Determination of the Presence of Early Sub-clinical Atherosclerosis in Erectile Dysfunction Patients by Measuring CIMT

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***Abstract*— Cardiovascular diseases are the main cause of death world-wide. Stiffing of the arterial wall is normally related with the beginning, or the progression, of atherosclerosis. Atherosclerosis plays an important role in the loss of the elastic properties of arteries walls. Thereby, atherosclerosis might cause harmful damage to arteries which in turn might cause cardiovascular disease and erectile dysfunction. Carotid intima-media thickness (CIMT) is used to measure atherosclerosis in parallel with the recording of Photoplethysmogram (PPG) from samples of erectile dysfunction subjects (68 patients). PPG and clinical indices were correlated to CIMT. An index extracted from PPG 2nd derivative (b/a ratio) found to be a good measure of high-risk of atherosclerosis in parallel with CIMT measurement. In addition, pulse pressure (PP) which is an indicator of arterial stiffness, found to be positively correlated to CIMT. PP, b/a index and subject's height (H) were used to predict a high-risk of atherosclerosis by means of a logistic regression model. The developed model showed a sensitivity of 76.4% and specificity of 64.7% in the prediction of high-risk of atherosclerosis. In addition, the Nagelkerke R-square was better in backward logistic regression (.372) compared to forward logistic regression (.288). Increases in thickness of the intima and media of the carotid artery, as measured by CIMT, are directly associated with a decreased of b/a index values and increased of PP values. Thereby, PPG is recommended to be used as an assistant technique in the prediction of high-risk of atherosclerosis.**

Keywords— PPG, CIMT, PP, Arterial stiffness and Arthrosclerosis.

I. INTRODUCTION

Coronary heart disease (CHD) or coronary artery disease (CAD) is generally caused by a condition called atherosclerosis, which occurs when fatty material and a substance called plaque builds-up on the walls of our arteries. Thickening and loss of elasticity of the coronary arteries, leading to progressive insufficiency of the arteries and they start narrowing. Understanding about the process of atherosclerosis would go a long way in serving to develop methods to prevent and treat such a disease. A marked increase in the incidence of coronary artery disease and death rates has been reported in both hemodialysis (HD) and diabetic patients when compared with an age-matched general population [1]. Atherosclerotic CVDs are a significant cause of morbidity and mortality for patients with end-stage renal disease (ESRD) [2-4]. The major risk factors for atherosclerosis are serum lipid concentrations, smoking, and hypertension. Carotid intima-media thickness (CIMT) test is an established method for the measurement of atherosclerosis. The common carotid artery in the neck is accessed by an ultrasound probe, which in turn allows the measurement of the thickness of the inner two layers the carotid called the intima and media by high frequency sound waves. CIMT is costly and operator dependent which raises the desire of having an assistance tool which can be used to predict the high-risk of atherosclerosis in an easier, simple, operator independent, and low cost method. Photoplethysmogram (PPG) is an optoelectronic method for measuring and recording changes of blood volume of a body part. PPG signals have been applied in many different settings including clinical physiological monitoring, vascular assessment and autonomic function [5]. Atherosclerosis plays an important role in the propagation of blood stream since it accelerates blood velocity and harms the elastic properties of arteries.

The second derivative wave had characteristic contours that facilitated the interpretation of the original PPG [6]. However, a sophisticated approach to contour analysis of the PPG has been developed by investigators in Japan [6-7]. Imanaga et al (1998) have proposed using the second derivative of PPG (SDPPG) [8]. This facilitates the distinction of five sequential waves called a, b, c, d and e waves. The relative heights of these waves (b/a, c/a, d/a and e/a ratios), have been related to age, arterial blood pressure, large artery stiffness and effects of vasoactive drugs. The indices calculated from the SDPPG waveforms are reported to correlate closely with both the distensibility of the carotid artery [8] and the central augmentation index (AIx) [6], suggesting the SDPPG indices may be a surrogate measure of arterial stiffness. Several previous studies showed that the SDPPG indices are associated with age [9-12], blood pressure (BP) [9, 11-12], the estimated risk of coronary heart disease [10], and the presence of atherosclerotic disorders [13]. The

This research is funded by the eScience grant (No. 03-01-02-SF0703) from the Ministry of Science, Technology and Innovation (MOSTI), Malaysia.

dyslipidemia was independently associated with the b/a. Fig.1 illustrates PPG waveform, its 1st and 2nd derivatives, and the process of points locating.

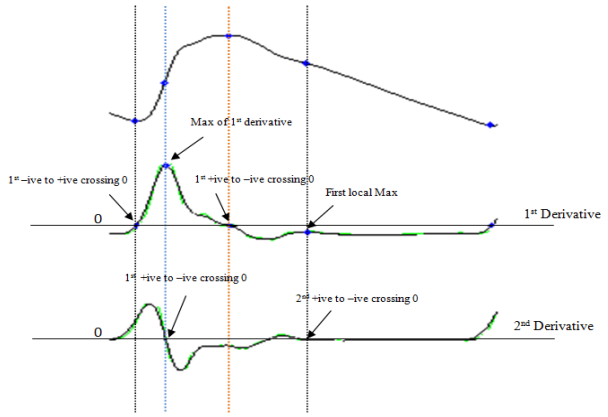

Fig. 1. Description of the process of locating points of interest from PPG waveform & its 1st and 2nd derivatives (recorded PPG and its derivatives)

Arterial stiffness is an independent risk factor of cardiovascular disease [14], and pulse pressure, a surrogate marker of increased arterial stiffness, is a powerful predictor of cardiovascular (CV) events [15-16]. The aim of our work was to study the characteristics of PPG that can be used to predict high-risk atherosclerosis and to explore any relation between CIMT and PPG indices in these patients. We determined HRART as an indicator of atherosclerosis

II. METHODOLOGY

A. Subjects and Protocols

The study is conducted in Urology Clinic in the National University of Malaysia Medical Centre (PPUKM). PPUKM is a teaching medical centre with 750 beds. The medical centre provides health services to most of the population around Kuala Lumpur as well the State of Selangor. The study was approved by the PPUKM ethics community review. Each patient was informed about the details of the study and their written consent was taken before the recordings were made. Patients were subject to obeying some inclusion criteria (high risks (Hypertension, Diabetes mellitus, Dyslipidaemia, Obesity, Smoking, and Significant family history) and no cardiovascular disease or risks at all) and to some exclusion criteria as well (establish cardiovascular disease, liver cirrhosis, Renal failure, Thyroid disease and Spinal cord injuries and finger or having Raynauld's). PPG measurements were collected from the right and left index fingers of the 68 participants with ages ranging from 30 to 78 years and median age 56 years (all male). The samples were classified into 2 groups, 34 each (case group who had a CIMT value greater than 0.7mm and control group who has CIMT value less than or equal to 0.7 mm). A written consent was taken from each participant. The data was recorded from a longitudinal study initially undertaken for the assessment of endothelium dysfunction in subjects presenting with erectile dysfunction. The subjects were from three different races in Malaysia (Malay, Chinese and Indian).

B. Hardware and Data Acquisition

PPG pulse measurements collected simultaneously from the right and left index fingers to study and analyze arterial conditions. After subjects were rested for five minutes, PPG recordings carried out for duration of 90 seconds. During the measurements, subjects were quiet, and breathed normally while resting in a supine position. PPG measurements were performed in hospital conditions at room temperature (24±1 °C). A special National Instruments with data acquisition board (NI cDAQ-9172) was used to digitize the signals locally and transmit the digital data to the personal computer with sampling rate of 5500 Hz. The recorded signals were analyzed off-line using customized algorithms developed in MATLAB (The MathWorks, Inc). These filters did not introduce phase delays or distortion to the waveforms. Utilizing PPG derivatives, PPG's points of interest can be located and determined [17-19].

C. Signal Processing

A customized algorithm written in Matlab is used to analyze the contour of PPG signal. Contour or morphology analysis depends mainly on the detection of PPG's inflection point (second peak or diastolic peak) since it tends to be less pronounced in most cases, especially aging and diabetic PPGs. However, among 12 variables extracted from PPG signal, an index derived from SDPPG (b/a ratio) is found to be a promising tool to assist the process of prediction of high-risk atherosclerosis. The algorithm loads PPG data (txt file), PPG signals were down-sampled (275 Hz), de-trended for removing outliers, drifts, offset and any movement artifacts. Next PPG signals were band-pass filtered (0.6–15 Hz) for removing the effect of the respiratory rhythm and higher frequency disturbances. PPG 1st derivative and 2nd derivative were evaluated. PPG inflection point is determined as the first local maximum of PPG1st derivative and it can be confirmed by the 2nd positive-to-negative crossing zero of SDPPG. The five waves of SDPPG were evaluated and the relative heights of these waves (b/a, c/a, d/a and e/a ratios) are extracted.

D. Statistical Analysis

Descriptive analysis was summarized by means and standard deviations Pearson correlation test was used to assess the relationship between CIMT and PPG. Bland-Altman test was performed to know the degree of agreement between CIMT and PPG. The value of CIMT greater than (0.7mm) is considered high-risk of atherosclerosis. A new index derived from CIMT named as HRART is used to represent the presence or absence of atherosclerosis. CIMT value $\leq$ 0.7 represents 0 (No-Risk) and CIMT value > 0.7 represents 1 (High-Risk)). Predictive equations of high risk of atherosclerosis were produced by using stepwise multiple logistic regression analyses. MedCalc software version 11.4.4 is used to obtain receiver operating characteristics (ROC) curve and area under curve (AUC). P-value with less than 0.05 was interpreted as statistically significant. All analysis' were carried out by using PASW Predictive Analytics Software (PASW,

formerly known as SPSS) version 11.5 and MedCalc software version 11.4.2.0. HRART was taken as dependent variable.

III. RESULTS

The baseline characteristics of the study subjects are shown in Table 1. The mean age was 56.5±9.8 years. The comparison between b/a index (the relative height of b wave to a wave) and CIMT data showed a good agreement which raised the ability of using b/a index as assistance tool for the prediction of risk of atherosclerosis. CIMT was significantly correlated with age, b/a, max ejection time (MET), pulse pressure (PP), and subject's height (H). The rest of the variables showed no significance statistically.

Logistic regression is used to identify the factors that contributed to the risk of atherosclerosis. All the factors (BMI, SP, DP, MAP, Age, H, PT, MET, ST, DT, PPT, SI, MEV, PM, DM, RI, b/a and c/a) are tested one by one using (ENTER) method. Only (Age, b/a, H, and PP) is significant. In the Multiple Logistic Regression, all the significant factors are included. Forward and Backward stepwise procedures were performed to identify the risk factors and controlling for the confounding effect. In the forward stepwise procedure, only b/a and height are significant. The characteristics of forward method are shown in table 2. In the other side, when (Backward: LR) logistic regression is used, the model performed better. The characteristics of backward: LR is shown in table3.

TABLE I: CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF SUBJECTS

	N	Mean	Std. Deviation
AGE	68	56.5	9.8
BMI	68	26	4.2
CIMT	68	84	.36
DP	68	82	7
H	68	167	6.4
MAP	68	101	7.3
PP	68	56	9
SP	68	138	10.6
Valid N (listwise)	68		

The values are expressed as mean±SD. H, subject's height; BMI, body max index; CIMT, carotid-intima-media thickness; DP, diastolic pressure; MAP, main arterial pressure; PP, pulse pressure; SP, systolic pressure.

TABLE II: FORWARD: LR CHARACTERISTICS

Factor-Model	B	S.E	Sig.	Exp (B)
b/a ratio	-5.465	1.9	.006	.004
H	-.117	0.5	.020	.890
Constant	23.796	8.7	.006	2.1025e+010
The Nagelkerke R^2 is 0.288				

TABLE III: BACKWARD: LR CHARACTERISTICS

Factor-Model	B	S.E	Sig.	Exp (B)
b/a ratio	-4.758	2.00	.019	.009
H	-.123	.050	.018	.884
PP	.066	.037	.040	1.069
Constant	20.696	8.90	.020	9.7310e+008
The Nagelkerke R^2 is 0.372				

In the forward: LR method, the Nagelkerke R-square was .288 which means that, b/a index and H contribute 28.8% to the risk of atherosclerosis, while other 71.2% are contributed by others factor that do not tested in this work.

However, backward: LR method gave better results since Nagelkerke R-square was .372 which means that, b/a index, H, and PP contribute 37.2% to the risk of atherosclerosis, while other 62.8% are contributed by other factors that are not tested in this work.

HRART was negatively correlated with b/a ratio. This indicated that, a reduction of b/a value may reflect the presence of high-risk atherosclerosis. In contrast, PP which is an indicator or atherosclerosis processes [20], was positively correlated with HRART which in turn, confirm the association between hypertension and atherosclerosis. The implemented model showed a sensitivity of 76.5 and a specificity of 64.7 in the detection of true-positive and true-negative respectively. The receiver operating characteristics (ROC) curve for b/a ratio vs. HRART is shown in Fig. 2. In addition, ROCs for all factors of the developed model are shown in Fig. 3.

Mainly, our interest is to use the logistic model to predict the outcome for a new subject. When we have a new subject, the developed model can used to predict the probability of having high-risk atherosclerosis. Let us say that, we have the inputs of b/a indx, PP and H of an individual subject and the output is a number between 0 to 1 which denotes the probability of the subject to having high-risk atherosclerosis. Therefore, the predictive equation from the developed statistical model given by with Y (Model's outcome) = 20.696 – 4.758*b/a + 0.066*PP – 0.123*H. Thereby, the probability of having high-risk atherosclerosis can be calculated as with HRART = Exp (Y) / (1+Exp (Y)). This tells us that increasing b/a value decreases the risk of atherosclerosis. Moreover, increasing PP increases the chance of being under high-risk atherosclerosis. Finally, increasing height decreases the risk of atherosclerosis.

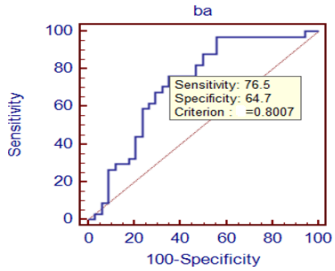

Fig. 2. ROC curve of b/a ratio in the prediction of high-risk atherosclerosis

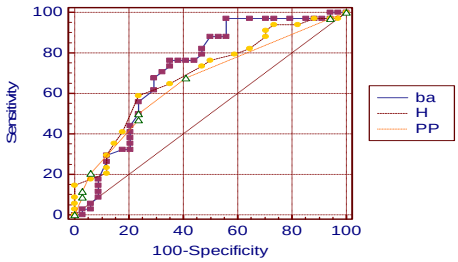

Fig. 3. ROCs of all factors of the developed model in the prediction of high-risk atherosclerosis

IV. DISCUSSION

The novelty of this work is the evaluation of the independent determinants of the SDPPG (b/a ratio) among subjects with high-risk of atherosclerosis as a factor for CVD by means of multiple logistic regression analysis. In our study, we determined the presence of early sub clinical atherosclerosis in erectile dysfunction patients by measuring CIMT. CIMT represents a marker of structural atherosclerosis. We found a significant increase in CIMT compared to age, PP which is found to be a marker of arterial stiffness. An important finding in our study was the demonstration of a negative correlation between atherosclerosis as indicated by CIMT and b/a ratio. Based on our findings, we suggest the use of b/a ratio in addition to PP and subject's height as determinants of high-risk of atherosclerosis in erectile dysfunction patients as an alternative method for the assessment of atherosclerosis. Fig. 4 represents the grouping of b/a ratio based on HRART index.

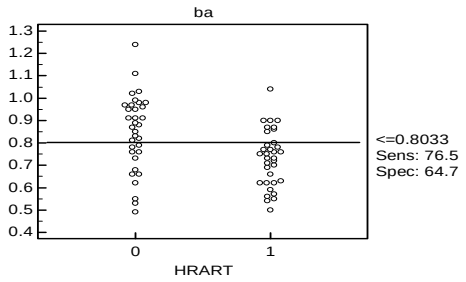

Fig. 4. The interactive dot diagram of b/a index in the prediction of HRART

The major limitation of the study was the small size of the sample. The study is conducted to study and investigate the characteristics of PPG's indices that might yield better results in exploring the effects of atherosclerosis on erectile dysfunction patients. However, our study was the first study demonstrating a negative correlation between HRART and b/a ratio and a positive correlation between HRART and PP.

V. CONCLUSIONS

Atherosclerosis disturbances play an important role in the loss of elastic properties of arterial system, thereby, affecting the propagation of blood stream. CIMT used to screen carotid intima-media arteries in order to provide a window to the amount of hardening and stiffness of arteries. PPG is a non-invasive technique which reflects blood volume changes in arteries close to the skin. However, SDPPG is shown to be useful in explaining and understanding the characteristics of PPG waveform variations. The index b/a ratio is found to be a useful in the assessment of the prediction of high-risk of atherosclerosis in parallel with CIMT. We concluded that, SDPPG's b/a ratio is a promising tool that might be used as a negative determinant of sub-clinical prediction of high-risk of atherosclerosis.

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