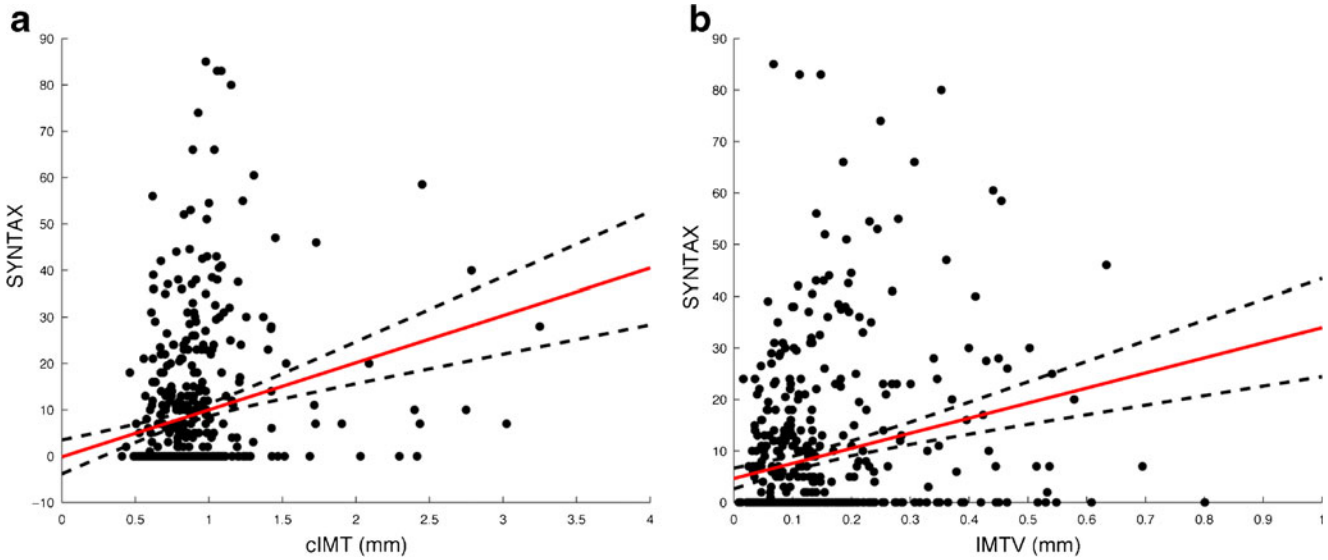

Fig. 3 **a** Correlation between the SYNTAX score and cIMT. **b** Correlation between the SYNTAX score and IMTV. The correlation coefficient, the 95 % confidence interval, and the *p* value are reported in Table 2

comparable to that of cIMT. This result is very important, since previous studies questioned the predictive value of cIMT as a single risk factor [30]. The negative results were partly attributed to the variability in the cIMT measurements. In our study, we adopted a validated [31] and automated system for cIMT measurement; therefore, we avoided any possible bias. Nevertheless, cIMT was not correlated with ABI and showed a correlation with the SYNTAX score that was equal to that of IMTV.

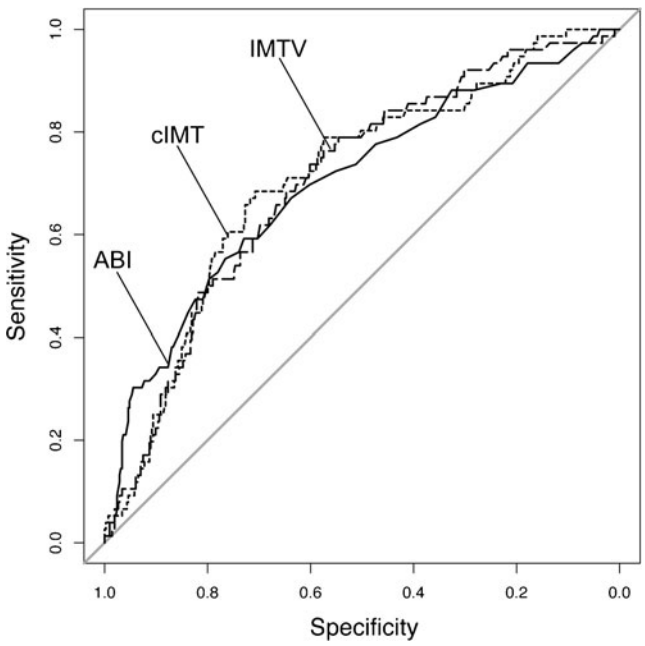

Fig. 4 Receiver operating characteristic curves for ABI (*solid line*), cIMT (*dotted line*), and IMTV (*dashed line*) with respect to the level of risk. The condition of high risk was determined as a SYNTAX score higher than 22

Ishizu et al. [32] evaluated the irregularity of cIMT and associated it with CAD. They showed that the IMT irregularity was a predictor of the presence of CAD. Labropulos et al. [33] associated higher values of the IMTV with increased cardiovascular risk. Specifically, they showed that patients who had increased risk factors showed an irregular wall/blood interface (i.e., an irregular LI interface). The technical limitation of this study was the manual measurement of the IMTV. In a previous study, we showed that manual and computer-based measurements of IMTV were not statistically different and that both measurements were correlated to the presence of symptoms in a cohort of Italian patients [15]. Therefore, for the first time, we applied automated IMTV measurement to the risk assessment of a population of CAD patients.

To further test the correlation between IMTV and ABI, we grouped the patients on the basis of the ABI. We considered patients with ABI greater than 0.9 (lower risk) and those with ABI of 0.9 or lower (higher risk),

Table 3 Logistic regression analysis results. The dependent variable was the level of risk based on the SYNTAX score and the independent variables were diabetes mellitus, hypertension, albumin concentration, and glucose concentration

Final independent variables	Coefficient	Standard error	*t*	*P*
ABI	−0.51996	0.08751	−5.942	5.40×10^{-9}
IMTV	0.23795	0.14495	1.642	0.1013
cIMT	0.08511	0.05530	1.539	0.1244
Diabetes mellitus	0.07524	0.04063	1.852	0.0647
Hypertension	0.07811	0.03109	2.513	0.0123

Table 4 Auto cIMT, Auto IMTV, and SYNTAX score in two groups of patients with a higher risk factor (ABI≤0.9) and a lower risk factor (ABI>0.9)

	ABI≤0.9 (*N*=120)	ABI>0.9 (*N*=380)	*P*
Auto cIMT (mm)	0.900±0.265	0.877±0.351	0.500
Auto IMTV (mm)	0.163±0.115	0.135±0.117	0.020[a]
SYNTAX score	14.1±18.0	7.0±13.5	0.0001[a]

[a] Statistically significant correlation

according to Fowkes et al. [7]. Table 4 reports the automatically measured cIMT and IMTV and the SYNTAX score for the two groups. It can be seen that patients with higher risk (ABI of 0.9 or lower) had statistically significant higher values of automatically measured IMTV and the SYNTAX score, but not of automatically measured cIMT. Therefore, in our population ABI had a significant correlation with automatically measured IMTV and other indexes of CAD, but not with automatically measured cIMT.

This study has some limitations. First, we studied a population of patients elected for coronary angiography. Hence, they had overall risk factors higher than those of the normal population. Further studies on other groups of patients are thus needed to fully validate the utility of automatically measured IMTV and its association with ABI. Second, about half of the patients had a SYNTAX score of zero and the overall SYNTAX score of the sample population was relatively low.

Conclusions

In conclusion, the results of our study showed that carotid IMTV automatically measured by AtheroEdge™ (from AtheroPoint, Roseville, CA, USA) was correlated with ABI, whereas the automatically measured cIMT was not. Even though larger studies are required, automated IMTV could be integrated with automated cIMT measurement to improve the assessment of CVD.

Compliance with Ethics Guidelines

Conflict of Interest Nobutaka Ikeda, Tadashi Araki, Kaoru Sugi, Masatako Nakamura, Martino Deidda, Filippo Molinari, Kristen M. Meiburger, U Rajendra Acharya, Luca Saba, Pier Paolo Bassareo, Michele Di Martino, Yoshinori Nagashima, Giuseppe Mercuro, Masataka Nakano, Andrew Nicolaides, and Jasjit S. Suri declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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