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The Assessment of Atherosclerosis in Erectile Dysfunction Subjects Using Photoplethysmography

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1. Introduction

Cardiovascular disease (CVD) is a major factor in mortality rates around the world and contributes to more than one-third of deaths in the United States [1]. The distribution of blood volume to different parts of the human vascular system can be seen in Figure 1. CVDs are the world’s largest killers, claiming 17.1 million lives a year [1]. Tobacco use, an unhealthy diet, physical inactivity and harmful use of alcohol increase the risk of heart attacks and strokes [2]. Table 1 introduces the common risk factors of CVD. In addition, Table 1 shows some common types of CVD risk factors.

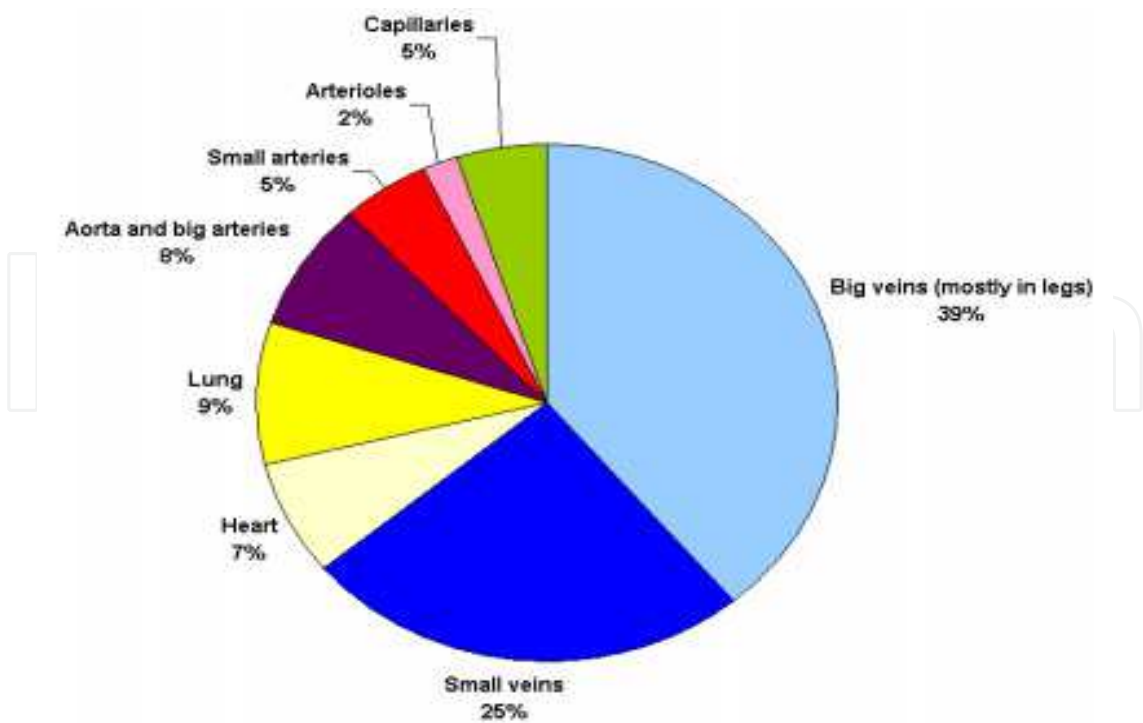


Fig. 1. Distribution of blood volume for the different parts of the human vascular system
Source: [3]

Risk factor	Risks can't be changed	Risks can be modified or treated	Factors contribute to heart disease risk
1	Increasing age	Tobacco smoke	Response to stress
2	Gender	High blood cholesterol	Drinking alcohol
3	Hereditiy	high blood pressure	Smoking
4	Family history	Physical inactivity	
5		Obesity	
6		Diabetes mellitus	

Table 1. Common types of CVD risk factors

The underlying cause of CV disease is atherosclerosis, a chronic inflammatory process that is clinically manifested as coronary artery disease, carotid artery disease, or peripheral artery disease [1; 4]. The frequency and prevalence of atherosclerosis are difficult to be assessed exactly. It has been predicted that atherosclerosis will be the primary cause of death in the world by 2020 [5]. Usually, atherosclerosis is an asymptomatic condition that might begin from childhood, whereas symptomatic organ-specific clinical manifestations often do not appear until 40 years of age or older when it is most commonly diagnosed [6]. Atherosclerosis can be characterized as a slow disease in which the arteries become hardened. In other words, it is characterized by the formation of arterial lesions or plaques as a result of an inflammatory response to endothelial injury [7]. Atherosclerosis eventually leads to artery enlargement, arterial stenosis, and may ultimately produce an arterial rupture [8]. The more commonly used subclinical vascular markers in the clinical setting are carotid intima media thickness (CIMT) and plaque measured by ultrasound, coronary artery calcium detected by cardiac computed tomography (CT), ankle–arm index pressure (AAI) measured by distal pressure Doppler measurement, and aortic pulse wave velocity (PWV) measured from carotid and femoral pressure wave recordings with a Doppler or mechanographic device [9-10]. Atherosclerosis can occur because of fatty deposits on the inner lining of arteries, calcification of the wall of the arteries, or thickening of the muscular wall of the arteries from chronically elevated blood pressure [11]. Atherosclerosis does not usually produce any symptoms until a CVD occurs. Therefore the prediction of atherosclerosis might contribute a lot to disease stratification and risk prevention. Figure 3 represents the process of developing atherosclerosis in the carotid intima-media arteries. It seems clearly that, inflammation affects the formation of arteries and the propagation of blood stream as well. Endothelial dysfunction is observed in the early stages of the atherogenic process, and it is initiated by injury to the arterial endothelium [1]. Such injury has been associated with CV risk factors including diabetes mellitus or impaired glucose metabolism, hypertension, cigarette smoking, dyslipidemia, obesity, and/or metabolic syndrome [12]. Endothelial dysfunction is the initial step of the atherosclerotic process involving many vascular districts, including penile and coronary circulation [13]. Endothelial dysfunction is associated with CVD risk factors [14-15]. Endothelial dysfunction has been proposed to be an early event of patho-physiologic importance in the atherosclerotic process [16-17] and provides an important link between diseases such as hypertension, chronic renal failure, or diabetes and the high risk of cardiovascular events in patients exhibiting these conditions [18].

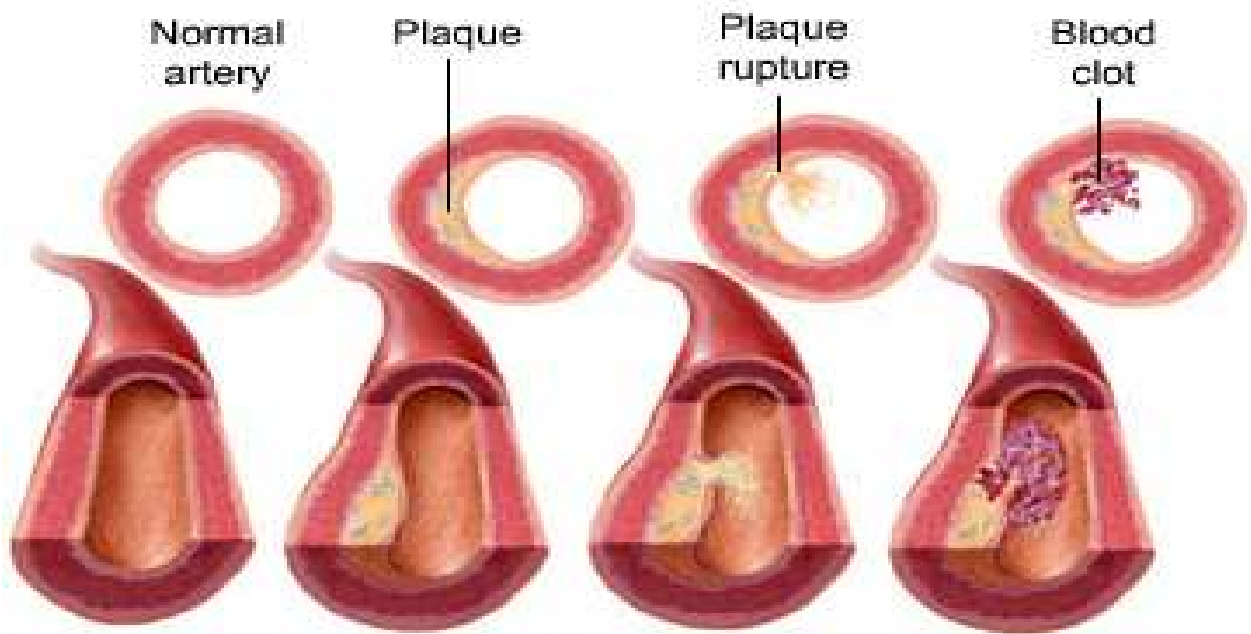


Fig. 2. The process of atherosclerosis development in general. Source: [38]

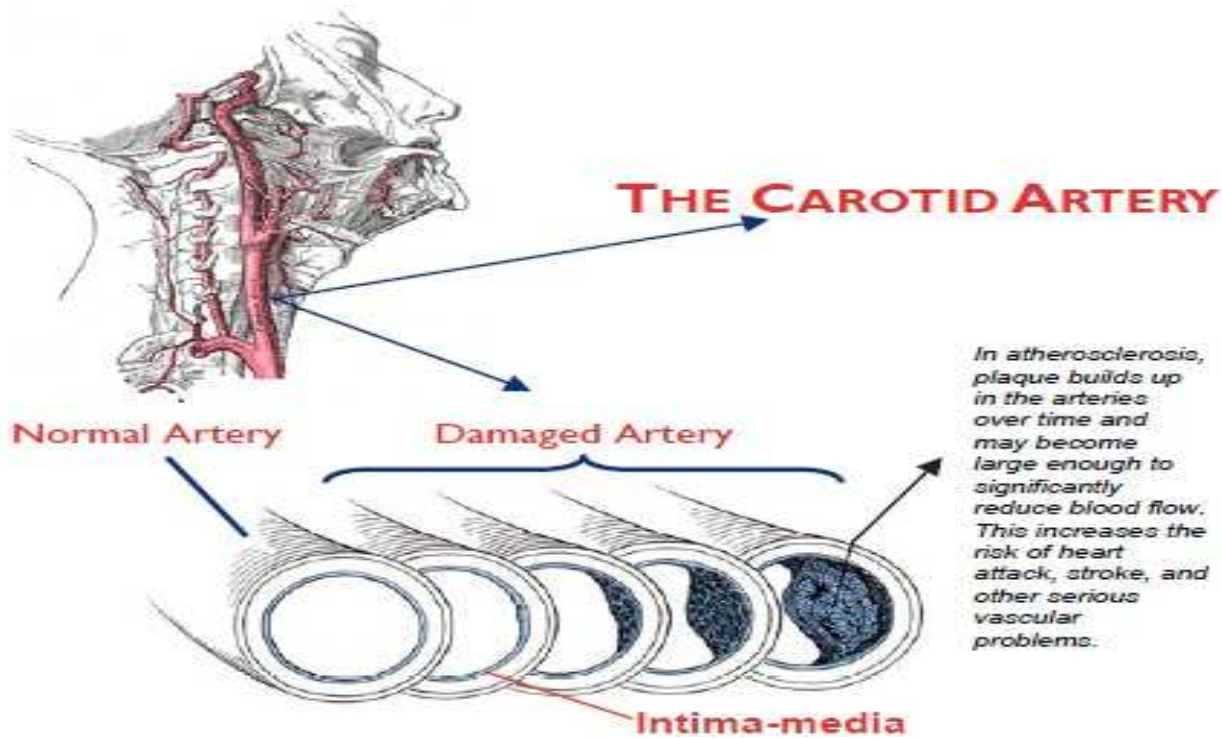


Fig. 3. Atherosclerosis risk at carotid intima-media arteries, Source: [39]

Elevated blood pressure reflects the existence of atherosclerosis. There is irresistible evidence that high blood cholesterol increases the risk of developing atherosclerosis; but cholesterol is not the damaging mechanism. In fact, the risk of atherosclerosis is more precisely assessed by measuring the proportional association between HDL cholesterol and LDL cholesterol [18]. Stiffening of large arteries predicts adverse cardiovascular outcomes [19-21]. Until now, measurements of arterial stiffness required the use of complex

ultrasound equipment or explanation tonometry at the level of the peripheral arteries, with the subjects in the supine or sitting position [22-23]. Medically, atherosclerosis is considered the dominant pattern of arteriosclerosis which affects primarily the elastic and large- to medium-sized muscular arteries. Therefore, hypertension is an established risk factor for the development of atherosclerosis [24]. Atherosclerosis is the term applied to a focal condition of the intima of arteries associated with medial changes. In fact, atherosclerosis can involve many of the body's blood vessels with a variety of presentations [25]. Pathological and epidemiological data confirm that atherosclerosis begins in early childhood, and advances seamlessly and inexorably throughout life [26]. Risk factors in childhood are similar to those in adults, and track between stages of life. When diagnosed, aggressive treatment should begin at the earliest indication, and continue for years. For those patients at intermediate risk according to global risk scores, C-reactive protein (CRP), coronary artery calcium (CAC), and carotid intima-media thickness (CIMT) are available for further stratification. Atherosclerotic lesions develop slowly, but continuously leading to the main causes of mortality in diabetic patients such as coronary arterial disease, stroke, and renal failure [27]. In diabetic children, the presence of subclinical atherosclerotic disease as a precursor of macrovascular complications has been shown in several studies [28]. Also, impaired endothelial function preceding atherosclerotic changes has been observed [29]. As the measurement of the intima-media thickness of the carotid arteries is considered a surrogate marker of subclinical atherosclerosis, this method has been used widely in these patients to assess vascular health [28]. CIMT is a noninvasive and reproducible method to detect and quantify subclinical atherosclerosis [30]. Autopsy studies have demonstrated a direct histological relationship between carotid and coronary atherosclerosis [31-32]. CIMT measurements have been used to measure differences in the progression of atherosclerosis in clinical trials [33]. In observational trials, increased CIMT is associated with prevalent and incident cardiovascular disease [34-36]. Although ultrasound measurement of CIMT has been recommended as a clinical screening tool, its use has been limited to research studies or selected institutions, in part because of labor- and time-intensive measurement protocols [37].

Mainly, atherosclerosis starts with oxidation of LDL particles in the arterial wall [40-41]. Oxidative modified LDL (oxLDL) damages the endothelium of the artery - a pathophysiology similar to that of vascular erectile dysfunction (ED) [41-42]. As a result, the elasticity of the arteries deteriorates. Impaired arterial elasticity and increased levels of circulating oxLDL as well as elevated fibrinogen and resting heart rate associate with subclinical atherosclerosis and increased risk of cardiovascular disease (CVD) events [43-48]. Besides similar pathophysiology, ED and CVD share same risk factors [49]. In addition, a high prevalence of both silent and clinical CVD has been reported among ED patients [49-50]. ED has also been reported as an independent predictor of incident CVD [51-52]. Since ED often precedes CVD symptoms from other vascular beds, it is thought to be an early clinical manifestation of systemic atherosclerosis [49; 53]. There is increasing evidence of a strong link between ED and atherosclerosis [54-55]. ED and atherosclerosis share similar risk factors and both conditions are characterized by endothelial dysfunction and impaired nitric oxide bioavailability [56]. Peripheral artery disease (PAD) as similar to ED is associated with atherosclerotic risk factors [57].

With advanced age, men experience decreases in important health indicators (muscle amount, muscle power, physical activity, bone density, blood generation, and sexual drive)

[58]. Various research [57-59] on the decrease in blood testosterone with aging suggests that many clinical characteristics related to age, including ED, are closely related to lack of testosterone. Recent research results indicate that testosterone and ED are closely related to one other [60-61], which suggests that supplementary therapy with testosterone may be one useful method in the treatment of ED [62]. However, the link between ED and atherosclerosis is well known to doctors. Doctors thought of atherosclerosis to be the main cause of ED. The thought was driven from the hypothesis that small arteries will be clotted before the large or medium ones. Since erection depends mainly on the amount of delivered blood to the penis, normal arteries thought to have no problem in supporting the process of blood delivering. In contrast, if the arteries become stiffen due to the deposition of atherosclerosis (which in turn will reduce their compliance as a result of the increment in arteries walls resistance), the amount of delivered blood will be declined which affects the process of erection. Atherosclerosis as an indicator of endothelium dysfunction, thought to be the underlying cause of CVDs and ED. Once the arteries start losing their elastic properties, the atherosclerosis is proven to be existed. The development of atherosclerosis prevents endothelial cell from regulating blood flow. Moreover, the accumulation of atherosclerosis affects the propagation of blood which can be detected by the recording of Photoplethysmogram (PPG) signal. PPG is an optoelectronic technique that reflects blood volume changes in arteries [63]. It functions by illuminating the skin with a light by light-emitting diode (LED) and recording the scattered lights by a photodetector.

ED as a vasculogenic disorder may indicate that, blood vessels anywhere in the body are not in perfect health. ED still has no establish method for diagnosing subjects to be subject with ED or normal subject (normal erection). Therefore, linking ED to atherosclerosis is the most acceptable thought in this area. ED may be a sign that coronary artery disease is developing some risk factors. That's why; being under-risk of atherosclerosis raises the chance of experiencing ED at any age. The endothelium can be damaged by high cholesterol, high blood pressure, smoking, or diabetes. They also cause atherosclerosis. Once damaged, the endothelium can't expand arteries to increase blood flow as well. Less blood flow into the penis means a less tumescence and consequently no satisfactory erection. In this study, a sample of 68 ED patients were hired to run a research that aims to investigate and evaluate the associations between atherosclerosis and ED. The PPG signal was used to predict the high-risk of atherosclerosis. Its noteworthy that, CIMT test was used to evaluate the risk of atherosclerosis. Since the CIMT method continues to be a measure of atherosclerosis, the value of 0.7 was determined as the critical point. As a result, any value below or equal to 0.7 ($\text{CIMT} \leq 0.7\text{mm}$) represents a normal case, otherwise, it represents a case under risk. And since the diagnostic test is used to reveal the health status of the subject, a new index derived from CIMT which is called high-risk atherosclerosis (HRART) was used to discriminate between at-risk-of-the-disease and normal subjects based on the critical value of 0.7. Statistically, HRART was taken as the dependent variable. All subjects were from Urology clinic at the medical center of the National University of Malaysia (PPUKM).

Thinking of atherosclerosis as the main cause that might cause ED represents a big motivation for the development of a predictive model for high-risk atherosclerosis assessment. Once atherosclerosis has been predicted, ED can be examined and checked by means of atherosclerosis. The measurement of CIMT and PPG were done at the same time. We started our research by hypothesizing that PPG is willing to predict high-risk atherosclerosis by utilizing PPG's contour analysis technique. Since PPG reflects changes in

blood volume, it will be affected clearly by aging and by atherosclerosis. Therefore, the aim was to extract some indices from PPG waveform morphology and relate these indices to atherosclerosis measured by CIMT test. Since the pulsatile components of PPG waveform are the important features due to their ability to reflect blood flow and blood volume changes in the arteries, we paid extra attention to PPG amplitude indices without neglecting PPG time indices. Atherosclerosis plays an important role in the process of blood propagation and blood volume changes. As we age, PPG amplitude is subject to reduction because of the accumulated atherosclerosis, which in turn increases the resistance of arteries and reduces arterial compliance. It is noteworthy that, atherosclerosis affects the elastic properties of the arterial wall, making it stiffer. As arteries become stiffer, blood propagation becomes faster and pulse amplitude becomes lower as well. In this research 12 main indices of PPG were extracted and evaluated Table 2 demonstrates the extracted parameters.

Index	B	S.E.	Wald	df	Sig.	Exp (B)
Age	.071	.028	6.198	1	.013**	1.07
BMI	-.025	.058	.179	1	.673	.976
SP	.04	.024	2.7	1	.1	1.04
DP	-.017	.034	.25	1	.614	.98
MAP	.016	.033	.23	1	.634	1.02
PP	.071	.032	4.8	1	.028**	1.07
H	-.114	.045	6.3	1	.012**	.89
PT	1.02	1.6	.4	1	.52	2.76
MET	52.8	32.5	2.6	1	.1	8.7E+22
ST	15.4	6	6.57	1	.01**	4732574
DT	4.96	6	.68	1	.41	143
PPT	-14.7	6.96	4.5	1	.034**	.00
SI	.04	.087	.23	1	.63	1.04
MEV	-552.3	1231	.2	1	.65	.00
PM	-1.08	10.2	.01	1	.92	.338
DM	1.76	15.2	.013	1	.9	5.8
RI	1.78	1.9	.88	1	.35	5.9
b/a	-5.43	1.88	8.3	1	.004**	72.6
c/a	-.073	3.75	.00	1	.98	.93

Note: Each index was tested separately to obtain any statistically significant against the dependent variable. The table represents their collection.

Table 2. Initial variables tested for model development

Given the importance of the medical data in pathogenesis of atherosclerosis, clinical interest has focused on the development of markers of risk. Therefore, blood pressure (SP, DP, PP, and MAP) in addition to body mass index were recorded as well. Among the medical data measurements mentioned, PP was found to be a significant factor contributing to the process of atherosclerosis. PP is an independent predictor of myocardial infarction (MI) [64]. The progression of atherosclerosis is accompanied by an increase in PP [65]. Our results supported such an observations by revealing a positively association between PP and atherosclerosis.

In addition, subject’s height (H) was inversely correlated with atherosclerosis in our results. Height was inversely associated with risk of MI [66], and an inverse association between height and risk of coronary heart disease (CHD) has been reported in several analytic studies [67-68]. Therefore, H and PP were statistically significant in this research. Detail on H and PP characteristics in the follow sections.

Basically, the first attention was to utilize PPG technique only in the assessment of high-risk atherosclerosis. But, as a result from the final research, PP and H were contributable to the risk of atherosclerosis. Which in turn resulted in a predictive model represents the contribution of PPG (b/a ratio), PP and H to the development of atherosclerosis. Obviously, it is worthy to investigate the contribution of PPG (b/a ratio) alone to atherosclerosis and the contribution of PP, H and PPG (b/a ratio) together. To make these investigations achieved, we conducted the analysis of logistic regression (Backward: LR). Logistic regression (LR) is used normally to model the relationship between a binary response variable and one or more predictor variables, which may either be discrete or continuous. Binary outcome data is common in medical applications. In our work, the binary response variable might be whether or not a patient is at risk of atherosclerosis. In multiple regressions, we are concerned with finding an appropriate combination of predictor variables to help explain the binary outcome. However, a logistic regression model was developed to assist in the early prediction of high-risk atherosclerosis, and to be used as an alternative rapid measure for screening for atherosclerosis.

The developed model went through three main methods of logistic regression. The first method (ENTER: LR) was used to test the significance of each index separately against the dependent variable, Risk of atherosclerosis initiated from CIMT test. The second method (Forward: LR) was used to test the significance of the significant indices against the dependent variable. The final method (Backward: LR) was used to test the significance of the significant indices against the dependent variable as well. Both forward and backward methods were used for the same techniques and they were fed with the same significant indices; and the one with a higher performance in terms of (Nagelkerke R-square and likelihood ratio) was used to implement the final model. The results revealed that some indices (age, PP, H, PPT, ST, and b/a) were statistically significant and that they could be used to initiate the model. The six chosen indices were fed to forward: LR and backward: LR methods. Table 3 shows the associated Nagelkerke R-square for each variable.

Index	R-square	Likelihood-ratio
Age	.133	87.14
PP	.11	88.4
H	.138	86.8
PPT	.094	89.3
ST	.135	87
b/a	.184	84.2

Note: R-square represents the amount that this index contributes to the process of high-risk of atherosclerosis.

Table 3. Nagelkerke R-square for the selected indices

However, to investigate the effects of the multiple variables together in the model, the forward: LR method was used first. After feeding the model with all the chosen variables, forward: LR responded as follows:

- Two out of six indices remained in the model (b/a and H), therefore age, PP, PPT, and ST were excluded from the calculations. Table 4 illustrates the model summary of the forward: LR method.
- The model revealed a value of Nagelkerke R-square (.288) and a likelihood ratio of 77.69
- Step 2, forward: LR was chosen to represent the model based on this method.

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	84.179	.138	.184
2	77.694	.216	.288

Note: Step 2 is used to represent the final decision about the model

Table 4. Model summary of forward: LR

On the other hand, backward: LR responded better than the forward: LR method. The model revealed a higher Nagelkerke R-square value (.372). A summary of the model is shown in Table 5. After feeding the model with all chosen variables, backward: LR responded as follows:

- Three out of six indices remained in the model (b/a, PP, and H); Therefore PPT, age and ST were excluded from the calculations. Table 5 illustrates the model summary of the backward: LR method.
- The model revealed a value of Nagelkerke R-square (.372) and a likelihood ratio of 74
- Step 4 backward: LR was chosen to represent the model based on this method.

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	71	.287	.383
2	71	.287	.383
3	72	.279	.372
4	74	.258	.372

Note: Step 4 was used to represent the final decision about the model

Table 5. Model summary of backward: LR

Moreover, it is helpful to demonstrate the relationship between the predicted outcome and certain characteristics found in observations. Table 6 represents the final characteristics of the developed model.

Our chief interest was to use the logistic model to predict the outcome for a new subject. How good was this model for prediction? When we have a new subject, we can use the logistic model to predict his probability of having high-risk atherosclerosis. Let us say we have a black box where we input the b/a index, PP and H of a subject and the output is a number between 0 and 1 which denotes the probability of the subject having a high-risk of atherosclerosis (Figure 4).

	B	S.E.	Wald	Df	Sig.	Exp(B)	95% EXP(B)	C.I.for
							Lower	Upper
BA	-4.758	2.020	5.55	1	.019	.009	.000	.450
H	-.123	.052	5.62	1	.018	.884	.798	.979
PP	.066	.037	3.27	1	.047	1.07	.994	1.148
Constant	20.696	8.924	5.38	1	.020	973357650		

Note: Model’s final selected factors and their characteristics

Table 6. The final factors included into the model and model characteristics

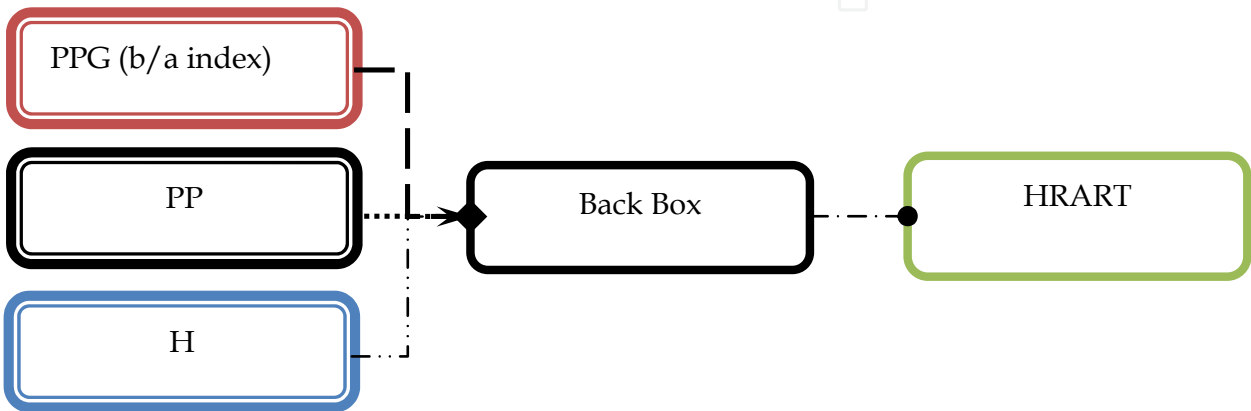


Fig. 4. The logistic regression predictive model

In the black box we have the equation for calculating the probability of having high-risk atherosclerosis, which is given by Y (Model’s outcome) = $20.696 - 4.758 \cdot b/a + 0.066 \cdot PP - 0.123 \cdot H$. Therefore, the probability of having high-risk atherosclerosis can be calculated as $HRART = \text{Exp}(Y) / (1 + \text{Exp}(Y))$. This tells us that increasing the b/a value decreases the risk of atherosclerosis. Moreover, increasing PP increases the chance of being under high-risk of atherosclerosis. Finally, increasing height decreases the risk of atherosclerosis. The classification table of the predictive model is shown in Table 7.

Observed		Predictive HRART		Percentage correct
		No-risk	High-risk	
Step 1	No-risk	24	10	70.6
	High-risk	9	25	73.5
Overall percentage				72.05
Step 2	No-risk	25	9	73.5
	High-risk	7	27	79.4
Overall percentage				76.5

Note: Classification table based on backward: LR

Table 7. Classification table of the predictive model

2. Agreement between the PPG and the CIMT

We often hope to have data on, for example, atherosclerosis or arteriosclerosis where direct measurement without adverse effects is difficult or impossible. The true values remain unknown. Therefore, indirect methods are used, and a new method has to be evaluated by comparison with an established method rather than with the true quantity. If the new method agrees adequately well with the old one, the new one may be used as an alternative measure, or the old one may be replaced. In this work, CIMT is an established method for the measurement of atherosclerosis. The PPG as a new method comes into this work to assist or replace CIMT. And since CIMT is the used method, the convention of assisting or interchanging use of the two methods was employed.

However, the Bland-Altman plot [69] is a graphical method to compare two measurement methods. In this graphical method the differences (or alternatively the ratios) between the two methods are plotted against the averages of the two methods. On the other hand [70] the differences can be plotted against one of the two methods, if this method is a reference or "gold standard" method. Horizontal lines are drawn at the mean difference, and at the limits of agreement, which are defined as the mean difference plus and minus 1.96 times the standard deviation of the differences. It is noteworthy that the agreement between the two methods must be done using the raw data (CIMT vs. b/a (PPG)).

A comparison between CIMT and PPG in the measurement of high-risk atherosclerosis is plotted in Figure 5. PPG is a new non-invasive method. Here the mean difference is 0.05 percentage points with a 95% confidence interval. The limits of agreement (-0.81 and 0.91) are small enough for us to be confident that the new method (PPG) can be used to assist CIMT for clinical purposes.

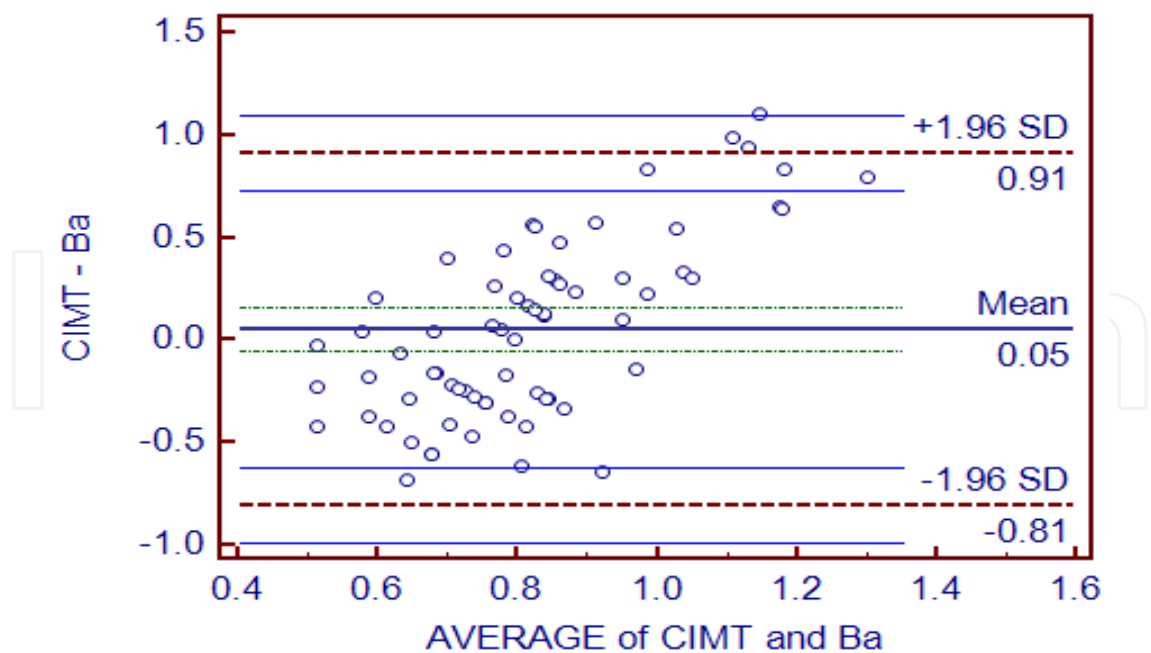


Fig. 5. Agreement of CIMT and PPG in the measurement of risk atherosclerosis

The plot reveals good agreement between the two methods, since the data are scattered around the mean. In addition, the mean value (0.05) is so close to zero that this strengthens

the agreement between CIMT and PPG. Such agreement raises the possibility of using PPG as an alternative rapid measure of high-risk atherosclerosis.

3. Model performance

The new proposed measure of high-risk atherosclerosis, (PPG's b/a index), needs to be evaluated to be used in clinical settings. Basically, the performance of any established test or any newcomer test must be assessed. The diagnostic performance of a test or the accuracy of a test to discriminate risky cases from non risky cases is evaluated using Receiver Operating Characteristic (ROC) curve analysis [71-72]. ROC curves can also be used to compare the diagnostic performance of two or more laboratory or diagnostic tests [73]. Moreover, a measure of how well an index can distinguish between two diagnostic groups (risky/non risky) can be evaluated by the area under the ROC curve (AUC). Since the CIMT method continues to be a measure of atherosclerosis, the value of 0.7 was determined as the critical point. As a result, any value below or equal to 0.7 (CIMT= ≤ 0.7 mm) represents a normal case, otherwise, it represents a case under risk. And since the diagnostic test is used to reveal the health status of the subject, a new index derived from CIMT which is called high-risk atherosclerosis (HRART) is used to discriminate between at-risk-of-the-disease and normal subjects based on the critical value of 0.7. HRART was taken as the dependent variable. Figure 6 demonstrates the error bar plot for b/a index based on HRART data.

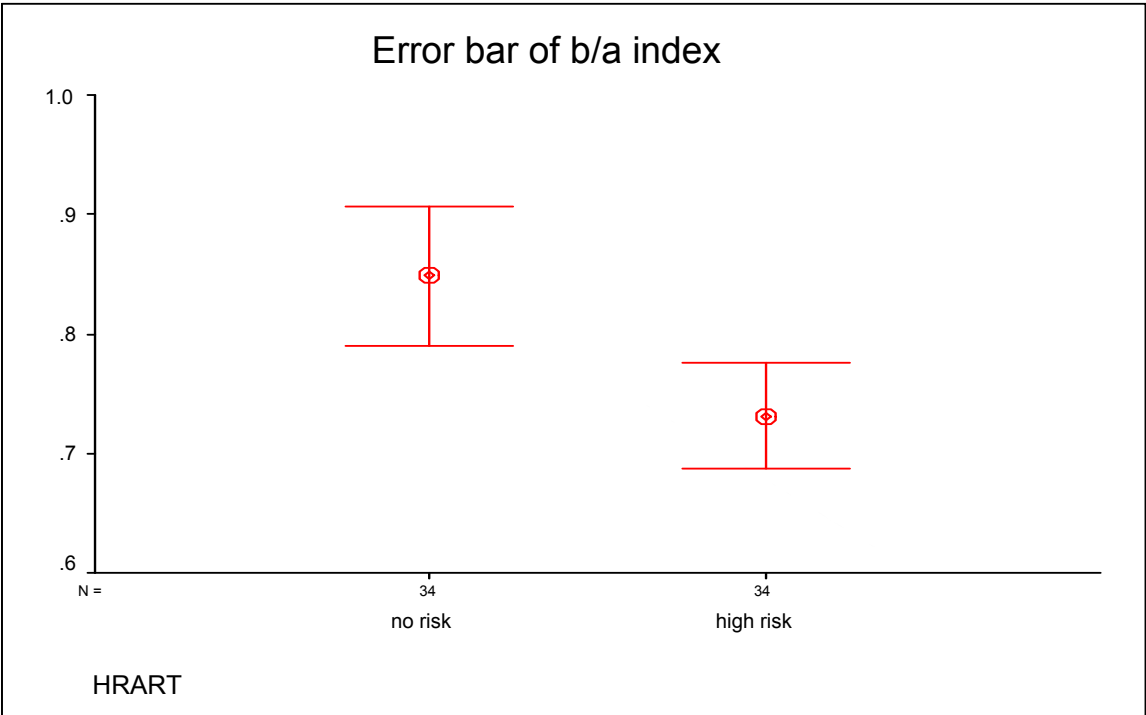


Fig. 6. Error bar of PPG (b/a index) based on HRART

Statistically, an ROC curve provides an objective measure of the discriminatory power of a screening test and also an idea of where to place the cut-off point. Therefore, a ROC test (HRART vs. b/a) was run to obtain the sensitivity (the true positive rate) and the 100-specificity (the false positive rate) for different cut-off points of the PPG (b/a ratio). MedCalc

software (version 11.4.4) was used to obtain the ROC curve and the AUC. The ROC curve for (HRART vs. b/a index) is shown in Figure 7.

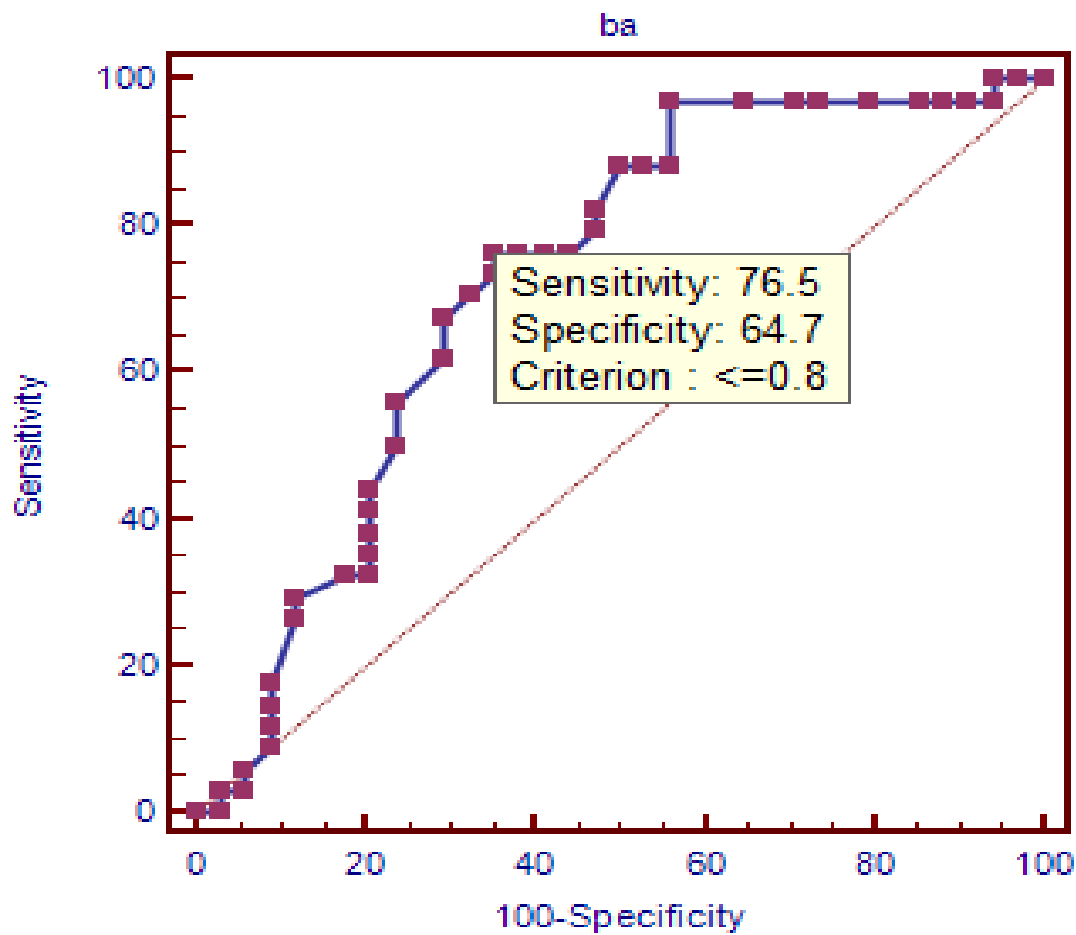


Fig. 7. ROC curve of HRART vs. PPG (b/a index)

As seen in Figure7, the ROC curve revealed a sensitivity of 76.5% and a specificity of 64.7% in the discrimination between risky and normal subjects. A sensitivity of 75% would be reasonable [74-76]. When the probability of disease and the sensitivity and specificity of the test are known, the predictive value positive (PVP) and the predictive value negative (PVN) can be calculated [77]. Moreover, the combination of ROC curves for all model factors can be obtained to reflect the relationship between each factor and the dependent variable. The three factors (b/a index, PP and H) contributed by some means to the process of atherosclerosis. Figure 8 represents the ROC curves for all the model’s factors.

The combined ROC for the model’s factors revealed the contribution of each factor to the development of atherosclerosis inside our arteries. As a result of that, each factor contributed separately to the atherosclerosis process, and all of them together contributed also to the process of atherosclerosis development partially. Partially means “not making a full contribution,” in other words, there are some other untested factors that might be contributing to atherosclerosis. However, the model produced a highly satisfactory Nagelkerke R-square value (0.372) which makes it a good rapid measure for the prediction of atherosclerosis risk. The effectiveness of the diagnosis is measured by the AUC.

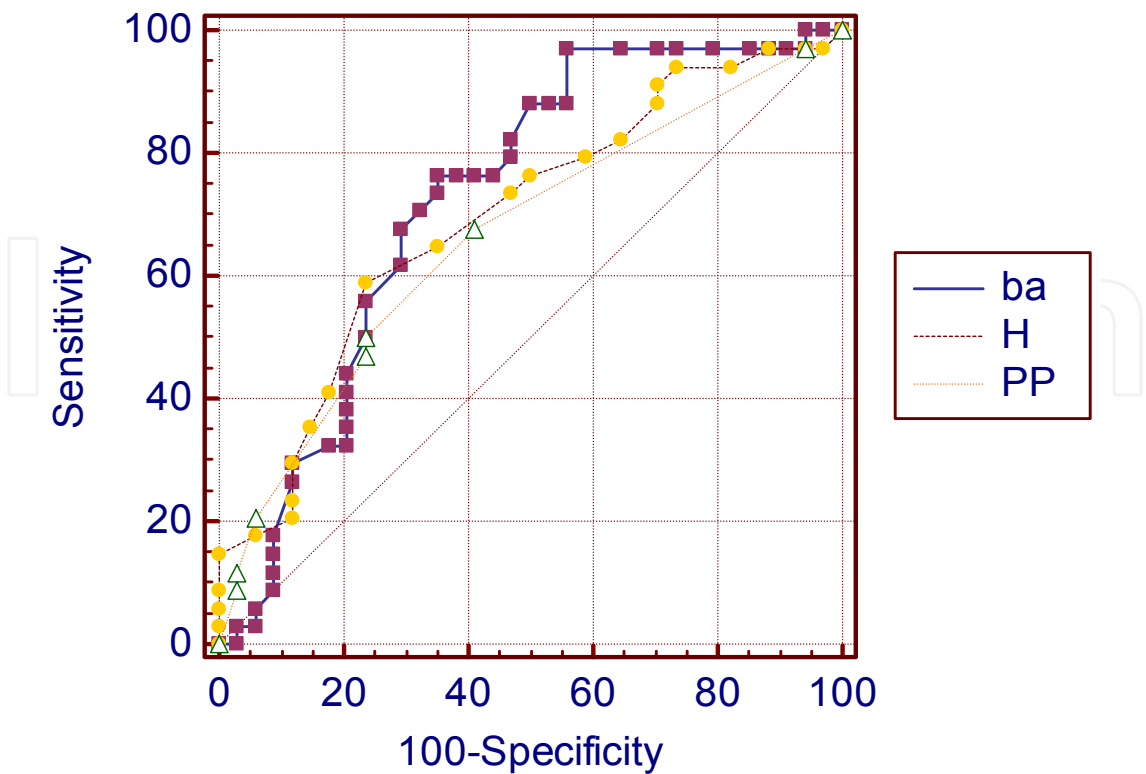


Fig. 8. The obtained ROC curves for b/a index, PP and H

3.1 Area Under the Curve (AUC)

The correctness of any medical test depends on how well the test separates the sample being tested into those with or without the disease. The area under the ROC curve (AUC) is frequently used as a measure for the effectiveness of diagnostic markers [78]. Moreover, AUC is an overall test for the performance of the test. Statistically, the area of 1 represents a perfect test which rarely appears in real empirical data. The analysis of our data produced an AUC of 0.724, which is fair enough to ensure that the test is reliable in discrimination between normal and risky specimens. The details of the AUC obtained can be seen in Table 8.

Variable	b/a index
Classification variable	HRART
Sample size	68
Positive group: HRART = 1	34
Negative group: HRART = 0	34
Disease prevalence (%)	50.0
Area under the ROC curve (AUC)	0.724
Standard error	0.06
95% Confidence interval	0.6 to 0.83
Z statistic	3.5
Significance level P (Area = 0.5)	0.0004

Table 8. The AUC obtained and its characteristics

Basically, AUC can be interpreted as the probability that the test result from a randomly selected diseased subject is more indicative of disease than that from a randomly selected non-diseased subject. Therefore, getting a value of AUC to be 0.724 can be an indicator of the good performance of the developed predictive model. The interactive dot diagram (Figure 9) illustrates a sensitivity of 76.5% and a specificity of 64.7%. During the present study we defined normal subjects (without risk of atherosclerosis) who had a value of b/a index to be greater than 0.8. Otherwise, the subject will be diagnosed as a subject at risk of atherosclerosis, which in turn will make the subject aggressive about his/ her health status.

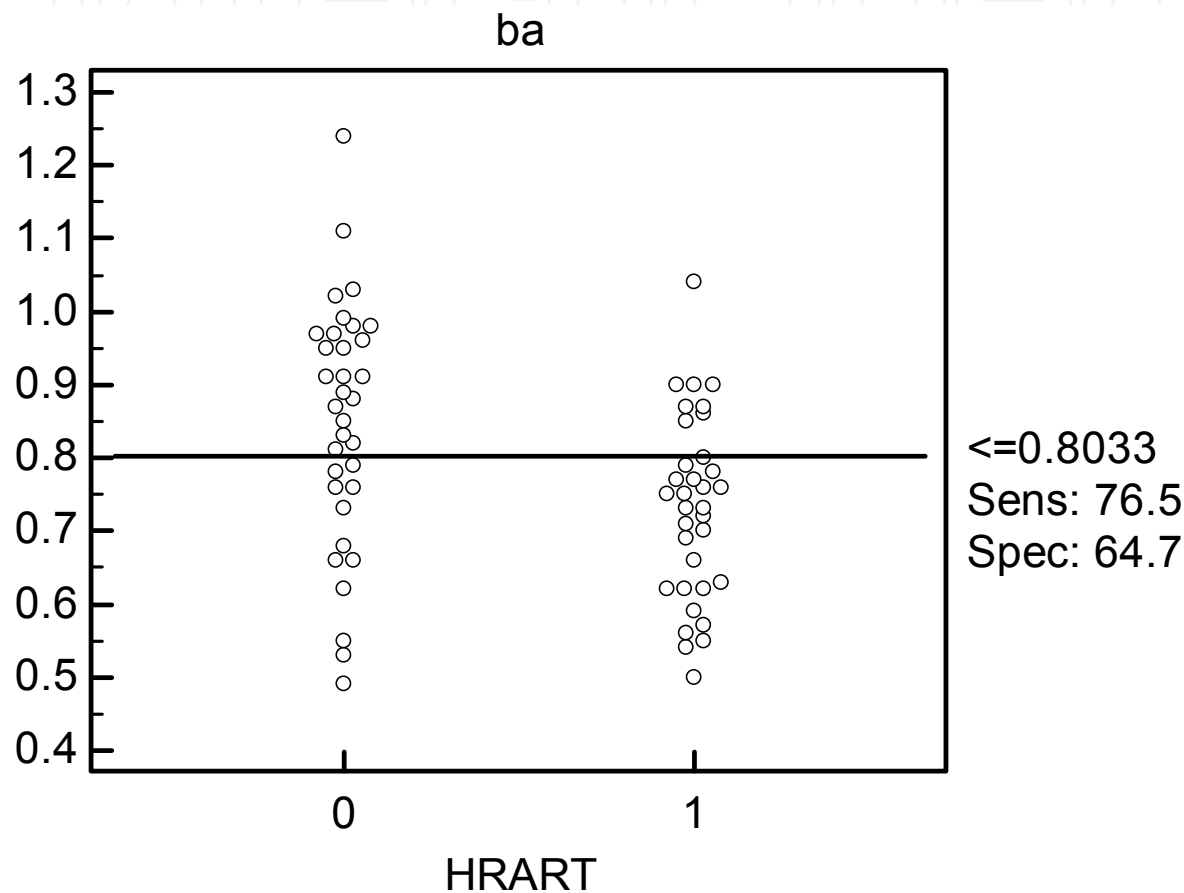


Fig. 9. Interactive dot diagram of b/a index based on HRART

In conclusion, this investigation introduced the acquired results based on our analysis. Moreover, a detailed discussion on the developed model and its characteristics were presented. The focus was completely on the association between atherosclerosis and the PPG signal indices. The developed model revealed a sensitivity of 76.5% and a specificity of 64.7% which in turn suggested that it could be a rapid measure for the assessment of the prediction of high-risk atherosclerosis. Mainly, thinking of atherosclerosis to represent an important cause of ED raises the important of this developed model. As the developed model successes to predict high-risk atherosclerosis, it can be used to assist ED as well. Therefore, predicting the high-risk atherosclerosis at early stages could really improve the prevention of experiencing ED and improve the treatment methods. The analysis can be further extended to other cardiovascular risk factors such as hypertension, hyperlipidemia and smoking. These factors are not analyzed in this study due to limitation in the number of

subjects with one of the particular above mentioned risk factors. However, there is no doubt that the assessment of arterial stiffness and the assessment of high-risk atherosclerosis will make a major contribution to the improved management of cardiovascular disease in clinical settings and to the process of diseases prevention.

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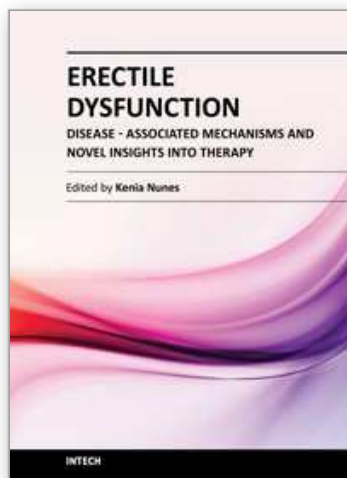
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Erectile dysfunction is a widespread problem, affecting many men across all age groups and it is more than a serious quality of life problem for sexually active men. This book contains chapters written by widely acknowledged experts, each of which provides a unique synthesis of information on emergent aspects of ED. All chapters take into account not only the new perspectives on ED but also recent extensions of basic knowledge that presage directions for further research. The approach in this book has been to not only describe recent popular aspects of ED, such as basic mechanism updates, etiologic factors and pharmacotherapy, but also disease-associated ED and some future perspectives in this field.

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