

Atherosclerotic coronary artery disease: The accuracy of measures to diagnose preclinical atherosclerosis

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Abstract. Different methods can be used to diagnose early pre-clinical stage atherosclerosis. The present study was carried out to evaluate the efficiency of these methods. Measures including carotid intima-media thickness (CIMT), pulse wave velocity (PWV), and coronary calcium score (CCS) were evaluated for the detection of coronary artery disease (CAD). We studied the clinical and biochemical profiles of individuals with non-CAD and CAD to assess measures of pre-clinical atherosclerosis. The association between CIMT, PWV and CCS on the one hand, and the coronary atherosclerosis on the other, was studied. In total, 150 cases of cardiovascular disease (CVD) participated in the present study and were subjected to computed tomographic (CT) coronary angiography to divide them into non-CAD (n=100) and CAD (n=50) groups. The patients were also subjected to pre-clinical atherosclerosis tests (CIMT, PWV and CCS). CAD patients had higher CIMT values on both sides (right side, 0.74 ± 0.09 vs. 0.62 ± 0.12 mm; left side, 0.78 ± 0.16 vs. 0.64 ± 0.19 mm; and average, 0.76 ± 0.12 vs. 0.63 ± 0.14 mm; all P-values <0.01). These patients also had significantly higher brachial-ankle PWV (baPWV) on left side (1638.8 ± 372.9 vs. 1498.6 ± 339.8 cm/sec, P<0.001). The overall CCS was significantly increased in CAD patients as compared to the patients without CAD (117.8 ± 118.6 vs. 8.6 ± 18.3 , P<0.001). In conclusion, the present study showed that among different measures of preclinical atherosclerosis, CCS had the best diagnostic accuracy. However, the combination of CIMT and baPWV had an excellent negative predictive value for atherosclerotic coronary vascular disease.

Introduction

Early detection of atherosclerosis in its pre-clinical stage has emerged as a promising approach to facilitate optimum cardiovascular (CV) risk stratification in asymptomatic individuals (1-4). Although definitive outcome data is absent, preliminary evidence suggested that addition of atherosclerosis imaging to conventional risk assessment tools may help us to achieve a better understanding about the nature and the aggressiveness of the preventive measures and can thus improve the clinical outcomes (5). There is scarce evidence suggesting that detection of structural evidence of atherosclerosis may improve patient compliance toward therapeutic measures (6-10). The endothelium has an important role in maintaining vascular homeostasis (3,4). Endothelial function can be measured in a variety of ways using invasive and non-invasive techniques in the coronary and peripheral circulation. The clinical examination of endothelial function involves assessing its ability to release NO in response to various exogenous and endogenous stimuli (11). Evaluation of reproducible, non-invasive techniques for assessing endothelial function should enable us to screen large populations and may guide us to design methods to reduce the individual's vascular risk.

Numerous tools have been developed for pre-clinical atherosclerosis assessments. This list includes carotid intima-media thickness (CIMT), brachial artery flow-mediated dilatation, pulse wave velocity (PWV) and coronary calcium score (CCS). Although these techniques can detect one or more atherosclerotic indicators, they have substantial methodological differences that are responsible for the differences in their availability, cost, ease of use, repeatability, and radiation exposure. Given these differences, it is imperative to determine their relative diagnostic accuracy in order to be able to accurately define their role in routine clinical practice. Although studies conducted in western populations suggested that CCS had the best predictive accuracy (12,13), few studies have compared different modalities of pre-clinical atherosclerosis detection in the Indian populations (14).

The present study was conducted to compare the strength of three commonly used and approved measures of pre-clinical atherosclerosis assessment methods, namely CIMT, PWV and CCS. In this study we evaluated the clinical and biochemical profiles of non-coronary artery disease (CAD) and CAD cases.

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We also verified the association of CIMT, PWV and CCS with coronary atherosclerosis.

Patients and methods

A total of 150 cases were recruited and participated in this study (irrespective to previous history of cardiovascular disease). Patients were divided into two groups: The non-CAD group, including those without any evidence of atherosclerotic coronary vascular disease (n=100) and the CAD group, which included patients with evidence of atherosclerotic coronary vascular disease (n=50). Patients were included in non-CAD group if they met all the following criteria: i) No previous history of documented CAD; ii) no atherosclerotic plaque seen on conventional or computed tomographic (CT) coronary angiography.

In contrast, the patients were assigned to CAD group if any of the following conditions was present: i) Any previous history of documented CAD, with or without coronary revascularization; ii) coronary angiography (conventional or CT) showing evidence of significant CAD defined as >50% luminal narrowing involving at least one epicardial coronary artery; or iii) evidence of coronary plaques, even with less significant luminal obstruction (<50%), on conventional or CT coronary angiography.

All cases underwent clinical evaluation, biochemical tests and assessment of pre-clinical atherosclerosis. Clinical evaluation included detailed history regarding the presence or absence of CV risk factors, duration of CV risk factors, and use of statins. Physical examination included height, weight and blood pressure measurement and the examination of CV system. Blood pressure was measured in the right arm in supine position, using a standard sphygmomanometer. Biochemical tests included fasting and 2-h postprandial blood glucose measurements, fasting lipid profile and the measurement of high-sensitivity C-reactive protein (hsCRP). Pre-clinical atherosclerosis assessment included CIMT measurement, PWV assessment and CCS estimation.

HT was defined according to Joint National Committee (JNC) 7 guidelines as systolic BP \geq 140 mmHg or diastolic BP \geq 90 mmHg or previous history of HT or self-reported use of anti-hypertensive medications (15). Diabetes mellitus was defined as fasting blood glucose >126 mg/dl or 2-h postprandial blood glucose >200 mg/dl or pharmacological treatment for diabetes or previous history of diabetes mellitus. Family history was considered positive if a coronary event had occurred in a male first-degree relative before the age of 55 years or a female first-degree relative before the age of 65 years. Smoking or tobacco use in any form during the preceding month was also considered to be a CV risk factor.

CIMT assessment. For CIMT measurement, distal common carotid artery (CCA) was imaged on both sides with a 7.5 MHz frequency linear array transducer, attached to any standard vascular ultrasound machine. The artery was imaged in a longitudinal plane to obtain optimal angle of incidence, defined as the plane in which the bifurcation of the carotid bulb into the internal and external carotid arteries can be visualized simultaneously with the bulb and distal CCA (also known as 'tuning fork'). Once this view was obtained, finer adjustments

in the transducer position was done to make sure that distal CCA was perfectly horizontal on the screen and 'double lines' of intima and adventitia were clearly visualized in the far wall of the CCA ('double-line' sign). From this view, the CIMT was measured as the distance between lumen-intima interface and the media-adventitia interface. Plaques, defined as >50% localized thickening of the intima compared to the rest of the wall, were included in the measurement of CIMT if present within the distal 1 cm of CCA.

The CCA was then imaged from two additional complementary angles, approximately 45° anterior and posterior to the first image and the CIMT measurements were performed. The three values thus obtained for each side were averaged and used for analysis. Reproducibility of CIMT measurement in our lab was documented (16).

PWV measurement. Measurement of PWV was performed using the PeriScope® device (Genesis Medical Systems Pvt. Ltd., Hyderabad, India) which was shown to have high degree of reproducibility for this purpose (17). This device was based on oscillometric method and records arterial pressure waveforms noninvasively. ECG-gated pressure waveforms were recorded simultaneously from both arms and both ankles. From these pressure waveforms, in-built software automatically calculates PWV for different vascular segments (18).

The procedure was performed during the morning hours, after overnight fast for 10 h. Participants were asked to refrain from smoking for at least 4 h before the procedure. On going medications were not discontinued but the morning dose was delayed until completion of the test. The procedure was performed in supine position. After 10 min of supine rest, four BP cuffs, which were connected to the PeriScope® device, were tied around both arms and both ankles. These BP cuffs carried oscillometric sensors to record pressure waveforms from the underlying arteries. ECG electrodes were put on the wrists and ankles to record ECG simultaneously. The machine then automatically inflated and deflated the cuffs simultaneously, while recording pressure waveforms from the four sites. From these pressure waveforms, right and left brachial-ankle PWV (baPWV) were calculated and used for analysis.

Coronary calcium scoring. Heart multidetector CT was performed using dual-source dual-energy Somatom Definition Flash (Siemens Healthcare, Erlangen, Germany) with 128x0.6 mm collimation, rotation time 75 msec and tube voltage of 80 and 140 kV. In single breath-hold, images were taken from the tracheal bifurcation level to the base of the heart using prospective ECG triggering with the center of the acquisition at 70% of the R-R interval. From the raw data, the images were reconstructed with standard kernel in 3-mm thick axial, non-overlapping slices and 25 cm field of view. All image analyses were performed on a dedicated workstation (MMWP and syngo.via; Siemens Healthcare). A coronary calcified lesion was defined as an area with a density >130 Hounsfield units and covering at least 6 pixels. The Agatston method was used to determine the CCS by multiplying each lesion area by a weighted CT attenuation score in the lesion (19).

Statistical analysis. The data analysis was done in line with study objectives. Statistical analyses were performed using

SPSS version 16.0. Values were expressed as mean \pm standard deviation or as percentages. Comparisons between the groups were carried out using Student's unpaired t-test or Chi-square test as appropriate. A P-value of 0.05 was considered to indicate a statistically significant difference.

Results

Patients in the non-CAD group were older (62.9 ± 3.2 vs. 39.6 ± 8.2 years, $P < 0.001$) than those in the CAD group. However, there was no significant difference between the two groups in terms of hypertension, diabetes, smoking and family history of premature CAD. The two groups did not show any significant difference in body mass index, systolic or diastolic blood pressure or hsCRP. However, as expected, the CAD patients were more likely to be on statin therapy (84.0 vs. 34.0%, $P < 0.001$) which probably accounted for their lower total cholesterol, low-density lipoprotein cholesterol and triglyceride levels (Table I).

CAD patients had increased CIMT values on both sides (right side, 0.74 ± 0.09 vs. 0.62 ± 0.12 mm; left side, 0.78 ± 0.16 vs. 0.64 ± 0.19 mm; and average, 0.76 ± 0.12 vs. 0.63 ± 0.14 mm; all P-values < 0.01). These patients also had significantly higher baPWV on the left side (1638.8 ± 372.9 vs. 1498.6 ± 339.8 cm/sec, $P < 0.001$). The overall CCS was significantly higher in CAD patients when compared to the patients in the non-CAD group (117.8 ± 118.6 vs. 8.6 ± 18.3 , $P < 0.001$) however, there were no significant differences in right side baPWV or the average of the two (Table II).

Discussion

Over the past few decades, atherosclerotic cardiovascular disease (CVD) has become the leading cause of death worldwide. The rapid increase in the incidence and prevalence of CVD has led to a growing recognition of the need to develop and implement effective strategies for its prevention. Raising awareness to CVD risk and the role of healthy life-style appears to be the most effective strategy for CVD prevention. Nevertheless, these efforts have been greatly limited by negligence and general apathy amongst public toward the healthy life-style measures. A more effective strategy may be to identify 'high-risk' individuals and focus all efforts and resources to prevent the development of disease in this group. Presently, CV risk assessment is generally performed using conventional CV risk factors and risk algorithms such as Framingham risk score. Several studies have shown that although these risk algorithms perform reasonably well at the population level, their accuracy at the individual level is rather dismal (20-23). Frequently we find individuals with multiple CV risk factors and high estimated CV risk who do not necessarily develop clinical CVD even in the long term, whereas there are other patients who present with acute CV event despite being free of all known major CV risk factors. To overcome this limitation, several diagnostic tools with the capability of detecting atherosclerotic vascular disease in early, pre-clinical stages have been developed recently. These tools can provide direct evidence on ongoing atherosclerotic process, irrespective of the presence or absence of known CV risk factors. Numerous large-scale studies have unequivocally

Table I. Clinical and biochemical characteristics of patients in both groups.

Parameters	Non-CAD group (n=100)	CAD group (n=50)	P-value
Age (years)	39.6 \pm 8.2	62.9 \pm 3.2	<0.001
Gender (Male)	78 (78.0%)	42 (84.0%)	0.64
Hypertension	76 (76.0%)	42 (84.0%)	0.06
Diabetes mellitus	15 (15.0%)	25 (50.0%)	0.003
Family history of premature coronary artery disease	48 (48.0%)	35 (70.0%)	0.01
Current smoking	39 (39.0%)	23 (46.0%)	0.08
Statin use	34 (34.0%)	42 (84.0%)	0.001
Total cholesterol (mg/dl)	192.0 \pm 32.6	168.0 \pm 25.2	<0.001
HDL-cholesterol (mg/dl)	42.0 \pm 11.3	40.4 \pm 10.5	0.31
LDL-cholesterol (mg/dl)	108.5 \pm 23.1	84.2 \pm 27.4	<0.001
Triglycerides (mg/dl)	162.6 \pm 35.0	132.9 \pm 41.8	0.002
Body mass index (kg/m ²)	29.2 \pm 2.1	28.3 \pm 2.8	0.48
Systolic blood pressure (mmHg)	134.4 \pm 9.6	131.9 \pm 10.2	0.77
Diastolic blood pressure (mmHg)	82.5 \pm 6.5	84.8 \pm 6.9	0.26
Fasting blood glucose (mg/dl)	104.3 \pm 25.7	112.4 \pm 31.7	0.09
hsCRP (mg/dl)	3.1 \pm 5.0	5.4 \pm 4.6	0.25

CAD, coronary artery disease; hsCRP, high-sensitivity C-reactive protein.

Table II. Pre-clinical atherosclerosis in patients in both groups.

Parameter	Non-CAD group (n=100)	CAD group (n=50)	P-value
CIMT (mm)			
Right side	0.62 \pm 0.12	0.74 \pm 0.09	0.008
Left side	0.64 \pm 0.19	0.78 \pm 0.16	0.005
Average	0.63 \pm 0.14	0.76 \pm 0.12	0.003
Pulse wave velocity (cm/sec)			
Right brachial-ankle	1632.0 \pm 376.5	1584.6 \pm 325.6	0.51
Left brachial-ankle	1498.6 \pm 339.8	1638.8 \pm 372.9	<0.001
Average brachial-ankle	1518.2 \pm 323.0	1589.2 \pm 307.7	0.58
CCS	8.6 \pm 18.3	117.8 \pm 118.6	<0.001

CAD, coronary artery disease; CIMT, carotid intima-media thickness; CCS, coronary calcium score.

demonstrated the incremental value of such techniques over conventional CV risk factors in prediction of future CV risk (4,18,24). The benefits of the incorporation of these diagnostic techniques into the standard risk assessment approach is still unclear, however existing evidence suggests that such a strategy can be very helpful. It can help us to

have a better understanding about the nature, timing and aggressiveness of anti-atherosclerotic therapy. Also it can help us in improving patient's compliance toward these measures and may aid in monitoring the response to therapy (1,2,4-10).

CIMT, brachial artery flow-mediated dilatation, PWV assessment, ankle-brachial index and CCS are the most commonly used pre-clinical atherosclerosis measures. All these tools are used to detect evidence of atherosclerosis in different vascular beds with the underlying rationale that atherosclerosis is a generalized disease and its presence in one vascular bed indirectly implies involvement, though not necessarily concurrently, also of other vascular beds. However, these techniques are methodologically vastly different from each other and therefore have significant differences in their availability, cost, ease of use, repeatability, and radiation exposure. As many of these techniques are already available for clinical use, it is important to determine their relative diagnostic accuracy in order to allow for their judicious, cost-effective and meaningful use in routine clinical practice.

In conclusion, the present study shows that among different measures of pre-clinical atherosclerosis, CCS is the most accurate diagnostic tool for the detection of coronary atherosclerosis. However, the combination of CIMT and baPWV has an excellent negative predictive value for atherosclerotic coronary vascular disease and can therefore be used as a simple, non-invasive, less expensive and radiation-free approach to initial CV risk stratification. Those with abnormal CIMT or baPWV can subsequently be subjected to CCS for further refinement of their CV risk.

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