

PREDICTIVE MODEL FOR THE ASSESSMENT OF HIGH-RISK
ATHEROSCLEROSIS USING PHOTOPLETHYSMOGRAPHY

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MODEL RAMALAN UNTUK PENILAIAN ATEROSKLEROSIS BERISIKO
TINGGI MENGGUNAKAN FOTOPLETISMOGRAFI

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TESIS YANG DIKEMUKAKAN UNTUK MEMPEROLEH IJAZAH
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DECLARATION

I hereby declare that the work in this thesis is my own except for quotations and summaries which have been duly acknowledged.

17 October 2011

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P46820

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DEDICATION

This project is dedicated to our Parents who have never failed to give us financial and moral support, for giving all our need during the time of my study. Also, this thesis is dedicated to my Brothers & Sisters who has been a great source of motivation and inspiration. Finally, this thesis is dedicated to all those who believe in the richness of learning.

ABSTRACT

Cardiovascular diseases (CVD) are the principal causes of death world-wide. Stiffening of the arterial wall is normally associated with the beginning, or the progression of atherosclerosis. As changes can be detected before the appearance of clinically apparent vascular disease, arterial stiffness may act either as a marker for the development of future atherosclerotic disease, or may be more directly involved in the process of atherosclerosis. Atherosclerosis plays an important role in the loss of the elastic properties of arteries walls, thereby, raises the chance of developing a vascular disease. Atherosclerosis can be measured by carotid intima-media thickness (CIMT) technique. CIMT test uses ultrasound technology to measure the thickness of the first two layers of the carotid artery located in the neck, where blood-flow-blocking plaque first develops. Thickness of the artery wall is an early indicator of vascular disease. The main disadvantages of CIMT technique are that it is costly, operator dependent and it causes discomfort to the patient (15-20 minutes procedure). The main objective of this work is to evaluate the potential use of Photoplethysmogram (PPG), a noninvasive optoelectronic method for measuring and recording changes of blood volume, routinely utilize in a clinical setup, to assist CIMT in the prediction of high-risk atherosclerosis. PPG signals and CIMT were in-parallel recorded from a sample of erectile dysfunction subjects (80 subjects). The carotid intima-media thicknesses were screened from both left and right neck side. PPG signals were acquired from index fingers of the right arm and left arm at a rate of 5500 Hz. Standard signal processing techniques, detrending, band pass filtering, resampling, and normalization and a customized algorithm for peaks detection were applied off-line. CIMT data were recorded into a new index called high-risk atherosclerosis (HRART), which represents the presence or the absence of high-risk atherosclerosis. A statistical model by means of logistic regression was developed to predict the atherosclerosis by means of b/a index from PPG signal, pulse pressure (PP) and subject's height. From statistical analysis, the findings of the research as follows: (i) The model showed a sensitivity of 76.5% in the prediction of true-positive cases (TP), (ii) The model showed a specificity of 64.7 in the prediction of true-negative cases (TN), (iii) Backward logistic regression showed better results compared to forward logistic regression, since Nagelkerke R-square were 0.288 and 0.372 respectively, and (iv) PPG (b/a) index, PP and subject's height were the main factors of the developed model. The results show that the proposed model is a potentially promising tool for the assessment of arterial stiffness, applicable to noninvasive and rapid assessment of atherosclerosis as a low cost, operator independent and ease of use measure compared to CIMT. In addition, the proposed technique can be used as alternative rapid measure of high-risk atherosclerosis which is a sign of developing CVD and erectile dysfunction.

ABSTRAK

Penyakit kardiovaskular (CVD) merupakan penyebab utama kematian di seluruh dunia. Kekakuan dinding arteri biasanya dikaitkan dengan permulaan atau perkembangan aterosklerosis. Perubahan boleh dikesan sebelum penyakit vaskular menjadi jelas secara klinikal. Kekakuan arteri boleh menjadi tanda perkembangan aterosklerosis atau berkaitan secara langsung dengan proses perkembangan aterosklerosis. Aterosklerosis akan menyebabkan kehilangan sifat-sifat kenyal dinding arteri dan meningkatkan kemungkinan untuk perkembangan penyakit vaskular. Aterosklerosis boleh diukur oleh teknik ketebalan media-intima karotid (CIMT). Ujian CIMT menggunakan teknologi ultrabunyi untuk mengukur ketebalan dua lapisan pertama arteri karotid di leher, di mana plak yang menyekat aliran darah mula bertapak. Ketebalan dinding arteri ialah satu petunjuk awal bagi penyakit vaskular. Kelemahan utama teknik CIMT ialah ianya mahal, pengendaliannya bergantung kepada operator dan prosedurnya tidak selesa (mengambil masa 15-20 minit). Objektif utama penyelidikan ini adalah untuk menilai potensi penggunaan Photoplethysmogram (PPG), kaedah optoelektronik tidak invasif untuk mengukur dan merakam perubahan isipadu darah yang secara rutin digunakan di klinik-untuk membantu CIMT dalam meramalkan aterosklerosis berisiko tinggi. Isyarat PPG dan CIMT dirakam secara selari daripada satu sampel pesakit disfungsi ereksi (80 subjek). Bagi ketebalan media-intima karotid diperiksa pada kedua-dua belah kanan dan kiri leher. Isyarat PPG telah dirakamkan daripada jari telunjuk tangan kanan dan kiri pada kadar 5500 Hz. Teknik pemprosesan isyarat yang piawai, detrending, penapisan jalur laluan, pensampelan semula dan penormalan dan algoritma pengesanan puncak digunakan secara luar talian. Data CIMT telah dirakamkan ke satu indeks baru yang dinamakan aterosklerosis berisiko tinggi (HRART), yang mewakili kehadiran atau ketiadaan aterosklerosis berisiko tinggi. Satu model statistik secara regresi logistik telah dibangunkan untuk meramalkan aterosklerosis dengan menggunakan indeks b/a daripada isyarat PPG, tekanan nadi (PP) dan ketinggian subjek (H). Daripada analisis statistik, penemuan penyelidikan adalah seperti berikut: (i) Model ini menunjukkan sensitiviti 76.5% dalam meramalkan kes-kes positif benar (TP), (ii) Model menunjukkan spesifisiti 64.7% dalam meramalkan kes-kes negatif benar (TN), (iii) Regresi logistik ke belakang menunjukkan hasil yang lebih baik berbanding dengan regresi logistik ke hadapan disebabkan *Nagelkerke R-square* ialah masing-masing 0.288 dan 0.372, dan (iv) Indeks b/a, PP dan ketinggian ialah faktor utama dalam model yang dibangunkan. Hasil ini menunjukkan model yang dicadangkan berpotensi untuk menilai kekakuan arteri dan boleh digunakan untuk menilai aterosklerosis dengan cepat dan tidak invasif. Teknik ini merupakan teknik kos rendah, tidak bergantung kepada operator dan senang digunakan berbanding dengan CIMT. Tambahan lagi, teknik yang dicadangkan boleh menjadi alternatif bagi meramalkan aterosklerosis berisiko tinggi yang merupakan satu tanda perkembangan CVD dan disfungsi ereksi.

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LIST OF ABBREVIATIONS

WHO	World Health Organization
CVD	Cardiovascular disease
CAD	Coronary artery disease
ED	Erectile dysfunction
PPG	Photoplethysmogram
CIMT	Carotid intima-media thickness
AHA	American Heart Association
LDL	Low-density lipoprotein
HDL	High-density lipoprotein
NWHIC	National women's health information center
LED	Light emitting diode
ΔT	Time between systolic and diastolic
PWV	Pulse wave velocity
SDPPG	Second derivative of Photoplethysmogram
CHD	Coronary heart disease
hs-CRP	High sensitivity C-reactive protein
NI	National instrument
IR-LED	Infrared light emitting diode
PPUKM	Pusat Perubatan Universiti Kebangsaan Malaysia
SD	Standard deviation
BMI	Body mass index
SP	Systolic pressure
DP	Diastolic pressure
PP	Pulse pressure
MAP	Main arterial pressure
RI	Reflection index
SI	Stiffness index

PM	Pulse maximum
DM	Diastolic maximum
PT	Pulse time
ST	Systolic time
DT	Diastolic time
MET	Maximum ejection time
MEV	Maximum ejection velocity
PPT	Peak-to-peak time
CI	Confidence interval
Sn	Sensitivity
Sp	Specificity
ROC	Receiver operation characteristics
AUC	Area under curve
ANOVA	Analysis of variance
H	Subject's height
HRART	High-risk atherosclerosis
LR	Logistic regression

CHAPTER I

INTRODUCTION

1.1 INTRODUCTION

The World Health Organization (WHO) reported that the number one leading cause of mortality and morbidity in the world population is cardiovascular disease (CVD). Recognising CVD as a continuum challenges the traditional concepts of primary and secondary prevention, with healthcare professionals adopting a “high-risk” approach to prevention (Emberson et al. 2004). CVD refers to the class of diseases that involves the heart and blood vessels, which make up the cardiovascular system. Because CVD can refer to many different types of heart or blood vessel problems, the term is also referred to atherosclerosis, the disease that affects the arteries due to narrowing and hardening from fatty deposits called plaque (Cohen 1992). The heart disease can be ischemic heart disease, which is characterized by reduced blood supply to the heart muscles, often due to coronary artery disease (CAD), will lead to heart attack and heart failure. High blood pressure and diabetes are associated with atherosclerosis and stroke. On top of the varieties of CVD, ischemic heart disease is top in the list and the leading cause of death in both males and females (WHO 2010).

There are many risk factors associated with CVD such as aging, male gender, diabetes mellitus, hypertension, hyperlipidemia, obesity, and cigarette smoking (Vita et al. 1990a; Black 1992; Davignon & Ganz 2004). Studies have suggested that before the symptoms of CVD are detectable, changes in the blood vessels have taken place (Anderson et al. 1995; Lüscher & Barton 1997) which eventually affected the vascular structures and functions (Glasser et al. 1997). It has been a great challenge to scientists, medical practitioners and researchers to be able to detect these anatomical

and physiological alterations of the vessels at early onset of CVD. Development of effective vascular monitoring techniques that would provide useful and valuable information for early diagnosis would be most beneficial in the prevention and control of the disease as well as improving risk stratification strategies (Verma & Anderson 2002). Identifying people at risk at early stage of the risk is a necessity for the prevention of damage to the vascular structure.

Arteriosclerosis which is known commonly as “hardening of arteries” is a common disease of coronary arteries and is a sign of CVD. Plaque is a combination of cholesterol and other fats, calcium and other elements carried in the blood, which builds up in the small blood vessels that feed the heart. When this condition exists in other parts of the body, it is called atherosclerosis (UCSF 2008). Often, there are no symptoms of arteriosclerosis until a heart attack occurs. The process of atherosclerosis can be a sign of alteration of the arteries’ elastic properties, which in turn can be a sign of CVD. Atherosclerosis and arteriosclerosis are thought to be the cause of heart disease and erectile dysfunction (ED). Having diabetes, being overweight or having high blood pressure or high blood cholesterol levels can cause ED (Gabe 2010). More than 80 percent of ED is caused by arteriosclerosis blocking arteries or diabetes, because erection needs an open artery and undamaged nerves (Zmuda et al. 1997). ED is characterized by a man's inability to have a firm sexual intercourse.

However, because of the increase of longevity in most developed societies, there is an increasing overlap between arteriosclerosis associated with normal vascular aging and atherosclerosis associated with cardiovascular risk factors. Therefore there is a need for improvement, both in the early identification of CVD risk, and in CV risk stratification. Arterial stiffness is an important determinant of cardiovascular risk and can now be measured in large populations simply and noninvasively. Photoplethysmogram (PPG) is a noninvasive technique which is used to reflect changes of blood volume at many sites of the body. The PPG signal is thought to reveal valuable information about the heart, the arteries and their associated diseases. Therefore PPG is used in this work as a rapid investigator in the prediction of high-risk atherosclerosis. The novelty of this research rises from the ability of using the non-intervention (no medical or physical interferes to the signal) PPG for the

prediction of atherosclerosis existence in human's arteries. However, the examination of changes in the PPG morphology in ED subjects, would add additional novelty to this work. Details on the PPG technique are explained in Chapter 2.

Basically, this is modeling and experimental based study. The study included ED subjects hired from the Urology clinic at the medical center of University Kebangsaan Malaysia (PPUKM). The study represented the collection of some medical data after running some experiments under the supervision of medical experts (doctors) side. Alongside with that, experiments of recording PPG signal and recording of CIMT data are included. However, the collected data and the conducted tools for analysis are used to model a predictive model for the assessment of high-risk atherosclerosis using the PPG signal.

1.2 PROBLEM STATEMENT

CVD and atherosclerosis gain a huge toll on our lives. Vascular disease starts as a ruin of specialized cells which line the arteries. These cells, called endothelial cells; they are the key to atherosclerosis and underlying endothelial dysfunction is the central feature of this killer disease. Atherosclerosis is relatively slow process, which typically starts in childhood and often progresses as we age. As the arteries experience atherosclerosis, damage to the arterial wall occurs. Moreover, atherosclerosis badly affects the functionality of the endothelium cells. This damage causes endothelial dysfunction and ultimately allows lipids and toxins to penetrate the endothelial layer and enter the smooth muscle cells. In addition, atherosclerosis is thought to be a key cause of erectile dysfunction due to the effects of atherosclerosis on the smooth muscles that lie on the penis. Generally, it is accepted that small arteries are worse affected by atherosclerosis than large or medium ones. Moreover, atherosclerosis is a systemic disease. Probably, if the patient has atherosclerosis in one part of his arterial system, let us say, the coronary arteries, he is more likely to have it in others, such as the cerebral circulation or the penile arteries. Therefore, considering atherosclerosis as a cause of erectile dysfunction is acceptable and logical thinking. The ability to detect alterations in the vascular structure and function in hypertension, diabetes mellitus, and atherosclerosis, such as by assessment of vascular compliance, has potential

advantages for improving risk stratification (Verma & Anderson 2002). Atherosclerosis readings in this work are generally measured by a test called CIMT, which stands for “carotid intima-media thickness.” An ultrasound probe is applied to the neck which facilitates the measurements of the thickness of the common carotid artery. High frequency sound waves allow us to measure the thickness of the inner two layers of the carotid called the *intima* and *media*. The test is noninvasive. However, being operator-dependent, costly, and a long procedure (15-20 minutes), it highlights the necessity of finding a rapid, noninvasive measure. Moreover, current lifestyles accelerate the need for rapid screening tools for the prediction of high-risk atherosclerosis. Besides, being noninvasive, low-cost, operator-independent, usable on different sites of the body, easy to use, and a rapid way of measuring, the PPG comes to the stage as a promising technique for providing valuable information about the cardiovascular system, which could make the PPG a useful clinical investigation tool (Allen & Murray 2000).

The motivation behind the proposed method of atherosclerosis assessment based on PPG analysis is attributable to the rapid procedure for measuring PPG hemodynamic indices; the simplicity of the instrumentation system; and the digital signal processing techniques that offer prospective advancement of the method. Add to that, the noninvasive quantification of PPG characteristics in the assessment of atherosclerosis in erectile dysfunction specimens.

1.3 RESEARCH OBJECTIVE

The main goal of this research was to develop a rapid, noninvasive technique for the prediction of high risk atherosclerosis by utilizing the PPG system and analysis of finger PPG signals. The proposed methodology of atherosclerosis assessment and prediction by PPG was evaluated in parallel with an established noninvasive technique of atherosclerosis assessment by ultrasound measurement (the CIMT test). The research involved experimentation on human subjects and data acquisition using both techniques followed by measurement analysis and method comparisons. More precisely, the specific objectives of the research were as follows:

- i. To identify significant characteristics of PPG in relation to CIMT by statistical analysis
- ii. To classify groups of healthy and at-risk subjects
- iii. To develop a predictive model for the assessment of the risk of atherosclerosis
- iv. To validate the PPG technique.

1.4 RESEARCH HYPOTHESIS

The hypothesis of this research was drawn to be twofold. First, PPG signal analysis of healthy individuals and of those with CVD risk factors would reveal significant trends as it would exhibit the characteristics of their vascular condition. Second, the PPG signal would respond to the alterations of vascular elastic properties, reflecting their compliance, which in turn could be used to predict the process of atherosclerosis as the main cause of arterial stiffness. The drawn hypothesis was formed due to the expectation of PPG behavior in responding to chronic atherosclerosis and its related changes of arterial characteristics.

1.5 SCOPE OF STUDY

The study is implemented and directed for pathology (ED) subjects from Malaysian races (Melayu, Chinese, and Indian). The study included subjects whom having an established ED only. Therefore, the association between ED and atherosclerosis is highlighted and examined.

1.6 THESIS ORGANIZATION

Thesis organization gained extra attention in order to describe the fundamentals of the work and the involved activities. Thesis dissertation organization follows closely the above research objectives and the research structure. The organization of the thesis is as follows:

Chapter I briefly explains the background, the problem statement, the listed objectives, and the motivation behind conducting this research. In addition, it describes the structure for the research, the research hypothesis and the organization of the dissertation.

Chapter II introduces a background to the cardiovascular system and the reviews of the main CVD risk factors and their impact on the vascular system. This chapter describes the process of arterial stiffness in general, and it provides an in-depth overview of atherosclerosis and the alteration of arterial characteristics caused by atherosclerosis. Moreover, a summary of the established methods used to measure and assist with the treatment of atherosclerosis are described. Therefore, a detailed background of the techniques used in this work (PPG) is introduced. The clinical applications, advantages and limitations of the PPG technique are discussed towards the end of the chapter.

Chapter III describes the instrumentation systems utilized in this research, including the specifications for the hardware and software for both the CIMA and PPG systems. Data collection, data organization and protocols for data acquisition are elaborated in this chapter. Descriptions of the algorithms used are also included. As statistical analysis was incorporated throughout the research, fundamental statistics and the relevant statistical tests are explained at the end of this chapter

Chapter IV presents the results and overall discussion of the research findings. First, it explains the results of parallel analysis of the PPG signals and the CIMA data. Then it illustrates the results of the PPG analysis using 1st and 3rd derivatives. The analysis of the PPG signals using 1st and 2nd derivatives is presented as well. Furthermore, this chapter presents the extracted parameters which resulted from the analysis of the PPG signal and its derivatives. Finally, the chapter ends up with the developed model, which includes the illustration of model factors, methods agreement and model performance. The developed statistical model represents a rapid measure of prediction of risk of atherosclerosis.

Chapter V summarizes the research, describes some limitations of the research, recommends necessary future improvements, and proposes future research directions initiated from this study.



CHAPTER II

LITERATURE REVIEW

2.1 THE CARDIOVASCULAR SYSTEM

The heart and circulation system make up the cardiovascular system. The heart works like a pump that provides blood to the organs, tissues, and cells of the body. The blood is responsible of delivering oxygen and nutrients to every cell and in removing the carbon dioxide and waste products made by those cells. Blood is carried out from the heart to the rest of the body through a complex network of arteries, arterioles, and capillaries; while it returns back to the heart through venules and veins. Figure 2.1 illustrates the process of blood circulation.

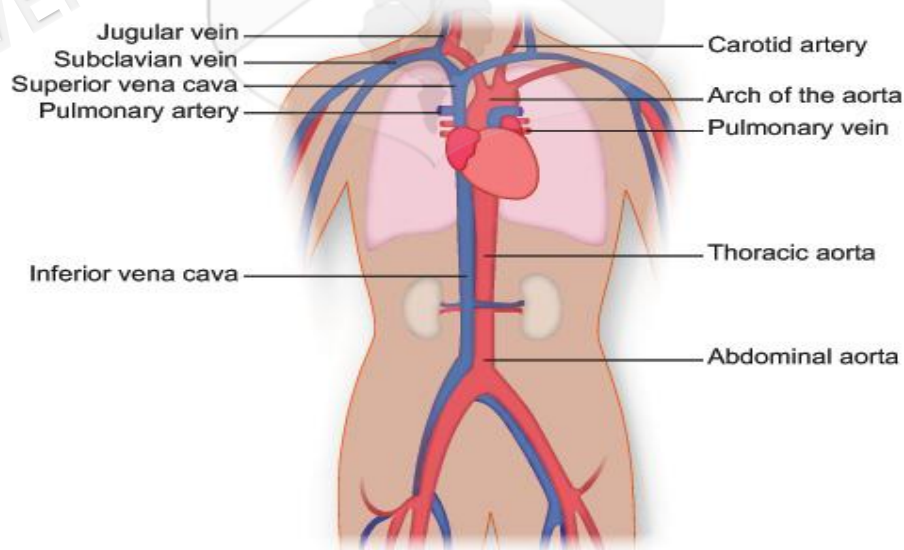


Figure 2.1: The blood circulation process

Circulatory disease is an important concern in today's preventive medicine because it is highly sustained by unhealthy cultural and lifestyle habits (WHO 2011). The cardiovascular system is accompanied by many risk factors. The term *cardiovascular disease* (CVD) is the class of diseases that involve the heart or blood vessels (arteries and veins). The distribution of blood volume to different parts of the human vascular system can be seen in Figure 2.2. CVDs are the world's largest killers, claiming 17.1 million lives a year. Tobacco use, an unhealthy diet, physical inactivity and harmful use of alcohol increase the risk of heart attacks and strokes (WHO 2011). Table 2.1 introduces the common risk factors of CVD.

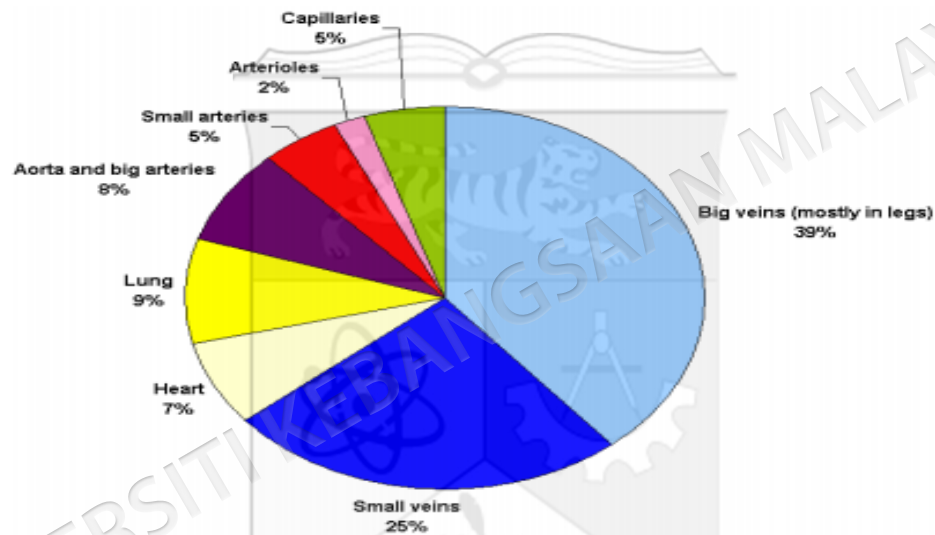


Figure 2.2 Distribution of blood volume for the different parts of the human vascular system

Source Blažeka et al. 2005

Table 2.1: Common types of CVD risk factors

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	

CVD includes dysfunctional conditions of the heart, arteries, and veins that supply oxygen to vital life-sustaining areas of the body like the brain, the heart itself, and other vital organs. If oxygen doesn't arrive, the tissue or organ will die. Ischemic Heart Disease is the technical term for obstruction of blood flow to the heart. In general this occurs because excess fat or plaque deposits are narrowing the veins that supply oxygenated blood to the heart. Excess build-up of plaque and fat are respectively termed *arteriosclerosis* and *atherosclerosis*. Both arteriosclerosis (calcium deposits) and atherosclerosis (fat deposits) involve a build-up on the inside of artery walls. In fact, atherosclerosis and arteriosclerosis are associated with the term of *endothelial dysfunction*. Atherosclerosis is characterized by thickening of the arteries, loss of elastic properties and endothelial dysfunction.

Endothelial dysfunction is the initial step of the atherosclerotic process involving many vascular districts, including penile and coronary circulation (Piero et al. 2009). Endothelial dysfunction is associated with CVD risk factors (Vita et al. 1990; Black 1992; Celermajer & Sorenson 1994). Endothelial dysfunction has been proposed to be an early event of patho-physiologic importance in the atherosclerotic process (Celermajer et al. 1992; Suwaidi et al. 2000) 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 (Dierk & Ernesto 1994).

Extensive clinical and statistical studies have identified several factors that increase the risk of developing CVD, including CAD and heart attack. These factors associated with the presence of CVD are referred to as the CVD risk factors. *Major risk factors* are those that research has shown significantly increase the risk of developing the disease; while other factors associated with increased risk, the significance and prevalence of which have not yet been precisely determined, are called *contributing risk factors* (AHA 2008). *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 (Munther 2008).

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 (the good kind) and LDL cholesterol (the bad stuff). Stiffening of large arteries predicts adverse cardiovascular outcomes (Benetos et al. 1997; Hayashi et al. 2002; Weber et al. 2004). 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 (Van et al. 2002; Yan et al. 2006). Medically, atherosclerosis is considered the dominant pattern of arteriosclerosis which affects primarily the elastic and large- to medium-sized muscular arteries.

2.2 ATHEROSCLEROSIS AND ARTERIOSCLEROSIS

Atherosclerosis is one of the main major causes of cardiovascular disease. Atherosclerosis can be described as a slow disease in which the arteries become hardened. However, *arteriosclerosis* can be defined as the hardening and thickening of the walls of the arteries. Hence, atherosclerosis is the main pattern of arteriosclerosis. Arteriosclerosis 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 (MedicineNet 2010). Arteriosclerosis 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. Figures 2.3 and 2.4 demonstrate the process of atherosclerosis and its main patterns.

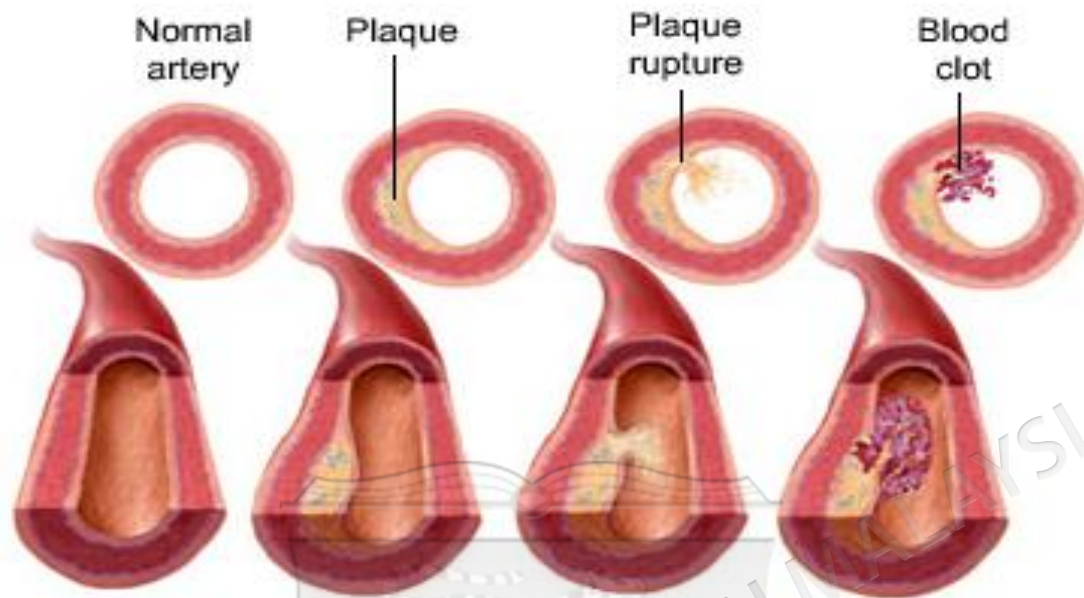


Figure 2.3 The process of atherosclerosis development in general

Source AHA 2010

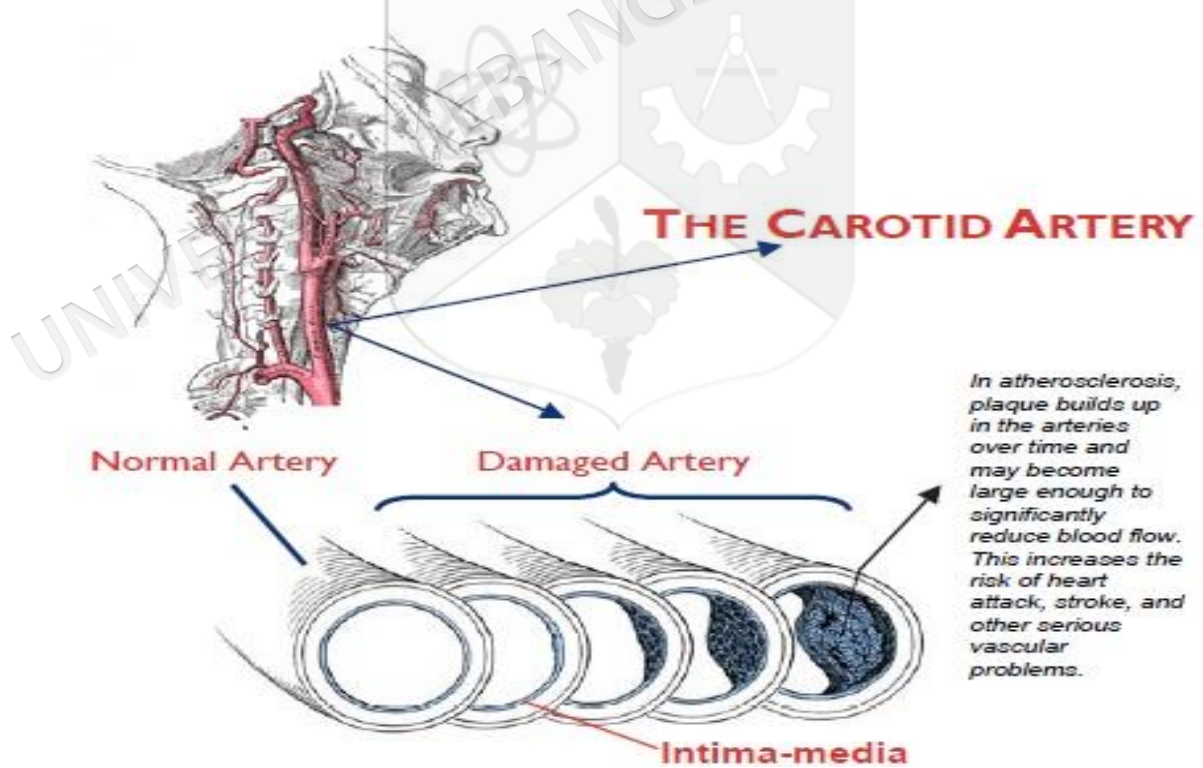


Figure 2.4 Atherosclerosis risk at carotid intima-media arteries

Source Site index (2011)

Atherosclerosis as a slow, complex disease that typically starts in childhood, and it often progresses when people grow older; moreover, it may progress rapidly in some old people (AHA 2010). Atherosclerosis risk depends on the amount of the deposited materials (blood clots, fat, and cholesterols). Figure 2.5 illustrates the deposited atherosclerosis inside the intima-media artery. Atherosclerosis can lead to clogged arteries in any part of the body. When the arteries to the heart are affected, angina (chest pain) or a heart attack may result. If arteries in the leg are affected, leg pain may occur. Atherosclerosis of the arteries to the brain can cause strokes (NWHIC 2011).

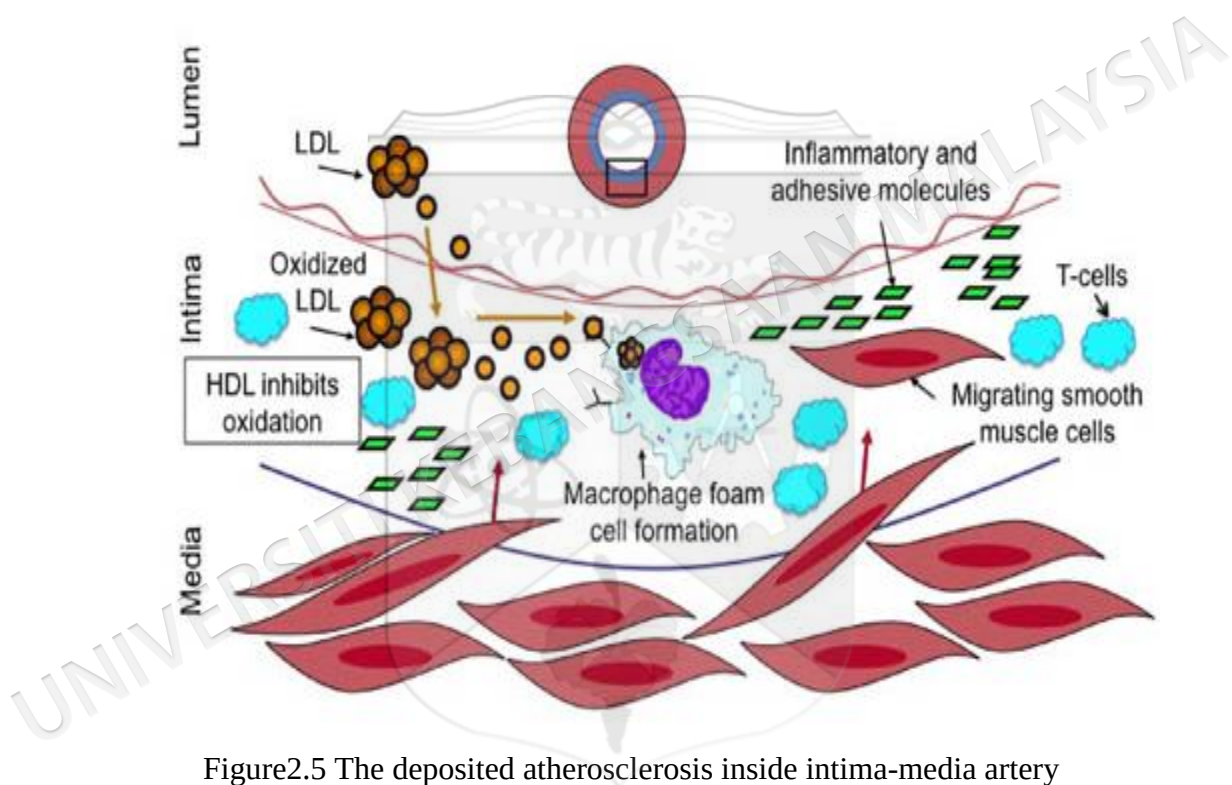


Figure2.5 The deposited atherosclerosis inside intima-media artery

Source Antonio 2009

2.3 MEASUREMENT OF ATHEROSCLEROSIS

Carotid artery intima-media thickness (CIMT) is now a well-validated tool to study the presence and progression of cardiovascular disease (Parikh & Daneman 2004). CIMT, determined by high resolution B-mode ultrasonography, is currently the best validated,

non-invasive surrogate marker for atherosclerosis available (Lipids Online 2011). Multiple studies have shown CIMT to be positively correlated with cardiovascular disease (CVD), primarily myocardial infarction (MI) and stroke. CIMT has also been associated with angiographic evidence of coronary artery stenosis. CIMT increases with age and generally is slightly higher in men compared to women (Lipids Online 2011). Moreover, CIMT found to be a marker of cardiovascular risk in Type 2 diabetic cohorts (Bernard 2005).

High resolution carotid ultrasonography has been used to obtain measurements of the thickness of the intima and media of the carotid arteries (Daniel et al., 1999). Previous studies have shown cross-sectional associations between common-carotid-artery intima-media thickness and cardiovascular risk factors (Poli et al. 1988; O'Leary et al. 1999; Mannami et al. 1997), the prevalence of cardiovascular disease (O'Leary et al. 1999; Mannami et al. 1997; Bots et al. 1992), and the involvement of other arterial beds with atherosclerosis (Burke et al. 1995; Allan et al. 1997). Changes in common-carotid-artery intima-media thickness have also been adopted as a surrogate end-point for determining the success of interventions that lower the levels of low density lipoprotein cholesterol (Blankenhorn et al. 1993; Furberg et al. 1994; Hodis et al. 1996). There are only a few studies showing an association between increased carotid-artery intima media thickness and new myocardial infarction or stroke (Salonen et al. 1991; Bots et al. 1997; Chambless et al. 1997; Hodis et al. 1998).

Physiology and anatomy interface at the inner (intima-media) thickness of our great vessels. It is within the intima-media that abnormalities in vascular biochemistry layer out soft, vulnerable plaque (Lorenz et al. 2006). It is within the IMT that vascular disease first progresses and it is within the IMT that vascular disease first regresses. The IMT is the leading edge of cardiovascular disease. CIMT measurement allows us to quantify, and then follow, the overall plaque generating status in a manner that is noninvasive, quantitative, and reproducible (Salonen & Salonen. 1991). Table 2.2 represents the factors associated with increased CIMT and/or rate of CIMT regression.

Table 2.2 The factors associated with increased CIMT and/or rate of CIMT regression

Factors associated with increased CIMT and/or rate of CIMT regression			
High LDL	Oxidized LDL	Low HDL	High Triglycerides
Lipoprotein	Hypertension	Smoking	Diabetics
Mercury	Arsenic	Low Antioxidant Defense Level	
Overweight	Homocysteine	Insulin Insensitivity	Low Vitamin D
Oxidative stress	Infectious Burden	Sleep Apnea	Hypothyroid
Low Selenium	Low Magnesium	High Fibrinogen	Kidney Failure
High Stress	Depression	Family Hy of CHD	Standing at Work
Low Testosterone +/- High Estradiol in men		Periodontal Disease	ADMA
Inflammation	Air Pollution	Allergy and Asthma	

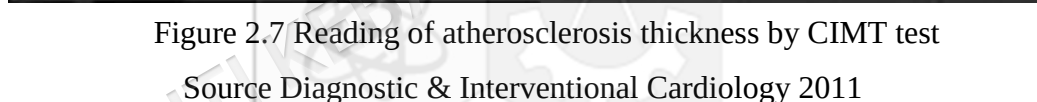
Atherosclerosis begins in the abdomen and ascends to the heart and the carotid arteries. The carotid artery, located on both sides of the neck, is the largest artery that is near the surface of the skin. It supplies blood to the brain, and it can therefore be examined noninvasively (NASA Spinoff 2007). The process of running a CIMT test is shown in Figure 2.6.



Figure 2.6 The process of CIMT test measurements

Source Diagnostic & interventional cardiology 2011

A limitation of the CIMT as a surrogate for detecting coronary artery disease is that it does not accurately assess the total atherosclerotic burden and therefore cannot predict the severity of coronary artery disease or distinguish patients with one-vessel, two-vessel, or more coronary artery disease (Regence 2011). The greatest weakness of CIMT is the lack of standardized protocols (Michael & Bradley 2010). In clinical practice, this weakness could result in an inaccurate estimation of the progression, or regression of atherosclerosis between measurements. However, the application of carotid intima border edge detection software programs has reduced reader variation and improved reproducibility. Gepner et al. (2006) demonstrated that an experienced or novice reader using a border detection program had absolute CIMT differences of $0.011 \text{ mm} \pm 0.004$



Source Diagnostic & Interventional Cardiology 2011

A limitation of the CIMT as a surrogate for d

A limitation of the CIMT as a surrogate for detecting coronary artery disease is that it does not accurately assess the total atherosclerotic burden and therefore cannot predict the severity of coronary artery disease or distinguish patients with one-vessel, two-vessel, or more coronary artery disease (Regence 2011). The greatest weakness of CIMT is the lack of standardized protocols (Michael & Bradley 2010). In clinical practice, this weakness could result in an inaccurate estimation of the progression, or regression of atherosclerosis between measurements. However, the application of carotid intima border edge detection software programs has reduced reader variation and improved reproducibility. Gepner et al. (2006) demonstrated that an experienced or novice reader using a border detection program had absolute CIMT differences of $0.011 \text{ mm} \pm 0.004$

and $0.022 \text{ mm} \pm 0.004$, respectively, when compared with CIMT measurements of the same images by a reference laboratory. Intra-observer reproducibility was high, with a mean absolute difference of $0.003 \pm 0.003 \text{ mm}$ (variation coefficient, 3.1%) and $-0.040 \pm 0.005 \text{ mm}$ (variation coefficient, 7.8%) for the experienced and novice readers, respectively (Gepner et al. 2006).

CIMT, however, is operator-dependent and requires high-cost ultrasound imaging instrumentation which could limit its usefulness for routine clinical assessments. Moreover, CIMT must be run in clinical environments, reflects atherosclerosis of carotid intima-media arteries only, is a relatively long procedure, and has no standard protocols of measurement. In addition, ultrasound method is gain-dependent, hence plaque morphology is difficult. Therefore there is a need to look for a rapid measure of atherosclerosis in clinical settings, daily activities, and in homes. All this is in addition to the need for a screening window to look inside the heart and arteries. Besides being noninvasive, operator-independent, easy to construct, usable on many sites of the body, a rapid test, low-cost and a simple method, PPG has shown potential for the assessment of endothelial function. It is much less costly than the ultrasound approach (Allen 2007). Therefore PPG is a promising tool in assisting with detection of high-risk atherosclerosis.

2.5 PHOTOPLETHYSMOGRAM

Several decades before the arrival of pulse oximetry, the simple PPG was used as a measure of tissue blood volume (Challoner 1979). It is related to, but not equivalent to, the measurement of pulsatile tissue volume, plethysmograph. Pulsatile tissue volume can be directly measured (Whitney 1953). The plethysmograph measures the sum total of volume changes in any and all blood vessels (Andrew et al. 2008). Arterial pulsations are the most significant (Whitney 1953). The underlying principle of the PPG is that it utilizes a photo transducer comprised of a pair of light-emitting diodes (LED), and the intensity of the emitted light received by the photodetector is modulated by the heart pumping action. The arteries, which contain more blood during systole than diastole,

increase in diameter (vasodilation) due to increased pressure (Webster 1997). Therefore, light intensity received by the PPG sensor during systole is less compared to that of during diastole. Thus, the dynamic changes of pulsatile blood volume produce the well-known PPG waveforms (Rosmina 2008).

The PPG is an optically obtained plethysmograph, which is a volumetric measurement of an organ. It can be used to detect blood volume changes in the microvascular bed of tissue (Challoner 1979). The PPG measures a function of the underlying circulation, but the relation is complicated by optical, biomechanical, and physiologic covariates that affect the appearance of the PPG (Andrew et al. 2008). The PPG is often obtained by using a pulse oximeter which illuminates the skin and measures changes in light absorption (Shelley & Shelley 2001). The PPG provides an estimation of cutaneous blood flow by measuring the dynamic attenuation of infrared light by the blood volume present in tissue (Jayasree et al. 2008). The contour of the pulsatile component of the PPG signal has been found to include content descriptive of vascular health (Brumfield & Andrew 2008). PPG pulse signals can be easily obtained from the tissue pads of the ears, fingers and toes where there is a high degree of superficial vasculature (Allen & Murray 2003). It has widespread clinical application, with the technology utilized in commercially available medical devices, for example in pulse oximeters, vascular diagnostics and digital beat-to-beat blood pressure measurement systems (Allen 2007). The electronic building blocks used in a typical PPG measurement system are shown in Figure 2.8.

Reproducibility is very significant in clinical physiological measurement (Allen 2007), for example in giving confidence in detecting significant responses to therapy. Many factors affect reproducibility: the method of probe attachment to tissue; probe-tissue interface pressure; pulse amplifier bandwidth; minimization of movement artifact; subject posture and relaxation; breathing; wakefulness; and room temperature and acclimatization (Teng & Zhang 2006; Zhang & Zhang 2006). Up to now, however, there are no internationally known standards for clinical PPG measurement. The PPG is multiple sites, which is a helpful technique in vascular assessment since it has the capability to make

simultaneous comparisons of pulses from different peripheral body sites (Allen & Murry 2000; Allen & Murry 2002; Allen & Murry 2003).

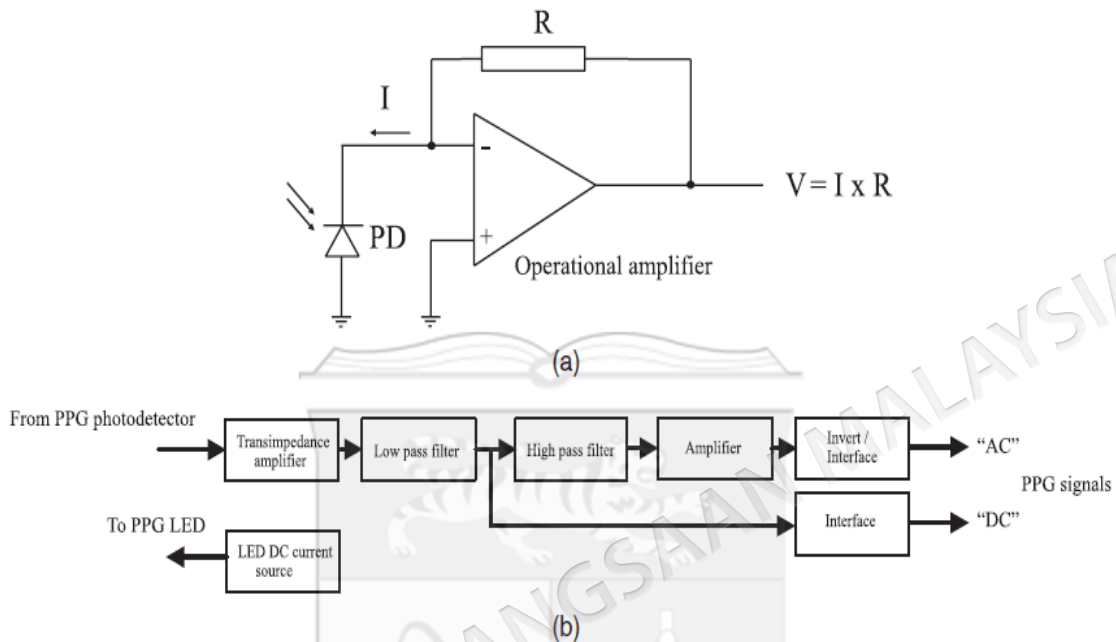


Figure 2.8 Electronic building blocks used in a typical PPG measurement system. (a) A transimpedance (current-to-voltage) amplifier stage that converts light intensity at the photodiode (PD) to an amplifier output voltage ($V = I \times R$, transimpedance gain proportional to feedback resistor value R). (b) The signal conditioning stages surrounding the transimpedance amplifier which include low pass filtering, high pass filtering and further amplification, inversion and signal interfaces.

Source Allen 2007

These waveforms are site dependent and usually comprise a pulsatile (AC) component synchronized to each heart beat, and are superimposed on a slowly varying (DC) baseline (Allen & Murry 2000; Bernardi et al. 1996; Sherebrin & Sherebrin 1990; Harness & Marjanovic 1989). The AC component is superimposed onto a large quasi-DC component that relates to the tissues and to the average blood volume. This DC component varies slowly due to respiration vasomotor activity. The lower frequency components are attributed to respiration (Allen et al. 2002), sympathetic nerve activity (Nitzan et al.

1998), and thermoregulation (Kamal 1989). The DC component of the signal is attributable to the bulk absorption of the skin tissue. DC component also contributes to the respiration, sympathetic nervous system activity and thermoregulation (Gonzalez et al. 2008). An illustration of the AC and DC components can be seen in Figure 2.9.

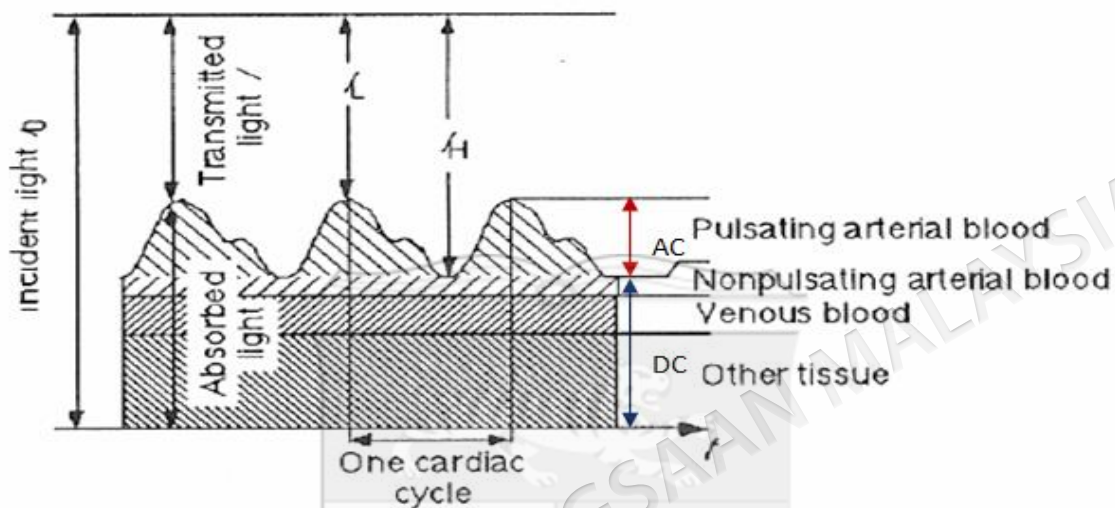


Figure 2.9 PPG waveforms generated from the variations of absorbed and transmitted light in living tissue

Source Webster 1997

Many of the studies reported in the PPG literature are for a single site, often the ear, finger or toe, where pulses can be easily detected (Sherebrin & Sherebrin 1990; Allen & Murray 1993; Chowienczyk et al. 1999; Hahn et al. 1999; Bortolotto et al. 2000; Foo et al. 2006; Millasseau et al. 2006). Many other skin measurement sites are available for vascular assessment (Tur et al. 1983). There have also been studies published which investigated PPG pulses at two sites simultaneously (Dillon & Hertzman 1941; Nijboer & Dorlas 1985; Cooke et al. 1985; Grossmann et al. 1987; Okada et al. 1986; Porret et al. 1995; Nitzan et al. 1998a, 1998b 2001). Three channel PPG research systems (Evans & Geddes 1988) and four channel research systems (Buchs et al. 2005; Erts et al. 2005) have also been established, but not commercialized. Multiple finger site pulse data have also been reported (Dyszkiewicz & Tendera 2006). Six channel PPG data have been published for simultaneous multi-bilateral site PPG data measurements (i.e. the right and

left ear lobes, index fingers or thumbs, and great toes) (Allen et al. 2000, 2002, 2003, 2004, 2005, 2006).

2.5.1 Analysis of the PPG Signal

Analysis of time domain techniques is used rather than frequency domain techniques (Shelley & GStout et al. 1999; Johansson 2003) to automatically detect the morphological changes in the contour of the PPG (Stephen & Suzanne 2006). The observed contour of the PPG contains similar information to that of the peripheral pressure pulse (Millasseau et al. 2000). The PPG pulse observed at the peripheral circulation is the result of the wave reflection phenomenon (Figure 2.10), which comprises a complex interaction between the left ventricle and the systemic circulation (Millasseau et al. 2002). PPG signal amplitude depends not only on the systemic intravascular pulse pressure, but also on the distensibility of the vascular wall, and hence on the autonomic nervous system (Burton 1954; Aymen et al. 2001).

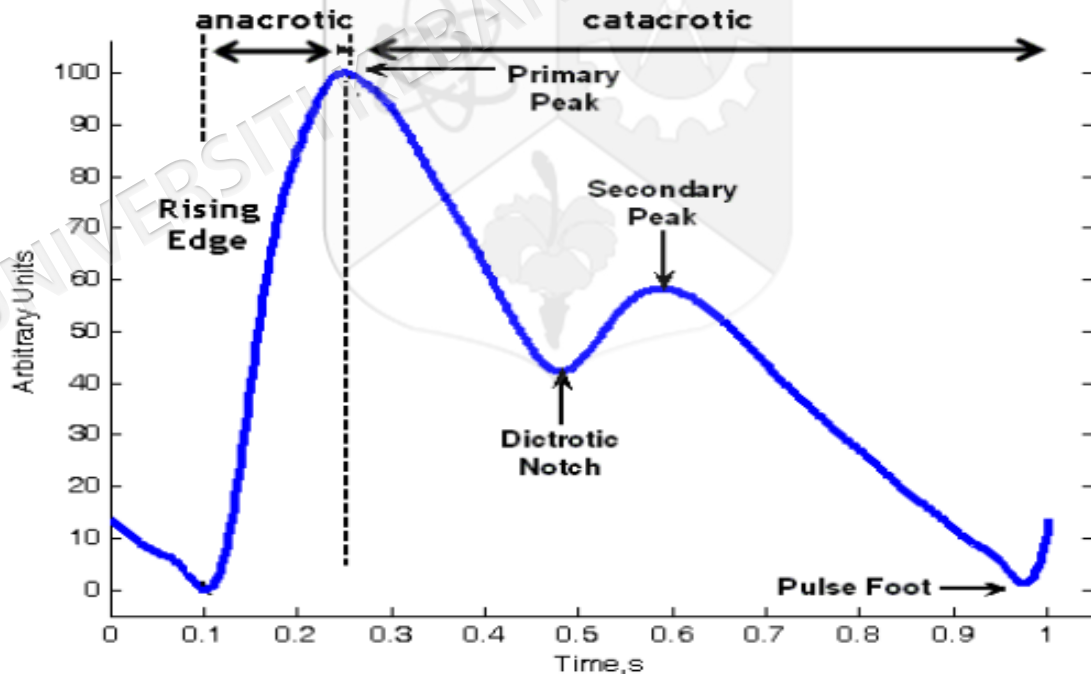


Figure 2.10 The characteristic of single pulse of PPG signal

Source Kalaivani 2009

The appearance of PPG can be defined as the anacrotic phase being the rising edge of the pulse, and the catacrotic phase being the falling edge of the pulse. A dicrotic notch is usually seen in catacrotic phase of subjects with healthy complaint arteries. The first peak is formed mainly by pressure transmitted along a direct path from the left ventricle to the finger (where it generates a change in blood volume) during the forward going pressure. The second peak is formed in part by pressure transmitted along the aorta and large arteries to sites of impedance mismatch in the lower body, where it is reflected back up the aorta during the propagation of the reflected wave (Gonzalez et al. 2008). The time delay between the systolic and diastolic peaks (ΔT) can be used to infer the transit time taken for pressure to propagate along the aorta and large arteries to the major sites of reflection in the lower body and back to the root of the subclavian artery. The ΔT decreases with age as a consequence of increased large artery stiffness and increased PWV of pressure waves in the aorta and large arteries (Millasseau et al. 2002). The dicrotic notch shifts up towards the right of the pulse cycle, and its diminution is consistent with age-related damping attributed to age-related increases in pulse wave velocity (Allen & Murray 2003). Therefore both dicrotic notch and inflection point of PPG tend to be less pronounced with age (Qawqzeh et al. 2010). In younger subjects the arteries are less distensible and the pulse wave velocity is high. Thus the dicrotic notch in the falling slope is prominent due to intense wave reflection (Hlimonenko et al. 2003). The PPG's points of interest can be seen in Figure 2.11. Moreover, the PPG differs in means of amplitude from one subject to another and from one site to the next. In addition, the PPG is found to have similar (or equal) values in the calculation of time intervals between each two points of PPG morphology for the same subject (e.g. right and left hand). However, it is found to differ in terms of amplitude value between right and left hand for the same subject. Table 2.3 summarizes some of the factors affecting the amplitude of the PPG.

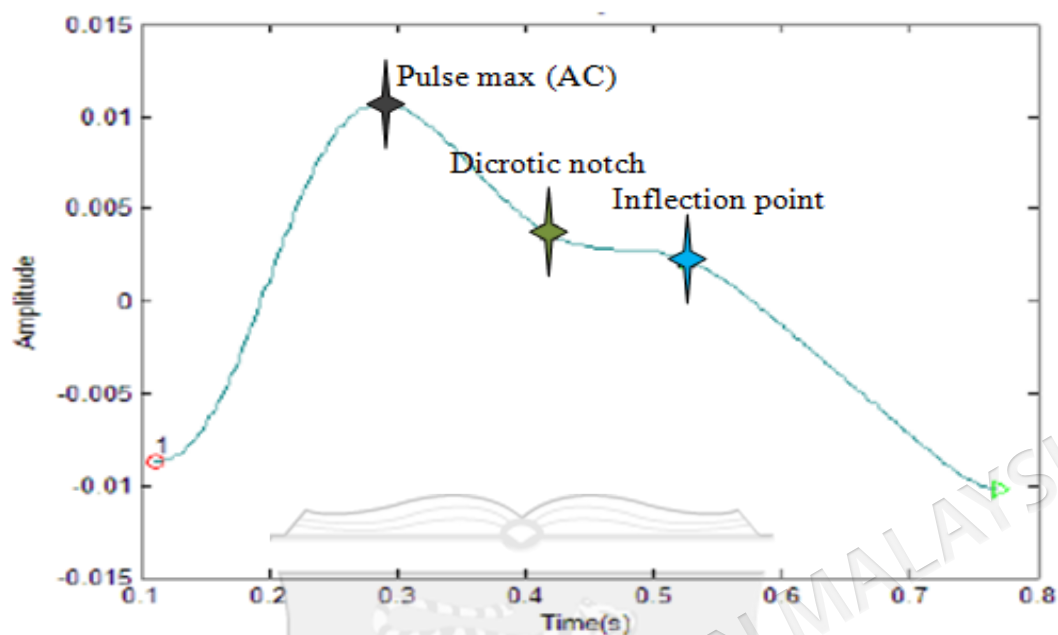


Figure 2.11 The characteristics of the recorded PPG signal. Analysis of PPG morphology variations in time domain (AC)

Table 2.3 Example of ambiguities in the PPG: Multiple processes can increase the absolute signal processing

Factor	Change	Effect	Result
↑ Arterial pulse pressure	Δ vascular state	→ ↓ vascular compliance	
↑ * Height of the hand	→ hand transmural	↑ pressures	→
↑ * Cuff/probe local pressure	→ ↓ compliance	transmural pressures in hand	→
↓ * Central mean arterial pressure	Δ ↓ compliance	transmural pressures in hand	→
↓ Volume pulse	→ manufacturer's postprocessing		
↓ Optic density in the tissue			
↑ Ambient light			
↑ increase;	Δ change;	↓ decrease;	→ cause

Source Modified from Andrew et al. 2008

Two main approaches have been developed to describe the characteristics of PPG waveform. The first method is the analysis of PPG second derivatives (Bortolotto et al. 2000; Imanaga et al. 1998; Takazawa et al. 1998; Qawqzeh et al. 2011; Gonzalez et al. 2008). The positions of the peaks and valleys of the second derivative give information

about PPG and its pulse parameters. The second method involves extracting the pulse parameters from the peaks of PPG directly, using the first (Millaseau 2002; Millaseau 2006) or third derivatives of PPG (Mustafa 1997). In fact, PPG derivatives facilitate the understanding of the morphological variations of PPG signal.

2.5.2 Analysis of PPG Derivatives

Takazawa et al. (1998) performed a drug administration study to evaluate the clinical application of the second derivative of the fingertip PPG waveform. They extracted an aging index ($AI = b-c-d-e/a$) based on SDPPG five waves. The developed aging index had a higher value for women than for men. Moreover, they concluded that the aging index might be useful for evaluation of vascular aging and for screening of arteriosclerosis. Moreover, a study by (Toshiaki et al. 2006) described the association of SDPPG indices, the risk of CHD and Framingham risk score. They recorded SDPPG from a community without apparent atherosclerotic disorders. Their findings showed that SDPPG indices significantly correlated with the Framingham risk score in both genders, as well as several coronary risk factors. For these reasons, they suggested that the SDPPG might be useful for the estimation of risk of CHD in the general population. The SDPPG characteristics can be shown in Figure 2.12.

Looking for a noninvasive indicator for vascular assessment, PPG augmentation indices have been extracted by Gonzalez et al. (2008) based on the analysis of SDPPG. They analyzed PPG signals by using a computer-based Photoplethysmographic analyzer. However, the extracted indices showed significant differences between normal and high-risk subjects. Toshiaki et al. (2007) sought to elucidate independent determinants of the SDPPG among various cardiovascular risk factors in middle-aged Japanese men. They observed no independent association between the SDPPG indices and blood leukocyte count or serum C-reactive protein levels. However, they concluded that SDPPG indices reflect arterial properties affected by several cardiovascular risk factors in middle-aged Japanese men.

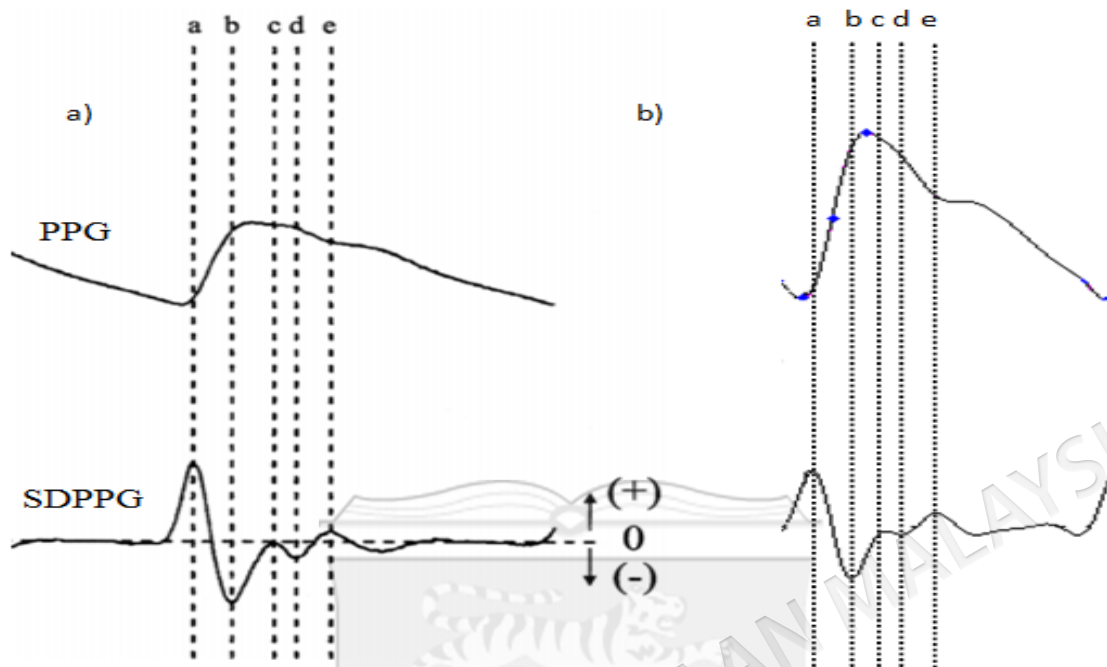


Figure 2.12 The characteristics of SDPPG. Part (a) represents SDPPG waves by Toshiaki et al 2006. And part (b) represents the recorded PPG and its SDPPG.

The length of the vascular system and the inner diameter and wall thickness of vessels may modify the SDPPG wave pattern in the growth period. Thereafter, as the effects of these factors decrease, the increase in intravascular pressure and decreasing wall elasticity due to aging may affect the wave pattern (Iketani 2000). Far away from adults and elderly people, a study by (Satoshi et al. 2010) demonstrated the altered characteristics of SDPPG in children and its reaction to vasodilator. They concluded that SDPPG might be useful for evaluation of some vascular diseases and for verifying the efficacy of a vasodilator, not only in adults but also in children.

2.6 ADVANTAGES AND LIMITATIONS OF THE PPG

The PPG demonstrates many advantages, due to the ease with which it can be set up, the simplicity of its use, and its low cost. In addition, the PPG has the ability to take measurements without having direct contact with the skin surface (Yue et al. 2009). For

these advantages, the PPG technology has attracted much attention in clinical applications (Allen 2007). Next to being non-invasive in nature, the PPG technique is advantageous because of its uncomplicated instrumentation system, ease of probe attachment, and convenience to both the operator and the patient (Rosmina 2008). With advancement of semiconductor technology, PPG sensors can be miniaturized, and thus the instrumentation is small and portable, making the application of PPG technique becoming interestingly popular in recent years (Allen 2007). The sampling time for PPG ranges from a few Hz to a few kHz, depending on the purpose of the monitoring. A low sampling frequency allows large data space and this will make the recorded data manageable and easy to store for future analysis.

The main limitation of PPG is that it is quite sensitive to motion artifacts, ambient light, skin pigments, dyes, nail polish, and dysfunctional hemoglobin (Webster 1997). Motion artifacts can have substantial effects on the DC signal, while the AC is still preserved. The method of probe attachment to tissue, subject posture, probe-tissue interface pressure, room temperature, pulse amplifier bandwidth are factors affecting the reproducibility of PPG signal. The DC component of the signal is attributable to the bulk absorption of the skin tissue. DC component also contributes to the respiration, sympathetic nervous system activity and thermoregulation. PPG signal amplitude depends not only on the systemic intravascular pulse pressure, but also on the distensibility of the vascular wall, and hence on the autonomic nervous system.

Extreme skin temperatures, such as excessive cold, are not good for recording PPG signals. This is because exposure of the body to extreme temperatures can cause changes in peripheral perfusion which will limit the blood circulation to the peripheries where the PPG sensors are attached. Besides that, for finger PPG signal recording, the patient should avoid using nail polish, as the presence of the colored paint on the nail will limit light transmission/reflection through the tissues, thus affecting the accuracy of the detected PPG signal.

Despite the few limitations of the PPG system, when precautions and preventive actions are taken during measurement, artifact-free and good PPG signals can be achieved. Recent developments in computing technology and software data analysis tools have enabled sophisticated pre- and post-processing of physiological waveforms. As such, even poor signals can be utilized and processed. The fact that many properties and valuable information are contained in the PPG signals is most important and worthwhile. Therefore the limitations are secondary issues. Therefore, the analysis of PPG waveform (contour analysis) is very important due to its simplicity and due to the ability of including it into clinical settings with a very low-cost as a non-invasive measure for arterial stiffness assessment. Its noteworthy that, the utilization of PPG technique in this study was to examine the ability of PPG (non-intervention PPG) in the predicting of high-risk atherosclerosis.

In fact, the proposed method of predicting high-risk atherosclerosis using Photoplethysmography can be implemented in many applications. Challenges remain with the technology, including the standardization of measurements, improving repeatability, and establishing comprehensive normative data ranges for comparison with patients and for evaluating responses to therapy (Allen 2007). Therefore, the proposed model can be implemented in applications for simple endothelial dysfunction assessments, and home diagnostics techniques.

2.7 CHAPTER SUMMARY

A brief summary of the cardiovascular system was introduced in the opening of this chapter. Some risk factors associated with the cardiovascular system were highlighted as well. The main focus of the chapter was on the atherosclerosis process, highlighting its causes, symptoms, risk factors, measurements, and its relation to arteriosclerosis. CIMA as an established method for the measurement of atherosclerosis in clinical settings was demonstrated along with its measurement procedure. There followed a list of CIMA disadvantages and limitations, as well. Then, a description was elaborated of the proposed new method for the prediction of high-risk atherosclerosis by means of PPG signal and its

techniques of analysis. The advantages and limitations of the PPG technique were discussed towards the end of the chapter. In view of the promising advantages, PPG was proposed to be used as a noninvasive technique for the prediction of high-risk atherosclerosis in this research study.



CHAPTER III

RESEARCH METHODOLOGY

3.1 EXPERIMENTAL DESIGN

A two channel PPG recording system was adopted in this research to obtain index finger PPG signals from both hands simultaneously. A special National Instrument unit with a data acquisition board (NI cDAQ-9172) was used to record, digitize the signals locally, and transmit the digital data to a personal computer with a sampling rate of 5500 Hz and amplitude of ± 6 V. Data were recorded into text files, to be analyzed offline using Matlab software. The experimental setup for this study can be seen in Figure 3.1. In addition, the used setup for PPG recording is shown in Figure 3.2. The setup unit consisted of two probes (Transmission type sensor), the NI unit for synchronization, and a personal laptop. The probes were attached to the patient's left and right index fingers. Each probe consisted of an infrared light emitting diode (IR-LED) and photodetector. The probes functioned on a transmission type sensor and worked synchronously to record index finger PPGs for each individual patient. The data were stored in text files inside the laptop to enable further analysis and investigation. The setup of the PPG was very simple, easy to use and operator-independent. The subject was asked to lie in a supine position and, after he had rested for five minutes, breathing normally and keeping quiet, the probes of PPG were then attached to both hands and the measurement was carried out for 90 seconds. The PPGs were stored in a text file which consisted of two columns representing the PPGs of the right hand and the left hand respectively. The computer was installed with National Instrument Lab View software (NI, LabVIEW 7.1 Development System).

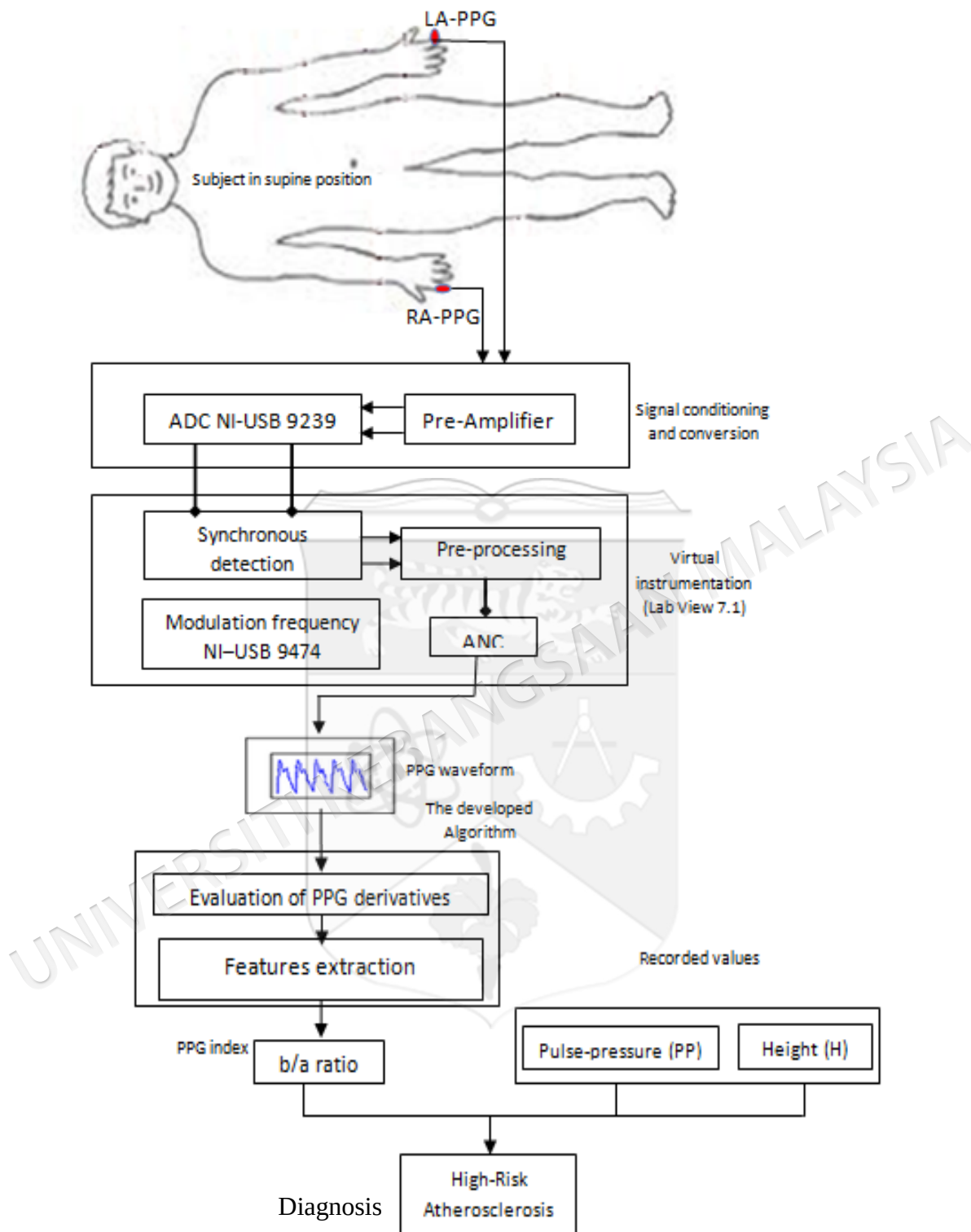


Figure 3.1 The experimental design of the study

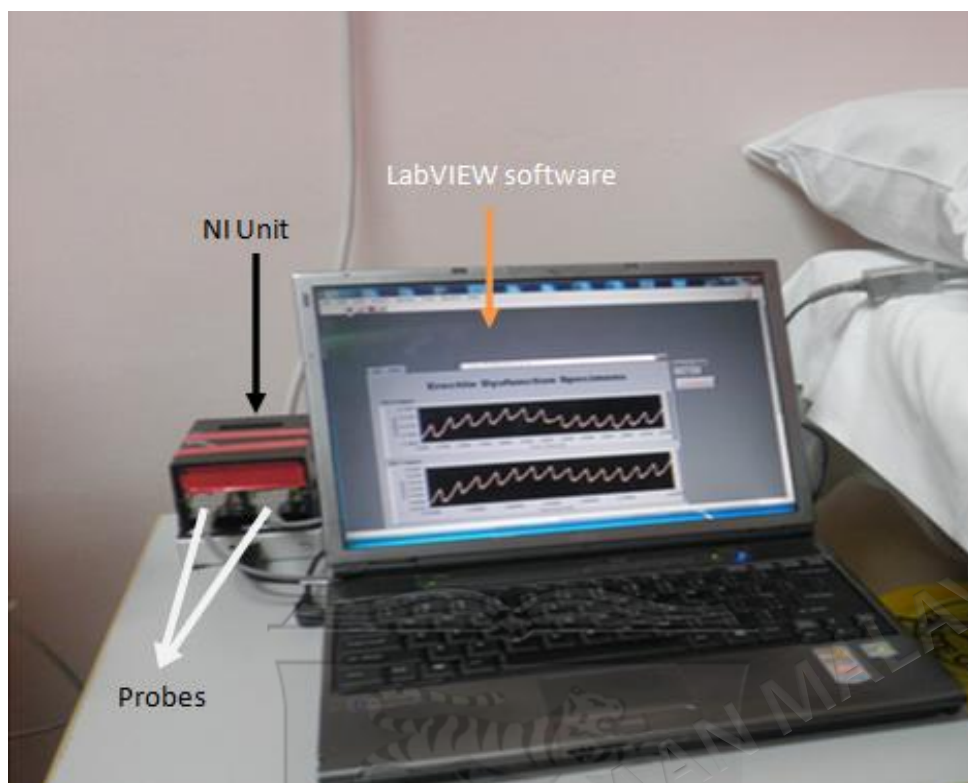


Figure 3.2 The setup used for PPG signal recording

3.1.1 DATA ACQUISITION

Ethical approval was obtained in order to proceed with this research (Appendix A). Consequently a total of 80 ED subjects participated in the data acquisition activity during the research (March 2009–February 2011). All subjects were selected from the Urology Clinic at the Medical Center of the National University of Malaysia (PPUKM). The study had two different protocols: Protocol A and Protocol B. Protocol A was adopted initially for the recording of the PPGs from the ED case subjects. Later on, another ethical committee approval was issued to form a new round of PPG recording for the control group. Both of the protocols used the same criteria for the process of recording the PPG signals; whereas different criteria were applied to the hiring of an individual to be the case or control group—the details are shown in Appendix B (information description for the participant) & Appendix C. All data were recorded in a clinical environment (hospital environment (PPUKM)). Figure 3.3 represents the recording of PPG signals based on the protocols used. The CIMT

measurement was carried out in the same room by a specialist operator to save patient time and to facilitate the whole process of recording. CIMT measurement was taken by using high resolution B-mode ultrasound equipment (GE Ultrasound, model: GE Vivid I Ultra and the probes types: 8L-RS). Figure 3.4 shows the process of CIMT measurement.

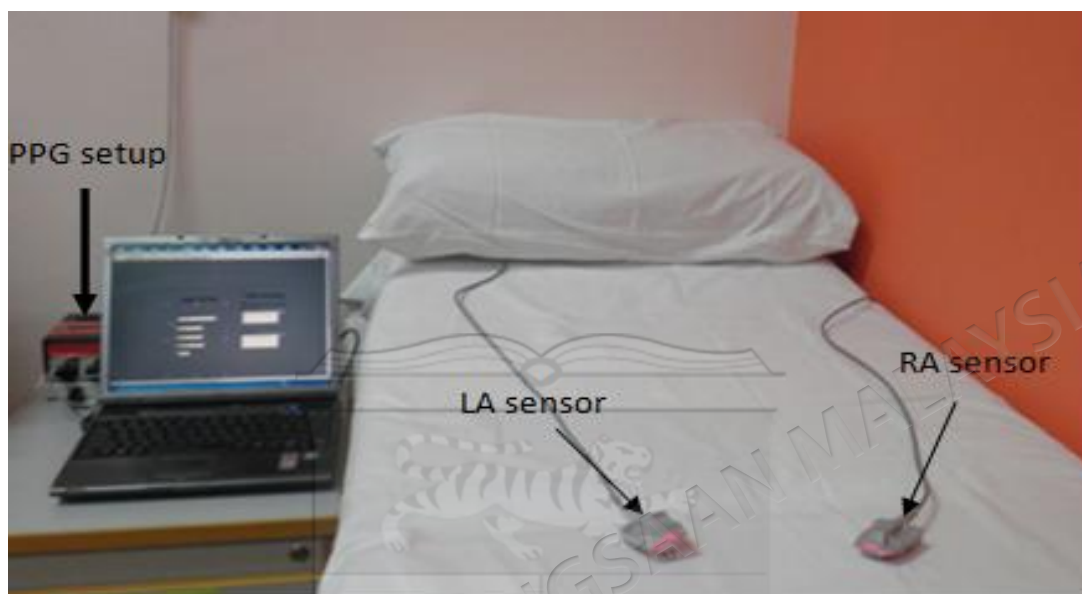


Figure 3.3 PPG instrumentation unit, probes, and the used laptop

PPGs can be recorded either at 660 nm or 905 nm. This work utilized the use of the red signal (905 nm) since it is more likely to be related to the arterial circulation (Seidel & LaRochelle 1987; Komori et al. 2002), and it is less noisy compared to the infrared signal. Figure 3.5 represents the process of recording PPG alongside with CIMT.



Figure 3.4 CIMT measurements by specialist



Figure 3.5 Parallel measurements of PPG and CIMT

Information recorded for each subject was categorized into two sections: demographic and clinical data. Demographic data concerned information such as the patient's age and sex. Clinical data was further grouped into physical findings and medical results. Physical findings were those detected by a physical examination of the patient such as height, weight, BMI, SP and DP. Medical results were those relating to recording CIMT for both right and left carotid intima-media thickness. Signal recording referred to recorded PPG signals according to the selected protocol, as in Appendix E.

Each subject was asked to rest for at least five minutes before the recording to allow cardiovascular stabilization. It was ensured that subjects had not consumed any meal or tea or coffee for three hours before the experiment, since caffeine causes deterioration in arterial stiffness and wave reflection (Vlachopoulos et al. 2003, 2004). Subjects were asked to breathe regularly and to stay quiet for the 90-second measurement period. As yet, however, there are no internationally recognized standards for clinical PPG measurement (Allen & Murray 2004). Published research tends to be based on studies using quite differing measurement technology and protocols.

Applications that utilize the beat-to-beat variation in PPG characteristics include the assessment of autonomic dysfunction and cardiovascular aging. The algorithms used enabled the selection of the most stable beats, selected a specific time period or a certain number of beats to be used for the analysis. However, the median of the selected beats was used for the recording of PPG characteristics. It can also be useful, however, to obtain an averaged pulse measure to represent an individual subject or site. In this work, no averaging was used due to the sensitivity of the PPG and due to its variations with noise and other artifacts. Details of the PPG analysis are illustrated in the PPG waveform analysis section.

3.1.2 SAMPLE SELECTION

Sampling is that part of statistical practice concerned with the selection of a subset of individual observations within a population of individuals intended to yield some knowledge about the population of concern, especially for the purposes of making predictions based on statistical inference. Sampling is an important aspect of data collection. Researchers rarely survey the entire population for two reasons: the cost is too high, and the population is dynamic in that the individuals within it may change over time. Results from probability theory and statistical theory are employed to guide practice. In business and medical research, sampling is widely used for gathering information about a population (Ken 2004). The present study used a sample of subjects with an established ED at any given age who had no risk or who had one or two risk factors. The study was approved by the Medical Center of Universiti Kebangsaan Malaysia (PPUKM) Ethics Committee and performed by the rules stipulated by the PPUKM Declaration. All subjects gave written consent (Appendix D). The histogram distribution of participants (68 out of 80 subjects, since 12 subjects were excluded from the analysis due to their noisy signals) can be seen in Figure 3.6.

PPG signals were obtained from a group of established erectile dysfunction subjects. The chosen group consisted of two subgroups: one without risk of atherosclerosis, and the other, with risk of atherosclerosis. The total sample varied from having no risk factors, to one or two risk factors. These risk factors were

confirmed through clinical investigation. The clinical characteristics for groups without and with high-risk atherosclerosis are shown in Table 3.1. Figure 3.6 shows a histogram of the age distribution for the total population, and Figure 3.7 a) and b) set out details of the two different groups.

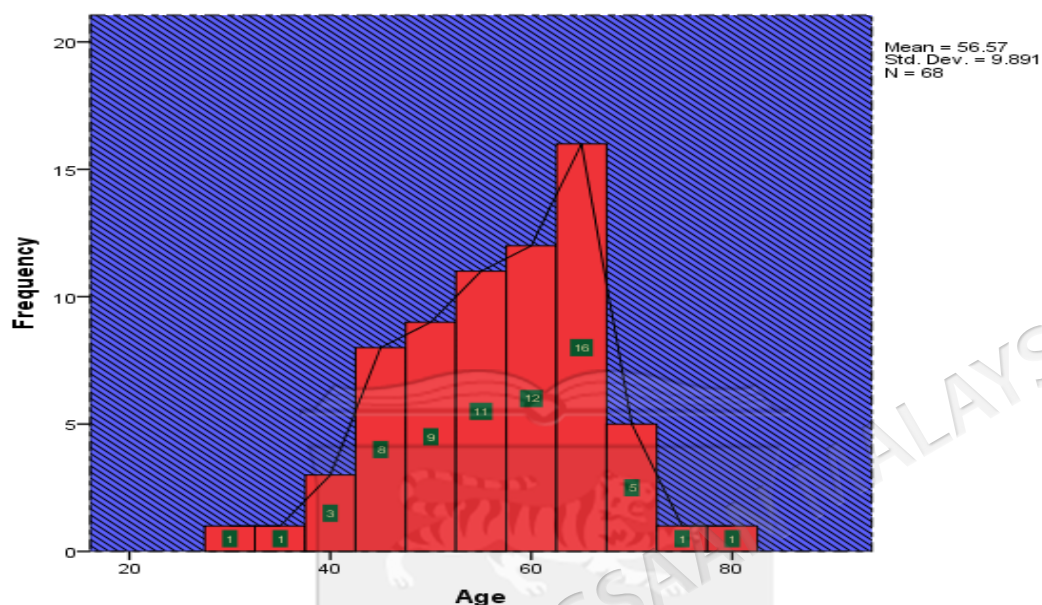


Figure 3.6 Age distribution histogram for the total population

Age distribution for the total selected subjects is elucidated. It can be seen that, most of subjects are above 40 years old. This phenomenon represents the age related associations to PPG waveform and atherosclerosis.

Table 3.1 Clinical Characteristics of the without and with high-risk atherosclerosis subjects

Clinical characteristic	No-risk n(34)	High-risk n(34)
Age range (years)	40.0	34.0
SD (Age)	10.7	7.90
Mean age (years)	53.5	59.7
Mean Height (cm)	169	165
BMI	26.7	26.3
SP (mm Hg)	137	141
DP (mm Hg)	83.0	83.0
PP (mm Hg)	53.0	59.0
MAP (mm Hg)	101	102
CIMT (mm)	0.55	1.10

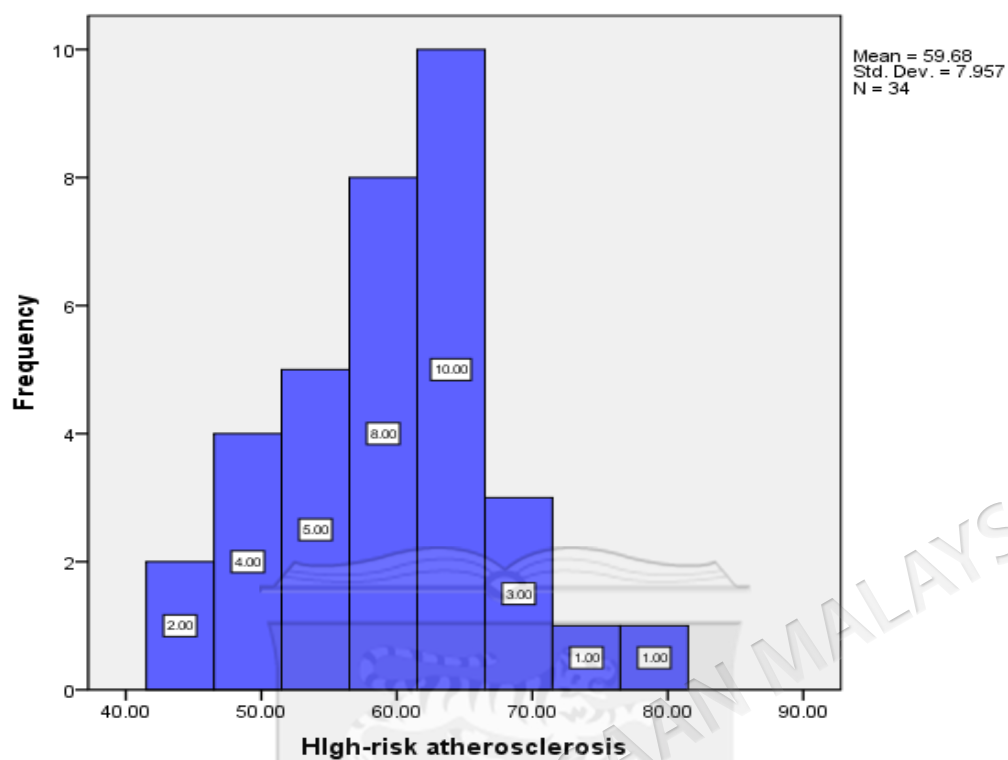


Figure 3.7 (a) Age distribution histogram of high-risk atherosclerosis subjects

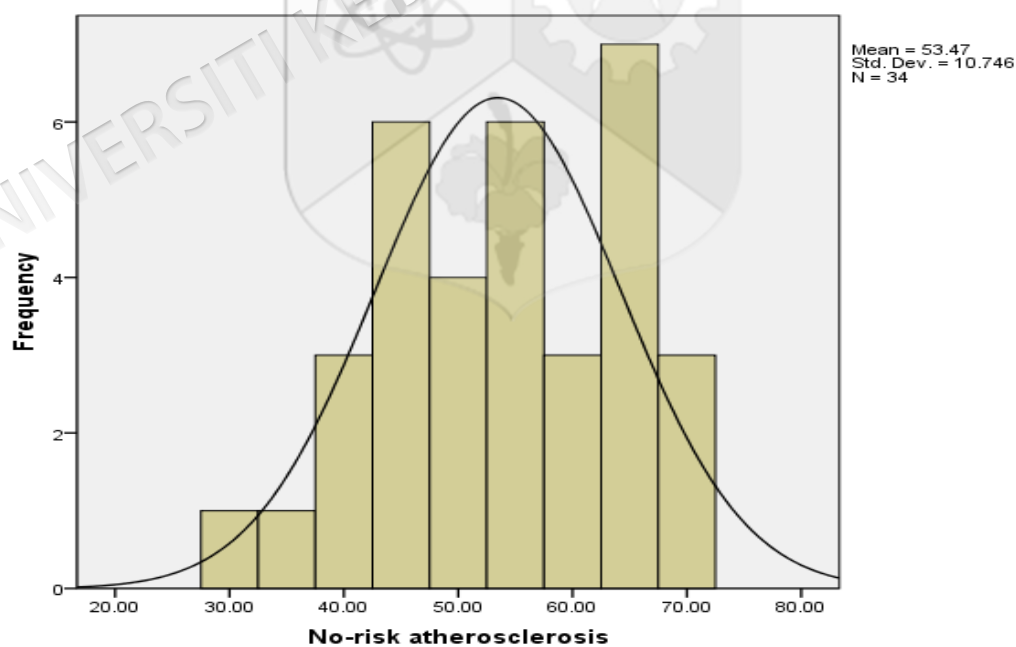


Figure 3.7 (b) Age distribution histogram of no-risk atherosclerosis subjects

3.2 ANALYSIS OF THE PPG WAVEFORM

It is well established that PPG measurements are quite sensitive to patient and movement artifacts (Kalaivani 2010). However, PPG signal pre-processing techniques have been employed in extracting certain information from its morphology to be used subsequently for signal analysis. This is implemented with several steps, as shown in Figure 3.8. First, the recorded PPG signal was de-trended to remove slow baseline drift, filtering the PPG signal to remove noise and any other artifacts, down sampling, chopping the middle part of the PPG signal to remove transits time (the start and end of the PPG); and finally a preprocessing algorithm was applied to locate certain points of interest on the PPG waveform morphology (evaluation of PPG derivatives). All the preprocessing and analysis was done in Matlab.



Figure 3.8 Block diagram of PPG waveform analysis

Furthermore, the PPG signal consists of a DC component that corresponds to changes in the venous pressure and other tissues, while it is the arterial blood volume changes that have a direct bearing on cardiovascular dysfunction. Therefore this quasi DC signal needs to be removed and the signal detrended before being subjected to analysis. A linear detrending was applied to the PPG data. Basically, only the AC component was of interest in this work. Therefore, band-pass filtering was used to extract the AC component (the pulsatile component). When analog filters with suitable cut-off frequencies are used, heart and respiratory signals can be distinguished in the PPG signal. Hence, PPG signals were band-pass filtered (0.6–15 Hz) for removal of the effect of the respiratory rhythm and higher frequency disturbances. In addition, these filters did not introduce phase delays or distortion to the waveforms (Zahedi et al. 2007). To ease visualization and comparison, PPG AC amplitude normalization was carried out. Resampling occurred in two forms: down sampling and up sampling. High frequency disturbance in data indicates that choice of sampling

interval and pre-sampling filters weren't appropriate (Ljung 1999). Therefore, to remedy these features either lowpass filtering or resampling of the data after filtering was implemented. In this work, a down sampling was done to minimize sampling rates from 5500Hz to 275Hz by using the built-in function “resample” in Matlab. Chopping of PPG was used to remove transits time in both ends, which in turn allows the cutting of the middle of PPG to be used for further analysis. The raw data of PPG can be seen in Figure 3.9 (a). And filtered PPG can be seen in Figure 3.9 (b).

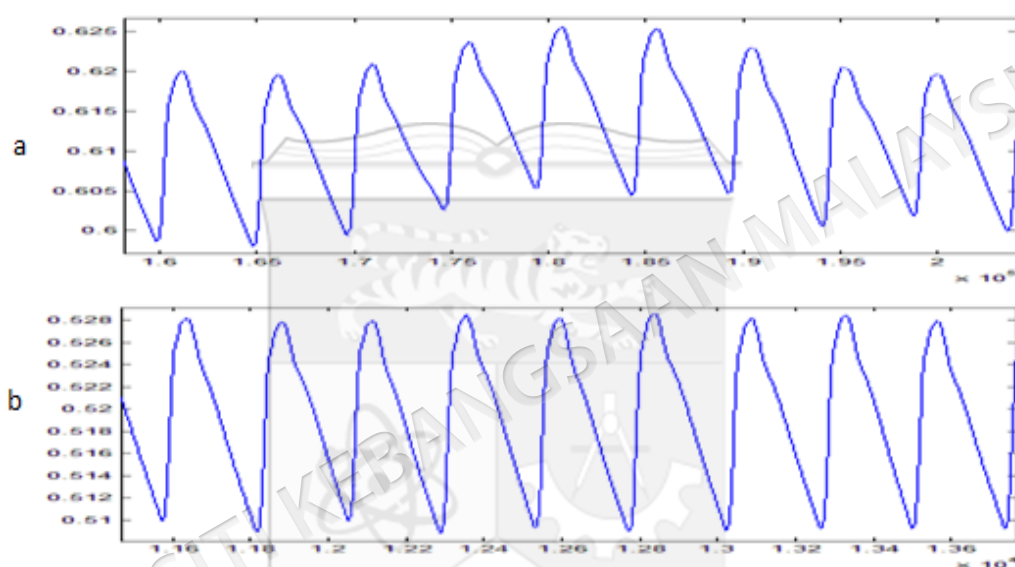


Figure 3.8 Example of PPG signal. (a) Raw PPG without filtering. (b) Filtered PPG signal using a band-pass filter.

Basically, seeking certain information from PPG signals was the essence of the analysis of its morphology variations. However, PPG consists of three main points of interest: Systolic point (AC peak); diastolic notch (valley); and inflection point (diastolic point (peak)). These points seem to be clearly pronounced in adult subjects since the discrimination between them can be simply visualized by eye (Figure 3.10 (a)). However, because of the smooth appearance of the PPG signal due to damping, other features, such as early and late systolic inflections, cannot be readily detected (Alberto 2002). In fact, those points tend to be less pronounced in most of the PPG signals due to the effects of aging, diabetes, atherosclerosis, arterial stiffness ...etc. Moreover, locating these points with the absence of the diastolic notch and/ or the

inflection point constituted a challenge. An example of a PPG signal that presents unseen inflection and dicrotic notch points can be explored in Figure 3.9 (b).

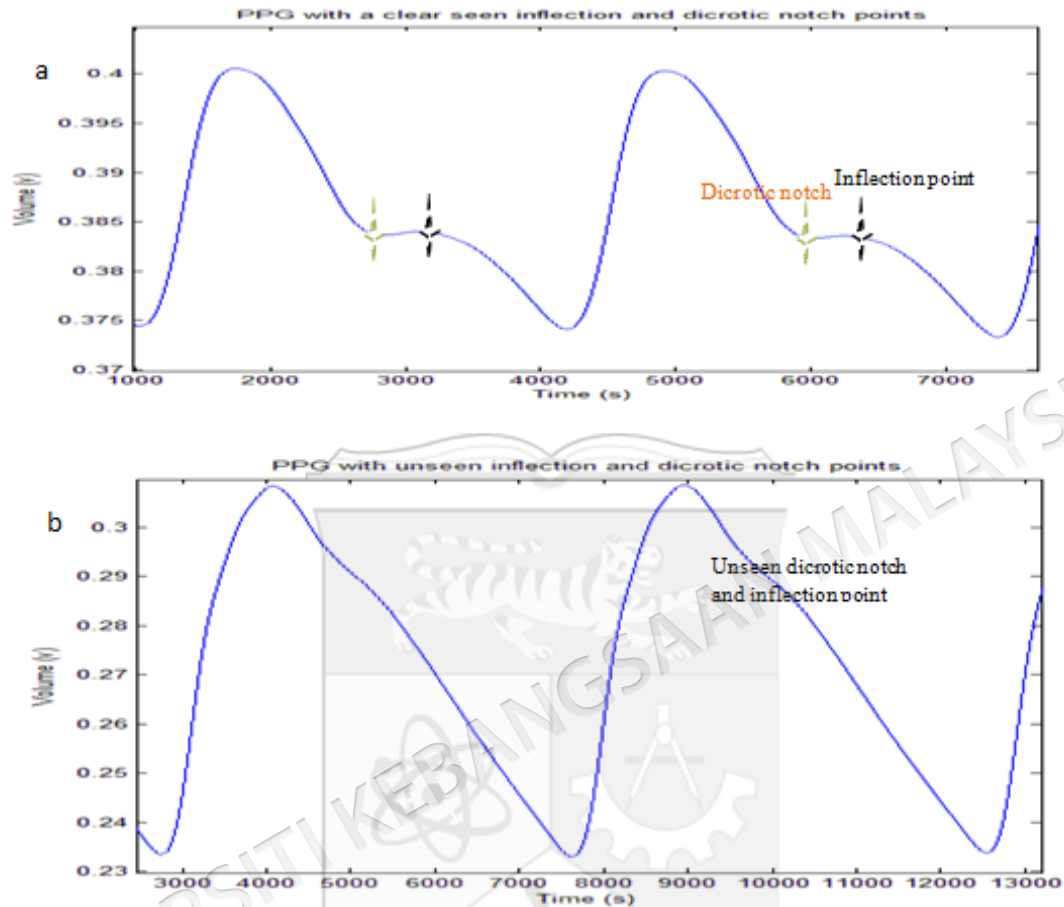


Figure 3.9 Recorded PPG signals with: (a) Clearly seen inflection and dicrotic notch, (b) Unseen inflection and dicrotic notch

As the main objective of this work was to develop a simple noninvasive technique for the prediction of high-risk atherosclerosis using PPG, obtaining the filtered PPG waveform, locating its points of interest, and extracting pulse parameters from its morphology were the main steps in developing a predictive model for evaluating high-risk atherosclerosis. Hence, extracting AC components from a PPG signal using good filtering would facilitate the process of point detection and features extraction. Figure 3.10 represents a sequence of filtered PPG pulses.

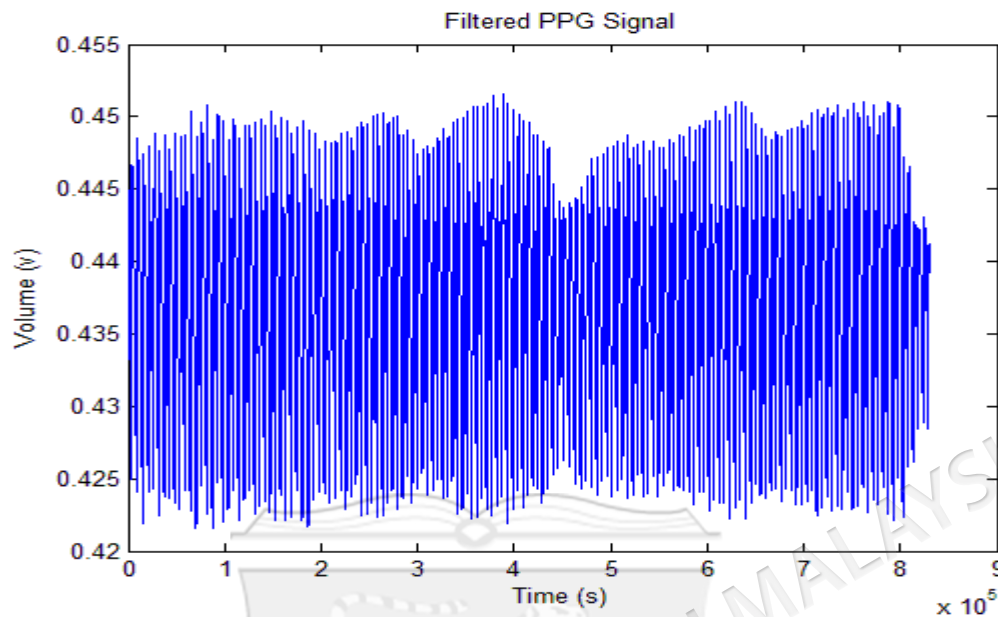


Figure 3.10 Sequence of the recorded filtered PPG pulses

Practically, peak and valley detection can be done by several techniques. Minimum and maximum algorithm can detect the changes of PPG values and locate the mentioned points based on the variation of the values of each two consequent points. For example, if the value of the current point is greater than the next point and the previous one, then the current point is considered as a peak. On the other hand, if the current point is lower than the previous and the next point, it is then considered as a valley. Definitely, a chosen threshold value must be determined practically to distinguish between the needed points. Therefore, such an algorithm is suitable for certain PPG signals where the dicrotic notch and inflection point are clearly seen. Moreover, minimum-maximum algorithm is useful for detecting the peaks and valleys of the PPG since PPG has a clearly visible peak (a systolic peak (AC Max)) and a clearly visible valley (a pulse foot). An illustrative example for the use of minimum-maximum algorithm for peaks and valleys detection is shown in Figure 3.11. Actually, this coding is simple and fast, but it is very restricted to those signals where the peaks and valleys are clearly visible. Unfortunately, this algorithm cannot be used in practical PPG analysis.

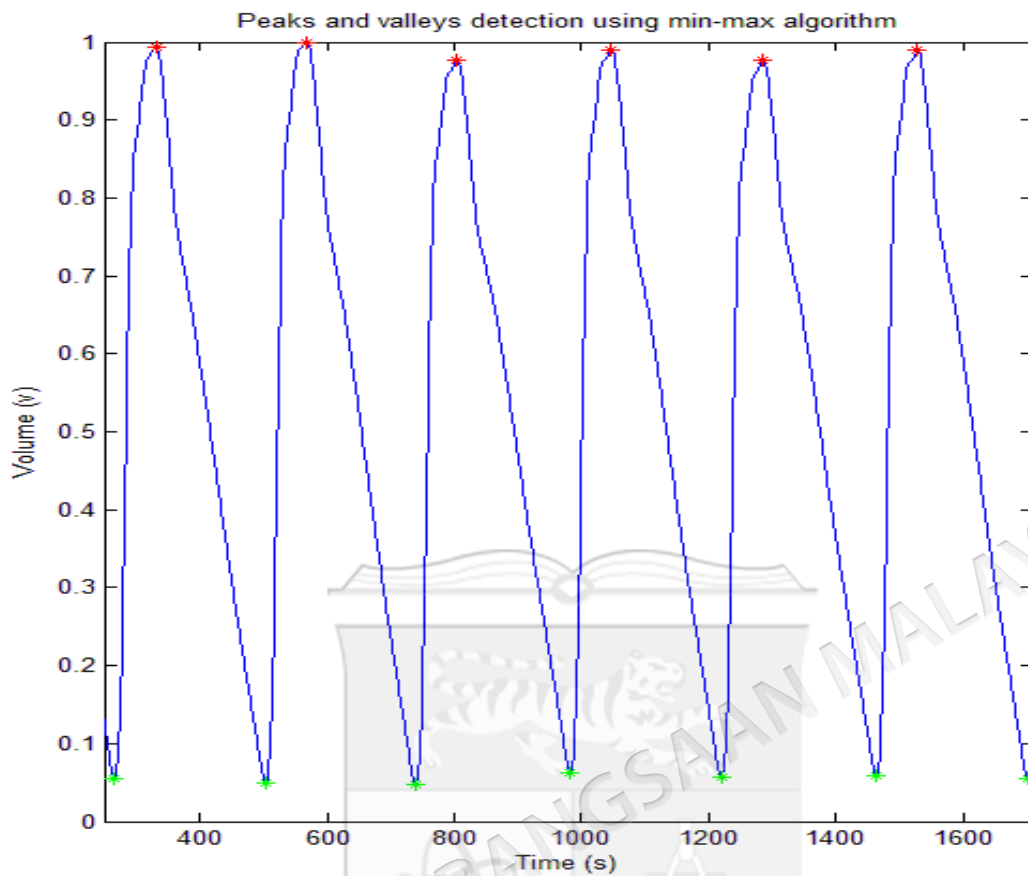


Figure 3.11 Peaks and valleys detection using min-max algorithm

Therefore, due to the limitations of such an algorithm, the use of PPG derivatives was implemented for the detection of inflection and dicrotic notch points. Basically, the PPG's 1st, 2nd and 3rd derivatives were utilized and evaluated in this work. The 1st derivative was evaluated by the differentiation of the PPG signal using the built-in gradient function in Matlab. The 2nd derivative was evaluated by the double differentiation of the PPG signal or by the differentiation of the PPG's 1st derivative. Finally, the PPG's 3rd derivative was evaluated by triple differentiation of the PPG or by the differentiation of the PPG's 2nd derivative.

3.3 EVALUATION OF PPG DERIVATIVES

The analysis of the morphology of PPG has become important because it contains much information about cardiovascular activity. Traditionally, pulse contour analysis requires 1st or higher derivatives to be calculated (Uldis 2008). There are two main

approaches that have been developed to describe the characteristics of the PPG waveform. The first method is the analysis of PPG 2nd derivatives (Bortolotto et al. 2000; Imanaga et al. 1998; Takazawa et al. 1998; Gonzalez et al. 2008). The positions of the peaks and valleys of the 2nd derivative give information about the PPG and its pulse parameters. The second method involves extracting the pulse parameters from the peaks of the PPG directly, using the 1st (Millaseau 2002; Millaseau 2006) or 3rd derivatives of the PPG (Mustafa 1997). In fact, PPG derivatives facilitate the understanding of the morphological variations of the PPG signal.

In this research, the detection of the inflection point was determined by utilizing both 1st and 2nd derivatives. In evaluation of the PPG 1st derivative, inflection points can be located as the first local maximum. Moreover, this point can also be detected by locating the 2nd positive to negative crossing zero of the 2nd derivative of the PPG. In addition, the PPG 1st derivative was utilized to determine the maximum point of the PPG pulse. The pulse maximum is thereby determined by the 1st positive to negative crossing zero of the PPG 1st derivative. Seeking information about ventricular ejection time can be obtained by locating the maximum ejection point, which in turn can be detected as the point corresponding to the maximum point of the PPG 1st derivative. This point also can be located as the 1st positive to negative crossing zero of the PPG 2nd derivative. Moreover, the foot of the PPG pulse can be determined as the 1st negative to positive crossing zero of PPG 1st derivative. An illustrative plot of PPG points of interest can be explored in Figure 3.12. All other points can then be expressed in relation to these points according to the flow chart shown in Figure 3.13.

It's noteworthy that this coding can detect PPG points of interest for almost all types of PPG signal. However, this coding might be unable to detect those points if the signal is very noisy. Moreover, once an inflection point is located by any one of the PPG derivatives, it can be confirmed by the use of another one. In other words, if we used the PPG 1st derivative to locate its inflection point (by locating the first local

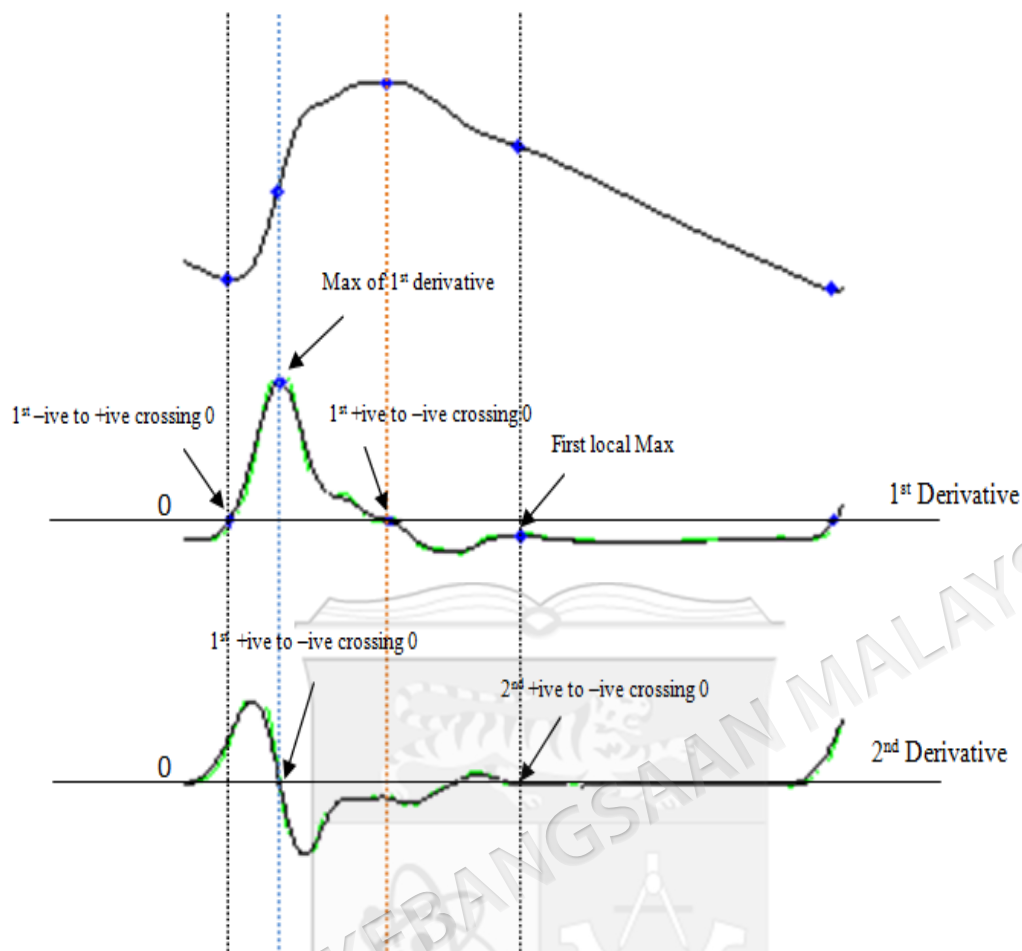


Figure 3.12 Description of the process of locating points of interest from PPG waveform its 1st and 2nd derivatives (recorded PPG and its derivatives)

maximum of the 1st derivative); then the PPG 2nd derivative can be used to confirm the detection of the inflection point by locating its 2nd +ive to -ive crossing zero. Furthermore, the 3rd derivative of the PPG was utilized to determine and locate the dicrotic notch. The dicrotic notch representing the end of ejection can be determined as the 3rd derivative's 1st -ive to +ive crossing zero which occurred after the 3rd derivative's +ive to -ive crossing zero point.

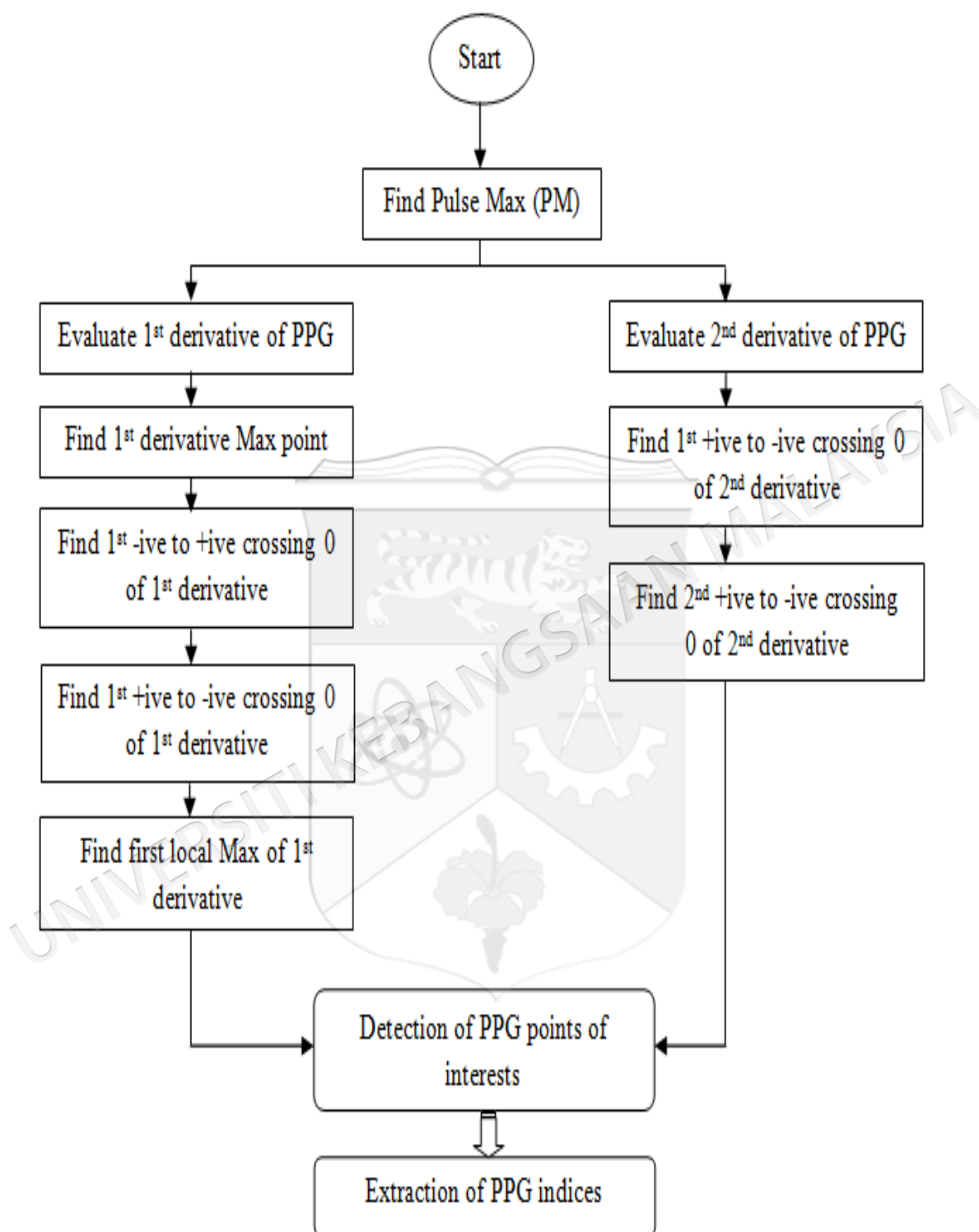


Figure 3.13 The flow chart for extraction of time domain features in the PPG waveform (1st and 2nd derivatives).

3.4 FEATURES EXTRACTION

After locating and determining the PPG's points of interest, the features extraction process took place. Basically, 12 indices were extracted and evaluated. Table 3.2 summarizes the extracted indices and their explanations. However, among the evaluated parameters an index (b/a ratio) derived from the SDPPG was utilized in the development of the statistical model for the prediction of high-risk atherosclerosis.

Table 3.2 Evaluated PPG parameters and their explanations

PPG's Index	Explanation
RI	Reflection index ($DM/PM \times 100$)
SI	Stiffness index ($H/\Delta t$)
PM	Maximum point of PPG pulse
DM	Amplitude of inflection point
PT	Time interval of PPG pulse
PPT	Peak-to-peak time (time between PM and DM)
ST	Time to reach systole (time to reach PM)
DT	Time to reach inflection point (time to reach DM)
MET	Maximum ejection time
MEV	Maximum ejection velocity
b/a ratio	Amplitude of b wave/ amplitude of a wave (SDPPG)
c/a ratio	Amplitude of c wave/ amplitude of a wave (SDPPG)

However, details on the extracted parameters and their statistical results are explained in Chapter 4. Statistical techniques were used to investigate, analyze and conclude the associations between the extracted indices, medical data and the recorded CIMT data.

3.5 STATISTICAL ANALYSIS

Statistics can be defined as the science of gathering, summarizing, and analyzing numerical data. Statistics makes it possible to predict the likelihood of events. Moreover, the field of statistics deals with the collection, presentation, analysis and use of data to make decisions and solve problems (Montgomery et al. 2003). It can also refer to the science of data collection and analysis for the purpose of drawing a conclusion. Statistics has become an essential part in most of biomedical research. This is because the practice of evidence based medicine, which can be defined as the conscientious, explicit, and judicious use of current best evidence in making decisions

about the care of individual patients (Sackett et al. 1996) has fascinated the attention of many researchers. Statistics was the core of this research. As the study involved working with data, obviously some knowledge of statistics is important especially to interpret and draw conclusions from the statistics. An introduction of the basics fundamentals of statistical concepts applied in the research work is introduced.

3.5.1 STATISTICS FUNDAMENTALS

a) *Population*

The large body of data that is the target of our interest.

b) *Sample*

The subset selected from the population

c) *Objective of statistics*

The main objective of statistics is to make an inference about a population based on information contained in a sample and to provide an associated measure of goodness for the inference. For example, in our work, we want to predict the absence or presence of high-risk atherosclerosis.

d) *Median*

The median is the value that is in the middle when the values are ordered

e) *Mean*

The mean is sum of the measurements divided by the total number of measurements.

f) *Correlation*

Correlation is a description of the degree of relationship between two variables

g) *Standard deviation*

Standard deviation (SD) is a measure of the dispersion of a set of data from its mean

h) *Normal distribution*

Normal distribution is the pattern for the distribution of a set of data which follows a bell shaped curve. It can be described completely by its mean and its

standard deviation. To test for normal distribution we used the Kolmogorov Smirnov (K-S) test of normality or analysis of the probability distribution p-p or Q-Q plots.

i) Variance

Variance is a mathematical expectation of the average squared deviations from the mean.

j) Statistical significance

The degree of certainty or confidence with which we can rule out chance. It can be represented by significance level (p -value) of a statistical test or the confidence interval (CI) of a population mean.

k) Sensitivity (S_n)

Sensitivity is a measure of the proportion of actual positives which are correctly identified.

l) Specificity (S_p)

Specificity is a measure of the proportion of negatives which are correctly identified. Sensitivity and specificity are the most widely used statistics used to describe a diagnostic test. Therefore, sensitivity $\rightarrow$ probability of a positive test among patients with disease and specificity $\rightarrow$ probability of a negative test among patients without disease

m) Receiver operating characteristics (ROC)

ROC is a graphical plot of the sensitivity vs. (1– specificity), for a binary classifier system, as its discrimination threshold is varied.

n) Area under ROC curve (AUC)

AUC is closely related to the ranking quality of the classification. It can be viewed as a measure based on pairwise comparisons between classifications of the two classes. It is an estimate of the probability P_{xy} that the classifier ranks a randomly chosen positive class higher than a negative class (Hanley & McNeil 1982).

o) Regression

Regression is a statistical measure that attempts to determine the strength of the relationship between one dependent variable and a series of other independent variables.

p) Logistic regression

Logistic regression is a type of predictive model that can be used when the dependent variable is dichotomous variable with two categories. To be precise, logistic regression makes no assumption about the distribution of the independent variables. They do not have to be normally distributed, linearly related or of equal variance within each group. The relationship between the predictor and response variables is not a linear function in logistic regression; instead, the logistic regression function is used

3.5.2 STATISTICAL TESTS

A statistical test provides a mechanism for making quantitative decisions about a process or processes. Hence, there are many statistical tests that can be conducted to justify the confidence of a finding, such as correlation, which is used for evaluating the linear relationship, t-test which studies the association between means, chi-square which concerns the association between proportions. Moreover, a paired t-test is used to compare the means between two independent groups; an unpaired/independent t-test is used to compare the means within one group; analysis of variance (ANOVA) is used to compare means among more than 2 independent groups; and there is regression, which is used to characterize the variation of the dependent variable around the regression function, which can be described by a probability distribution. In this study we used logistic regression modeling for the prediction of high-risk atherosclerosis. The level of significance was set at $p < 0.05$, indicating that we are 95% confident that the probability of a relation is true. Tests of correlation were included as well.

3.6 MODELING THE PPG USING LOGISTIC REGRESSION

The associations between PPG indices and CIMT measurements were evaluated by means of correlation. Those parameters that remained statistically significant were used to initiate the predictive model. The final listed parameters to be used for PPG modeling were age, pulse pressure (PP) and subject's height (H) from one side and peak-to-peak time (PPT), b/a ratio and systolic time (ST) from the PPG signal. Age is an important factor since it is considered to be an accompaniment to all underlying vascular diseases. Age distribution based on categorical groups no-risk and high-risk atherosclerosis is shown in Figure 3.14. Moreover, the scatter plot of age against the recorded index of atherosclerosis demonstrated a tendency of atherosclerosis to be increased as we age (Figure 3.15).

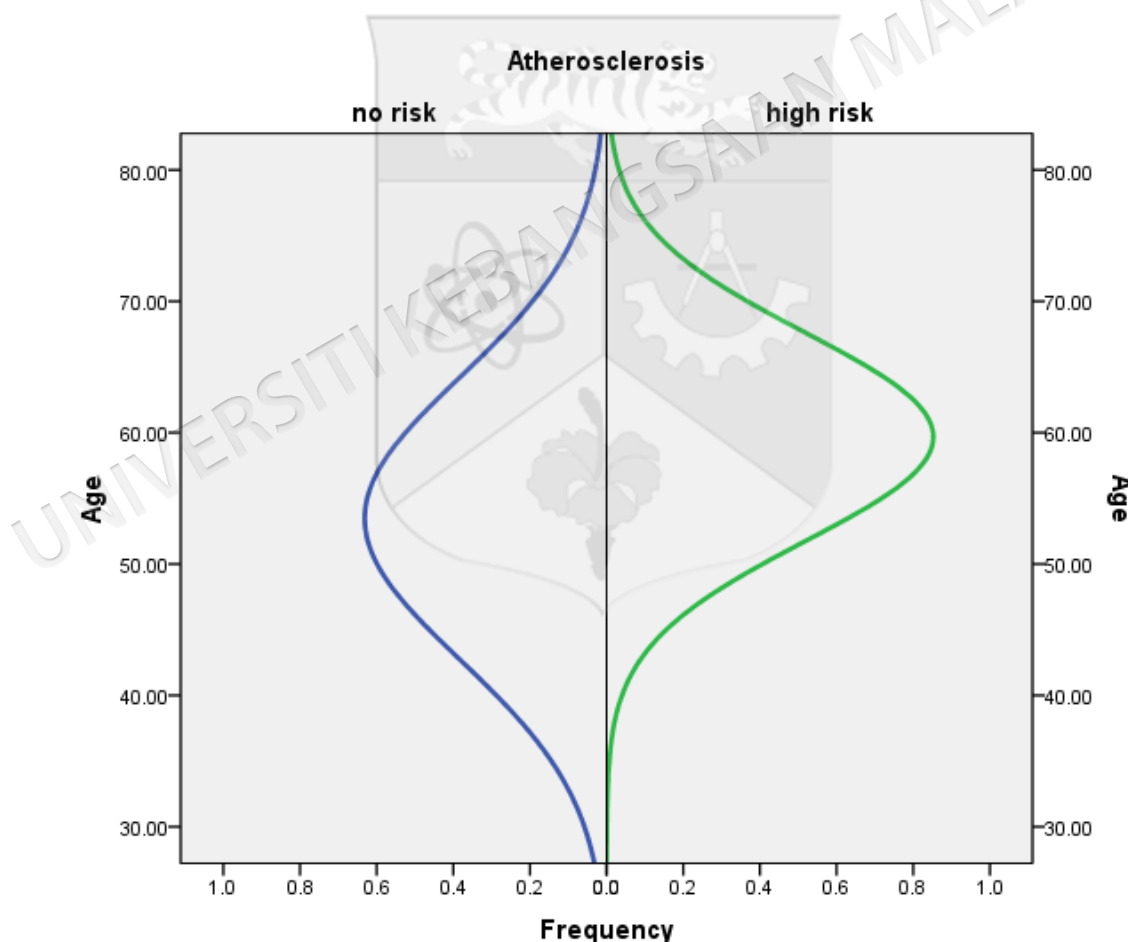


Figure 3.14 Age distribution among no-risk and high-risk atherosclerosis

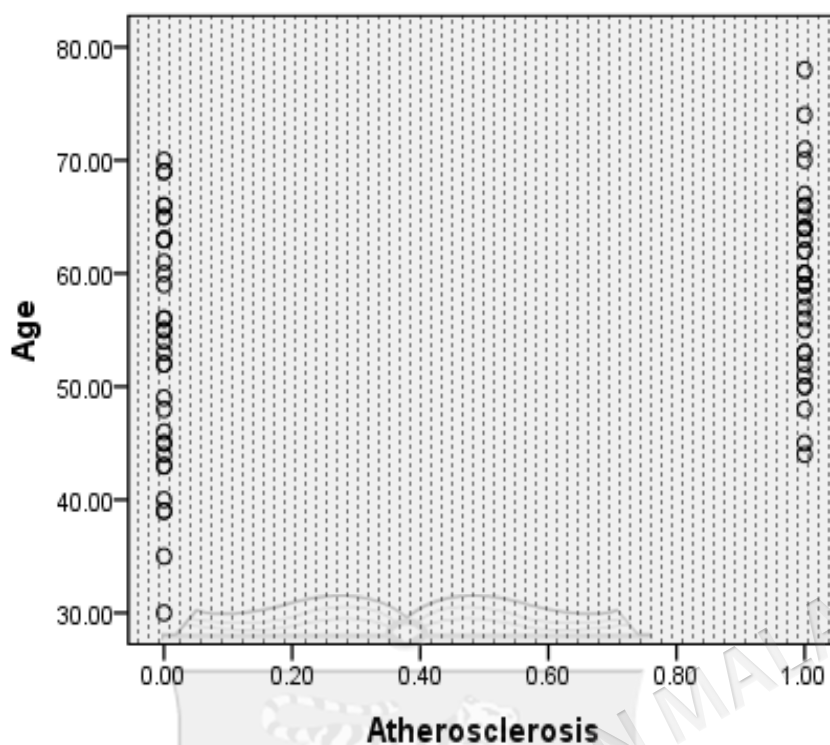


Figure 3.15 Scatter plot of age against HRART

In regards to pulse pressure, PP is an independent predictor of myocardial infarction (Mourad et al. 2010). PP is an index of large artery stiffness, and has been associated with coronary events (Girish et al. 2005). Increased levels of baseline pulse pressure are associated with subsequent progression of coronary atherosclerosis in postmenopausal women (Girish et al. 2005). PP correlated positively with the occurrence of cardiovascular events (Safar & Frohlich 2007). The greater the PP, the stiffer and more injured the vessels are thought to be. Moreover, in this work, PP correlates positively with CIMT. The scatter plot of PP and CIMT is shown in Figure 3.16, while the Boxplot of PP based on HRART grouping is shown in Figure 3.17.

It can be visualized from Figure 3.16 that, PP values tend to increase as well as CIMT values increase. This is a reflection of the effect of atherosclerosis in blood pressure measurement. Since PP is another marker of hypertension, accumulated atherosclerosis is accompanied with elevated blood pressure which might cause injury and inflammatory to arterial wall, which in turn makes them stiffer.

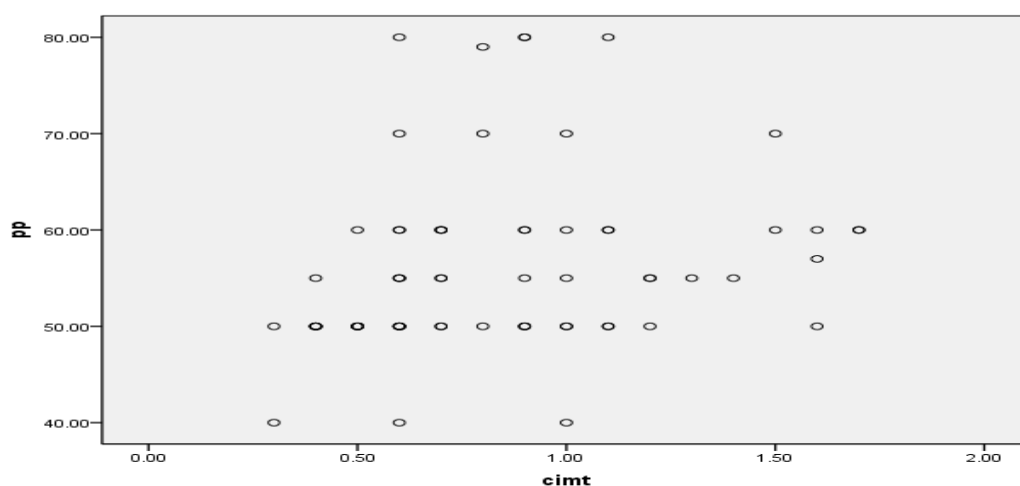


Figure 3.16 Scatter plot of PP and CIMT

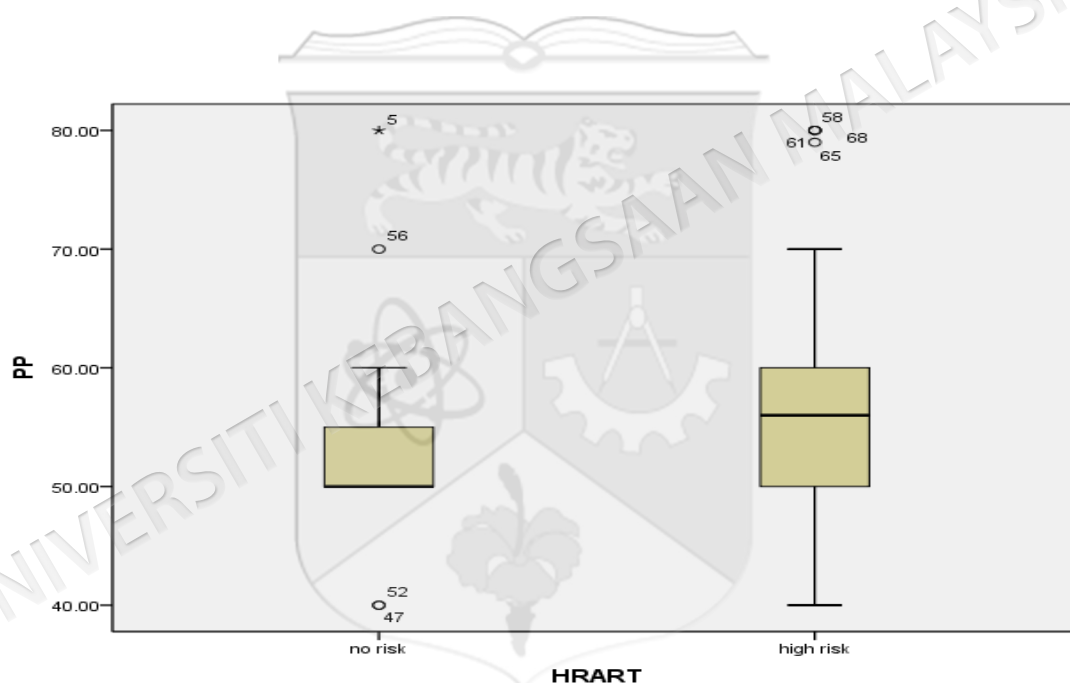


Figure 3.17 Boxplot of PP based on HRART grouping

There is an inverse relationship between body height and cardiovascular risk (Harold et al. 1998). There is a general tendency towards atherosclerosis and arterial dilatation (Päivänsalo et al. 2000). A relationship between generalized arterial dilatation and increased CIMT has been observed outside of TS with the “Glagov phenomenon” (Swerdlow et al. 2001; Julia et al. 2006). Body height is associated with the diameters of the common iliac arteries in both genders (Päivänsalo et al. 2000). The early systolic arrival of reflected waves in short people acts to stiffen the aorta and increase the pulsatile effort of the left ventricle (Harold et al. 1998). Although

indirect, this evidence supports a physiological hypothesis for the body height–cardiovascular risk association. The results of this work revealed an inverse correlation between body height and atherosclerosis (CIMT). Figure 3.18 demonstrates the tendency of atherosclerosis to be increased in shorter subjects.

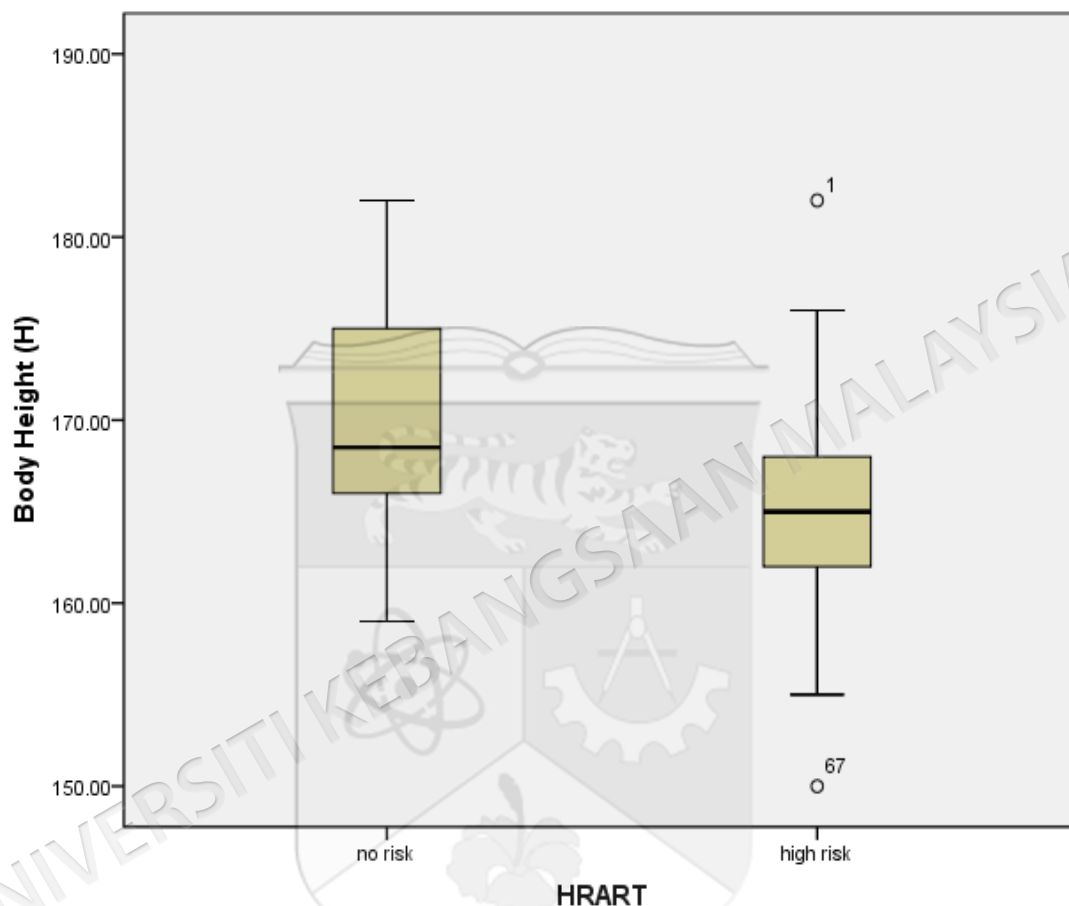


Figure 3.18 Association between atherosclerosis and body height

In addition to the mentioned factors, the b/a index that was extracted from the PPG's second derivative correlates negatively with CIMT as well. The scatter plot of b/a and CIMT is shown in Figure 3.19.

Therefore those factors were used to initiate the predictive model. Logistic regression modeling was used. The model was fitted with all the significant indices together; then, the model evaluated the entered parameters by either forward or backward regression techniques. The technique that revealed higher Nagelkerke R-square and better likelihood ratio was chosen to implement the final predictive model.

Figure 3.20 illustrates the block diagram of the developed model. Details on the developed model were given in Chapter IV.

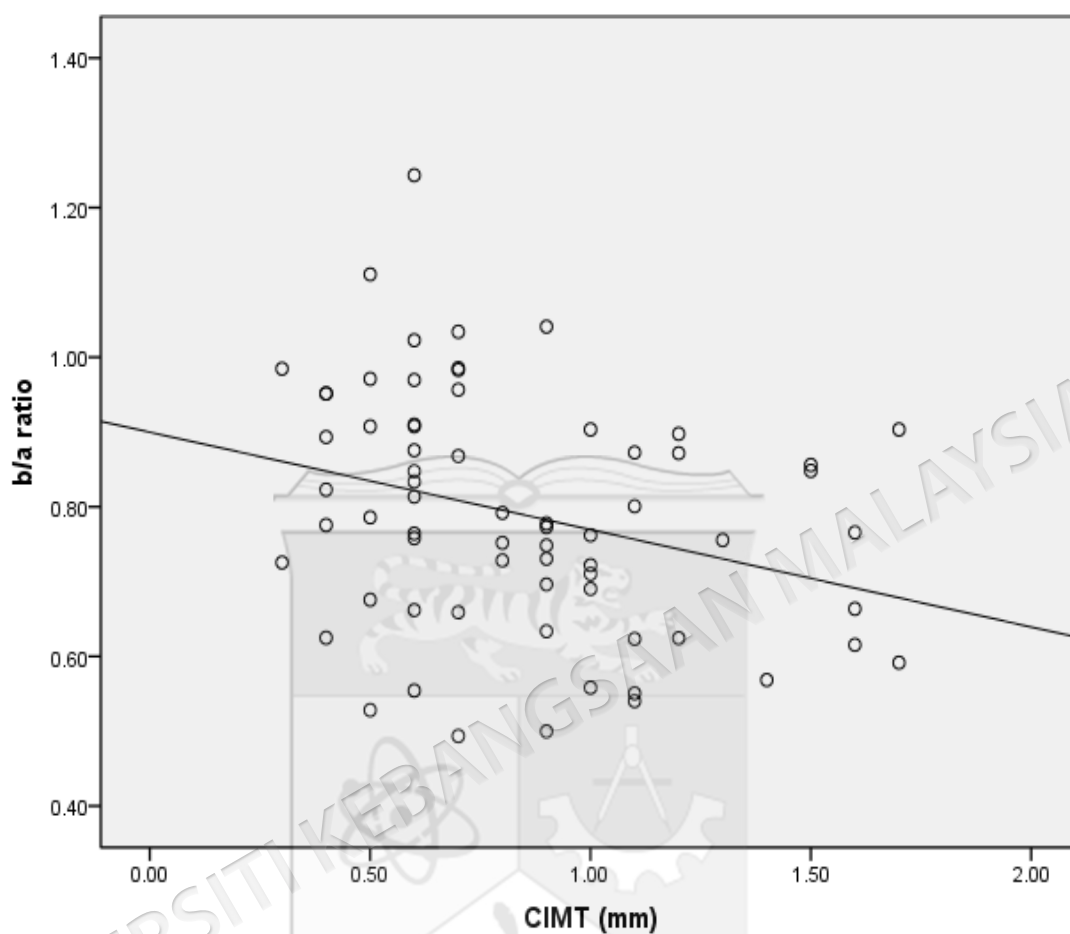


Figure 3.19 The scatter plot of CIMT and b/a ratio.

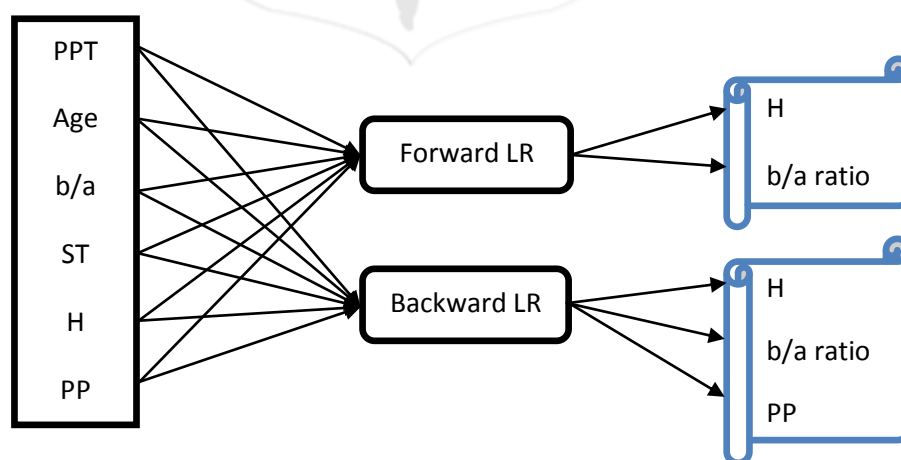


Figure 3.20 Block diagram of the developed model, forward and backward logistic regression

3.7 CHAPTER SUMMARY

The instrumentation systems for both ultrasound measurement and PPG recording have been detailed in this chapter. CIMT data recording was illustrated. PPG signals were processed and analyzed. Extraction of PPG points of interest and calculating of PPG indices were demonstrated and detailed in this chapter. Moreover, brief illustrations of some statistical fundamentals were elaborated. Finally, a brief description of the developed predictive model was highlighted.



CHAPTER IV

RESULTS AND DISCUSSION

4.1 PARALLEL ANALYSIS OF PPG SIGNALS AND CIMT DATA

As the early start of this work, data collection was running in parallel consisting of PPG, C-reactive protein (CRP) and CIMT data. Unfortunately, CRP profile data were dropped from the study since there was an error in the analysis of the blood samples. The first step was in the trend of analyzing the PPG's shape (morphology) in means of points of interest of the shape itself. Moreover, PPG shape varies from one subject to another and from one site to another, in addition to having a dependency on age. The prime consideration was to obtain the most important points of the morphology of the PPG waveform, as a starting point for the analysis with the CIMT data. Therefore, after looking for the most appropriate and relevant papers on PPG shape analysis, we started coding our algorithm for the detection of the PPG inflection point and the PPG dicrotic notch.

These two points represent the most important and difficult points to obtain, especially in their tendency to be less pronounced with aging. The first code written in Matlab utilized PPG 1st and 3rd derivatives to locate these points. However, an optimized coding for treating all types of PPG signals, including the noisy ones, was developed utilizing the PPG 1st and 2nd derivatives. This chapter will explain the two algorithms in detail; it will highlight the extracted indices and illustrate the developed statistical model as well.

4.2 PPG ANALYSIS USING 1st and 3rd DERIVATIVES

PPG waveform analysis depends mainly on the detection of its points of interest. Those points of interest reflect the characteristics of the PPG signal in both the time and frequency domains. Our analysis was mainly on the time domain (especially the AC components). The derivatives of the PPG waveform helped in understanding the process of the variation of PPG morphology; the variations are the result of the effects of many related factors like age and disease. However, the early analysis of the PPG waveform depended mainly on the detection of its minimum and maximum values (minimum-maximum algorithm). Moreover, such analysis was dependent on the appearance of PPG second peak (inflection point), which normally tends to be less pronounced with age and disease. In addition, the need to evaluate and calculate some points of interest which cannot be extracted directly from the PPG waveform itself motivated us to use PPG derivatives as a facilitator for improving our understanding of PPG variations.

The idea adopted from Mustafa (1997) for the analysis of blood pressure waveform using the 1st and 3rd derivatives was the starting point for utilizing PPG derivatives in this work. Therefore, the 1st and 3rd derivatives of PPG were evaluated for achieving a certain target, which was to calculate RI and SI from the PPG. These two indices were the main parameters we were looking for at the time the proposal was being drawn up, at the early stage of this work. As the association between RI, SI and atherosclerosis as a cause of erectile dysfunction was under consideration, the use of the PPG 1st and 3rd derivatives seemed pertinent. Locating pulse maximum is possible through many techniques, e.g., min-max algorithm. The difficulty intensified around the detection of the PPG inflection peak, which in turn was assessed by the 1st and 3rd derivatives. The coding started with the loading of the PPG data (2-channels (text file)); after that, the loaded data was filtered using a band-pass filter which had two cut-off frequencies: 0.6 Hz & 15 Hz. The filter was used for removing the effect of the respiratory rhythm and higher frequency disturbances. These filters did not introduce phase delays or distortion to the waveforms (Zahedi et al. 2007). As the feature points of PPG could be described as inflection points along its morphology, the PPG's 1st and 3rd

derivatives were evaluated. In this way the process of locating points was implemented (details about points location and detection and indices calculations can be found in Chapter 3). This coding detected four points of the PPG, and all other points could then be expressed in relation to these points (Figure 4.1). The only limitation of this code was in its dependency on the quality of the pre-selected pulses, since the PPG data was chopped from both sides to remove transits time. Therefore, if there were some up normal pulses (due to any noise source intervention), the calculated parameters would be subjected to non precision. In terms of the calculated parameters, Table 4.1 summarizes the indices obtained using the mentioned coding.

Table 4.1 Calculated indices based on 1st and 3rd derivatives of PPG

PPG Amplitude Indices	PPG Time Indices
Reflection index (RI)	Pulse time (PT)
Pulse maximum (PM)	Systolic time (ST)
Diastolic amplitude (DM)	Diastolic time (DT)
Dicrotic notch amplitude (DnA)	Peak-to-peak time (PPT(Δt))
	Stiffness index (SI)

Note: Indices calculated based on 1st and 3rd derivates of PPG

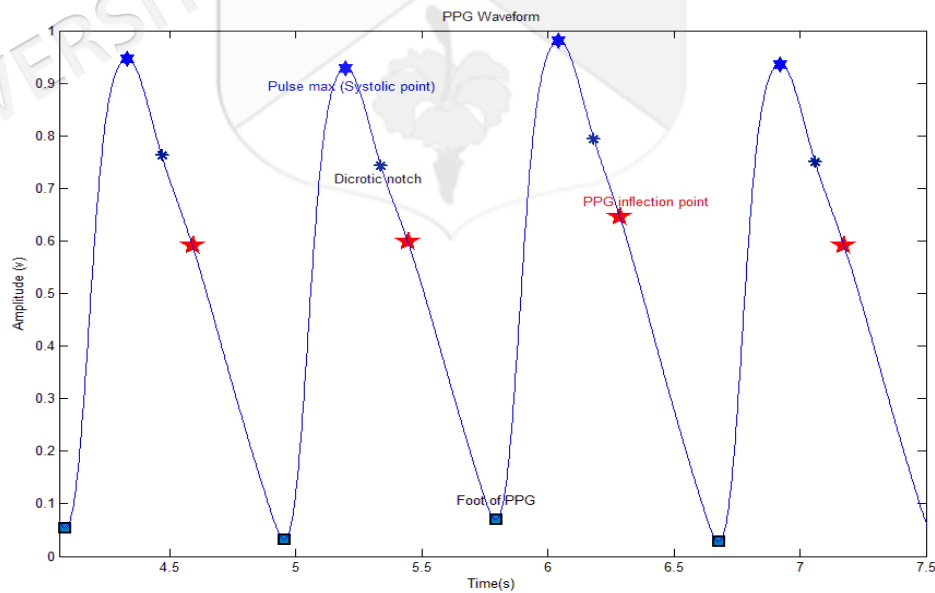


Figure 4.1 PPG waveform characteristics

It should be noted that, this coding can perform better and it definitely gives very good results when the pulses are selected for quality. Generally, the coding is used to study the differences and the correlations between recorded PPG signals from both the right index finger and the left index finger. The analysis revealed identical results between the two sites (right and left hands) by means of time indices PPG. On the other hand, a strong correlation (small difference) between the PPG amplitude indices was obtained. The need to obtain the most suitable pulses, and therefore to have better results (in terms of slow variations of PPG), a new algorithm which could perform faster, calculate more indices and offer a fruitful window for processing and visualizing of PPG data was developed, utilizing both 1st and 2nd derivatives of the PPG signal.

4.3 PPG ANALYSIS USING 1st and 2nd DERIVATIVES

Since the process of optimization is accompanied normally with research areas, a new coding of PPG waveform analysis was developed. The new code utilized the use of 1st and 2nd derivatives of PPG to assist the previous coding and to extract additional indices from the PPG. Moreover, this coding allowed visualizing and selection of the most appropriate pulses to be processed in the analysis. Smoothing of the PPG and its derivatives took place as well. The algorithm of PPG waveform analysis contains the following main parts: 1) signal filtering, removing of DC component and noise; 2) separation of AC signal to individual beats and finding of inflection points by 1st and 2nd derivative analysis; 3) detection of maximum ejection points; 4) evaluation of the SDPPG (a, b, and c waves); and 5) evaluation of hemodynamic parameters in every beat. A detailed scheme of the algorithm is shown in Figure 4.3. Basically, this algorithm allows the selection process of the most suitable pulses to be processed and analyzed. By scrutinizing the loaded data from the PPG, the noisy or bad pulses can be avoided. Therefore, the later analysis will be carried out on the good pulses, resulting in better results. Figure 4.2-a demonstrates a part of a PPG signal which seems to be influenced with a noise source. However, running the analysis for the good pulses can be seen in Figure 4.2-b.

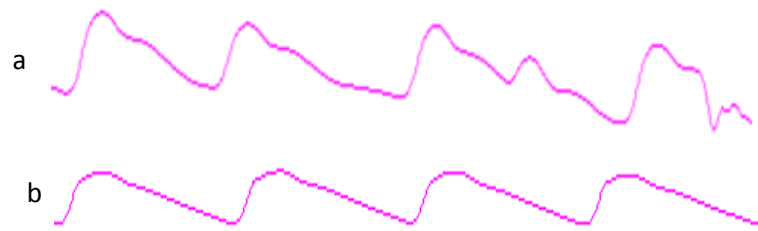


Figure 4.2 Recorded PPG signal a) bad pulses b) good pulses

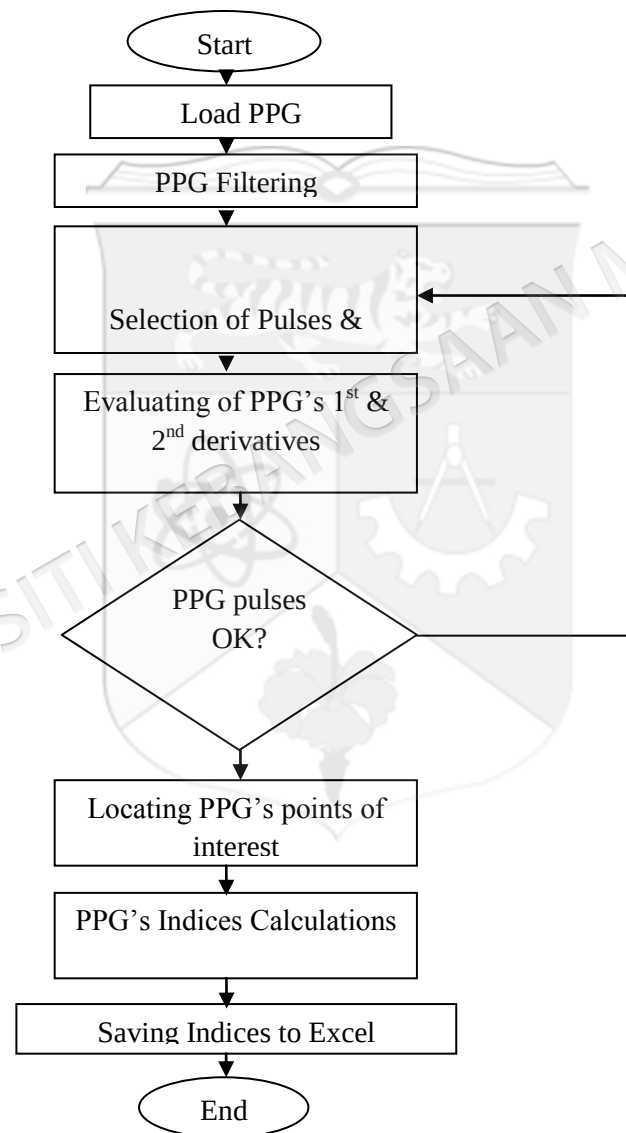


Figure 4.3: Block-diagram of PPG indices extraction using its 1st and 2nd derivatives

Since PPG is very sensitive to noise and artifacts, this coding allows the process of choosing the most suitable pulses. This algorithm has been developed to ensure the quality of the selected pulses and to improve the accuracy of the measurement in this study. Moreover, the visualization of every single pulse can be obtained by moving the cursor to that pulse. PPG derivatives are very sensitive to noise and artifacts despite the use of filtering. Getting suitable pulses can improve and optimize the processing of PPG and thereby improve the processing of its derivatives. As shown in Figure 4.4, the PPG derivatives look stable and noiseless due to the selection of the most suitable pulses. In addition, the selected pulses can be plotted together to investigate the variations of the pulses (Figure 4.5).

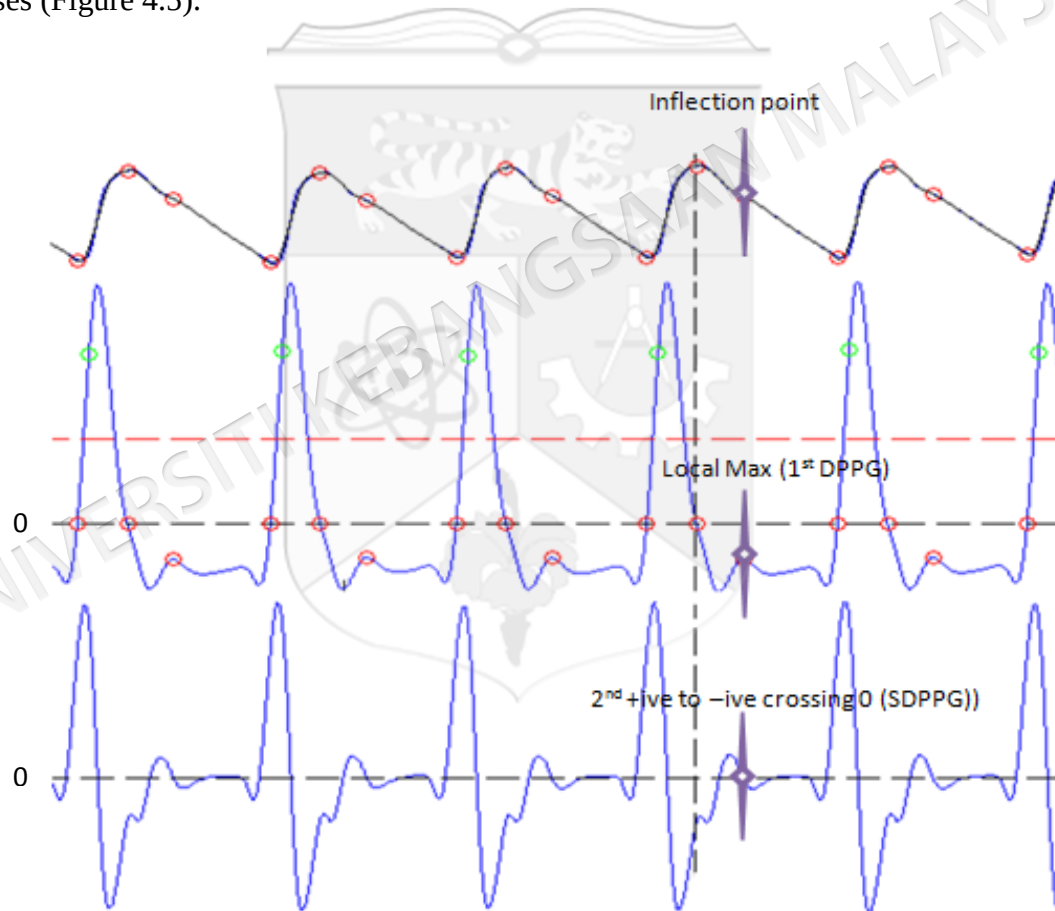


Figure 4.4 Selected PPG pulses and their 1st and 2nd derivatives

The variability of the selected pulses can be reduced, which achieves better results and a decrease of the standard deviation values, thereby optimizing the total quality of the measurements. In Figure 4.5 a total of 20 selected pulses were plotted together. It's noteworthy that the morphology of the signal is still maintained, due to the decrease in variability among the selected pulses. In addition, the main characteristics of the signal can be noticed clearly.

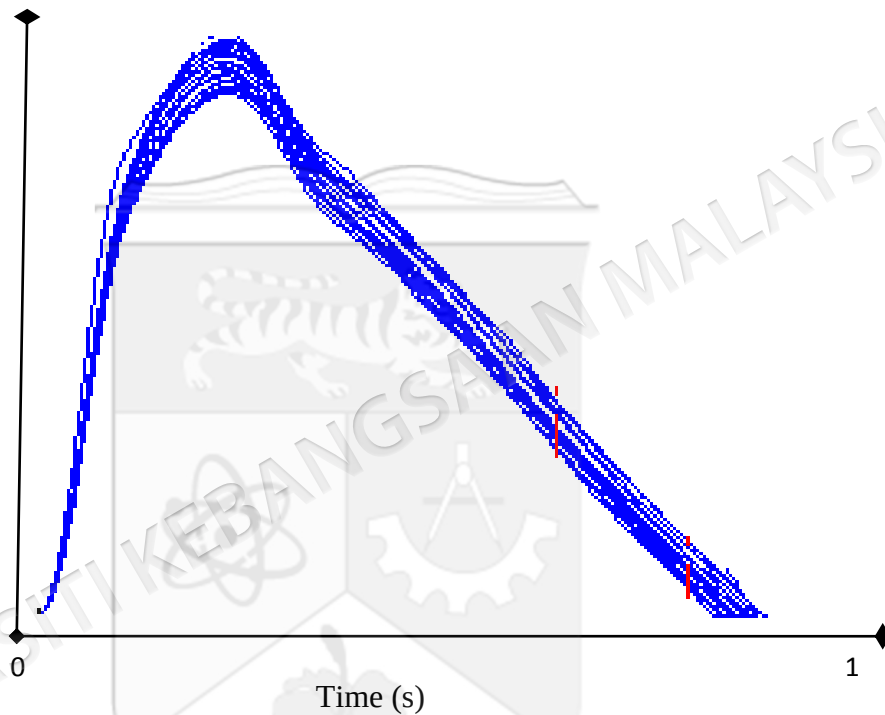


Figure 4.5 The plot diagram of the selected pulses

After the selection of the most suitable pulses to be used for further analysis, the features extraction process can be started. Basically, the parameters extracted based on the analysis of PPG using its 1st and 2nd derivatives were used to implement the predictive model. Those parameters were divided into timing indices and amplitude indices. The next section illustrates those indices in detail.

4.4 EXTRACTED PPG INDICES

The extracted indices of the PPG signal represented the analysis of the time domain (the AC components). Since the most obvious feature of blood flow in arteries is that it is pulsatile (Nichols & O'Rourke 2005), the derived indices were classified into time indices and amplitude (volume) indices. Time indices represent the time between two consequence points on the PPG waveform; while PPG amplitude indices represent the difference in amplitude between any point of a PPG waveform and the baseline. The baseline (the minimum point of the pulse) is normally scaled to zero to ease the visualization of the signal. Table 4.2.1 illustrates PPG time indices in means and median values. However, the PPG time indices showed no difference between the right and left index fingers, while the PPG amplitude indices revealed a difference between the right and left fingers (refer to our paper. Table 4.2.2 represents the PPG amplitude indices characteristics.

Table 4.2.1 PPG time indices characteristics

Index	Mean	Median	S.E.	Range	Variance
TP	.8500	.8500	.1500	.69	.024
MET	.0900	.0900	.0080	.04	.000
ST	.2200	.2300	.0450	.17	.002
DT	.4100	.4200	.0400	.25	.002
PPT	.1800	.1850	.0400	.18	.002
SI	9.500	9.000	2.800	17	8.20
MEV	.0002	.0002	.0002	.00	.000

Note: The median values were used for further calculations...

Table 4.2.2 PPG amplitude indices characteristics

Index	Mean	Median	S.E.	Range	Variance
RI	.69	.700	.100	.60	.017
DM	.02	.0160	.016	.07	.000
PM	.03	.020	.020	.10	.001
b/a	.79	.770	.150	.75	.020
c/a	.73	.730	.060	.30	.004

Note: The median values were used for further calculations...

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 evaluated.

4.4.1 PPG AMPLITUDE INDICES

In this section a description of each amplitude index is given. In addition, the motivation behind calculating each index is highlighted.

Reflection index (RI)

RI is derived as a ratio of pulse inflection point amplitude (second peak) divided by the pulse max amplitude. RI is a measure of small and medium arterial stiffness. RI mainly depends on the detection of PPG second peak, which tends to be less pronounced with aging. From our analysis, RI was found to increase with age and CIMT which addresses the effects of aging and atherosclerosis on arterial properties. Figure 4.6 illustrates the variations of RI based on five age groups.

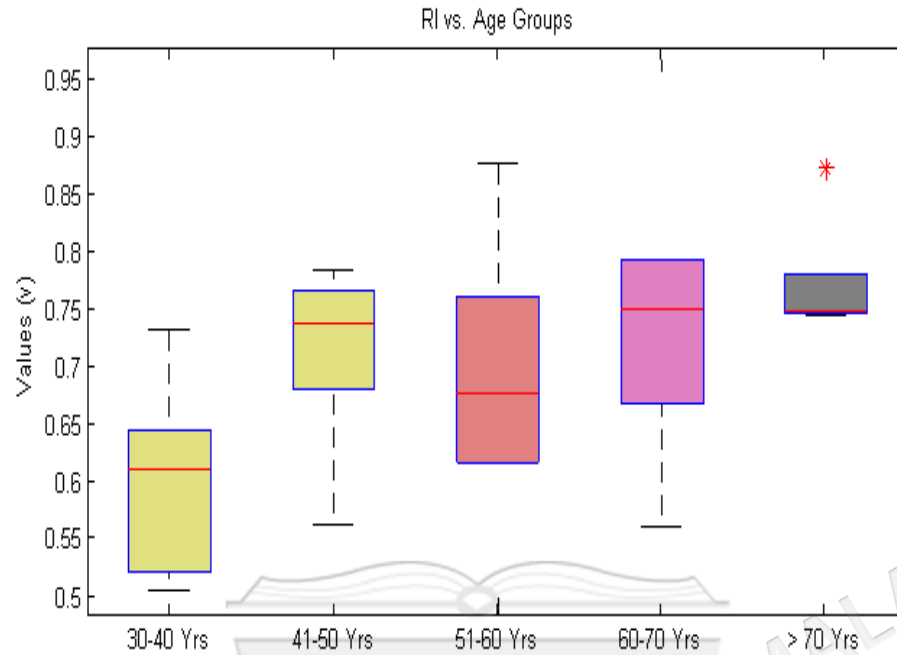


Figure 4.6: Variations of RI among five age groups

Age effect on RI is clearly seen. RI tends to increase as we age. This figure aims to examine the variation of RI among each age group, therefore, it helps in visualizing aging effects on PPG's peaks. However, even the variations of RI due to accumulated atherosclerosis are not distinguished clearly; they still increase as CIMT values increases. Such a phenomenon can be noticed in Figure 4.7. The process of atherosclerosis as measured by CIMT is chronic operation which thought to be a sign of CVD and an accompaniment to many underlined diseases. In fact, the inciting event of atherosclerosis is likely an inflammatory insult that occurs decades before the disease becomes clinically apparent (Crowther 2005).

Defiantly, the accumulated atherosclerosis plays an important role in stiffening arterial wall. Utilizing RI as a measure for medium to large arteries stiffness, it could reveal the existence of atherosclerosis and its effects on the compliance of that artery. RI sought to represent an independent indicator of arterial stiffness. RI represents the peak of anacrotic phase (pulse max) and the peak of catacrotic phase (inflection point max), which in turn might contain descriptive contents of arterial compliance.

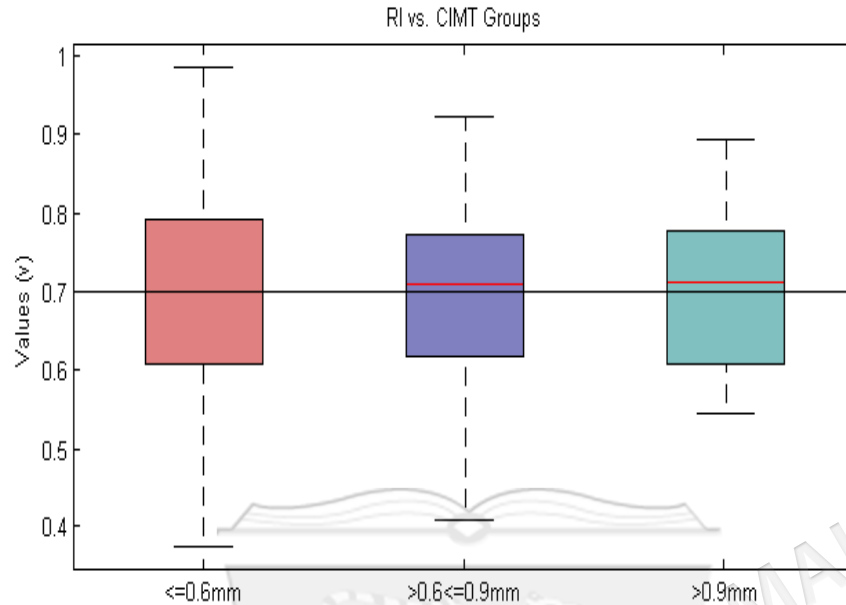


Figure 4.7 RI vs. CIMT groups

Pulse Maximum (PM)

While the PPG signal reflects blood volume changes, it also reflects the response of the arterial wall to the pressure initiated by blood propagation. The PM index represents the maximum point of the PPG waveform (the maximum systolic point), which can be used as a measure of arterial distensibility. decrease of PM values, due to the increase of arterial stiffness and the acceleration of pulse wave velocity. The tendency of PM to decrease as we age can be observed in Figure 4.8.

Since the amplitude of PPG depends on the distensibility of the vascular wall, it would be useful to examine the variations of PPG amplitude (PM) as a measure of the distensibility of arterial wall in response to the pressure initiated by blood steam propagation. I normal arteries the compliance is high; therefore they can respond to the force of blood pressure making them more distensible. It follows that a loss of the arteries' elastic properties might result in a reduction of PM values. Its noteworthy that, sympathetic nervous system activity and thermoregulation affect the amplitude of PPG waveform as well.

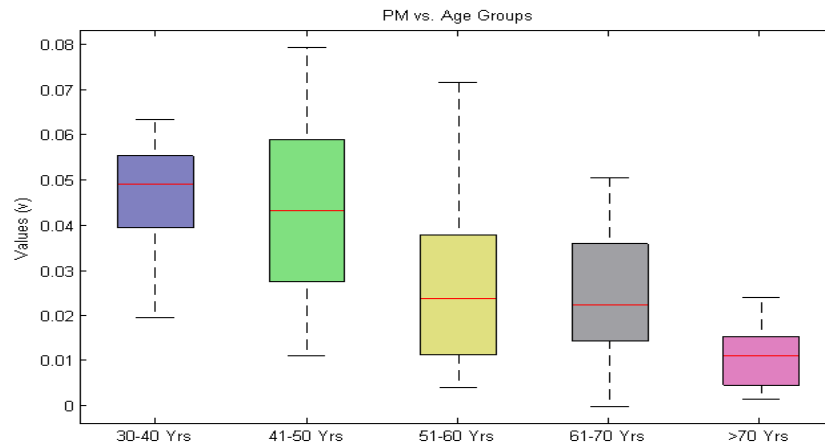


Figure 4.8 PM variations among five age groups

Diastolic Maximum (DM)

The positions of the DM points reflect the amount of the augmented diastolic blood into the systolic side. With age, the inflection point (diastolic point) becomes closer to the systolic point (PM). This phenomenon can be noticed through the reduction of peak-to-peak time (PPT or ΔT) (the time between the systolic and diastolic points). The DM can be used as a measure of small and medium arterial stiffness due to its ability to reflect the response of PPG to the loss of arterial elastic properties. Moreover, the DM tends to be increased slightly with age and atherosclerosis. The analysis of DM values against CMT values showed a slight increase of DM values (Figure 4.9).

Anderwsplot was plotted for RI, PM, and DM in order to visualize the outliers of the three multivariate variables (Figure 4.10). The plot was used to represent the variations of each variable. In addition, RI, PM, and DM implemented the changes of PPG volume due to changes of its morphology.

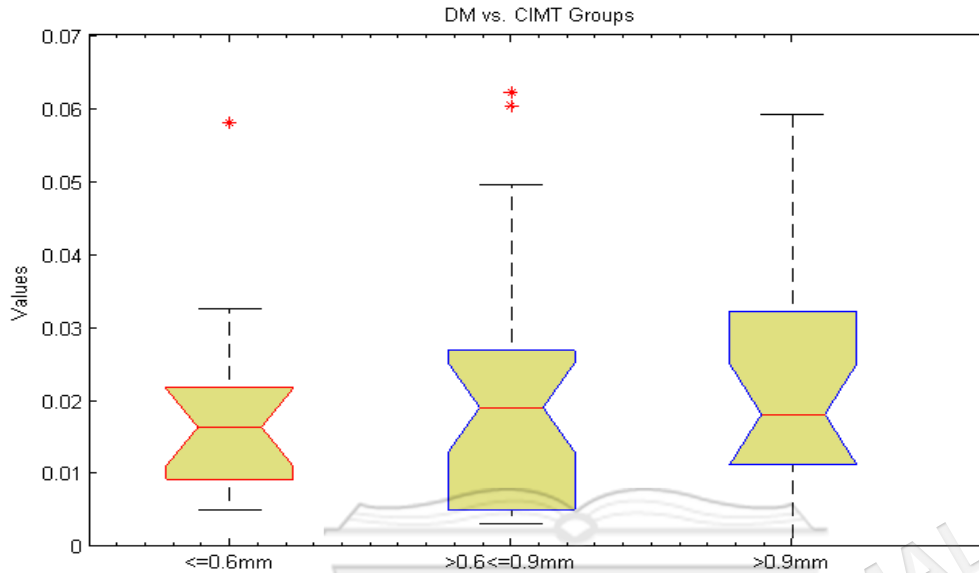


Figure 4.9 DM variations among CIMT groups

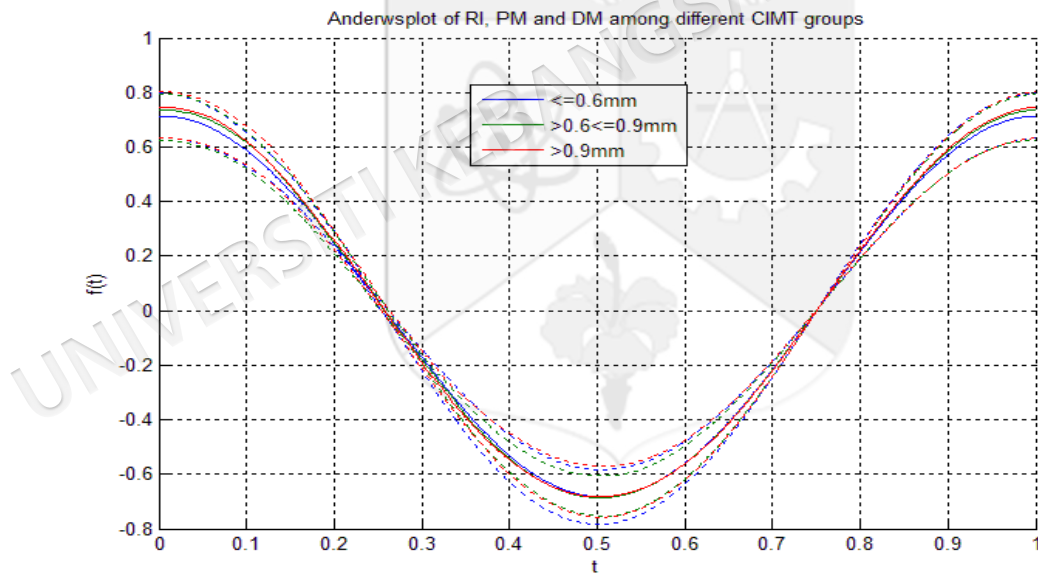


Figure 4.10 Anderwesplot of RI, PM and DM among different CIMT groups

Examining RI, PM, and DM as measures of PPG's amplitude, would enhance the ability of understanding the trends of PPG amplitude to increase or decrease in response to alterations of arterial compliance such as the ones caused by accumulated atherosclerosis.

b/a and c/a Ratios

The focus of this part of our thesis is on the SDPPG indices (b/a and c/a ratios), which may be used as a surrogate measure of arterial stiffness. Moreover, the use of PPG derivatives in general and the SDPPG in a special case were intended to facilitate understanding of the process of the variations of the PPG waveform and to help the process of locating the points of interest of the PPG morphology. The waves (a, b, and c) represent a direct measure for the distensibility of arterial wall. As we age, the amplitude of these waves tends to be declined. The analysis revealed that the c/a ratio is not correlated with age or the CIMT data. However, the b/a index was found to be correlated with both age and CIMT data. Aging is the dominant influence of atherosclerosis. Therefore, analyzing the changes of the mean values of b/a ratio among each age group revealed a reduction of b/a values as we age. Such a phenomenon can be seen in Figure 4.11.

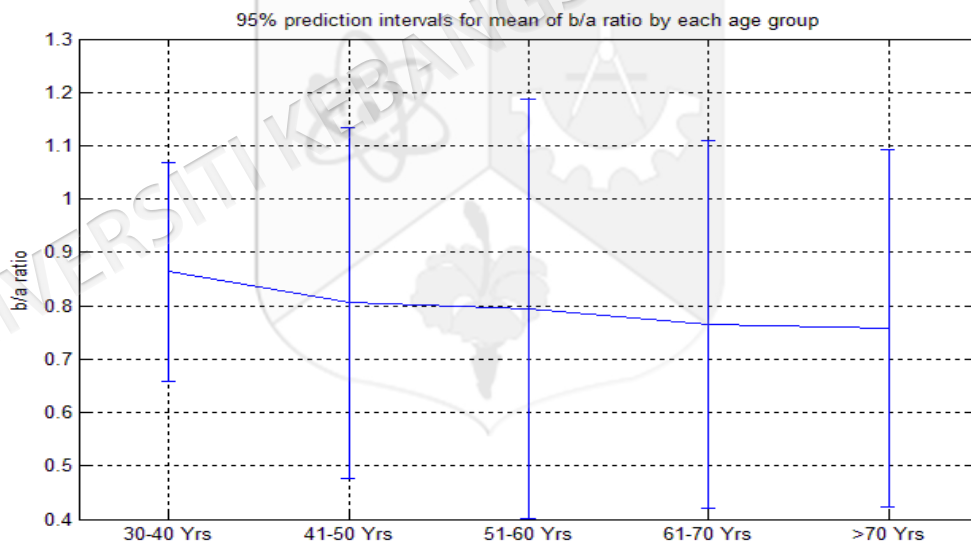


Figure 4.11: Changes of b/a ratio mean values with each age group

It is also noteworthy that the b/a ratio was associated with the increase of CIMT values; therefore an increase of CIMT value corresponds to a decrease of b/a value. The utility of the b/a ratio in the prediction of high-risk atherosclerosis had a great impact on the development of the final predictive model, since it maintained a statistical significance through all stages of the analysis. Changes of the b/a mean values among different CIMT groups confirmed these results and improved the negative relation between the b/a index and the CIMT (Figure 4.12).

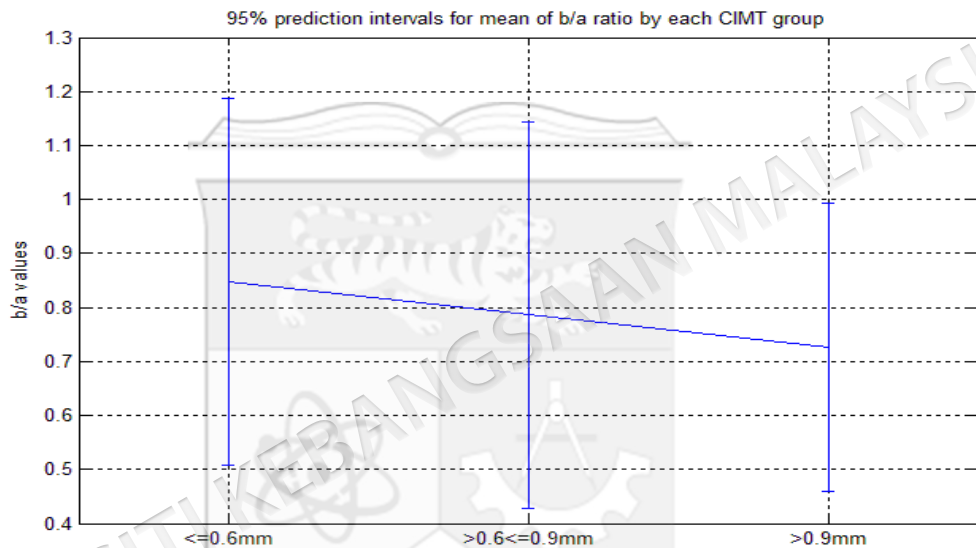


Figure 4.12 Changes of b/a ratio mean values among each CIMT group

4.4.2 PPG TIME INDICES

Pulse Time (PT)

The time interval between each two consequence pulses is represented by PT. However, since PPG signals are affected by the effects of atherosclerosis, PT tends to be altered due to the accumulation of atherosclerosis (Figure 4.13).

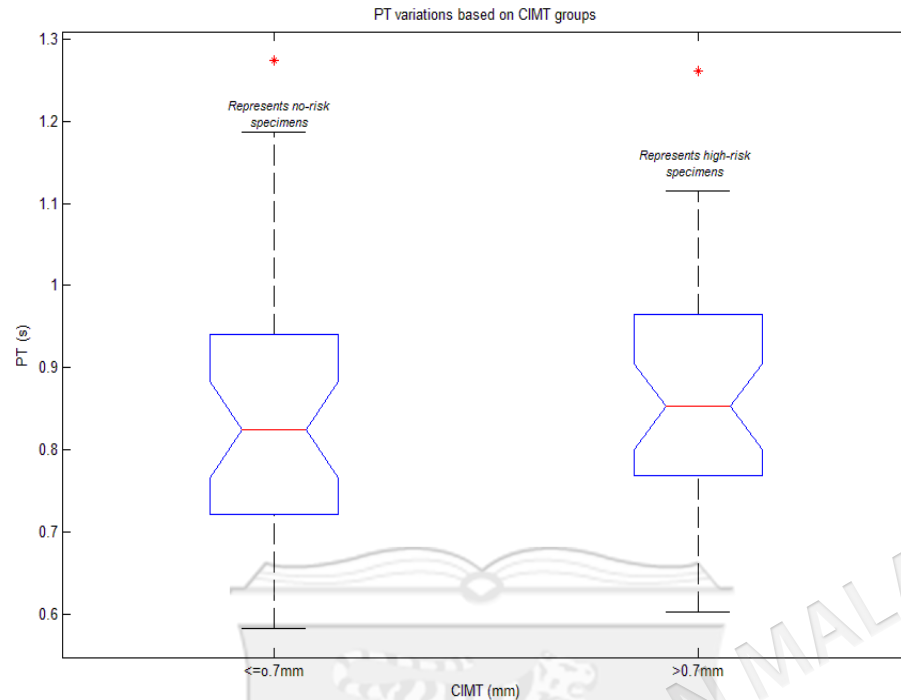


Figure 4.13 Variations on PT based on CIMT groups

In addition to the alterations of PT by atherosclerosis, PT is age-related. The analysis showed a trend of PT being increased as CIMT values increased. This strengthens the hypothesis of relating atherosclerosis to aging. As mentioned earlier, age is the dominant influence of atherosclerosis, PT showed a tendency to increase as we age. The variations of PT with age groups can be explored in Figure 4.14.

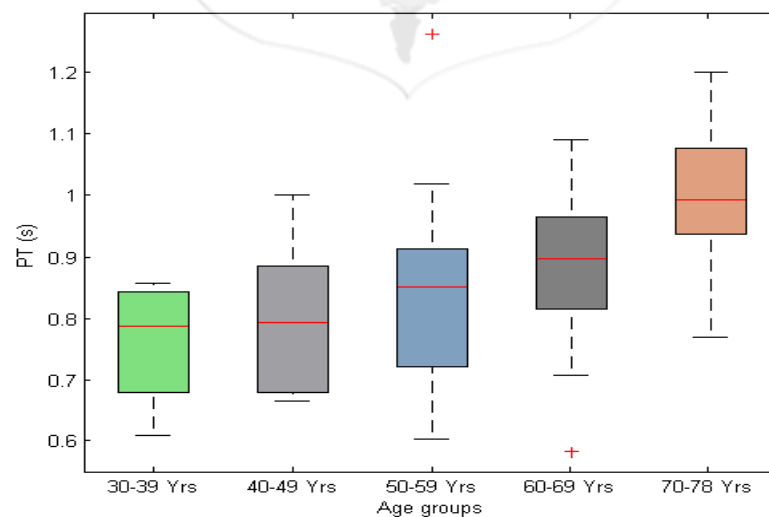


Figure 4.14 The variations of PT over different age groups

Peak to Peak Time (PPT)

It is accepted that older subjects have increasing arterial stiffness resulting in changes in the propagation of the pulse to the periphery, thereby influencing the peripheral pulse timing and shape characteristics (Allen & Murry 2003). As discussed earlier as age is the dominant influence of atherosclerosis, the influences of atherosclerosis on PPG signal morphology variations tend to be clearly affected. In terms of timing influences, PPT represents the time interval between the systolic point and the inflection point; however, inflection peak tends to be closer to the systolic peak due to the augmentation of the diastolic into the systolic. As the inflection point becomes closer to the systolic peak, PPT becomes smaller in value, which in turn can be used as an indicator of the loss of arterial elastic properties, thereby reflecting arterial stiffness. Figure 4.15 demonstrates the variations of PPT means through several CIMT groups using ANOVA plot.

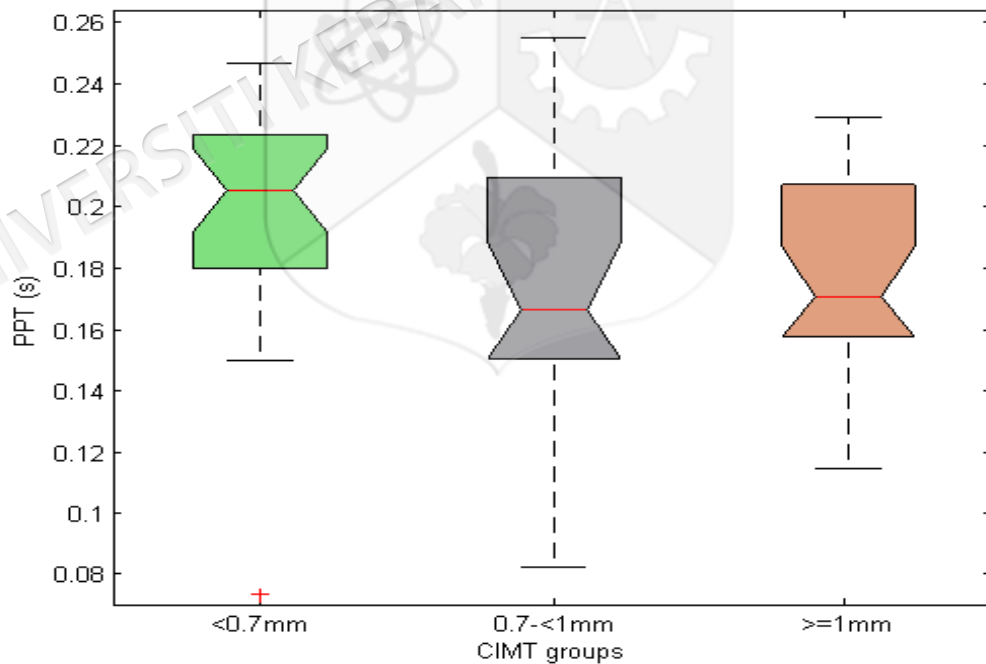


Figure 4.15 ANOVA plot diagram for PPT among various groups of CIMT

Statistically, PPT is found in this work to be significant during many stages of the analysis. It correlated negatively with age and with CIMT. Nevertheless, it dropped out when it was used to initiate the predictive model, since it was not significant in either the forward or the backward logistic regression. Details of the predictive model as well as PPT can be found in Section 4.5. Table 4.3 presents the correlations of PPG time indices against age and CIMT.

Table 4.3 Correlations of PPG time indices against age and CIMT data

Index	Age	CIMT
PT	.26/.035	.04/.770
MET	.40/.001	.28/.022
ST	.27/.029	.24/.045
DT	.24/.045	.03/.840
PPT	-.05/.96	-.25/.045
SI	-.04/.75	.18/.152

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 in parallel with CIMT and PPG data. Among the medical data measurements mentioned, PP was found to be a significant factor contributing to the process of atherosclerosis. The progression of atherosclerosis is accompanied by an increase in pulse pressure (Amar & Chamontin 2007). Our results support such an observation by reflecting an increment of PP as atherosclerosis increases. Figure 4.16 illustrates the trend of PP to be influenced by the accumulation of atherosclerosis.

Fortunately, PP was statistically correlated for both CIMT and HRART parameters. Details on (SP, DP, MAP) were demonstrated in Chapter 3. The association between PP and age is illustrated in Figure 4.17. Statistically, PP is found to be an important factor contributing to high-risk atherosclerosis. Therefore, it was used as secondary factor in the developed model for the prediction of atherosclerosis. However, the alterations and influences on atherosclerosis of PP might be a significant sign of the high-risk of developing CVD and other risk factors. Mainly, PP is used as independent predictor of arterial stiffness and myocardial infarction (MI) (Fang et al 1995). Therefore,

examine the variations of PP among age groups would reveal the response and tendency of blood pressure to the advancement of age.

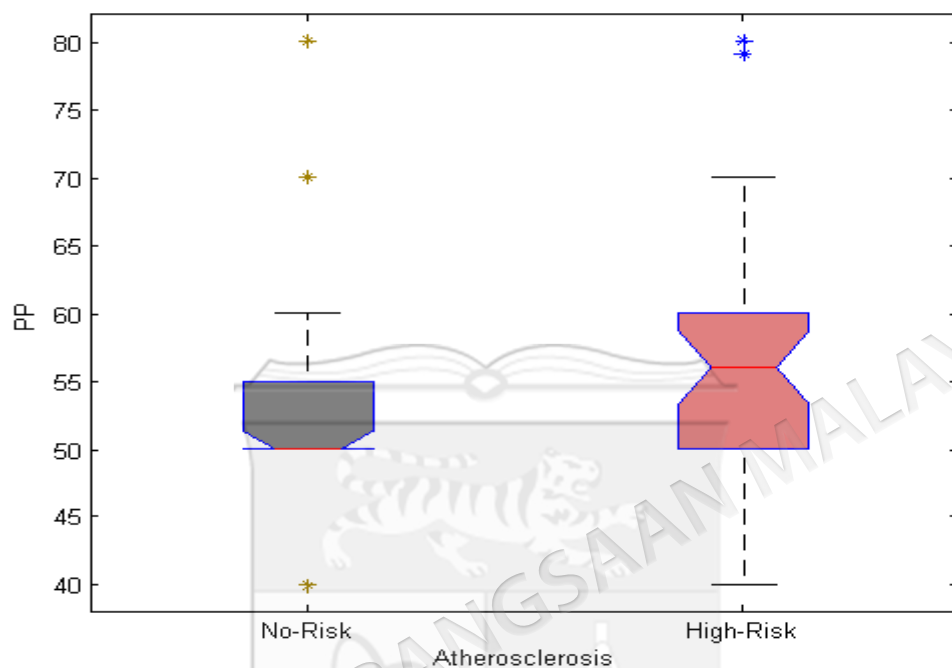


Figure 4.16 The influence of atherosclerosis on PP

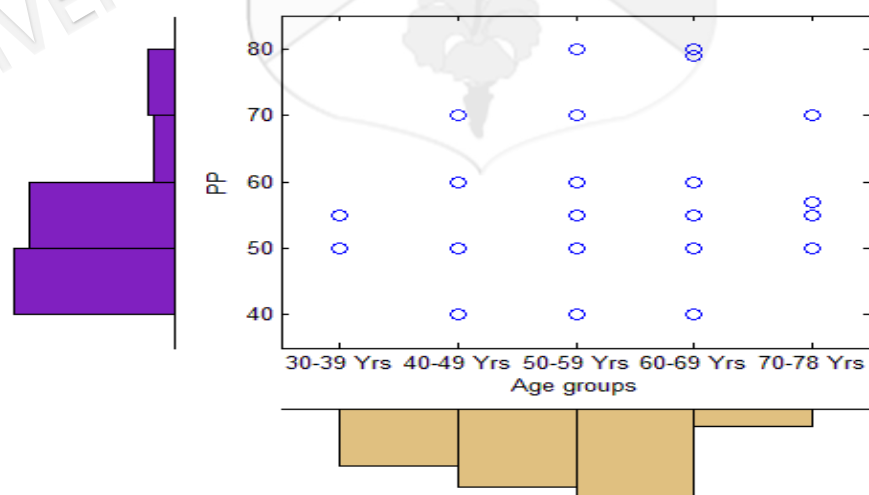


Figure 4.17 Associations between PP and several age groups

Furthermore, with respect to the connections observed between CIMT, some cardiovascular risk factors, age and pulse pressure, subclinical atherosclerosis might also underlie these relationships. In the present work, a statistical predictive model was developed for the purpose of prediction of high-risk atherosclerosis. Details of the model, its factors, factor characteristics, and model performance are introduced in the follow section.

4.5 THE DEVELOPED PREDICTIVE MODEL

4.5.1 Model Indices Analysis

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. From

the analysis Table 4.4 illustrates the initial parameters used to be tested prior to model development.

Table 4.4 Initial variables tested for model development

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.

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 4.5 shows the associated Nagelkerke R-square for each variable.

Table 4.5 Nagelkerke R-square for the selected indices

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.

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 4.6 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.

Table 4.6 Model summary of forward: LR

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

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 4.3.4. 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 4.7 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.

Table 4.7 Model summary of backward: LR

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

In addition to the data presented in Tables 4.3.3 and 4.3.4, it is helpful to demonstrate the relationship between the predicted outcome and certain characteristics found in observations. Table 4.8 represents the final characteristics of the developed model.

Table 4.8 The final factors included into the model and model characteristics

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							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

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 4.18).

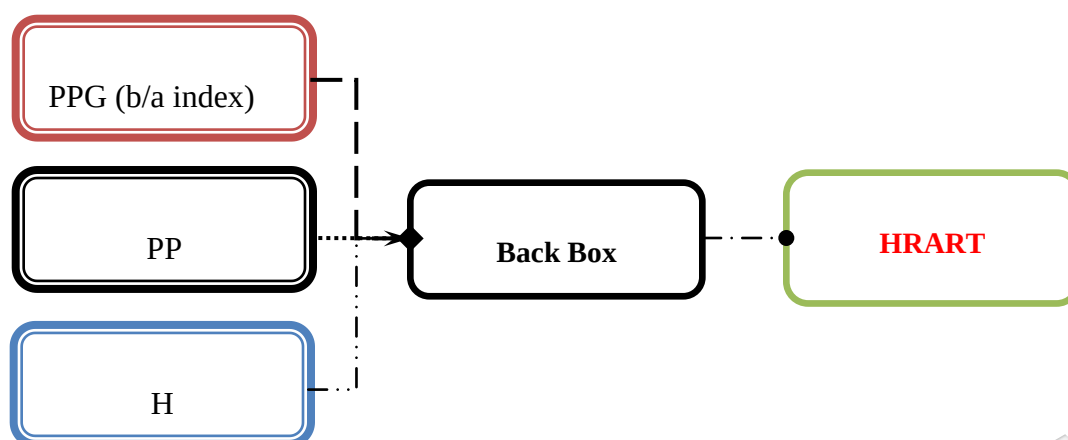


Figure 4.18 The logistic regression predictive model

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 4.9.

Table 4.9 Classification table of the predictive model

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

4.6 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 (Bland & Altman 1986, 1999) 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 (Krouwer 2008) 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 4.19. 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.

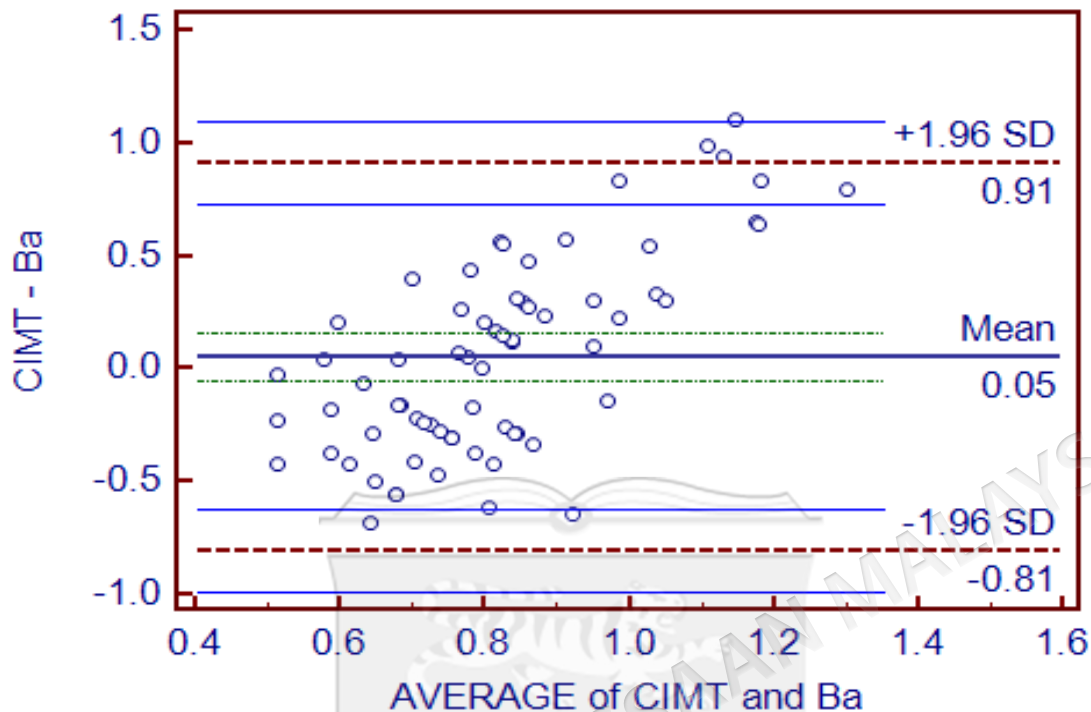


Figure 4.19 Agreement of CIMT and PPG in the measurement of risk atherosclerosis

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.

4.7 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 (Metz 1978; Zweig & Campbell 1993). ROC curves can also be used to compare the diagnostic performance of two or more laboratory or diagnostic tests (Griner et al. 1981). 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). Details on ROC and AUC were described in Chapter 3 and Chapter 2.

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= $\leq$ 0.7mm) 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 4.20 demonstrates the error bar plot for b/a index based on HRART data.

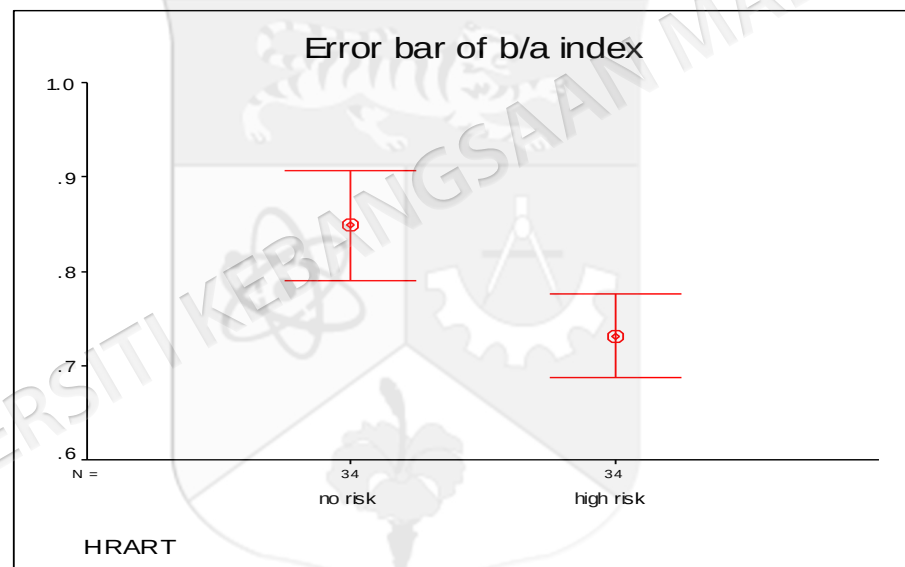


Figure 4.20 Error bar of PPG (b/a index) based on HRART

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 4.21.

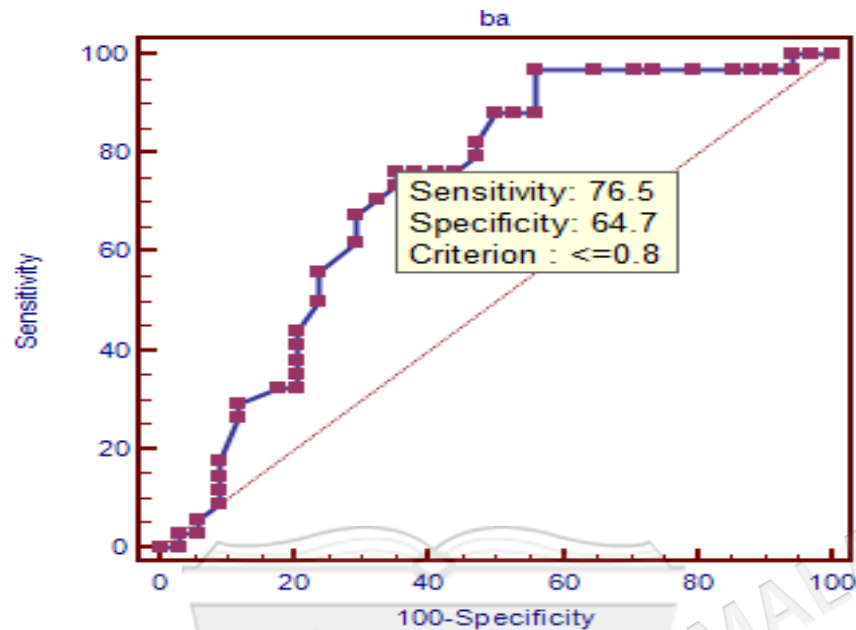


Figure 4.21 ROC curve of HRART vs. PPG (b/a index)

As seen in Figure 4.21, 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 (Diamond & Forrester 1979; Goldschlager 1982; Rifkin & Hood 1977). 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 (David & John 1990). 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 4.22 represents the ROC curves for all the model's factors. To examine the performance of the model by including the three contributed factors (b/a index, PP, and H), the model performs better by means of sensitivity, specificity and AUC values. Figure 4.23 demonstrates the combined ROC curve for the final factors in the model.

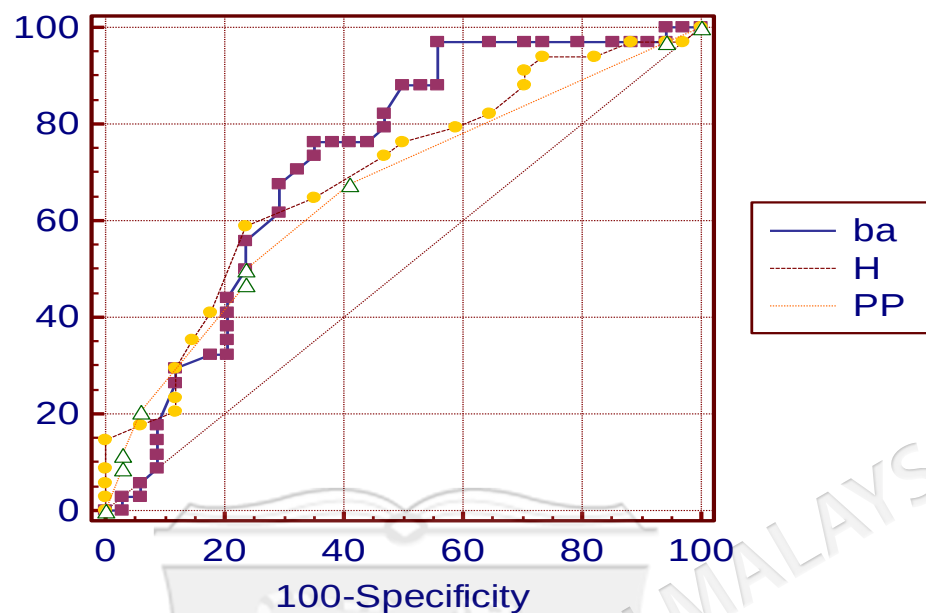


Figure 4.22 The obtained ROC curves for b/a index, PP and H

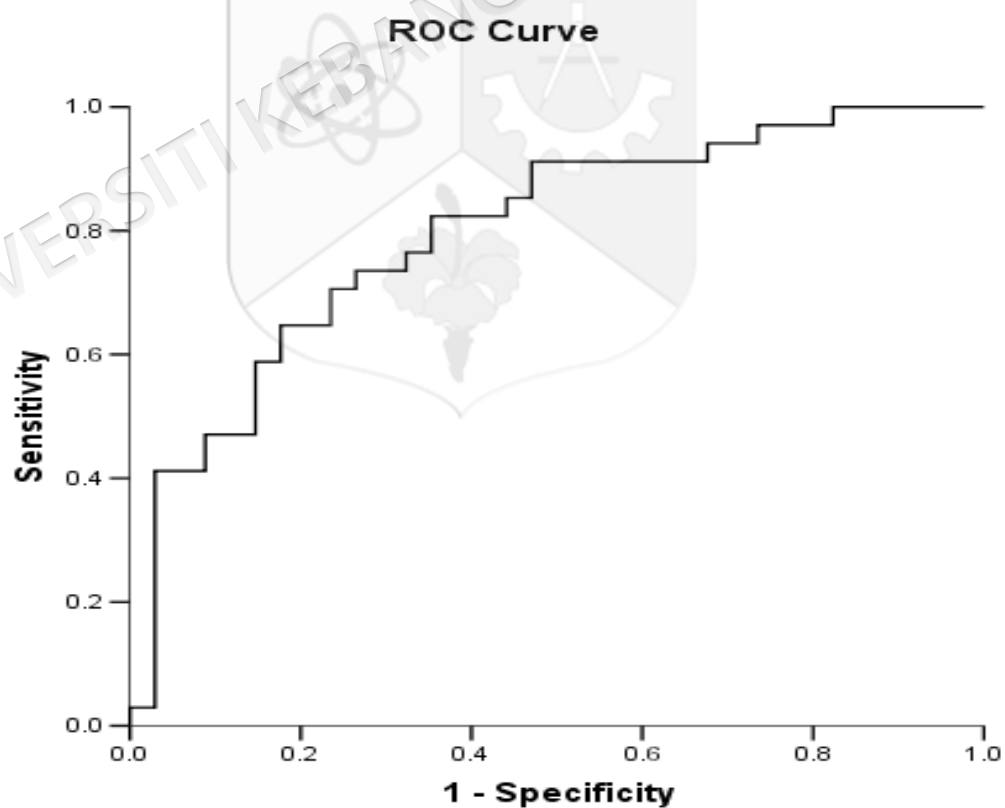


Figure 4.23 The combined ROC curve for the final factors in the model.

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. As seen in Figure 4.23, the final model (b/a, PP, and H) performs better than b/a ratio alone. The model showed a sensitivity of 81.8% and a specificity of 64.7%. 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.

4.8 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 (David & Benjamin 2002). 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 by (b/a index) can be seen in Table 4.11. As AUC is an overall measure for the performance of any developed model, the final model which includes b/a ratio, PP and subject's height, showed higher AUC (0.798) which increases the total accuracy of the model. Table 4.10 demonstrates the characteristics of AUC for the final model.

Table 4.10 The obtained AUC for the whole model and its characteristics

Classification variable	b/a index, PP, and H
Sensitivity & Specificity	81.8% & 64.7%
AUC	0.798

Table 4.11 The obtained AUC for b/a ratio and its characteristics

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

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 4.23) illustrates a sensitivity of 76.5% and a specificity of 64.7% for b/a ratio alone. 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. However, the three factors performed better when they used to classify subject into healthy or at-risk subject by means of

atherosclerosis. The final model revealed a sensitivity of 81.8% and a specificity of 64.7%. The best cut-off point for the developed model is 0.4335. For any new selected random subject to be diagnosed, the value greater than the cut-off point represents high-risk subjects. Otherwise, it represents a healthy subject. For both interactive diagrams, each circle represents a real subject under examination.

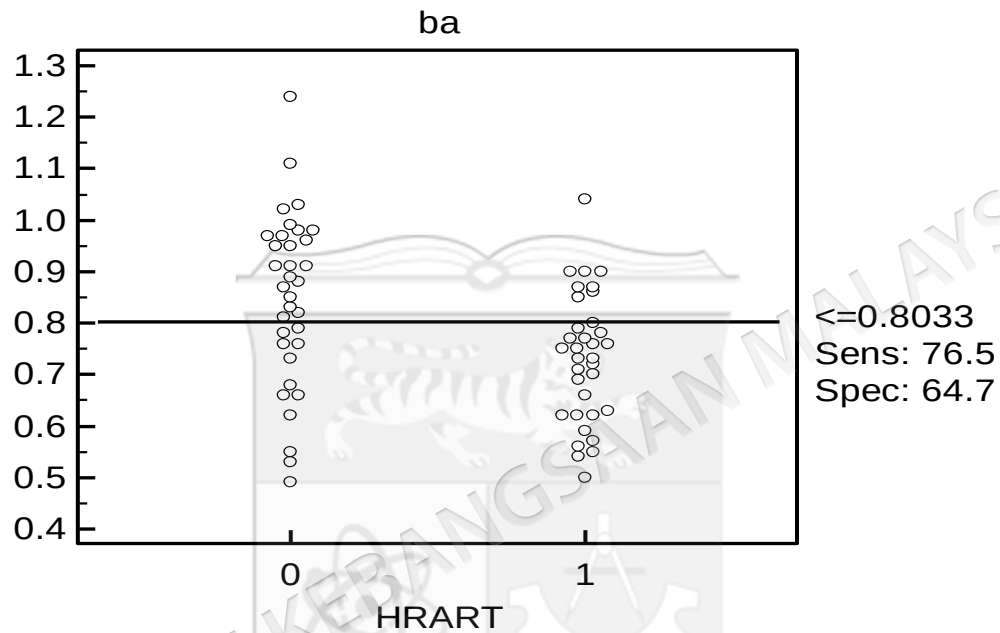


Figure 4.23 Interactive dot diagram of b/a index based on HRART

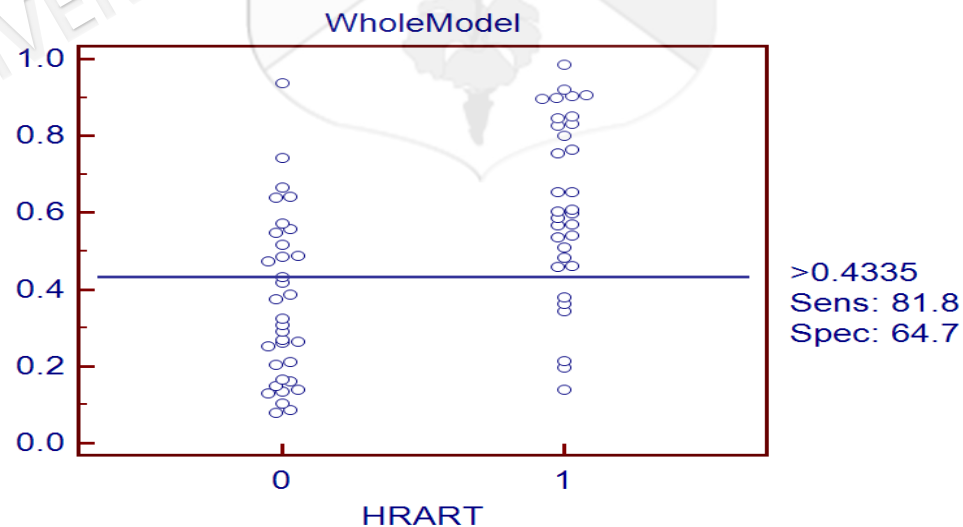


Figure 4.24 Interactive dot diagram of the whole model based on HRART

In conclusion, this chapter 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% by using the b/a ratio only. But when the three variables joined together, the model performs better revealing a sensitivity of 81.8%, specificity of 64.7% and an AUC to be 0.798. These results strengthen the ability of using PPG as a rapid measure for the assessment of the prediction of high-risk atherosclerosis. 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.

CHAPTER V

CONCLUSIONS AND FUTURE WORK

5.1 CONCLUSIONS

The availability of powerful methods for signal processing are allowing for a renaissance in the field of PPG research. Therefore, to uncover the true potential of PPG, there is a need for standardization and quantification of PPG as it is presented to the clinician. In addition, clinician has a vital role to play in the discovery and verification of new uses of PPG.

However, a new approach for the assessment of arterial stiffness and prediction of high-risk atherosclerosis as a special case was developed based on the analysis of PPG morphology. The developed approach was initiated as a low-cost and non-invasive optical measurement. The proposed method of the high-risk atherosclerosis assessment utilized information from PPG morphology amplitude changes in response to blood stream propagation and its effect on arterial alterations as a result of the accumulated atherosclerosis. The originality of this work can be noticed mainly in the utilizing of the non-intervention PPG signal. Additionally, the originality in this research in the first use of PPG's (b/a index) as an independent predictor for atherosclerosis. Moreover, the analysis of the PPG signal for ED subjects is considered originality in this area. More specifically, the final results obtained were based on the analysis of the PPG second derivative. The use of the PPG second derivative can facilitate the understanding of various PPG characteristics.

The analysis of PPG contour variations through its derivatives helped locate some points of interest on the PPG signal. In addition, analysis of the PPG second derivative and obtaining its five consequent waves (a, b, c, d, and e waves) enhanced understanding of changes in PPG

morphology. PPG second derivative was used in many applications. Some works aimed to calculate aging index utilizing its consequent waves. The important thing of utilizing PPG second derivative is to visualize and examine the original waveform. However, it would be a great challenge to relate PPG second derivative indices to the real measurements (diagnostic tests, medical data). This piece of research obtained the ability of bringing PPG and its second derivative to a real utility in predicting and assessing high-risk atherosclerosis in their original form (non-intervention PPG). Moreover, PPG second derivative waves (a and b) were used to calculate b/a ratio, which in turn was used as the main predictive index of high-risk atherosclerosis together with PP and the subject's height. The results obtained by the PPG showed promising outcomes as a means of assessment of high-risk atherosclerosis

This new method of assessing vascular function and prediction of high-risk atherosclerosis was shown to be a good and rapid measure for the screening of vascular diseases. The b/a index of PPG maintained significant statistics during all statistical stages. Hence, the cut-off point of b/a index (0.8) was used to discriminate between high-risk and no-risk atherosclerosis. In addition, the final predictive model (logistic regression model) had a cut-off point of 0.5. The sensitivity and specificity of predicting no-risk or high-risk atherosclerosis subjects through analysis of the PPG signal is reliable enough to be used in clinical settings as a rapid screening tool for atherosclerosis and its consequential diseases.

The analysis of PPG signals can provide a simple, inexpensive and non-invasive means for studying vascular function. Moreover, the PPG technique potentially has the advantage of being able to predict alterations in the vascular structure and function before the onset of clinical disease and before the clinical symptoms are detectable. By that means, PPG can assist CIMT; or it can be used as an alternative measure as an early prediction of high-risk atherosclerosis in homes and in clinical settings. Therefore, PPG is valuable for clarifying CVD risk, particularly for patients with intermediate risk, as assessed by conventional risk assessment.

The limitation of the proposed method was the shortage of subjects recruited, especially below the age of 40 years old. The arteries in younger subjects are generally more elastic and have higher compliance compared to older ones. This imbalance was unavoidable, and may have introduced an aging effect rather than the disease's effect. In addition, the study was restrictive in the sampling of pathology subjects (erectile dysfunction specimens). Therefore, in order to obtain more convincing results and to have higher confidence levels in the results, it would be necessary to conduct further investigations on many more subjects of a wider age range.

To conclude, this study contributed to the assessment of high-risk atherosclerosis using PPG waveform, without any intervention from physical, physiology or medical sides. The novelty of this work raised the ability to utilize PPG technique in the prediction of atherosclerosis and therefore the prediction of the ability to experience erectile dysfunction. The study came out with a quantified index (b/a ratio), which gives the start point of quantifying of PPG technique in clinical settings. As mentioned above, the value of b/a (0.8 v) was used as a cut-off point in the discrimination between normal and case subjects. Such findings opened the possibilities of quantifying other parameters from PPG. Therefore, allowing the researchers to work towards the establishment of PPG technique in clinical settings, since PPG technique still a method under study.

5.1 SUGGESTIONS AND FUTURE WORK

The standardization of measurement and obtaining results from PPG data recording has shortcomings; therefore the need for establishment of a standard protocol to be used as a reference for recording PPG data will be a distinctive target. PPG measurement at the index finger seems to be the most suitable for use in recording of PPG signals. Therefore, it is highly recommended that incoming data recording needs to be made using index finger PPG. It is also suggested that subjects be classified into groups, for example, diabetic subjects should be analyzed separately since their PPGs morphologies look more rounded. Moreover, the b/a index was extracted, and it was the important factor in the developed model. Therefore, in terms of PPG's indices, it is highly recommended to pay

extra attention to ST and PPT parameters, since they were strongly significant in this study. We hypothesized that ST and PPT would be great indices of interest to be investigated further. In fact, many studies claimed that PPG is age-related; therefore, our results showed a strong association between PPG and age, which in turn reflects the need to consider age in future investigations of PPG morphological changes and its association to pathological abnormalities.

In the early stages of this research, the Dolphin system was used to record PPG data (five subjects, all excluded from the analysis). Later on, the use of National Instrument (NI) was utilized to obtain index finger PPG. It seems that NI is much better, since the given signal is more stable and less noisy compared to the one obtained by the Dolphin system. Therefore, we can recommend the use of NI rather than current methods available.

Due to the shortfall in the sample size used, it is highly recommended to increase the number of the specimens in any coming round of PPG data recording. And as mentioned in many places in this thesis, normal subjects (normal erection) should be included in future data recordings. The current study utilized the discrimination between participants as having no-risk atherosclerosis or under high-risk atherosclerosis. Therefore, hiring normal subjects with normal erection might facilitate the process of predicting the subject's erection status. In terms of erection and erectile dysfunction, another submitted protocol for conducting a study that administrates PDE-5 inhibitor medications might be utilized to relate the effects of PDE-5 inhibitors on vascular activities and, thereby, relating PPG morphological changes to erectile dysfunction characteristics (Appendix E).

Studying PPG signals to assist vascular activities at the same time with high-sensitivity C-reactive protein (hsCRP) might be a great idea for implementation. hsCRP is an indicator of cardiovascular risk such as heart attack or stroke. As a result, it might reveal valuable information by means of PPG analysis. It is therefore of interest to know whether the PPG can predict hsCRP and/or its consequences. In addition, the A1c test,

which is a good general measure of diabetic care, is recommended to be conducted alongside hsCRP. A1c test indicates a person's average blood glucose level over the past few months. Therefore, as future work, both hsCRP and A1c tests might be useful independent indicators of erectile dysfunction.

As a by-product of the project and contribution to the scientific community, it is proposed that data acquired during the project be made available to a public data-base of biological signals (www.physionet.org) maintained by MIT in the USA.



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Appendix A

Ethical Committee Approval


UNIVERSITI KEBANGSAAN MALAYSIA
National University of Malaysia

PUSAT PERUBATAN UKM • UKM MEDICAL CENTRE
Sekretariat Penyelidikan Perubatan • Medical Research Secretariat

UKM 1.53.5/244/SPP3
February 2009

Clinical Associate Professor Dr Oteh Maskon
Department of Medicine
UKM Medical Centre
Cheras.

Dear Dr.,

Approval to conduct research in UKM

Title : *'Photoplethysmography (PPG) in Predicting Endothelial Dysfunction in Patients Presenting with Erectile Dysfunction (ED)'*

Project Code : **FF-074-2009**

With reference to the above, the Research Ethics Committee, UKM has approved the following research proposal:

Duration of Study : February 2009 until January 2010

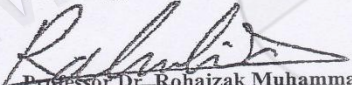
Financial Support : RM 5,000.00 from UKMMC Fundamental Research Fund

- Deal with UKMMC Financial Department for claims

Please submit your **Progress Report** every 6 months and **Final Report** upon completion of the research to the Medical Research Secretariat.

Thank you.

Yours truly,


Professor Dr. Rohaizak Muhammad
Deputy Dean (Research & Industry)
UKM Medical Centre
& Chairman
Research Ethics Committee
UKM, Cheras

Cc.

- Circulation file
FF-074-2009



Pemenang Anugerah Kualiti Perdana Menteri 2006
Winner of Prime Minister's Quality Award 2006

Sekretariat Penyelidikan Perubatan, Tingkat 1 Blok Klinik, Pusat Perubatan Universiti Kebangsaan Malaysia, Jalan Yaacob Latiff, Bandar Tun Razak,
56000 Cheras, Kuala Lumpur, Malaysia. Telefon: 03-9145 5046/5047/5048/6718 Faksimili: 03-9172 5339
Laman web: <http://www.ukm.my/mrs/>

APPENDIX B

INFORMATION FOR PATIENT/PARTICIPANT

Research Title

A Predictive Model for the Assessment of High-Risk Atherosclerosis Using Photoplethysmography

Introduction

Endothelial dysfunction is characterized by a shift of the actions of the endothelium toward reduced vasodilatation, a proinflammatory state, and prothrombic properties. It is associated with most forms of cardiovascular disease, such as hypertension, coronary artery disease, chronic heart failure, peripheral artery disease, diabetes, and chronic renal failure (Endemann and Schiffrin, 2004) which represent some forms of cardiovascular disease (CVD).

Because of its easy and mature nature of measurements and calculations (Zhang et al, 2008), PPG utilized in this study to investigate and analysis the relationship between CVD and erectile dysfunction (ED). ED is the inability to maintain an erection firm enough to have sexual intercourse. Unfortunately, millions of men are suffering from ED world wide nowadays. It has long been understood that the cause of this disorder in many men is related to the health of the blood vessels that serve or are within the penis (JAMA, 2005). PPG provides a means of determining properties of vascular tree during the cardiac cycle and changes with aging and diseases (Bhattacharya and Kaniljal, 2001).

What would the research involve?

PPG signals from the patient/participant will be collected and saved for further analysis. Besides that, the information regarding the analysis of PPG morphology will be analyzed along with the conducted tests in PPUKM for each individual subject. CIMT, hsCRP and physical measurement will be collected as well in order to allow comparisons with the new measurements introduced by PPG.

Research benefits

The research conducted will contribute greatly to the advancement of science and health care industry. It will also improve understanding of the endothelial functions and it will help in the prevention as well as treatment for

cardiovascular risks in the future. Mainly, our research focuses on the utility of PPG signal morphology in reflecting the associations between arterials stiffness's and CV disorders especially erectile dysfunction.

The Risks

There is no added risk as there is no known danger of taking pulse signal from the finger. We are using the pulse oximetry probes. Therefore, the procedure for measurement is very similar to that of the pulse oximetry where doctors obtained information regarding the oxygen saturation in the blood. As a matter of fact, the pulse oximetry signal has been widely accepted by physicians as an important diagnosis tool.

Confidentiality

The results obtained will be reported in a collected manner with no reference to a specific individual. Hence, the data from each individual will remain confidential. Nevertheless, you have the right to know the results of the analysis.

Do I have to participate?

The participation into this study is voluntary. If you prefer not to take part, you do not have to give a reason and it will not affect the treatment given. You may also withdraw at any point in time during the study.

Payment and compensation

You do not have to pay in order to participate in this research. Similarly, no payment is available to you for participating. In the event that this study results in the development of any marketable product, you will have no ownership interest in the product and no right to share in any profits from its commercialization whatsoever.

If I have questions, to whom can I ask?

PhD Candidate Yousef Qawqzeh: 017-6 930960
 Prof. Dr. Mohd Alauddin Moh Ali: 03-8921 6302
 Prof. Dr. Oteh Maskon : 012-9 187915
 Jabatan Kejuruteraan Elektrik, Elektronik & Sistem,
 Fakulti Kejuruteraan, UKM, Bangi

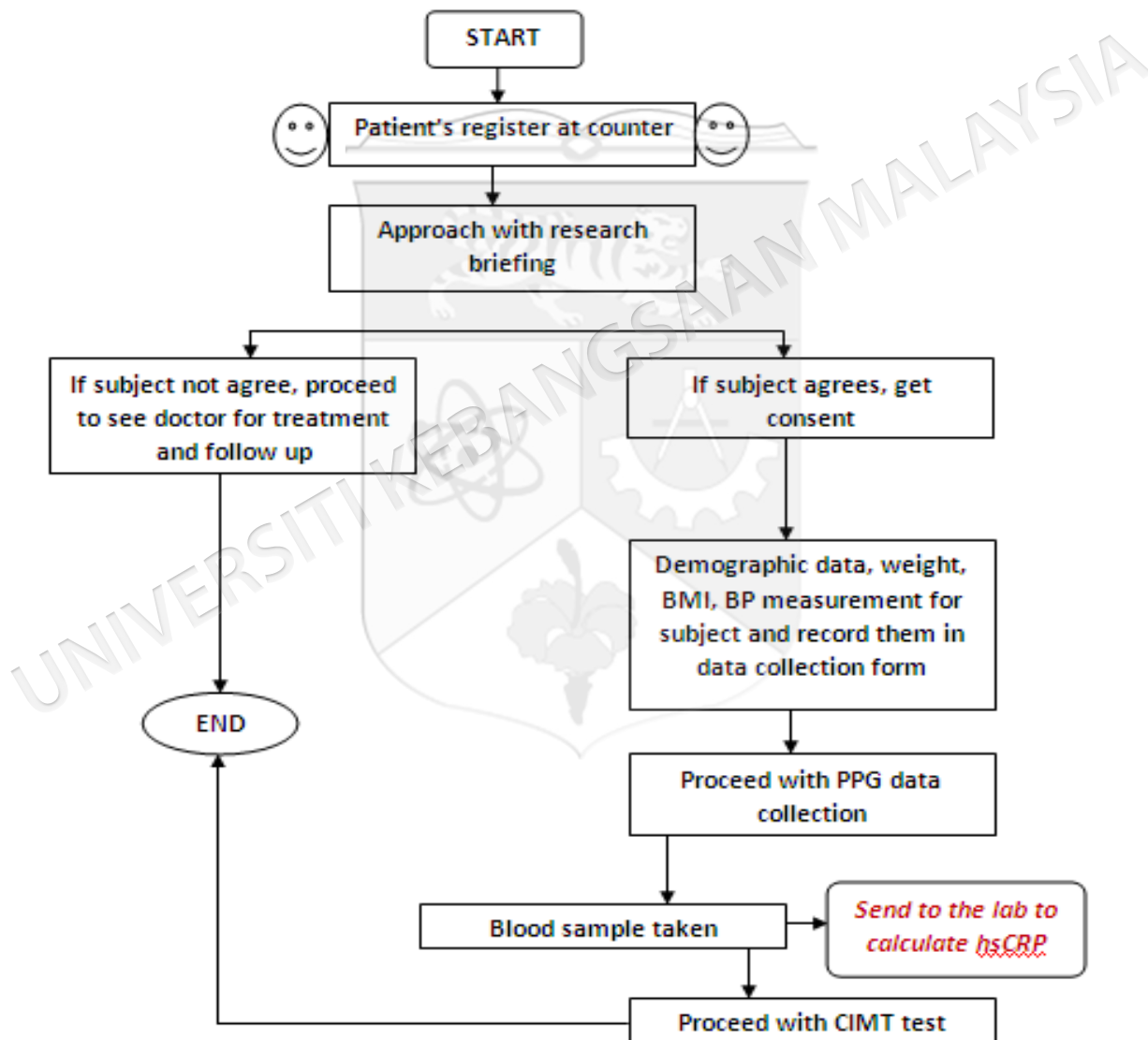
Appendix C

Data Collection Protocol

The flowchart demonstrates the initial process flow for subject recruitment and data acquisition.

Protocols of experiment:

- Supine position
- PPG for right and left finger tips
- CIMT for right and left sides
- hsCRP test



APPENDIX D

CONSENT FORM FOR A RESEARCH PROJECT

I, _____ (patients' name), bearing a postal address
at

_____, have agreed
to take part in the study:

“Development of a non-invasive technique for endothelial dysfunction investigation and assessment using PPG”

The nature and purpose of the study has been explained to me in detail by Dr _____, who is carrying out the study. I was able to ask him/her questions regarding all aspects of the study.

In addition, he/she had given me a copy of the participant information leaflet. My identity will not be disclosed and I can withdraw from the study at any time, and it will not affect my treatment.

Signature of patient: _____

I/C No: _____

Date: _____

Signature of doctor: _____ Name: _____

Date: _____ I/C No: _____

Signature of witness: _____ Name: _____

Date: _____ I/C No: _____

APPENDIX E

Data Collection Form and PPG Recording Protocol

Patient ID sticker here

A. Visit date: _____

Form completed by: _____ Doctor Signature: _____

B. Demographics

Patient Last Name: _____ Patient First Name: _____
 Date of Birth (mm/dd/yyyy): ____/____/____ Patient Age: _____ **System Calculation**
 Sex: **Male** **Female**
 Social Security #: _____ Medical Record Number: _____
 Health Insurance Claim Number: _____ Patient ZIP Code: _____
 Race: **Malay Chinese Indian / Other (please specify)** _____
 Referring Cardiologist: _____ Referring Physician: _____
 Address: (_____)
 Contact number: _____
 E-mail address: (optional) _____

C. Risk Factors

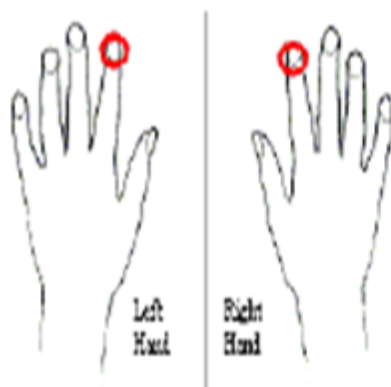
Weight (kg): _____ **Height (cm):** _____

D. CVD History

Do you have any established CVD? **Yes** **No**

Current or Recent Cigarette Smoker:	Yes	No			
Family History of Coronary Artery Disease:	Yes	No			
Diabetes:	Yes	No			
If Yes → Diabetes Control: (select one)	None	Diet	Oral	Insulin	Other
Dyslipidaemia:	Yes	No			
Renal Failure – Dialysis:	Yes	No			
Hypertension:	Yes	No			
Chronic Lung Disease:	No	Mild	Moderate	Severe	
Peripheral Arterial Disease:	Yes	No			
Morbid Obesity:	Yes	No			

Probes location



Data Acquisition Protocol

- ✚ Each subject relaxes for 5 minutes in supine position
- ✚ Attach the probes to both left and right hands
- ✚ Start data recording for 90 seconds and save the file based on patient's ID sticker number
- ✚ Stop data recording
- ✚ Release the probes
- ✚ Proceed for the next subject

Note: If the above locations are impractical for a particular subject, please use another finger and mark on the figure location used in the experiment

Steps	Probe location	Conditions	File name
1	LA RA	Supine position (arms at bed level)	Subject ID sticker
2		One and half minute (90 seconds) of data recording	

APPENDIX F

Listing of MATLAB program codes

1. Min-Max Algorithm

```
% Peak detection
clear all; clc;
sr = 5500;
% Open the dialog box for choose data file (txt format)
ppg=load ('S01_01.txt');
ppg=ppg(:,1);

left =450500;right = 451901;
ppg = ppg(left:end-right);
%Band-Pass-Filtering
length(ppg)
ppg = -detrend (ppg);
ppg=resample (ppg,1,20);
ppg=BPF(ppg,275,0.6,15);
ppg = ppg - min (ppg);
ppg = ppg/max (ppg);
t = 0: length(ppg)-1; % time scale
% figure (1); plot(ppg);
% [maxtab, mintab] = peakdet(ppg, 0.05);
% % hold on;
% plot(mintab(:,1), mintab(:,2), 'g*');
% plot(maxtab(:,1), maxtab(:,2), 'r*');
% figure (1); plot(t,ppg);
[maxtab, mintab] = peakdet(ppg, 0.05, t);
figure (1); plot (t,ppg)
hold on;
plot(mintab(:,1), mintab(:,2), 'g*');
plot(maxtab(:,1), maxtab(:,2), 'r*');

function [maxtab, mintab]=peakdet(v, delta, x)
%PEAKDET Detect peaks in a vector
%
% [MAXTAB, MINTAB] = PEAKDET(V, DELTA) finds the local
% maxima and minima ("peaks") in the vector V.
% MAXTAB and MINTAB consists of two columns. Column 1
% contains indices in V, and column 2 the found values.
%
% With [MAXTAB, MINTAB] = PEAKDET(V, DELTA, X) the indices
%
% in MAXTAB and MINTAB are replaced with the corresponding
% X-values.
%
% A point is considered a maximum peak if it has the maximal
% value, and was preceded (to the left) by a value lower by %
DELTA.

% Eli Billauer, 3.4.05 (Explicitly not copyrighted).
% This function is released to the public domain; Any use is allowed.
```

```

maxtab = [];
mintab = [];

v = v(:); % Just in case this wasn't a proper vector

if nargin < 3
    x = (1:length(v))';
else
    x = x(:);
    if length(v) ~= length(x)
        error('Input vectors v and x must have same length');
    end
end

if (length(delta(:))) > 1
    error('Input argument DELTA must be a scalar');
end

if delta <= 0
    error('Input argument DELTA must be positive');
end

mn = Inf; mx = -Inf;
mnpos = NaN; mxpos = NaN;

lookformax = 1;

for i=1:length(v)
    this = v(i);
    if this > mx, mx = this; mxpos = x(i); end
    if this < mn, mn = this; mnpos = x(i); end

    if lookformax
        if this < mx-delta
            maxtab = [maxtab ; mxpos mx];
            mn = this; mnpos = x(i);
            lookformax = 0;
        end
    else
        if this > mn+delta
            mintab = [mintab ; mnpos mn];
            mx = this; mxpos = x(i);
            lookformax = 1;
        end
    end
end
end
end

```

2. PPG Analysis Algorithm

```

function varargout = PPG_analysis(varargin)
% Begin initialization code - DO NOT EDIT
gui_Singleton = 1;
gui_State = struct('gui_Name',       mfilename, ...
                  'gui_Singleton',   gui_Singleton, ...
                  'gui_OpeningFcn', @PPG_analysis_OpeningFcn, ...
                  'gui_OutputFcn',  @PPG_analysis_OutputFcn, ...
                  'gui_LayoutFcn',   [] , ...
                  'gui_Callback',    []);
if nargin && ischar(varargin{1})
    gui_State.gui_Callback = str2func(varargin{1});
end

if nargout
    [varargout{1:nargout}] = gui_mainfcn(gui_State, varargin{:});
else
    gui_mainfcn(gui_State, varargin{:});
end

% --- Executes just before PPG_analysis is made visible.
function PPG_analysis_OpeningFcn(hObject, eventdata, handles, varargin)
% Choose default command line output for PPG_analysis
handles.output = hObject;

% Initialize variables
clc
handles.mouseflag = 0;
handles.xc = zeros(2,1);
handles.peaks = cell(3,1);
handles.sm = ones(3,3);

% Set graphs
handles.plot1 = plot(handles.axes1, 0,0,'m-', 0,0,'m-', 0,0,'k-', 0,0,'b.',
0,0,'b.', 0,0,'b.', 0,0,'b.', 0,0,'k-.');
handles.plot2 = plot(handles.axes2, 0,0,'m-', 0,0,'m-', 0,0,'k-', 0,0,'b.',
0,0,'b.', 0,0,'b.', 0,0,'b.', 0,0,'k-.');
handles.plot3 = plot(handles.axes3, 0,0,'m-', 0,0,'m-', 0,0,'k-', 0,0,'b.',
0,0,'b.', 0,0,'b.', 0,0,'b.', 0,0,'k-.');
handles.plot4 = plot(handles.axes4, 0,0,'b-', 0,0,'g-', 0,0,'r-', 0,0,'k-',
0,0,'k-', 0,0,'k-', 0,0,'m-', 0,0,'m-');
% SPPG
handles.plot5 = plot(handles.axes5, 0,0,'b-');
% derivatives
handles.plot6 = plot(handles.axes6, 0,0,'g-', 0,0,'k-', 0,0,'b.', 0,0,'b.',
0,0,'b.', 0,0,'b.', 0,0,'k--', 0,0,'k-', 0,0,'y-', 0,0,'go');
handles.plot7 = plot(handles.axes7, 0,0,'g-', 0,0,'k-', 0,0,'b.', 0,0,'b.',
0,0,'b.', 0,0,'b.', 0,0,'k--', 0,0,'k-');
% parameters
handles.plot8 = plot(handles.axes8, 0,0,'b.-', 0,0,'k-.');

% Update handles structure
guidata(hObject, handles);

% --- Outputs from this function are returned to the command line.

```

```
function varargout = PPG_analysis_OutputFcn(hObject, eventdata, handles)
varargout{1} = handles.output;
```

```
% -----
% -----
% --- Executes on button press in load.
function load_Callback(hObject, eventdata, handles)

%P = get(handles.axes1,'OuterPosition')
% itais maina poziciju: set(handles.axes1,'OuterPosition',[P(1) P(2)-5
P(3) P(4)+5]);
handles = load_ppg(handles);
guidata(hObject, handles);
% -----
```

```
% -----
% --- Executes on button press in save.
function save_Callback(hObject, eventdata, handles)
handles.param
xlswrite([handles.path handles.fname(1:end-3) 'xls'], handles.param,
'Hemodynamic parameters');
% -----
```

```
% -----
% --- Executes on signal smooth slider movement.
function smooth1_Callback(hObject, eventdata, handles)
handles.dataflag = 0;
handles.sm(handles.ch,1) = get(handles.smooth1,'Value');
handles = ppg_feet(handles,handles.ch);
handles = parameters2(handles); % parameters from all channels
guidata(hObject, handles);
% -----
```

```
% --- Executes during object creation, after setting all properties.
function smooth1_CreateFcn(hObject, eventdata, handles)
% Hint: slider controls usually have a light gray background.
if isequal(get(hObject,'BackgroundColor'),
get(0,'defaultUiControlBackgroundColor'))
set(hObject,'BackgroundColor',[.9 .9 .9]);
end
```

```
% -----
% --- Executes on 1st derivative slider movement.
function smooth2_Callback(hObject, eventdata, handles)
handles.dataflag = 0;
handles.sm(handles.ch,2) = get(handles.smooth2,'Value');
handles = ppg_feet(handles,handles.ch);
handles = parameters2(handles); % parameters from all channels
guidata(hObject, handles);
% -----
```

```
% --- Executes during object creation, after setting all properties.
function smooth2_CreateFcn(hObject, eventdata, handles)
% Hint: slider controls usually have a light gray background.
```

```

if isequal(get(hObject,'BackgroundColor'),
get(0,'defaultUicontrolBackgroundColor'))
    set(hObject,'BackgroundColor',[.9 .9 .9]);
end

% -----
% --- Executes on 2nd derivative slider movement.
function smooth3_Callback(hObject, eventdata, handles)
    handles.dataflag = 0;
    handles.sm(handles.ch,3) = get(handles.smooth3,'Value');
    handles = ppg_feet(handles,handles.ch);
    handles = parameters2(handles); % parameters from all channels
guidata(hObject, handles);
% -----

% --- Executes during object creation, after setting all properties.
function smooth3_CreateFcn(hObject, eventdata, handles)
% Hint: slider controls usually have a light gray background.
if isequal(get(hObject,'BackgroundColor'),
get(0,'defaultUicontrolBackgroundColor'))
    set(hObject,'BackgroundColor',[.9 .9 .9]);
end

% -----
% --- Executes on mouse motion over figure - except title and menu.
function figure1_WindowButtonMotionFcn(hObject, eventdata, handles)
handles = mouse_move(handles);
guidata(hObject, handles);
% -----

% -----
% --- Executes on mouse press over figure background, over a disabled or
% --- inactive control, or over an axes background.
function figure1_WindowButtonDownFcn(hObject, eventdata, handles)
handles = mouse_click(handles);
guidata(hObject, handles);
% -----

% --- Executes when selected object is changed in uipanel_mouseclick.
function uipanel_mouseclick_SelectionChangeFcn(hObject, eventdata, handles)

if get(handles.zoom,'Value') == 1
    handles.mouseflag = 0;
    zoom on
    pan off
%    linkaxes([handles.axes1 handles.axes2 handles.axes3], 'x');
    handles.xc = zeros(2,1);
end
if get(handles.move,'Value') == 1
    handles.mouseflag = 0;
    zoom off
    pan on
%    linkaxes([handles.axes1 handles.axes2 handles.axes3], 'x');
    handles.xc = zeros(2,1);
end

```

```

if get(handles.edit1,'Value') == 1
    handles.mouseflag = 1;
    zoom off
    pan off
    handles = ppg_window(handles);
    handles.dataflag = 0;
    handles = ppg_feet(handles,1); % parameters from channel 1
    handles = ppg_feet(handles,2); % parameters from channel 2
    handles = ppg_feet(handles,3); % parameters from channel 3
    handles.ch = 3;
    handles = parameters2(handles); % parameters from all channels
end
guidata(hObject, handles);

% --- Executes on button press in feet_method.
function feet_method_Callback(hObject, eventdata, handles)
    handles.dataflag = 0;
    handles.sm(handles.ch,3) = get(handles.smooth3,'Value');
    handles = ppg_feet(handles,handles.ch);
    handles = parameters2(handles); % parameters from all channels
guidata(hObject, handles);

% --- Executes on selection change in parameter.
function parameter_Callback(hObject, eventdata, handles)
X = handles.peaks(handles.ch);
x1 = X(:,1); x1 = x1(1:end-1);
t = handles.data(:,1);
par = handles.param(:,1+get(hObject,'Value'));
set(handles.plot8(1),'XData',t(x1),'YData',par);
set(handles.axes8,'YLim',mean(par)+3*(std(par)+eps)*[-1 1]);
drawnow

% --- Executes during object creation, after setting all properties.
function parameter_CreateFcn(hObject, eventdata, handles)
% hObject    handle to parameter (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    empty - handles not created until after all CreateFcns called

% Hint: popupmenu controls usually have a white background on Windows.
%         See ISPC and COMPUTER.
if ispc && isequal(get(hObject,'BackgroundColor'),
get(0,'defaultUiControlBackgroundColor'))
    set(hObject,'BackgroundColor','white');
end

function h = load_ppg2(h)

% Set data file
[h.fname, h.path] = uigetfile('*.dat','Open data file');
set(h.ch_txt,'String',['Loading...']); drawnow

% Load data into matrix
h.ch = 1;
sr = 1000; % sample rate of Zbigeva data
fid = fopen([h.path h.fname]);
Data = fread(fid,'int16');
fclose(fid);

```

```

% Data transform
N = length(Data);
t = (1:N/3)'/sr;
p1 = Data(1:3:N);
p2 = Data(2:3:N);
p3 = Data(3:3:N);
h.Data = [t p1 p2 p3];
s = fix(length(t)/50000);
set(h.ch_txt, 'String', ['Channel: ' num2str(h.ch)]);

% Plot the signal
set(h.axes1, 'Color', [1 1 1]);
set(h.axes2, 'Color', [.9 .9 .9]);
set(h.axes3, 'Color', [.9 .9 .9]);
set(h.plot1(1), 'XData', t(1:s:end), 'YData', p1(1:s:end));
set(h.plot2(1), 'XData', t(1:s:end), 'YData', p2(1:s:end));
set(h.plot3(1), 'XData', t(1:s:end), 'YData', p3(1:s:end));
set(h.axes1, 'XLim', [t(1) t(end)], 'YLim', [min(p1) max(p1)]);
set(h.axes2, 'XLim', [t(1) t(end)], 'YLim', [min(p2) max(p2)]);
set(h.axes3, 'XLim', [t(1) t(end)], 'YLim', [min(p3) max(p3)]);
set(h.plot4(1), 'XData', t(1:s:end), 'YData', p1(1:s:end));
set(h.plot4(2), 'XData', t(1:s:end), 'YData', p2(1:s:end));
set(h.plot4(3), 'XData', t(1:s:end), 'YData', p3(1:s:end));
mini = min(min(h.Data(:,2:4)));
maxi = max(max(h.Data(:,2:4)));
d = (maxi-mini)/3;
set(h.axes4, 'XLim', [t(1) t(end)], 'YLim', [mini-d maxi+d]);
drawnow

zoom on
linkaxes([h.axes1 h.axes2 h.axes3], 'x');

set(h.zoom, 'Value', 1);

function h = mouse_click(h)

mc = get(gca, 'currentpoint');
if mc(1,1)<h.X(1) || mc(1,1)>h.X(2)
    return
end

ax = get(gcf, 'CurrentAxes');
[z,h.ch] = find(ax-[h.axes1 h.axes2 h.axes3]==0);

set(h.ch_txt, 'String', ['Channel: ' num2str(h.ch)]);
h = ppg_feet(h,h.ch);

function h = mouse_move(h)

if h.mouseflag == 0;
    return
end

ax = get(gcf, 'CurrentAxes');
[z,h.ch] = find(ax-[h.axes1 h.axes2 h.axes3]==0);

```

```

mc = get(gca, 'currentpoint');
if mc(1,1)<h.X(1) || mc(1,1)>h.X(2)
    return
end
set(h.plot1(8), 'XData', [mc(1,1) mc(1,1)], 'YData', [-10000 10000]);
set(h.plot2(8), 'XData', [mc(1,1) mc(1,1)], 'YData', [-10000 10000]);
set(h.plot3(8), 'XData', [mc(1,1) mc(1,1)], 'YData', [-10000 10000]);
set(h.plot4(6), 'XData', [mc(1,1) mc(1,1)], 'YData', [-10000 10000]);
set(h.plot6(8), 'XData', [mc(1,1) mc(1,1)], 'YData', [-10000 10000]);
set(h.plot7(8), 'XData', [mc(1,1) mc(1,1)], 'YData', [-10000 10000]);
set(h.plot8(2), 'XData', [mc(1,1) mc(1,1)], 'YData', [-10000 10000]);
drawnow

if get(h.edit1, 'Value') == 1
    h = ppg_beat(h, mc(1,1));
end

function h = parameters(h,ch)

X = h.peaks{ch};
x1 = X(:,1); x2 = X(1:end-1,2); x3 = X(1:end-1,3); x4 = X(1:end-1,4);
v = X(1:end-1,5); ba = X(1:end-1,6); ca = X(1:end-1,7);
N = length(x2);
%[N h.dataflag size(h.param,1)]
h.sp = cell(N,1); % single period ppg matrix
t = h.data(:,1); p = h.data(:,ch+1); % ppg signal matrix
if h.dataflag == 0
    h.param = zeros(N,16); % parameters matrix
end
h.dataflag = 1;
if N~=size(h.param,1)
    set(h.ch_txt, 'String', 'Signal is too bad[3] Please change
conditions!');
    drawnow
    h.mouseflag = 0;
    return
end
H = str2double(get(h.height, 'String'))/100; % body height

% Parameters -----
dp = diff(p(x1)); % foot-to-foot amplitude variations
for j = 1: N
    sp = p(x1(j):x1(j+1))-p(x1(j))-dp(j)*(0:x1(j+1)-x1(j))/(x1(j+1)-x1(j)); %
single beat
    h.sppg{j} = sp;
    h.param(j,8) = v(j); % 8-Max ejection velocity
    h.param(j,9) = sp(x3(j)-x1(j)+1)-sp(1); % 9-Sistolic pulse amplitude
    h.param(j,10) = sp(x4(j)-x1(j)+1)-sp(1); % 10-Diastolic pulse amplitude
end
h.param(:,11) = h.param(:,10)./h.param(:,9); % 11-Reflection index
h.param(:,12) = ba; % 12-parameter b/a (2nd derivative)
h.param(:,13) = ca; % 13-parameter c/a (2nd derivative)
h.param(:,2) = diff(t(x1)); % 2-Pulse durations
x1 = x1(1:end-1);
h.param(:,1) = t(x1); % 1-Feet time
h.param(:,3) = t(x2)-t(x1); % 3-Max Ejection time
h.param(:,4) = t(x3)-t(x1); % 4-Sistolic peak time
h.param(:,5) = t(x4)-t(x1); % 5-Diastolic peak time

```



```

h.param(:,6) = t(x4)-t(x3); % 6-Sistolic/Diastolic peak shift
h.param(:,7) = H./(t(x4)-t(x3)); % 7-Stiffness index (SI)

```

```

par = h.param(:,1+get(h.parameter,'Value'));
set(h.plot8(1),'XData',t(x1),'YData',par);
set(h.axes8,'YLim',mean(par)+3*(std(par)+eps)*[-1 1]);
drawnow

```

```

function h = parameters2(h)

```

```

% Parameters evaluated from all channels -----
x1 = h.peaks{1}(:,1); x1 = x1(1:end-1);
x2 = h.peaks{2}(:,1); x2 = x2(1:end-1);
x3 = h.peaks{3}(:,1); x3 = x3(1:end-1);
if length(x1)~=length(x2)||length(x1)~=length(x3)
    set(h.ch_txt,'String','Signal is too bad[4] Please change
conditions!');
    drawnow
    return
end
h.param(:,14) = x2-x1; % 14-pulse wave transit time 1->2
h.param(:,15) = x3-x2; % 15-pulse wave transit time 2->3
h.param(:,16) = x3-x1; % 16-pulse wave transit time 1->3

t = h.data(:,1);
par = h.param(:,1+get(h.parameter,'Value'));
set(h.plot8(1),'XData',t(x1),'YData',par);
set(h.axes8,'YLim',mean(par)+3*(std(par)+eps)*[-1 1]);
drawnow

```

```

function h = parameters2(h)

```

```

% Parameters evaluated from all channels -----
x1 = h.peaks{1}(:,1); x1 = x1(1:end-1);
x2 = h.peaks{2}(:,1); x2 = x2(1:end-1);
x3 = h.peaks{3}(:,1); x3 = x3(1:end-1);
if length(x1)~=length(x2)||length(x1)~=length(x3)
    set(h.ch_txt,'String','Signal is too bad[4] Please change
conditions!');
    drawnow
    return
end
h.param(:,14) = x2-x1; % 14-pulse wave transit time 1->2
h.param(:,15) = x3-x2; % 15-pulse wave transit time 2->3
h.param(:,16) = x3-x1; % 16-pulse wave transit time 1->3

t = h.data(:,1);
par = h.param(:,1+get(h.parameter,'Value'));
set(h.plot8(1),'XData',t(x1),'YData',par);
set(h.axes8,'YLim',mean(par)+3*(std(par)+eps)*[-1 1]);
drawnow

```

```

function h = ppg_feet(h,ch)

```

```

set(h.ch_txt,'String','Calculating...'); drawnow
sr = 1/diff(h.Data(1:2,1));

```

```

t = h.data(:,1);

% -----
% Smoothing signal using Savitsky-Golay filter
sm1 = 5+2*fix(sr/10*h.sm(ch,1));
set(h.smooth1, 'Value', h.sm(h.ch,1));
set(h.smooth1_val, 'String', num2str(fix(sm1)));
p = sgolayfilt(h.data(:,ch+1),3,sm1);

% Derivatives of signal and smoothed versions
k = 1.875*1e-2; % design filter
b = [1 1 0]; a = [1 -.7265 0]; % for sample rate 1000 Hz
sm2 = fix(20*h.sm(ch,2));
set(h.smooth2, 'Value', h.sm(h.ch,2));
set(h.smooth2_val, 'String', num2str(fix(sm2)));
sm3 = fix(20*h.sm(ch,3));
set(h.smooth3, 'Value', h.sm(h.ch,3));
set(h.smooth3_val, 'String', num2str(fix(sm3)));
% -----
dp1 = gradient(p); % 1st derivative
f = dp1;
for i = 1: sm2
    f = k*filtfilt(b,a,f);
end
dp1s = f;
%
dp2 = gradient(dp1s); % 2nd derivative
f = dp2;
for i = 1: sm3
    f = k*filtfilt(b,a,f);
end
dp2s = f;
% -----

% -----
% find reference to feet by standard deviation of dp/dt
st = 1*std(dp1s);
dx0 = fix(sr/12); % Initial foot-> SD time shift
x1 = find(dp1s(1:end-dx0-1)<0 & dp1s(2:end-dx0)>0 & dp1s(2+dx0:end)>st);
N = length(x1);
x2 = zeros(N-1,1); x3 = zeros(N-1,1); x4 = zeros(N-1,1);
v = zeros(N-1,1); ba = zeros(N-1,1); ca = zeros(N-1,1);

if get(h.feet_method, 'Value')==1
for i = 1: N-1
    [z,ind] = max(dp2s(x1(i):x1(i)+100));
    x1(i) = x1(i)+ind;
end
end

dx1 = fix(sr/55); % Initial foot-> sistolic time shift
%dx3 = fix(sr/3); % Initial diastolic->sistolic time shift
dx3 = 0; % Initial diastolic->sistolic time shift
for i = 1: N-1
    % sistolic peaks
    ind = find(dp1s(x1(i)+dx1:x1(i+1))<0,1, 'first');
    x3(i) = x1(i)+dx1+ind;
    % max ejection velocity
    [v(i),ind] = max(dp1s(x1(i):x3(i)));

```

```

    x2(i) = x1(i)-1+ind;
    % diastolic peaks
    ind = find(dp2s(x3(i)+dx3:x1(i+1)-1)>0 &
dp2s(x3(i)+dx3+1:x1(i+1))<0,1,'first');
    if isempty(ind)==1
        set(h.ch_txt,'String','Signal is too bad[2] Please change
conditions!'); drawnow
    return
    end
    x4(i) = x3(i)+dx3+ind;
    if dp1s(x4(i))>0
        ind = find(dp1s(x4(i):x1(i+1)-1)>0 &
dp1s(x4(i)+1:x1(i+1))<0,1,'first');
        x4(i) = x4(i)-1+ind;
    end
    % 2nd derivative parameters "b/a", "c/a"
    ba(i) = -min(dp2s(x1(i):x1(i+1)))/max(dp2s(x1(i):x1(i+1)));
    ca(i) = max(dp2s(x3(i):x1(i+1)-1))/max(dp2s(x1(i):x1(i+1)));
end

% draw graphs
switch ch
case 1
    set(h.plot1(3),'XData',t,'YData',p);
    set(h.plot1(4),'XData',t(x1),'YData',p(x1));
    set(h.plot1(5),'XData',t(x2),'YData',p(x2));
    set(h.plot1(6),'XData',t(x3),'YData',p(x3));
    set(h.plot1(7),'XData',t(x4),'YData',p(x4));
    set(h.axes1,'Color',[1 1 1]);
    set(h.axes2,'Color',[.9 .9 .9]);
    set(h.axes3,'Color',[.9 .9 .9]);
case 2
    set(h.plot2(3),'XData',t,'YData',p);
    set(h.plot2(4),'XData',t(x1),'YData',p(x1));
    set(h.plot2(5),'XData',t(x2),'YData',p(x2));
    set(h.plot2(6),'XData',t(x3),'YData',p(x3));
    set(h.plot2(7),'XData',t(x4),'YData',p(x4));
    set(h.axes1,'Color',[.9 .9 .9]);
    set(h.axes2,'Color',[1 1 1]);
    set(h.axes3,'Color',[.9 .9 .9]);
case 3
    set(h.plot3(3),'XData',t,'YData',p);
    set(h.plot3(4),'XData',t(x1),'YData',p(x1));
    set(h.plot3(5),'XData',t(x2),'YData',p(x2));
    set(h.plot3(6),'XData',t(x3),'YData',p(x3));
    set(h.plot3(7),'XData',t(x4),'YData',p(x4));
    set(h.axes1,'Color',[.9 .9 .9]);
    set(h.axes2,'Color',[.9 .9 .9]);
    set(h.axes3,'Color',[1 1 1]);
end

set(h.plot6(1),'XData',t,'YData',dp1);
set(h.plot6(2),'XData',t,'YData',dp1s);
set(h.plot6(3),'XData',t(x1),'YData',dp1s(x1));
set(h.plot6(4),'XData',t(x2),'YData',dp1s(x2));
set(h.plot6(5),'XData',t(x3),'YData',dp1s(x3));
set(h.plot6(6),'XData',t(x4),'YData',dp1s(x4));
set(h.plot6(7),'XData',[0 t(end)],'YData',[0 0]);
set(h.plot6(9),'XData',[0 t(end)],'YData',[st st]);
set(h.plot6(10),'XData',t(x1+dx0),'YData',dp1s(x1+dx0));
set(h.axes6,'YLim',[min(dp1) max(dp1)]);

```

```

set(h.plot7(1), 'XData', t, 'YData', dp2);
set(h.plot7(2), 'XData', t, 'YData', dp2s);
set(h.plot7(7), 'XData', [0 t(end)], 'YData', [0 0]);
set(h.axes7, 'YLim', [min(dp2) max(dp2)]);
set(h.ch_txt, 'String', ['Channel: ' num2str(ch)]);
set(h.beats_txt, 'String', [num2str(N) ' beats']);
drawnow

% -----

h.peaks{ch} = [x1,[x2;0],[x3;0],[x4;0],[v;0],[ba;0],[ca;0]]; % pulse param
% -----

h = parameters(h, ch); % calculate parameters

function h = ppg_window(h)
clc
% Selecting of window of data
ax = get(gcf, 'CurrentAxes');
X = get(ax, 'Xlim'); h.X = X;
sr = 1/diff(h.Data(1:2,1));
xmin = fix(sr*X(1)); xmax = fix(sr*X(2));

if xmax-xmin >= 80000
    xmax = xmin+80000;
end

t = h.Data(xmin:xmax,1);
N = length(t);

h.data = zeros(N,4);
h.data(:,1) = t; % the time window
p = zeros(N,4); % for wavelet (4?)
p(:,1:3) = h.Data(xmin:xmax,2:4); % the signal window

% Denoising signal using wavelet decomposition
level = 5; wname = 'sym4'; tptra = 'sqtwolog'; sorh = 's';
npc_app = 4; npc_fin = 4;
ps = wmulden(p, level, wname, npc_app, npc_fin, tptra, sorh);
h.data(:,2:4) = ps(:,1:3);

set(h.plot1(2), 'XData', t, 'YData', p(:,1));
set(h.plot2(2), 'XData', t, 'YData', p(:,2));
set(h.plot3(2), 'XData', t, 'YData', p(:,3));
set(h.plot1(3), 'XData', t, 'YData', h.data(:,2));
set(h.plot2(3), 'XData', t, 'YData', h.data(:,3));
set(h.plot3(3), 'XData', t, 'YData', h.data(:,4));
set(h.plot4(4), 'XData', [X(1) X(1)], 'YData', [-100000 100000]);
set(h.plot4(5), 'XData', [X(2) X(2)], 'YData', [-100000 100000]);

set(h.axes1, 'XLim', [t(1) t(end)], 'YLim', [min(p(:,1)) max(p(:,1))]);
set(h.axes2, 'XLim', [t(1) t(end)], 'YLim', [min(p(:,2)) max(p(:,2))]);
set(h.axes3, 'XLim', [t(1) t(end)], 'YLim', [min(p(:,3))-eps
max(p(:,3))+eps]);
set(h.axes6, 'XLim', [t(1) t(end)]);
set(h.axes7, 'XLim', [t(1) t(end)]);
set(h.axes8, 'XLim', [t(1) t(end)]);
drawnow

```

```

function h = initialize(h)

h.mouseflag = 0;
h.xd = .5*ones(2,3);
h.dxd = .08;
h.peaks = cell(3,1);
h.sm = [.5 .05 .05; .5 .05 .05; .5 .05 .05];
h.err = 1;

for j = 1: 6
h.param_all{j} = [];
end
h.sd = [0 0 0];

% Set graphs
h.plot1 = plot(h.axes1, 0,0,'m-', 0,0,'m-', 0,0,'k-', 0,0,'b.', 0,0,'b.',
0,0,'b.', 0,0,'b.', 0,0,'k-.');
h.plot2 = plot(h.axes2, 0,0,'m-', 0,0,'m-', 0,0,'k-', 0,0,'b.', 0,0,'b.',
0,0,'b.', 0,0,'b.', 0,0,'k-.');
h.plot3 = plot(h.axes3, 0,0,'m-', 0,0,'m-', 0,0,'k-', 0,0,'b.', 0,0,'b.',
0,0,'b.', 0,0,'b.', 0,0,'k-.');
h.plot4 = plot(h.axes4, 0,0,'b-', 0,0,'g-', 0,0,'r-', 0,0,'k-', 0,0,'k-',
0,0,'k-', 0,0,'m-', 0,0,'m-');
set(h.plot4,'LineWidth',2);
% Single beats
h.plot5 = plot(h.axes5, 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-'
...
, 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-',
0,0,'b-' ...
, 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-',
0,0,'b-' ...
, 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-',
0,0,'b-' ...
, 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-',
0,0,'b-' ...
, 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-',
0,0,'b-' ...
, 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-',
0,0,'b-' ...
, 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-',
0,0,'b-' ...
, 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-',
0,0,'b-' ...
, 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-',
0,0,'b-' ...
, 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-', 0,0,'b-',
0,0,'b-' ...
, [.5 .5],[0 10000],'r--', [.5 .5],[0 10000],'r--');
% derivatives
h.plot6 = plot(h.axes6, 0,0,'g-', 0,0,'k-', 0,0,'b.', 0,0,'b.', 0,0,'b.',
0,0,'b.', 0,0,'k--', 0,0,'k-', 0,0,'g--.', 0,0,'go');
h.plot7 = plot(h.axes7, 0,0,'g-', 0,0,'k-', 0,0,'b.', 0,0,'b.', 0,0,'b.',
0,0,'b.', 0,0,'k--', 0,0,'k-.');
% hemodynamic parameters
h.plot8 = plot(h.axes8, 0,0,'b.-', 0,0,'k-.');

function plot_param(h)

% Plot parameters .....
pid = 1+get(h.parameter,'Value');

```

```

if pid <= 13
    par = h.param_all{h.ch}(:,pid);
    set(h.plot8(1), 'XData', h.param_all{h.ch}(:,1), 'YData', par);
elseif pid==14 || pid==17
    par = h.param_all{4}(:,2+(pid-14)/3);
    set(h.plot8(1), 'XData', h.param_all{4}(:,1), 'YData', par);
elseif pid==15 || pid==18
    par = h.param_all{5}(:,2+(pid-15)/3);
    set(h.plot8(1), 'XData', h.param_all{5}(:,1), 'YData', par);
elseif pid==16 || pid==19
    par = h.param_all{6}(:,2+(pid-16)/3);
    set(h.plot8(1), 'XData', h.param_all{6}(:,1), 'YData', par);
end

set(h.axes8, 'YLim', mean(par)+2*(std(par)+eps)*[-1 1]);
drawnow

```



APPENDIX G

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