ORIGINAL ARTICLE

Aortic velocity propagation: A novel echocardiographic method in predicting atherosclerotic coronary artery disease burden

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Background: **The major burden of cardiovascular disease mortality around the globe is due to atherosclerosis and its complications. Hence its early detection and management with easily accessible and noninvasive methods are valuable. Aortic velocity propagation (AVP) through color M-mode of the proximal descending aorta determines aortic stiffness, reflecting atherosclerosis. The aim of this study was to find the utility of AVP in predicting coronary artery disease (CAD) burden assessed through SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) score and compared with carotid intima-media thickness (CIMT), which is an established surrogate marker of atherosclerosis.**

Methods: **In this cross-sectional comparative study, we measured AVP by color M-mode and CIMT by using Philips QLAB-IMT software in 100 patients, who underwent conventional coronary angiogram (CAG) between May 2013 and November 2014. Coronary artery disease is considered significant if >50% diameter stenosis is present in any epicardial coronary artery and insignificant if otherwise.**

Results: **Initially, to know the normal range we measured AVP and CIMT in 50 patients without any major risk factors for CAD but CAG was not done. Aortic velocity propagation ranged from 46 cm/s to 76 cm/s (mean = 58.62 þ 6.46 cm/s), CIMT ranged from 0.50 mm to 0.64 mm (mean = 0.55 þ 0.03 mm). Among 100 patients who underwent CAG we found 69% had significant CAD, 13% had insignificant CAD, and 18% had normal coronaries. Those with significant CAD had significantly lower AVP (41.65 þ 4.94 cm/s) [F (2,97) = 44.05, $p < 0.0001$] and significantly higher CIMT (0.86 þ 0.11 mm) [F (2,97) =35.78, $p < 0.0001$]. AVP had significant strong negative correlation with CIMT ($r = -0.836$, $p < 0.0001$, $n = 100$) and SYNTAX score ($r = -0.803$, $p < 0.0001$, $n = 69$), while CIMT was positively correlated with SYNTAX score significantly ($r = 0.828$, $p < 0.0001$, $n = 69$).**

Conclusions: **AVP and CIMT can predict CAD burden in a robust way. AVP may emerge as an exquisite bedside tool to predict atherosclerotic burden and guide in implementing preventive therapy for cardiovascular disease.**

Keywords: Aortic stiffness, Atherosclerosis, Intima-media thickness, Propagation velocity

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Introduction

The prevention of atherosclerosis and its complications is a major goal of cardiovascular health care. Currently, identifying patients who are at high risk for cardiovascular disease (CVD) prior to its development and disease prevention has taken a higher priority. Atherosclerosis involves a combination of fatty degeneration (atherosis) and vessel stiffening (sclerosis) of the arterial wall. Sclerotic changes have attracted less attention than atherosis because of the greater difficulty entailed in its assessment. Standard evaluation by histopathology and serial angiography is a sensitive method to determine atheromatous but not sclerotic changes. Atherosclerosis increases thickness and stiffness of the arterial wall and therefore it leads to increased arterial resistance. Increased arterial resistance results in decreased flow propagation velocity within the arterial lumen [1]. The color M-mode-derived aortic velocity propagation (AVP) of descending thoracic aorta by measuring arterial stiffness has been shown to be inversely correlated with coronary artery disease (CAD) [1,2], while other methods to assess arterial stiffness such as pulse wave velocity, aortic distensibility, and aortic strain are difficult to apply in practice. Also, a recent study found AVP was on par with pulse wave velocity and aortic distensibility in assessing arterial stiffness, with added advantage of ease and reproducibility in clinical practice.

Carotid intima-media thickness (CIMT) is increasingly used as a surrogate marker for atherosclerosis. The American Heart Association Writing Group 3, National Cholesterol Education Program Adult Treatment Panel III, the American Society of Echocardiography, Screening of Heart Attack Prevention and Education guideline, and European Society of Hypertension recommend measuring CIMT for redefining CVD risk assessment in patients with subclinical atherosclerosis [3]. Carotid intima-media thickness and brachial artery flow-mediated dilatation have been shown to be correlated with coronary atherosclerosis [4,5].

This study was done to find the utility of AVP in predicting CAD burden and compare with CIMT, which is an established surrogate marker of atherosclerosis.

Abbreviations

CVD	cardiovascular disease
AVP	aortic velocity propagation
CAD	coronary artery disease
SYNTAX	Score SYNergy between PCI with TAXus and cardiac surgery Score
CIMT	carotid intima-media thickness
CAG	coronary angiogram
NCEP-ATPIII	National Cholesterol Education Program Adult Treatment Panel III
SHAPE	Screening of Heart Attack Prevention and Education
TC	total cholesterol
TG	Triglycerides (TG)
HDL	high density lipoprotein
DT	deceleration time
IVRT	isovolumetric relaxation time
ANOVA	Analysis of Variance
ROC curve	receiver operating characteristic curve
SPSS	Statistical Package for Social Sciences
SVD	single vessel disease
DVD	double vessel disease
TVD	triple vessel disease

Methods

This was a cross-sectional comparative study in which 100 patients who required conventional coronary angiogram were included. Patients with severe valvular heart disease, aneurysm of the aorta, renal failure (serum creatinine >2 mg/dL), atrial fibrillation, frequent premature beats, left bundle branch block on electrocardiography, or poor echocardiographic image quality were excluded.

A baseline examination was performed, which included detailed medical history taking, physical examination, laboratory testing, and assessment of CVD status. The blood sample was taken after 12 hours of overnight fasting. Baseline biochemistry included serum lipid profile, fasting blood sugar, creatinine, urea, and liver function tests to rule out any other systemic illness or a secondary cause of dyslipidemia.

Total cholesterol, triglycerides, and high-density lipoprotein–cholesterol were analyzed using enzymatic methods, while low-density lipoprotein–cholesterol was computed from the Friedewald formula [6].

Informed consent was obtained from all individual participants included in the study. This study was approved by the hospital ethics committee.

Transthoracic echocardiographic examination

Two-dimensional transthoracic echocardiographic examination was performed at rest with S5-1 transducer using a commercially available echocardiographic machine (iE 33; Philips, Eindhoven, The Netherlands), according to established standards. Left ventricular diameters and the left atrial systolic diameter determined

from M-mode traces recorded from parasternal long-axis view. The pulsed Doppler sampling volume was placed between the tips of the mitral valve leaflets to obtain maximum filling velocities. Early diastolic flow (E), atrial contraction signal (A), E/A ratio, and E deceleration time were measured. Isovolumetric relaxation time was determined as the interval between the end of the aortic outflow and the start of the mitral inflow signal. Early diastolic mitral annular velocity by tissue Doppler was determined and then E/early diastolic mitral annular velocity was calculated. Left ventricular (LV) ejection fraction measured in parasternal short axis view at papillary muscle level and severity of LV systolic and diastolic dysfunction was graded based on American Society of Echocardiography guidelines [7,8].

Assessment of AVP

With the patient supine and from suprasternal view, color M-mode Doppler recordings were obtained with the cursor parallel to the main flow of direction in the descending thoracic aorta. Color Doppler Nyquist limit was set at 30–50 cm/s and switched to M-mode with a recorder sweep rate of 200 mm/s; an M-mode spatiotemporal velocity map in the shape of a flame was displayed. If the slope of the flame was unclear, baseline shifting was used to change the aliasing velocity until a clear delineation of the isovelocity slope was seen. The aortic flow propagation velocity was then calculated by dividing the distance between points corresponding to the beginning and end of the propagation slope with the duration between corresponding time points in cm/s.

Thus, AVP corresponds to the velocity at which the flow was propagating down the artery. The mean of three measurements was recorded as the AVP value, similar to Gunes et al. [1] (Fig. 1).

CIMT assessment

Both common carotid arteries of the patients were scanned longitudinally with an L11-3 MHz linear transducer using a commercially available echocardiographic machine (iE 33 with QLAB-IMTl; Philips). The bulb dilation served as a landmark to indicate the border between the distal common carotid artery and the carotid bulb. Images were obtained from the distal portion of the common carotid artery, 1–2 cm proximal to the carotid bulb.

The two bright echogenic lines represent the intima and media lines. The intima-media thickness was measured as the distance from the leading edge of the first to the second echogenic line. Only far wall intima-media thickness of the distal 1-cm portion of the common carotid artery, just before bifurcation, was measured at end-diastole using QLAB-IMT software (Philips) [9,10].

Coronary angiography

Coronary angiography was done percutaneously via femoral or radial artery with standard Judkins or Tiger catheters respectively by modified Seldinger technique using the Artis zee cardiac angiography system (Siemens, Munich, Germany). Coronary angiograms were interpreted visually and always analyzed in two orthogonal views and considered significant if $\geqslant$50% diameter stenosis and insignificant if <50% diameter stenosis was seen [11]. CAD burden was assessed by computer-assisted SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) scoring algorithm [12].

Statistical analysis

We analyzed normality of distribution for variables using Kolmogorov–Smirnov and

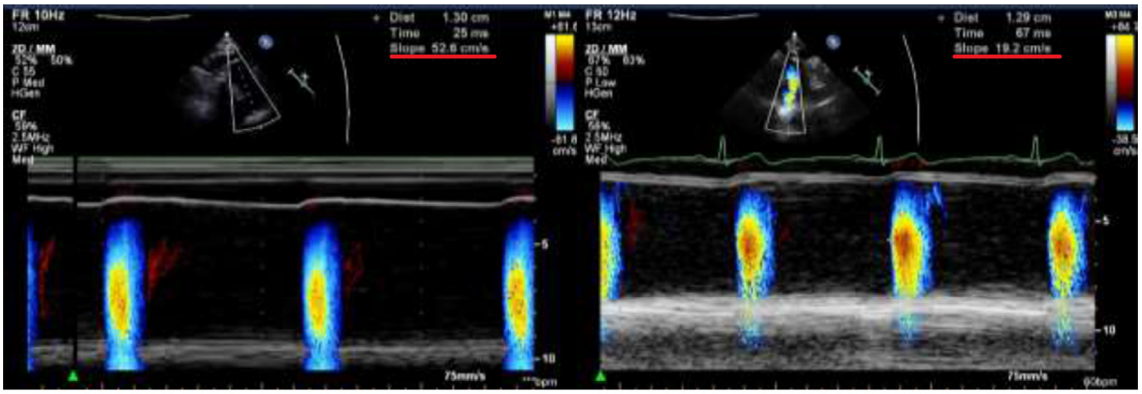

Figure 1. Measured (A) aortic velocity propagation in a patient with normal coronaries versus (B) a patient with significant coronary artery disease.

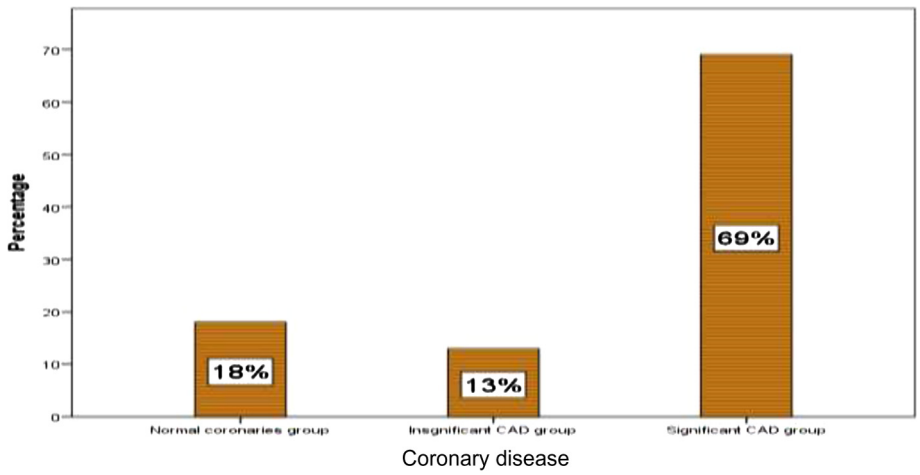

Figure 2. Bar chart showing distribution of study population based on coronary angiogram subgroups. CAD = coronary artery disease.

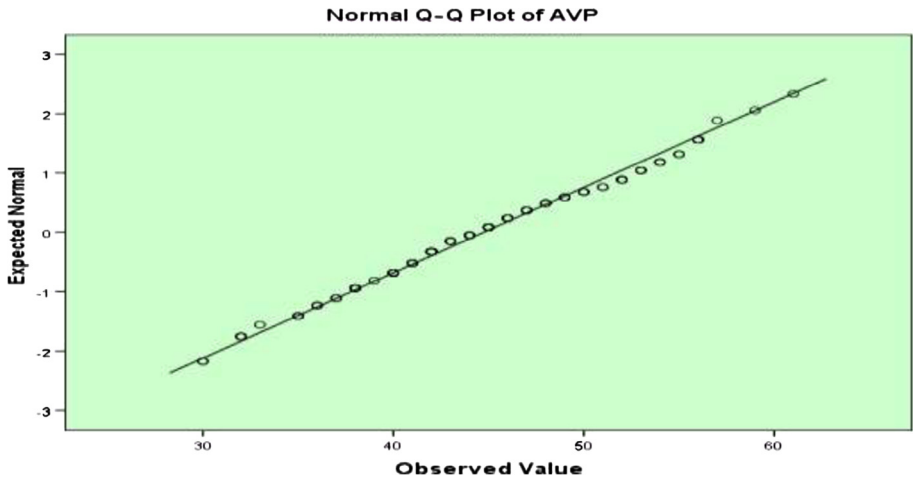

Figure 3. Normal Q-Q plot for distribution of aortic velocity propagation in the study population. AVP = aortic velocity propagation.

Table 1. Clinical and demographic characteristics of study population.

	Normal coronaries group (n = 18)	Insignificant CAD group (n = 13)	Significant CAD group (n = 69)	p
Mean age (y)	51.50 ± 10.5	56.77 ± 10.1	54.81 ± 9.4	0.29
Male sex	9.2%	7.7%	83.1%	<0.0001*
Smoking	5.4%	13.5%	81.1%	0.04*
Hypertension	6.4%	10.6%	83%	0.008*
Diabetes mellitus	3.6%	17.9%	78.6%	0.06
Family history of premature CAD	33.3%	33.3%	33.3%	0.37
Total cholesterol (mg/dL)	204.9 ± 53.5	199.5 ± 40.9	202.4 ± 43.7	0.94
Triglycerides (mg/dL)	212.8 ± 61.9	190.1 ± 58.1	219.9 ± 86.0	0.46
LDL-cholesterol (mg/dL)	127.1 ± 50.4	126.5 ± 38.6	123.8 ± 43.6	0.94
HDL-cholesterol (mg/dL)	35.2 ± 5.0	34.9 ± 5.8	34.61 ± 5.1	0.89
LVEF (%)	59.1 ± 5.3	50.85 ± 12.6	50.16 ± 10.3	0.004*

CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = high-density lipoprotein; LVEF = left ventricular ejection fraction.
* Indicates significant at $p < 0.05$.

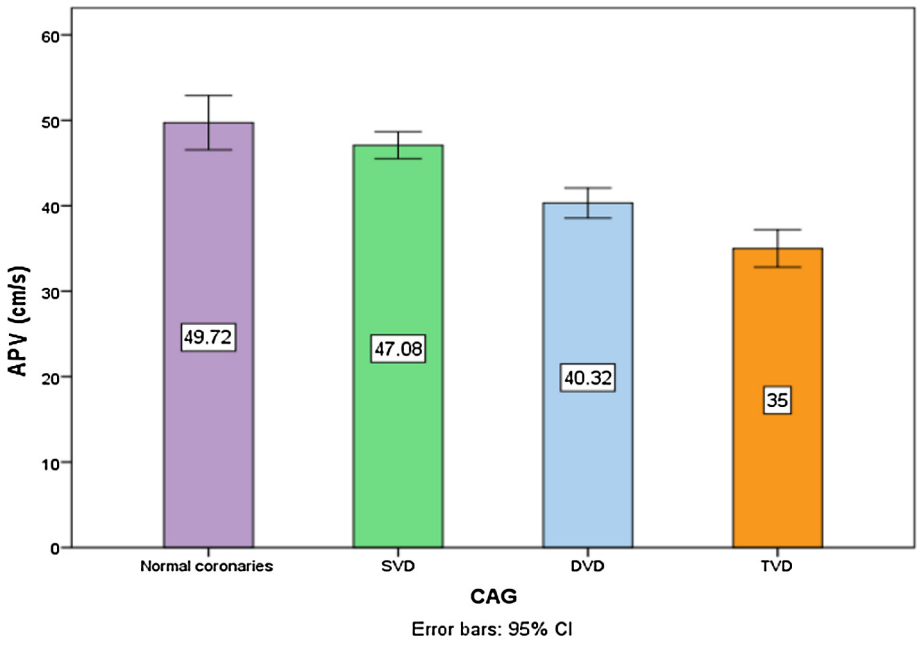

Figure 4. Bar chart with error bars showing mean aortic velocity propagation ± 95% confidence interval based on number of coronaries involved. AVP = aortic velocity propagation; CAG = coronary angiogram; DVD = double vessel disease; SVD = single vessel disease; TVD = triple vessel disease.

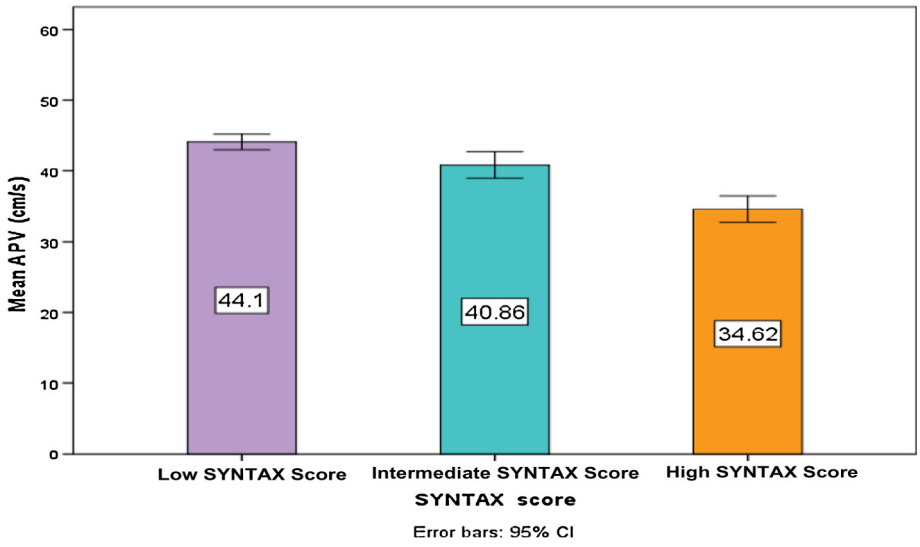

Figure 5. Bar chart with error bars showing mean aortic velocity propagation ± 95% confidence interval based on SYNTAX score. AVP = aortic velocity propagation; CI = confidence interval.

Shapiro–Wilk tests. Quantitative variables were expressed as mean ± standard deviation and qualitative variables as numbers and percentages. Differences between conventional coronary angiogram (CAG) groups were assessed by one-way analysis of variance (ANOVA) test and univariate ANOVA to compare groups based on coronaries involved. Mann–Whitney *U* test for variables without a normal distribution, and the Chi-square test for qualitative variables. Pearson correlation analysis was used to assess the relation between AVP and CIMT and also between other quantitative variables. Simple linear regression and multivariate regression analysis were performed with AVP as the dependent variable. Receiver operating characteristic (ROC) curve analysis was done for AVP to assess its sensitivity, specificity, and likelihood ratio in predicting CAD.

Data analysis was performed using SPSS for Windows version 21 (SPSS Inc., Chicago, IL, USA). Microsoft Word and Excel were also used to generate tables and graphs. All results were

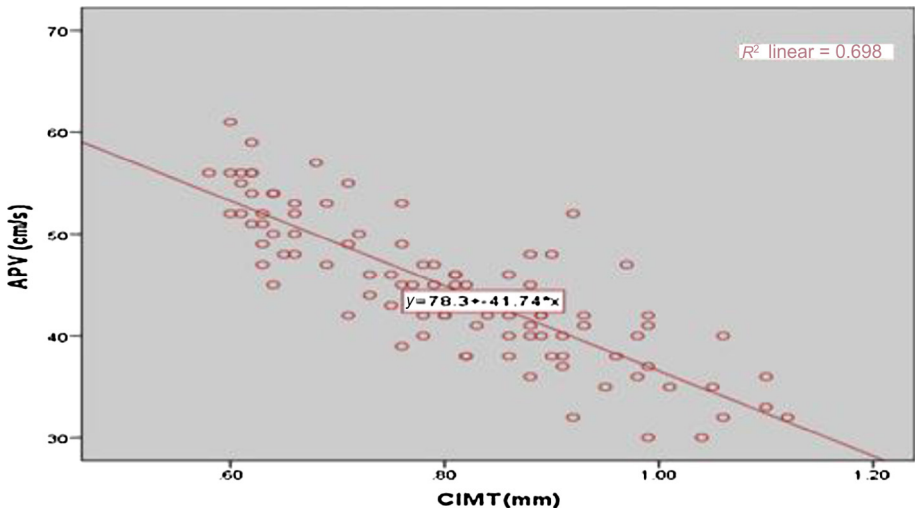

Figure 6. Scatter plot of showing simple linear regression equation of aortic velocity propagation from carotid intima-media thickness. AVP = aortic velocity propagation; CIMT = carotid intima-media thickness.

considered statistically significant at the level of $p < 0.05$.

Results

Initially, to know the normal range in the population, we measured AVP and CIMT in 50 patients without any major risk factors for CAD but CAG was not done. In this, 30% were women and the mean age was 40 ± 6.8 years. Aortic propagation velocity ranged from 46 cm/s to 76 cm/s with a mean of 58.62 ± 6.46 cm/s, CIMT ranged from 0.50 mm to 0.64 mm with a mean of 0.55 ± 0.03 mm.

In the study population, the clinical and demographic characteristics were similar among CAG subgroups except for male sex, smoking, hypertension, and LV ejection fraction (Table 1). In the study population, 49% had single vessel disease, 22% had double vessel disease, 11% had triple vessel disease, and 18% had normal coronaries. Based on coronary artery disease on CAG the study population was analyzed as three subgroups: normal coronaries group, insignificant CAD group, and significant CAD group (Fig. 2).

AVP was normally distributed on testing with Kolmogorov–Smirnov test and Shapiro–Wilk test with acceptable skewness and kurtosis (Fig. 3). The mean AVP in significant CAD group was low (41.65 ± 4.94 cm/s) compared with 49.72 ± 6.38 cm/s in normal coronaries group. There was a statistically significant difference between the groups and within the groups, as determined by one-way ANOVA [F (2,97) = 44.05, $p < 0.0001$].

A Fisher least significant difference (LSD) *post hoc* test showed significantly lower AVP in the 'significant CAD' group when compared with other two groups. We found statistically significant difference between the groups and within the groups based on the number of epicardial coronaries involved, as determined by univariate ANOVA [F (3,96) = 27.03, $p < 0.0001$]. A Fisher LSD *post hoc* test showed significantly lower AVP (35.00 ± 3.26 cm/s) in the triple vessel disease group when compared with the other two groups (Fig. 4). For those with significant CAD on CAG, we further calculated SYNTAX score for CAD burden, categorized as low SYNTAX score if $\leqslant 22$, intermediate if the score was 22–32, and high SYNTAX score if $\geqslant 33$.

We found a statistically significant difference between the groups and within the groups as determined by one-way ANOVA [F (2,66) = 39.30, $p < 0.001$]. A Fisher LSD *post hoc* test showed significantly lower AVP (34.62 ± 3.12 cm/s) in the high SYNTAX score group when compared with the other two groups (Fig. 5).

We found a statistically significant difference in CIMT among CAG subgroups as determined by one way ANOVA [F (2,97) = 35.78, $p < 0.0001$]. A Fisher LSD *post hoc* test showed significantly higher CIMT in the significant CAD group when compared with the other two groups ($p < 0.0001$), but found no significant difference between insignificant CAD and normal coronaries groups ($p = 0.693$). Also, when mean CIMT was compared between SYNTAX categories we found a significantly higher CIMT (1.00 ± 0.07 mm) in the high SYNTAX score group compared with the other two groups ($p = 0.008$).

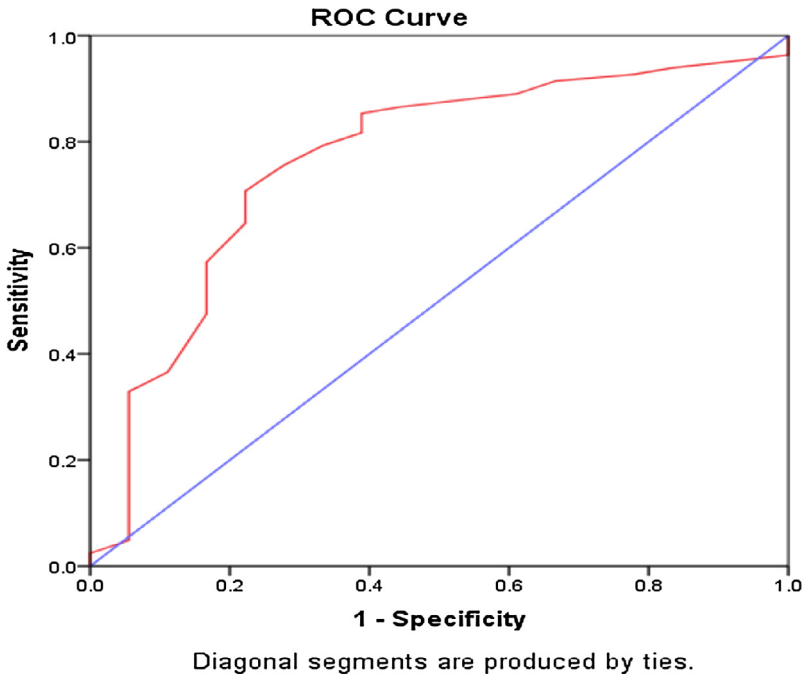

Figure 7. Receiver operating characteristic curve of aortic velocity propagation for predicting coronary artery disease. ROC = receiver operating characteristic.

Correlation of AVP and CIMT with major risk factors for CAD

On Pearson correlation analysis, we found that AVP and CIMT were inversely correlated with systolic blood pressure (SBP), age, duration of diabetes mellitus, and low-density lipoprotein–cholesterol levels but attained statistical significance for SBP only ($r = -0.252$, $p = 0.01$).

Correlation of AVP with CIMT and SYNTAX score

Pearson correlation analysis was conducted to examine the relationship between AVP and CIMT. Results showed a significantly strong negative correlation between AVP and CIMT ($r = -0.836$, $p < 0.0001$, $n = 100$). Also, AVP was inversely correlated with SYNTAX score in significant CAD group ($r = -0.803$, $p < 0.0001$, $n = 69$), while CIMT was positively correlated with SYNTAX score ($r = 0.828$, $p < 0.0001$, $n = 69$).

Regression analysis

On simple linear regression analysis, AVP can be regressed from CIMT as AVP = 78.3 + (−41.74) × CIMT with R^2 linear being 0.698, $p < 0.0001$ (Fig. 6).

On multivariate analysis, AVP was significantly associated with CIMT, SYNTAX score, and SBP but on multiple linear regression analysis, AVP can be regressed from CIMT and SYNTAX score significantly, excluding SBP as AVP = 69.61 + (−27.13 × CIMT) + (−0.18 × SYNTAX score).

ROC curve analysis of AVP for predicting CAD

The area under the curve was 0.764, rejecting the null hypothesis (Fig. 7). Based on the ROC curve, the optimal cutoff value of AVP was ⩽47.5 cm/s, which had 76% sensitivity and 72% specificity with positive likelihood ratio being 2.71. The diagnostic cut-off value of AVP in predicting CAD was ⩽40.5 cm/s with 99% specificity and positive likelihood ratio of 3.3 and cut-off value for screening was ⩽53.5 cm/s with 92% sensitivity.

Discussion

This is the first study to compare AVP by color M-mode of proximal descending aorta (a novel echocardiographic method to assess aortic stiffness reflecting atherosclerosis) with documented CAD burden assessed through SYNTAX score (searched PubMed, Medline, EMBASE, Scopus EBSCO, web of science, IndMed, Medind). We also compared AVP with CIMT, which is an established surrogate marker of atherosclerosis.

Aortic stiffness is associated with cardiovascular risk factors such as smoking, obesity, hypertension, diabetes, and older age. As the extent and the severity of the atherosclerosis increases, aortic

distensibility and aortic strain decrease. As atherosclerosis progress, tunica media increases in thickness and tunica media gets stiffer. It is very valuable to detect atherosclerotic disease before clinical disease manifests using a noninvasive method. Endothelial dysfunction is the first stage of atherosclerosis. Atherosclerosis increases arterial wall thickness and the stiffness of the aorta. The arterial resistance will increase as the arterial wall gets stiff and thick and the increase in arterial resistance decreases the flow AVP.

Fazio et al. [13] reported that the presence of atherosclerotic plaque in the thoracic aorta was a marker for significant CAD at angiography with a sensitivity of 90% and a specificity of 90% (positive predictive value 95%, negative predictive value 82%) [14]. Hence aortic stiffness reflecting atherosclerosis was studied by various methods of which pulse wave propagation velocity and AVP drew attention in view of ease and noninvasiveness in their assessment.

CIMT measurement with B-mode ultrasonography has been frequently used for the detection of atherosclerosis in many epidemiological studies due to its ease, reproducibility, noninvasiveness, and economy.

Mean AVP in significant CAD group was 41.65 ± 4.94 cm/s compared with 49.72 ± 6.38 cm/s in normal coronaries group. Gunes et al. [1] and Sen et al. [15] also found lower AVP in CAD group, which was in support of this study.

Correlation of CIMT with CAD

In this study, we found mean CIMT is significantly higher in significant CAD group compared with the normal coronaries group [$F(2,97) = 35.78$, $p < 0.0001$], which was also observed by Sen et al. [15].

We also found no significant difference in CIMT between the insignificant CAD group and normal coronaries group, emphasizing higher CIMT with significant CAD. We also assessed relation between CIMT and CAD burden by SYNTAX score, which showed a significant strong positive correlation with SYNTAX score ($r = 0.828$, $p < 0.0001$, $n = 69$) which was in accordance with Ikeda et at study [16] in which only CIMT was compared with SYNTAX score.

Correlation of AVP with CAD

Few studies compared AVP with documented coronary artery disease by conventional coronary angiography. One of the major findings of our study is that AVP is inversely correlated with severity of CAD which is similar to those published by Gunes et al. [1] and Sen et al. [15]. Sen et al. [15] compared AVP with Gensini score but found it to be not significant. Unique to this study is that we found that AVP has strong and inverse correlation with SYNTAX score ($r = –0.803$, $p < 0.0001$) which is now appropriate with the guidelines instead of Gensini score. Also found significantly lower AVP in those with high SYNTAX score compared with intermediate and low SYNTAX score groups [$F(2,66) = 39.30$, $p = < 0.001$] which was not shown in any of the previous studies.

Correlation of AVP with CIMT

Similar to Simsek et al. [2], Sen et al. [15], and Guntekin et al. [17], we also found that AVP was significantly inverse correlated with CIMT ($r = –0.836$, $p < 0.0001$). Mohan et al. [18] and Geroulakos et al. [19] assessed CIMT in Indian individuals as mean of six measurements manually, but we used Philips QLAB-IMT advanced software. According to the guidelines of European Society of Cardiology, the level of CIMT >0.9 mm was accepted as the target organ injury cut-off point [20]; in our study mean CIMT in significant CAD group was 0.86 ± 0.10 mm (0.76–0.96 mm). Also, AVP was relatively better at predicting CAD burden when compared with CIMT.

Clinical perspective

Since AVP through color M-mode is noninvasive and economical, this novel method will be useful in screening larger population. This may be valuable in detection and management of individuals at high risk for CVD events. It can also be integrated into cardiac risk stratification of individuals for primary prevention in addition to other CVD risk prediction scores.

Limitations

Measurement and reproducibility of AVP with color M-mode is a limitation, however, with the present advanced echocardiography machines and by using Garcia et al.'s method [21] one can reduce intra- and interobserver variability. Poor echo image quality with suprasternal views in short-necked, obese individual is a limitation. In view of positive results a larger study is underway.

Conclusions

This novel transthoracic color M-mode propagation velocity of the descending thoracic aorta (AVP) may emerge as an exquisite bedside tool to predict atherosclerotic burden and guide in

implementing preventive therapy for cardiovascular disease.

This study showed that by assessing AVP with transthoracic echocardiography and CIMT with B-mode ultrasound, one can predict CAD burden in a robust way and AVP was relatively better at predicting CAD burden compared with CIMT.

The strength of this study lies in it being the first to compare AVP and CIMT with CAD burden assessed through SYNTAX score, which is more validated now with the guidelines [22].

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