THE RELATIONSHIP BETWEEN SONOGRAPHIC PARAMETERS OF BRACHIAL ARTERY AND SMOKING

By

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DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE RADIOLOGY

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Supervisors:

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DEDICATION

I would like to dedicate this thesis to my family and my wife Dr Kokila Rajapathy who has shown an incredible amount of strength and faith in me.

ACKNOWLEDGEMENT

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMNS

CVD	Cardiovascular disease
CAD	Coronary artery disease
CHD	Coronary heart disease
WHO	World Health Organization
DM	Diabetic mellitus
IMT	Intima-media thickness
RI	Resistive index
PSV	Peak systolic velocity
SD	Standard deviation
IQR	Inter-quartile range
HUSM	Hospital Universiti Sains Malaysia.
CT-Scan	Computed-tomography scan
MRI	Magnetic resonance imaging

ABSTRAK

Tajuk: **Hubungan antara Parameter Sonografi daripada Arteri Brakial dan Merokok**

Latar Belakang

Perubahan dalam struktur arteri brachial seperti penambahan ketebalan initima-media (IMT) telah menunjukkan perkaitan dengan proses perkembangan aterosklerosis. Perubahan ini akan membawa kepada hakikat manifestasi penyakit vaskular jantung seperti penyakit arteri koronari dan strok, yang telah menyebab 17.3 juta kes kematian di seluruh dunia, sama ada di negara yang maju ataupun yang sedang membangun. Jumlah kes kematian akan terus meningkat jika langkah pencegahan tidak diambil untuk mengawal faktor-faktor yang berkaitan dengan aterosklerosis. Sonografi resolusi tinggi telah menunjuk kebaikannya sebagai alat klinikal tidak invasif dan bebas radiasi dalam pengukuran IMT arteri. Nilai IMT ini dapat yang memberi gambaran secara keseluruhan kepada perkembangan aterosklerosis dalam kalangan kumpulan berisiko tinggi termasuk perokok.

Objektif

Kajian ini bertujuan untuk menentukan perkaitan antara parameter sonografi arteri brachial dan merokok.

Kaedah/Metodologi

Resolusi tinggi ultrasonografi telah digunakan untuk memeriksa arteri brachial dalam kalangan perokok dan bukan perokok yang terdiri daripada kakitangan Hospital

Universiti Sains Malaysia. Arteri brachial diimbas di bahagian lekuk antecubital dengan posisi membujur. Imej optimum arteri brachial boleh diperolehi pada lokasi kira-kira 5-10 cm di atas lipatan antecubital. Lokasi ini ditandai, dan semua imej berikutnya diperolehi di lokasi yang sama. Bahagian dinding jauh IMT diukur secara langsung di jarak antara lumen-Intima dengan media-adventitiadi bahagian distal daripada brachial (5-10cm di atas lipatan siku). Pengukuran halaju sistolik puncak (PSV) dan indeks rintangan (RI) diambil dengan sonografi Doppler pada sudut <60°.

Keputusan

Sejumlah 45 kakitangan Hospital Universiti Sains Malaysia (HUSM) telah menawarkan diri untuk mengambil bahagian dalam kajian ini. Antara peserta kajian in, 20 (44.4%) daripada mereka adalah perokok manakala 25 (55.6%) daripada mereka tidak merokok. Purata ketebalan media intimal adalah 0.36 ± 0.01 mm untuk perokok dan 0.30 ± 0.01 mm untuk bukan perokok. Purata PSV untuk perokok adalah $57.50 \pm 14,79$ cm/saat dan $48,94 \pm 5.19$ cm/saat bagi peserta yang tidak merokok. Purata RI adalah 0.90 ± 0.03 untuk perokok dan 0.85 ± 0.13 untuk peserta bukan perokok. Terdapat perbezaan yang ketara untuk IMT dan RI antara perokok dan bukan perokok (p<0.01), tetapi bukannya nilai PSV. Di antara kedua-dua pemboleh ubah ini, hanya nilai IMT menunjukkan perkaitan dan regresi yang signifikan dengan tempoh merokok dalam kalangan perokok(r=0.754; r^2=0.568, p<0.01).

Kesimpulan

Kajian ini mendapati penambahan ketebalan IMT adalah ketara dalam kalangan perokok berbanding peserta bukan perokok dalam kalangan kakitangan HUSM. Ini mencadangkan potensi penggunaan sonografi resolusi tinggi dalam pengimejan IMT

dalam kalangan perokok, yang merupakan kumpulan berisiko tinggi untuk aterosklerosis.

ABSTRACT

Title: **The Relationship between Sonographic Parameters of Brachial Artery and Smoking**

Background

Anatomical changes in brachial artery like thickening of initima-media thickness (IMT) has shown to significantly associated with progression of atherosclerosis. This changes will ultimately lead to manifestation of cardiac vascular disease like coronary artery disease and stroke, which causes 17.3 millions of death cases worldwide, in both developed and developing countries. The number of death cases will continue to increase if preventive measure is not taken to control the risk factors associated with the atherosclerosis. The high-resolution sonography has shown to be a non-invasive and radiation-free clinical tools in measuring IMT value of artery, which provide insight to the progression of atherosclerosis in high risk group including smokers.

Aim and Objective

The present study aimed to determine the association between sonography parameters of the brachial artery and smoking.

Method

High resolution ultrasonography was used to examine the brachial artery among smoker and non-smokers, which recruited from the staff of Hospital Universiti Sains Malaysia. The brachial artery is scanned in the antecubital fossa in a longitudinal fashion. Optimal brachial artery images were obtained at about 5-10 cm above the antecubital crease.

This location was marked, and all subsequent images were obtained at the same location. The IMT at the far wall is measured directly as the distance between the lumen-intima and media-adventitia border at the distal portions of the brachial (5-10cm above elbow). Measurement of PSV and RI are taken. Doppler angle is keep at $<60^{\circ}$.

Result

There were 45 staff of Hospital Universiti Sains Malaysia (HUSM) volunteered to participate in this study. Among these participants, 20 (44.4%) of them were smokers while 25 (55.6%) of them were non-smokers. The mean of the intimal media thickness is 0.36±0.01 mm for smokers and 0.30±0.01 mm for non-smokers. The mean of the peak systolic velocity is 57.50±14.79 cm/sec for smokers and 48.94±5.19 cm/sec for non-smokers. The mean of the resistive index is 0.90±0.03 for smokers and 0.85±0.13 for non-smokers. There is significant difference of brachial artery intimal media thickness and resistive index between smokers and non-smokers ($p<0.01$), but not the peak systolic value. Among the two significant variables, only intimal media thickness and duration of smoking showed significant correlation and regression ($r=0.754$; $r^2=0.568$, $p<0.01$).

Conclusion

The present study revealed significant thickening of IMT in smokers compared to non-smokers among HUSM staff. This suggested the application of high resolution ultrasonography in screening of IMT among smokers, which is consider as high risk group for atherosclerosis.

SECTION ONE

INTRODUCTION

SECTION 1

INTRODUCTION

1.1 Background of the Study

Coronary artery disease (CAD) is the major cause of death in the world. According to World Health Organization (WHO) estimates, in 2008 around 17.3 million people died of CVD, which indicates about 30% of global deaths (Mendis et al., 2011). Majority of the incidence were attribute to coronary artery disease (CAD) and stroke. The incidence of CAD in Malaysia is around 141 per 100,000 population (Azman and K.H., 2006, Wan-Azman Wan-Ahmad and Sim, 2013). CAD and stroke is a slow progressing chronic disease, which may remain silent for years, eventually lead to myocardial infarction, and sudden death. About half of all sudden deaths are reported to be due to undiagnosed heart disease, and two-thirds of these patients died before reaching the hospital (Enas and Kannan, 2005).

Atherosclerosis is the principal cause for both CAD and stroke. The disease is also known as slowly progressive chronic inflammatory vascular disease. It initiated post event of minor endothelial damage, and slowly progress throughout the lifetime (Shah, 2010). The rate of progressing varies depending on the risk exposure in an individual like smoking, hypertension, hyperlipidemia, physical inactivity, and diabetic mellitus. It occurs in the intimal layer of the arterial wall which thickens with time as the disease progresses. On the contrary to this, the medial layer of the artery does not thicken significantly as compared to the intimal layer. Therefore, an imaging modality like an ultrasound examination that is capable of measuring the intimal thickness is useful for prediction of cardiovascular risk (de Korte et al., 2011).

Much interest has been focused on both noninvasive and minimally invasive detection and measurement of early atherosclerosis, for the use in presymptomatic diagnosis and studies of the disease progression and regression (Crouse and Thompson, 1993). As the coronary circulation is difficult to study noninvasively, other means of determining the morphological and functional changes in early atherosclerosis can be obtained by measuring the brachial artery intimal media thickness (IMT), peak systolic velocity (PSV) and resistive index (RI), which can be detected using high resolution ultrasound B mode imaging (Bai et al., 2007, Iwamoto et al., 2012)

Atherosclerosis is a systemic artery disease which commonly affects large and medium-sized arteries. It initiates with thickening of the IMT and slowly loss of elasticity, eventually end up with atherothrombotic disease (Lahoz and Mostaza, 2007). Studies has shown significant association between CAD and structural changing in arteries, which include brachial, carotid, coronary and radial arteries. The most establish parameter was the association between carotid IMT and CAD. Carotid IMT has been used as clinical predictor for risk stratification of CAD. Studies has also shown significant association between brachial artery with the presence and severity of coronary and carotid atherosclerosis with a correlation coefficient of 0.4 to 0.7. The degree of association was the highest among younger adult. In older adult, the lesion are usually in advanced stage, and it showed higher prevalence in coronary artery, while advanced lesion is rarely found in brachial artery (Sorensen et al., 1997).

On the other hand, study has also revealed significant association between the brachial artery and the left anterior descending coronary artery ($r = 0.54$, $p = 0.002$). These findings support the use of brachial artery studies to enhance our understanding

of early atherogenesis, and even as surrogate markers for atherosclerosis in the other major systemic arteries (Sorensen et al., 1997). Morphological change of the brachial artery is associated with the extent of coronary artery stenosis and atherosclerotic wall changes in the carotid arteries in CAD patients. These indicate the potential of brachial artery IMT in the diagnostic and prognostic evaluation of patients with suspected CAD (Montalcini et al., 2012). Incidence of CAD increases in relation to the increase in brachial IMT. In addition, brachial IMT is positively related to Framingham risk score, which is a risk calculator and an index of cumulative cardiovascular risk commonly used for assessing the probability of myocardial infarction or death from heart disease within 10 years. Therefore brachial IMT is helpful for estimation of the extent of atherosclerosis and for risk stratification of patients with cardiovascular risk factors (Iwamoto et al., 2012).

Non-invasive technology for direct imaging of artery is useful for monitoring of structural changes in follow up study. It can be performed repeatedly without expose to invasive and radiation risk. Ultrasound examinations of brachial artery have been increasingly used for the non-invasive assessment of early atherosclerotic changes including functional, morphological, and mechanical properties. The brachial artery offers the opportunity to perform all of these non-invasive measurements in one single examination session. Besides, it is relatively more convenient to perform ultrasound on brachial artery, compared to carotid, coronary, and femoral artery, as the patient is only required to be positioned at sitting rest position.

Cigarette smoking is well established as a major risk factor for CAD. According to WHO estimation, there are around 1.1 thousand million smokers in the world, which

is approximately one third of the global population whom are aged 15 years and over (WHO, 2008). The 2006 Malaysia National Health & Morbidity Survey showed that 21.5% of Malaysian adults smoke. 49% of all adult males and 5% of all adult females are now current smokers. Today there are about 5 million smokers in Malaysia, each an average of 14 cigarettes per day according to Tobacco CPG Malaysia 2003 (IPH, 2012). Smokers have a 2-4 fold increase in the incidence of coronary heart disease and sudden death (O'quin, 2012). Active smoking was found to play a major role in the progression of atherosclerosis, as did the duration of smoking measured by pack-years of exposure (Howard et al., 1998).

Generally, clinicians have difficulty in convincing smokers to quit smoking. This is due to the physical- and psycho-addictive effect of smoking. Clinician can make a relatively more firmed statement to persuade an individual to stop smoking if evidence is attached. A simple, easy and portable tool that can provide evidence on early atherosclerotic changes in the vessels in someone will definitely increase the motivation to stop smoking. It is easier to explain the correlation smoking to the CAD mortality and morbidity risks if the evidence on endothelium changes can be provided instantly.

In conclusion, it is very crucial to screen the smokers to predict the CAD risk in a noninvasive, radiation free and low cost method by ultrasound. The early identification of individuals at of high cardiovascular risk and those with atherosclerosis is paramount to successful prevention treatment.

SECTION TWO

LITERATURE REVIEW

SECTION 2

LITERATURE RIVIEW

2.1   Cardiac Vascular Disease

Cardiovascular diseases (CVDs) is a major cause of death worldwide affecting people in developing and developed countries. It caused by the dysfunction of blood vessels supplying the heart muscles. In 2008, an estimation of 17.3 million people died from CVDs, which account for 30% of global deaths. Coronary artery disease and stroke is the two major manifestations of CVDs, which caused 7.3 million and 6.2 million of death, respectively. The number of death due to these two manifestations is estimated to reach 23.3 million by 2030 (Alwan, 2011, Mathers and Loncar, 2006).

About 300 risk factors associated with CAD and stroke have been studied, but only those meet the following criteria are considered as major risk factor: (i) a high prevalence in many populations; (ii) show significant independent impact on the CAD and stroke; and (iii) the incidence of CAD and stroke show reduction in response to the treatment and control of the respective risk factor. These risk factors are characterized into modifiable and non-modifiable risk factors (Table 2.1). According to WHO report, at least one third of all CVD cases in the world is associated with the five main risk factors, which are tobacco use, alcohol use, high blood pressure, high cholesterol and obesity (Mendis et al., 2011, Wilson, 1994). Study has shown that people with CVD risk factors-free at younger-middle age have lower probability of age-related CVD risk, as well as other non-communicable disease, and subsequently have longer life-expectancy (Lloyd-Jones et al., 1999). This will lead to reduce in cost of gerontological care during late life-time (Moarreaf, 2004).

Table 2.1   Major risk factors for cardiovascular disease

Risk Factor	Impact
(a) Major modifiable risk factors	
High Blood Pressure	Hypertension is also a major risk for heart attack and the most important risk factor for stroke (Diamond and Phillips, 2005, Vidt and Prisant, 2005). Chronically increase in blood pressure increase the workload of the heart and pressurize vascular system as well. About 90% of the hypertension is attributed to essential hypertension, while the remaining is attributed to secondary hypertension. Framingham Study has revealed hypertension accounts for about one quarter of heart failure cases (Kannel and Cobb, 1992), especially among the elderly from which hypertension accounts for as high as 68% of the heart failure cases. Men are at two times risk of developing heart failure as compared to women among the patients with hypertension.
Abnormal Blood Lipids	Studies revealed that high total cholesterol, LDL-cholesterol and triglyceride levels, and low levels of HDL-cholesterol increase risk of coronary heart disease and ischemic stroke (Mendis et al., 2011).
Tobacco Use	Cigarette smoking is still the major modifiable risk factor of CVD. Increases risks of cardiovascular disease, especially in people who started young, and heavy smokers (Ambrose and Barua, 2004). Over 4,000 substances has been identified in cigarette smoke, some of the chemicals are toxic, mutagenic, carcinogenic, and pharmacologically active. In the aspect of CVD, cigarette smoking can alter the normal physiological structure and function of blood vessels (Rahman and Laher, 2007), raise blood pressure (Al-Safi, 2005), and unhealthy cholesterol levels (Bernaards et al., 2005). Smoking also reduces efficiency of oxygen delivery to body tissues (Jensen et al., 1991). Besides, passive smoking is also exposed to the risk of CVD (Celermajer et al., 1996).
Physical Inactivity	According to WHO report, physical inactivity can increases risk of heart disease and stroke by 50%. Active lifestyle has been a preventative policies for CVD among individuals of all ages (Mendis et al., 2011, O'Donnell and Elosua, 2008).
Obesity	Obesity is one of the major risk factors for coronary heart disease and diabetes (Mendis et al., 2011). The higher degree of obesity associated the higher chances of developing the antecedents of atherosclerosis such as high blood pressure and diabetes, consequently increase the probability of developing heart disease. Obese aspect alone can cause extra 30% likelihood of getting heart disease. The commonly found obese patterns among male and female are fat accumulation around belly (apple shape) and hip (pear shape), respectively (Zaret et al., 1992).
Unhealthy Diets	Low fruit and vegetable intake is estimated to cause about 31% of coronary heart disease (He et al., 2007, Bhupathiraju and Tucker, 2011) and 11% of stroke (He et al., 2006) worldwide; high saturated fat intake increases the risk of heart disease and stroke through its effect on blood

Risk Factor	Impact
	lipids and thrombosis (Mendis et al., 2011).
Diabetic Mellitus	DM is a metabolic syndrome that post major risk for coronary heart disease and stroke (Zaret et al., 1992). Hypertension is at two fold prevalence among the diabetic patient than the non-diabetic patient. Study by Sowers et al. (2001) revealed DM patient prone to develop hypertension and consequently make CVD as the major cause of mortality among the patient. Thus a suggestion of maintaining blood pressure below 130/85 mm Hg might reduce or delay the death outcome. Type 2 DM patient during and after middle age without history of CAD are carrying equivalent risk to patient of non-DM with history of CAD, thus DM patient can be identify as high risk group for CAD (Haffner et al., 1998).
(b) Other modifiable risk factors	
Low socioeconomic status	Socioeconomic status (SES) is a strong determining factor for CAD incidence and outcomes. There is established negative relationship between CAD and SES (as defined by occupational position, income, education, etc.). SES often associated with other CVD risk such as unhealthy lifestyle and chronic psychosocial stress (Mendis et al., 2011, Strike and Steptoe, 2004).
Mental ill-health	Depression is three times more prevalence among patients with CAD than controls (Strike and Steptoe, 2004). Depression enhance the development of CAD through both behavioral and biological pathways. Depression might promote other unhealthy lifestyle habits that increase CAD risk, like smoking, unhealthy diet and physical inactivity. Depression also impose stress on body physiology, such as activation of immune system, hyperactivity of physiological stress system (e.g. hypothalamic pituitary adrenal axis), etc. (O'Donnell and Elosua, 2008, Mendis et al., 2011).
Psychosocial stress	Chronic life stress, social isolation and anxiety increase the risk of heart disease and stroke. Most studies revealed positive correlation between work stress and CAD, among the blue- or white-colar employee; and among both men and women. Stoke is more common among patients with CAD than the controls (Strike and Steptoe, 2004, Mendis et al., 2011).
Alcohol use	One to two drinks of alcohol per day may lead to a 30% reduction in heart disease including CAD and atherosclerosis. The mechanism of alcohol intake increase HDL cholesterol, protective agent against CVD, remained under-discovered. However, heavy alcohol consumption, four or more drinks per day can have harmful effects on the body. It raises blood pressure, causes significant liver damage, central nervous system complications, damages the heart muscle, etc (Mendis et al., 2011, Zaret et al., 1992).
Use of certain medication	Some oral contraceptives and hormone replacement therapy increase risk of heart (Mendis et al., 2011).
Lipoprotein	High LDL-cholesterol level interfere with the normal blood clot lysis

Risk Factor	Impact
	(dissolving) effect, formed clot unlikely to reduce in size, thus increase the risk for CVD, especially indicated in CAD and stroke (Mendis et al., 2011, Zaret et al., 1992).
Left ventricular hypertrophy	It is a powerful marker of cardiovascular death (Mendis et al., 2011). Left ventricle of heart plays role in pumping blood to all body compartment, except lung compartment. Changing in anatomical structure of left ventricle can alter normal physiological function of the heart. It can lead to heart failure, arrhythmias, and sudden death (Zaret et al., 1992).
(c) Non-modifiable risk factors	
Advancing age	Age is the most powerful independent risk factor for CVD. The progression of plaque formation is continued either in fast or slow pace in relation to individual genetic or lifestyle factors (NHLBI, 2014). Sign and symptom onset as the plaque built up to significant size that disturbed normal vascular function. The risk for CVD increase as age increased corresponding to the progressing of plaque built up. The risk is significantly increased in men after age 45 and in women after age 55. The risk of stroke doubles every decade after age 55 (Keller and Fleury, 1999).
Heredity or family history	CAD shows as high trend of family inherited disease (Keller and Fleury, 1999). According to WHO atlas of CVD, an individual will have increased risk of CVD if a first-degree blood relative has had coronary heart disease or stroke before the age of 55 years for a male relative, or 65 years for a female relative (Mendis et al., 2011). Both environment and genetic factors play role as contributing agent to CVD in a family. The established genetic factors like hyperlipidemia and increase blood fibrinogen level, has been identified through animal and human clinical studies (Keller and Fleury, 1999).
Gender	Men are at higher risk of CVD than women at all ages (Wilson et al., 1998, Keller and Fleury, 1999). However, observational studies has revealed that incidence of morbidity and mortality caused by CVD increased in women after menopause and at the same ratio as in men (Antonicelli et al., 2008). This is due to detrimental effect of estrogen withdrawal on cardiovascular function and body metabolism, like changes in body fat distribution from a gynoid to an android pattern, reduced glucose tolerance, abnormal plasma lipids, increased blood pressure, increased sympathetic tone, endothelial dysfunction and vascular inflammation.
Ethnicity or race	Increased stroke noted for Blacks, some Hispanic Americans, Chinese, and Japanese populations. Increased cardiovascular disease deaths noted for South Asians and American Blacks in comparison with Whites (Winkleby et al., 1999, Liebson, 2009).
(d) "Novel" risk factors	
Excess homocysteine in	Elevated homocysteine level is directly associated increase risk for CVD. Hyperhomocysteinemia is known to be related to depressive

Risk Factor	Impact
blood	symptoms, as plasma homocysteine levels are elevated during hostility and anger (Strike and Steptoe, 2004, Mendis et al., 2011).
Inflammation	Atherosclerosis, the antecedent for CAD and stroke is actually progressing through a continuous inflammatory response, and end up with thrombotic complication. Increase of inflammatory markers are associated with increased cardiovascular risk, such as elevated C-reactive protein (CRP) during low-grade chronic inflammation (Mendis et al., 2011, Libby et al., 2002).
Abnormal blood coagulation	Elevated serum fibrinogen, or other component of blood clotting cascade, increase the risk for CVD. Fibrinogen level elevates as aging progressed (Mendis et al., 2011, Zaret et al., 1992).

2.2   Arteriosclerosis

Arteriosclerosis is a chronic systemic disease that affects most major arteries of cardiovascular system. It is characterized by accumulation of lipids, inflammatory cells, and connective tissue within the arterial wall. It is the commonest cause of premature death in the western world. This disease progresses in a silent mode, and first onset manifestation often attributes to sudden cardiac death, stroke or myocardial infarction (Davies et al., 2004). It is the major contributing factor for CAD and stroke (Scannapieco et al., 2003). This disease is commonly been explained as hardening of the arteries. The first detection sign was the histological observation of lipid deposition in the intima endothelial layer. The progressing of the disease in human is started as early as after childhood, which is evidenced by the report on the detection of fatty streaks in aortas of children which aged more than 3 years, and coronary arteries during adolescence (Stary, 1988). The affected arteries become narrowed, weaken and loosen its elasticity. The diameter of the artery reduce, decrease blood flow, which lead to reduced oxygen supply to the body tissues. The narrowing of the lumen is usually caused by slowly formation of plaque that consisting of cholesterol, fatty substances, cellular metabolite waste, calcium deposition and fibrin blood clotting agent. Atherosclerosis development can progress in any artery in human body, such as heart, brain, arms, and kidneys. Any disease could raise up according to the affected organ. Many diseases can be related to atherosclerosis, including coronary heart disease/coronary artery disease, carotid artery disease, peripheral artery disease, stroke and chronic kidney disease.
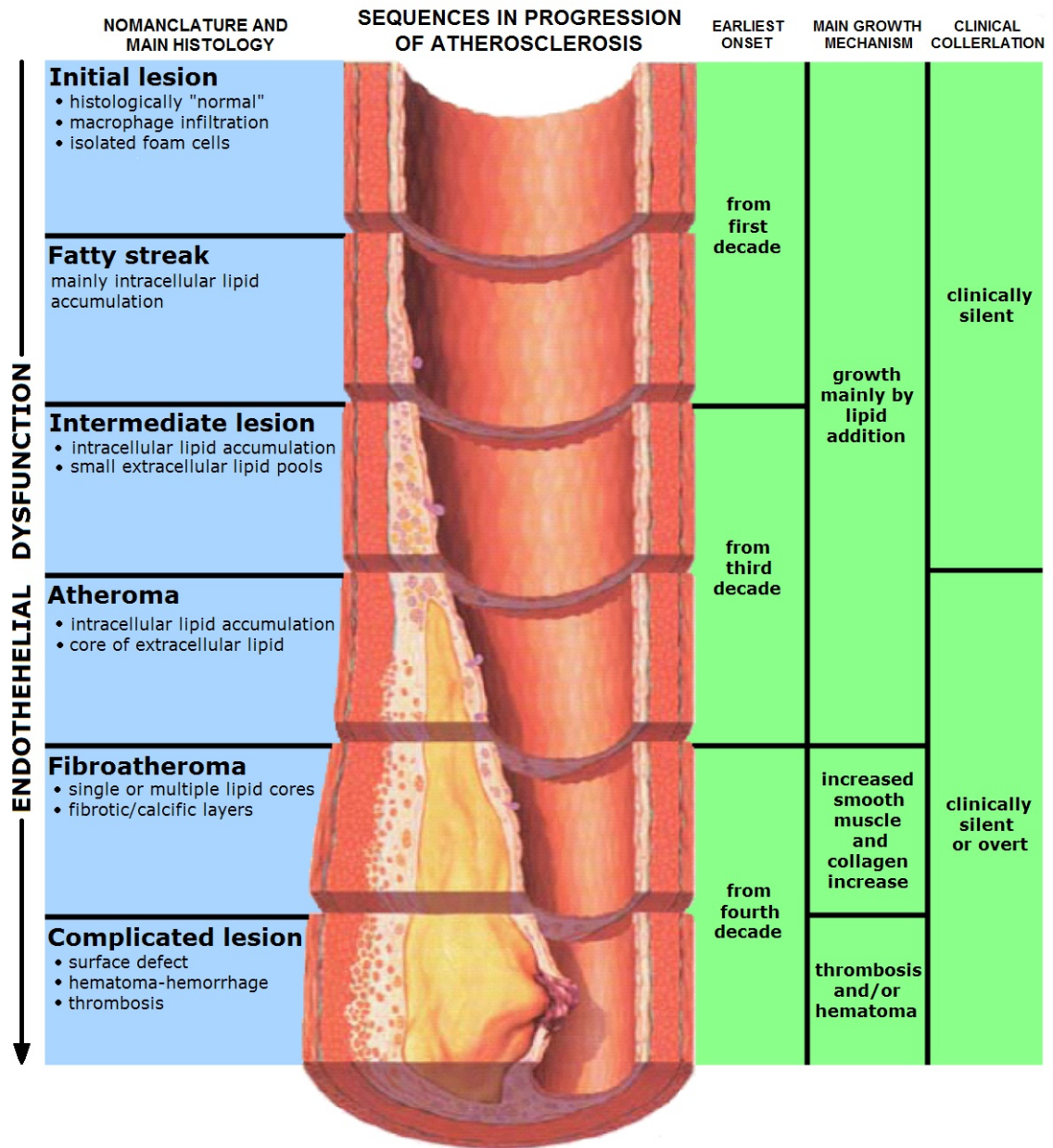
Figure 2.1   Sequential events in development and progression of atherosclerosis

2.3 Diagnosis Tools for Detection of Subclinical Atherosclerosis

There are many established methods for detection or risk evaluation of atherosclerosis among known patient or high risk group. These methods include direct imaging techniques like ultrasound, EBCT scanning, and 64-slice CT angiography; and indirect detection techniques like ultrasonography and monitoring of biomarkers level, e.g. C-reactive protein and homocysteine.

2.3.1 Electron-beam Computed Tomography (EBCT) Scanning

This is one of the methods for direct plaque imaging and evaluation. It help to identify coronary calcification Figure 2.2. It is also useful screening method that can identify individuals at-risk, as well as for monitoring of calcification progressing. To date, invasive angiography is still referred as the gold standard technique for diagnosis of CAD.

Calcium Score	Hazard Ratio	Annual Number and Rate of Coronary Events
0 (n = 3,409)	1	15 (0.10%)
1–100 (n = 1,728)	3.6	39 (0.59%)
101–300 (n = 752)	7.73	41 (1.43%)
>300 (n = 833)	9.67	67 (2.87%)

Note that 90% of all events occurred in subjects with coronary calcification, and nearly 50% of the subjects had no coronary calcification. Adapted from Detrano et al. (24).

Figure 2.2   Standard risk factor-adjusted coronary event rates in 4 racial/ethnic groups of asymptomatic subjects based on coronary calcium score (multi-ethnic study of atherosclerosis

2.3.2 64-slice CT angiography

Multi-slice CT coronary angiography (CTA) enable visualization of the coronary arteries in a complete fashion, including the arterial wall, vessel dimensions and tortuosity, and calcified and non-calcified plaques (Schmermund et al., 2009). This is a

powerful state-of-art direct imaging technique that enable identification of bulky plaque underlying beneath the blood vessel. This is currently the gold standard for diagnosis of CAD. It enables visualization of the arteries structure, incorporate diagnosis and treatment at one time. However, the procedure is invasive in nature. It unable to perform functional assessment of the CAD. There is possibility of bleeding at the access site. It exposes individuals to the risks of anaphylaxis and renal failure due to the contrast agent use. Individuals are also exposed to the radiation dose that equivalent to few hundred times of common chest X-ray. The risk-benefit ratio for a high risk group undergone CT scan is still controversy. However, it is definitely helpful during emergency and life-saving critical moment.

2.3.3   Ultrasonography

Ultrasonography enable imaging procedure been carry out outside of human body. It is at low cost compared with other imaging techniques. The procedure for ultrasound imaging is simple, patient will feel relatively more comfort during the procedure. This procedure is free of any radiation exposure and intravenous injection for improvement of image contrast. To date, no clinical complication was associated with repeatedly use of ultrasonography on an individual. Ultrasonography tools and equipment has been improved to enable ease for screening of CAD associated parameters like IMT, pulse wave velocity and ankle-brachial index.

2.3.4   Blood Biomarkers

Many blood biomarkers has been associated with progression of CAD, such as

- B-type natriuretic peptide (BNP) (Bassan et al., 2005)

- CRP (Danesh et al., 2004)

- Homocysteine (ARNESEN et al., 1995)

- Renin (Unger, 2002)

- Urinary albumin-to-creatinine ratio (Klausen et al., 2004)

Among the listed biomarkers, BNP and the urinary albumin-to-creatinine ratio has shown to be the most informative predicting factor for CAD events.

2.4 Prevalence of Smoking in Malaysia

Smoking is a well-known modifiable risk for prevention of many diseases, such as high blood pressure, atherosclerosis, premature death, abortion, and cancer (WHO, 2008). However, it has become a cultural habit among people in many population, even in Malaysia, in all ages and both gender. It is estimated that ten thousand of death are contributed by the smoking related diseases. According to Malaysian National Health and Morbidity Survey, the prevalence of smoking among adults 18 years old and older is above 20%, which in referred as extremely high. This phenomenon is particularly found among men. Smoking is more prevail among the men with prevalence of 46.4% from the total men; whereas smoking among women is relatively less (~1.6%).

Smoking among the young people has indicated continued high rate of mortality and morbidity related to smoking-related disease (Tachfouti et al., 2014). The 2009 Global Youth Tobacco Survey revealed 19.5% of 13-15 years old youth use some form of tobacco products, with 18.2% smoking cigarettes and 9.5% using other tobacco products. In Malaysia, prevalence of adolescent male cigarette smokers (30.9%) is higher than adolescent female (5.3%). However, the prevalence of 5.3% adolescent

female is much higher than the adult female smokers (1.6%), indicates the possibility of increased smoking prevalence in the future (IPH, 2012).

2.5   Smoking-Related Disease

Smoking is the most preventable and modifiable risk that affect many chronic diseases. It is estimated that 40 thousands of deaths from CVD are related to passive smoking. Immediate determination of smoking cessation can lead to both immediate and long-term benefit. If someone stop smoking before 50 years old, he/she will experience 50% less risk of dying in next 15 years, compared with those who are still active smokers (O'quin, 2012).

Smoking exert direct effect to our respiratory system. It can cause lung cancer, chronic obstructive pulmonary disease (including chronic bronchitis, and emphysema), exacerbates asthma, and chronic bronchitis. Some of the clinical manifestation can be reversed while some cannot be reversed. Emphysema which lead to loss of lung tissue is a permanent effect. Lung tissue are loss at twice rate in smokers than normal people, but these tissue will slowly recover once the smoker quit smoking (Health and Services, 2004).

Smoking is a significant risk for CVD which lead to double risk of developing CAD and 2-4 fold increase in sudden death, compared to non-smokers. Smoking accelerate the aging effect on atherosclerosis development in major body arteries, such as aorta and peripheral arteries, leading to CAD and peripheral vascular disease. It increases the risk of stroke by two time. However, if someone stop smoking, the established risk will reduce to one-half after one year of smoking cessation and

approaching the risk having by the non-smokers at year two (Howard et al., 1998, Bernaards et al., 2005).

Study by Bernaards et al. (2005) revealed the, increased tobacco consumption will lead to reduce in blood pressure, high-density lipoprotein cholesterol (HDL-c), body weight, and waist-to-hip ratio (WHR). Increase in tobacco consumption also lead to increase of ratio between total serum cholesterol and HDL-c. By stopping or reducing tobacco consumption, all the stated abnormal parameters will slowly return to normal range. Both men and women exhibit the similar trend.

2.6   Vascular Screening among Healthy and High Risk Groups

Unconditional screening (angiography, vascular imaging) and preventive interventions (such as lifestyle, medications) of vascular structure and function for everyone is an ideal preventive measure for CAD. This enable early detection of vascular changes during atherosclerosis development. This idea would be practical and ideal if the screening and intervention were both safe, risk-free, affordable, indicates high compliance and sustainable. However, there is no perfect idea present in the real world. Lifestyle improvement, which mean living a disease risk-free and health promoting lifestyle, is significantly effective in reducing disease. Many unseen obstacles like social, cultural, and economic factors need to be overcome to gain the positive outcome from worldwide intervention program.

Non-invasive screening tool is very useful for identifying subclinical atherosclerosis, early vascular impairment and dysfunction (Mullen et al., 1997). These include ultrasonography, coronary calcium score assessment by computed tomography

(CT), non-invasive CT angiography, and magnetic resonance imaging. Each of the stated techniques possess relatively strengths and limitations. Recently, high resolution B-mode ultrasonography has been extensively study for its usefulness in detecting IMT thickening in carotid artery, brachial artery and femoral artery have the potential to be suitable screening tools for the detection of subclinical atherosclerosis. It is a non-invasive tool, simple and relatively inexpensive modality for detection of subclinical atherosclerosis. Beside, this technique is safe, as this procedure does not expose an individual to radiation, which is needed in coronary calcium scanning, and other invasive imaging technique (Shah, 2010).

An effective screening and prevention measure is important for reducing the burden of the disease and cost-of-illness impose to the nation or institution. An individual carrying CVD risk will has reduced in quality of health and quality of life in the late adult. A sudden death of an employee or civilian of an nation will also lead organization or nation lost, subsequently cause reduce in investment (Cahalin et al., 2014). Thus a good CVD screening program would be good in reduce the unseen lost due to CVD.

2.7 Sonographic Parameters of Brachial Artery for Assessment of Endothelial Structure and Function

Brachial IMT was predictive of cardiovascular outcome is in line with studies using carotid or femoral artery IMT. Sorensen et al. (1997) revealed atherosclerosis is common in the human brachial artery and is significantly correlated with both coronary and carotid disease. These results suggest that the brachial circulation may serve as a reasonable "surrogate" for studying atherosclerosis, particularly in younger adults.

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2.7.1 Brachial Intima-Media Thickness

Thickening IMT is one of the process associated with atherosclerosis. Abnormal IMT value indicates structural changes in the artery. Carotid and femoral IMT values have been study for their association with CAD, as a risk factor or predictor for CAD event (Peters and Bots, 2013, Iwamoto et al., 2012). Recent study has shown increasingly interest in screening of brachial IMT for prediction of CAD event. This is due to the simpler procedure in measurement of brachial IMT compared with carotid and femoral IMT, as well as its significant association with hypertension and CAD. Intima-media thickness of the brachial artery predicted long-term (up to four years) cardiovascular events in a population with chest pain with or without underlying CAD (Frick et al., 2005).

Focus on brachial IMT has been initiated since 1997, a study on the association between atherosclerosis and human brachial artery through autopsy of human body. The study has shown significant correlation between atherosclerosis lesions found in brachial artery and coronary artery (r = 0.41, p = 0.003), brachial artery and carotid artery (r = 0.53, p = 0.0001), as well as brachial artery and left anterior descending coronary artery among patient less than 50 years old (r = 0.54, p = 0.002) (Sorensen et al., 1997).

Iwamoto et al. (2012) reported that brachial IMT in the CVD group was significantly larger than that in either the no risk group or at-risk group (no risk group, 0.21±0.05 mm; at-risk group, 0.32±0.09 mm; CVD group, 0.37±0.09 mm; *P*<0.001, respectively). Brachial IMT in the at-risk group was significantly larger than that in the no risk group (*P*<0.001). There was a significant difference in carotid IMT among

groups (no risk group, 0.50±0.05 mm; at-risk group, 0.72±0.16 mm; CVD group, 0.88±0.16 mm; respectively, *P*<0.001 for CVD group or at-risk group versus no risk group; *P*=0.01 for CVD group versus at-risk group (Figure 2.3). Based on the report, anatomical thickness of brachial artery IMT is thinner than carotid artery IMT in general. This is associated with the difference in blood pressure exert to the artery wall between brachial and carotid arteries.
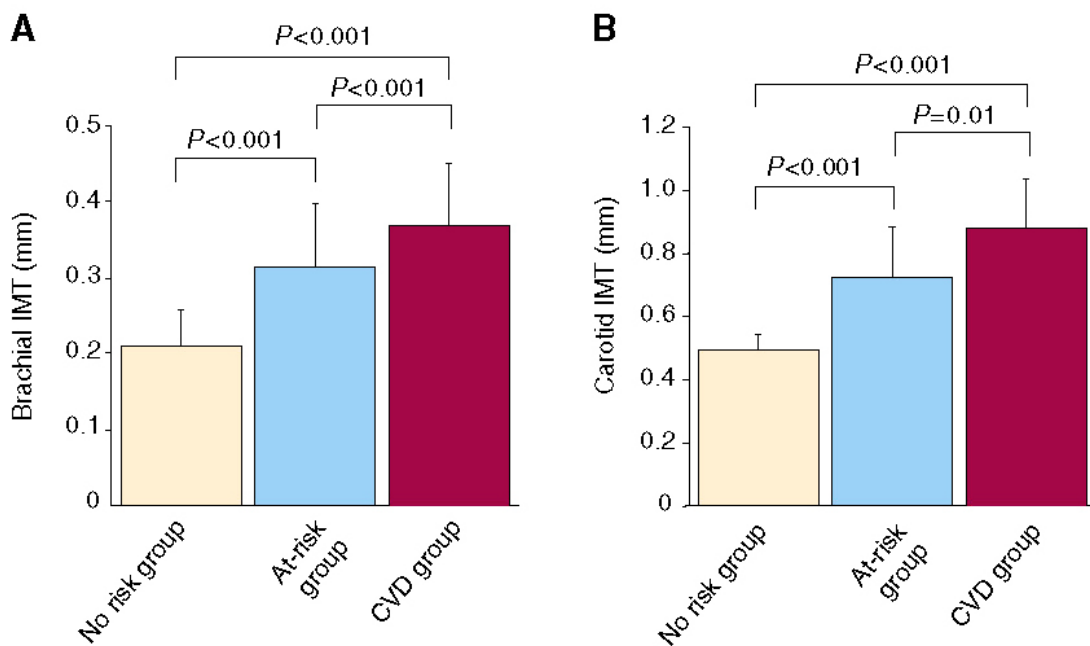

Figure 2.3   Comparisons of brachial artery and carotid artery thickness among no-risk, at risk, and CDV group

Note: A, Bar graphs show intima-media thickness (IMT) of the brachial artery in the no risk factor group, at-risk group, and cardiovascular disease (CVD) group. B, Bar graphs show IMT of carotid artery no risk factor group, at-risk group, and CVD group.
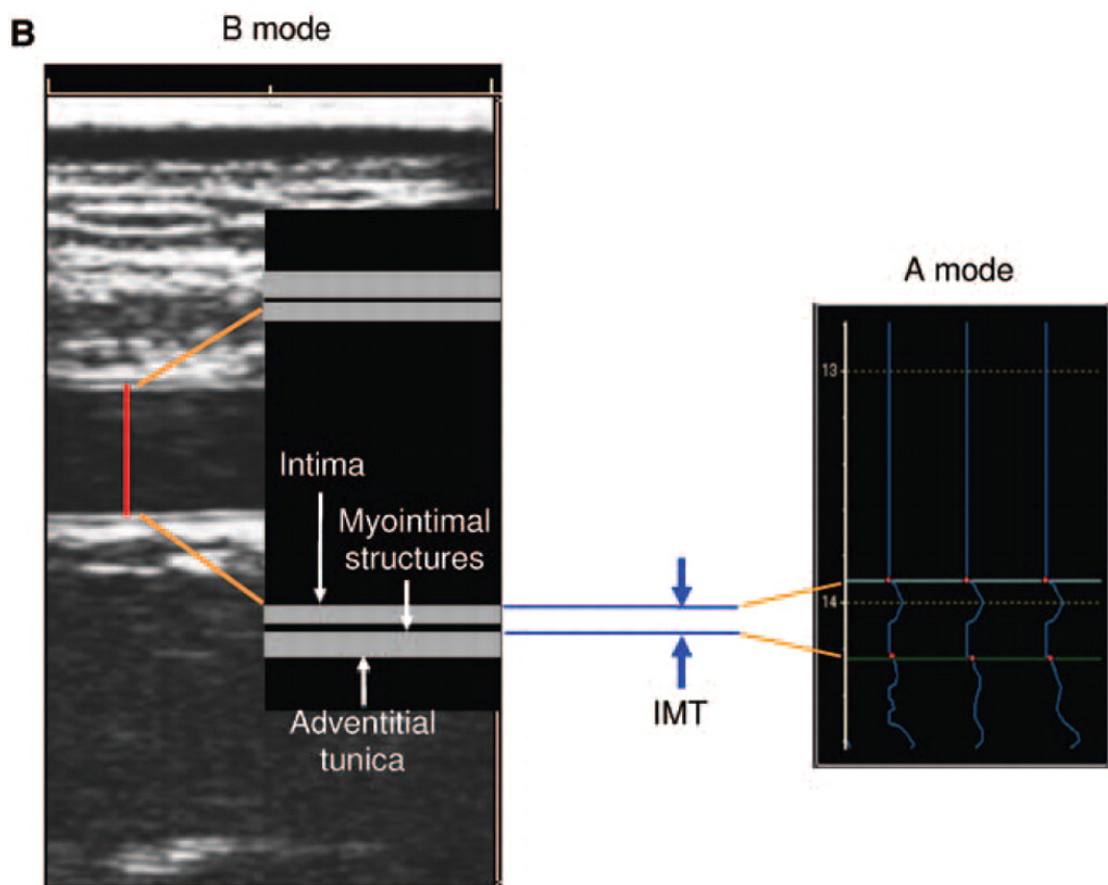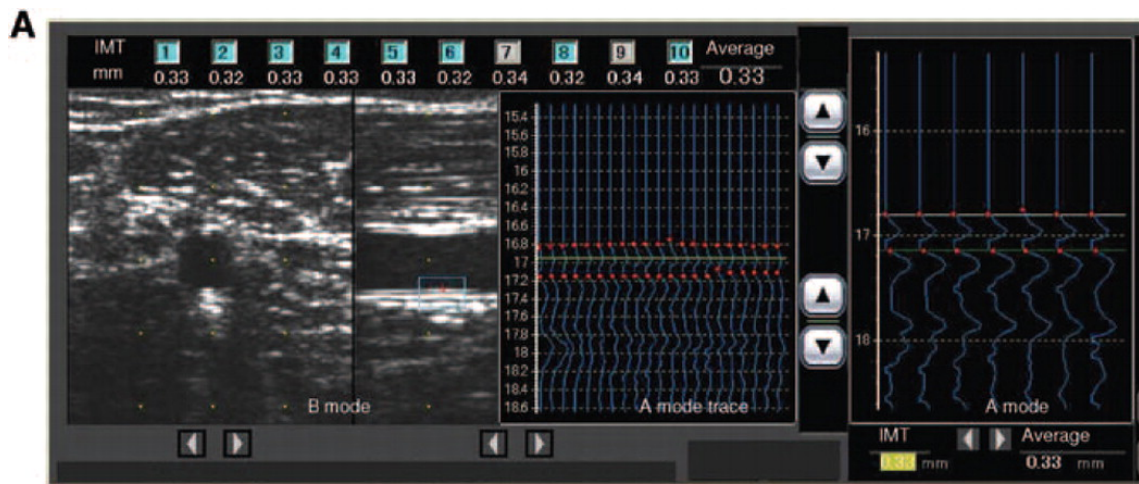
Figure 2.4   Measurement of IMT in brachial artery using ultrasonography

A, Analysis displays show vessel images of B-mode and A-mode of the brachial artery. Intima-media thickness (IMT), defined as the distance between the starting point of the first curve, indicating the intimal interface, and that of the second curve, indicating the media-adventitia interface, on the A-mode image of the far wall depicted in the middle and right displays, was measured automatically. A total of 21 points over the 3-mm length of IMT were measured and the mean value of IMT in each of the 10 images was automatically calculated. The average of mean values, defined as brachial IMT, was automatically calculated with exclusion of the outliners (gray panels). B, The scheme shows a close up of analysis displays and annotated anatomic landmarks for measurement of IMT. [Adopted from Iwamoto et al. (2012)]

2.7.2 Peak Systolic Velocity

PSV is one of the important parameters provided by the Doppler ultrasound. Is it also a useful measurement in determine the degree of stenosis in artery. Report has shown the possibility of using PSV for grading of carotid stenosis. Generally, PSV increases with the narrowing of the lumen in an artery. Study has shown PSV increases proportionally in with increasing stenosis and decreased to 0 cm/sec at occlusion (Figure 2.6). PSV increases in direct proportion to severity of angiographically-determined degree of internal carotid artery stenosis as shown in Figure 2.5 (Grant et al., 2000). Nevertheless, the correlation and regression of PSV with stenosis was suggested to showed variation in different population (Alexandrov et al., 1997). Several factors can affect the variability in PSV measurement as illustrated in Table 2.2.
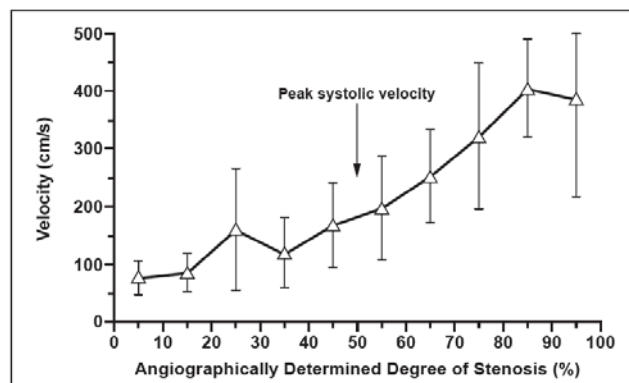
Note: Adopted from Grant et al. (2000)

Figure 2.5   Peak systolic velocity (PSV) versus angiographically-determined degree of stenosis.
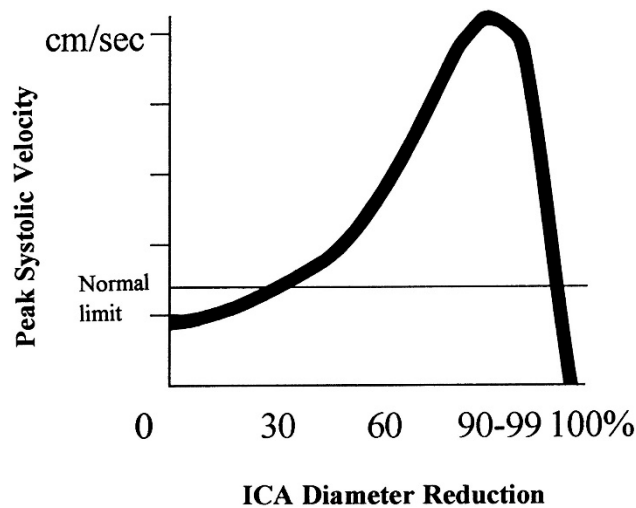
cm/sec

Peak Systolic Velocity

Normal
limit

0   30   60   90-99 100%

ICA Diameter Reduction

Figure 2.6   Profile of PSV changes versus reduction in internal carotid artery

Table 2.2   Factors cause errors in PSV measurement

Factors
1. Factor intrinsic to the artery being studied
a. Vessel site
b. Vessel size
c. Vessel depth
d. Vessel tortuosity
e. Plaque calcification
f. And vessel acoustic impedance (reflection and refraction)
2. Variations attributable to equipment
a. transducer beam pattern (steering vs nonsteering)
b. signal processing
c. signal-to-noise ratio
d. factors that affect frequency spectral shape, such as aperture size, transit time, and geometric broadening
e. sample volume length, and shape, the later being affected by depth (attenuation), acoustic impedance, and frequency
3. Factors related to the examination technique by the technologist
a. Experience
b. Accurate sample volume size, and three-dimensional placement in the vessel at the site of maximum stenosis
c. Angle of isonation in relation to the velocity vector, which is not necessary parallel to the vessel axis
d. Choice of color Doppler and gain setting

2.7.3 Resistive Index

RI is also known as Pourcelot Index, one of the parameters provided by Doppler ultrasound. It is use for characterizing the arterial waveform at Doppler ultrasonography. RI is defined as $(S-D)/S$, where S is the height of the systolic peak and D is the height of the end-diastolic trough. RI often been associated with vascular resistance and compliance (Bude and Rubin, 1999). Vascular resistance is the force that opposes the flow of blood through a vascular bed. It is equal to the difference in blood pressure across the vascular bed divided by the cardiac output. The vascular compliance is an index of the vascular elasticity, referred as one of the risk of cardiovascular disease. At normal or low constant vascular compliance, the RI value shows linear increment with the vascular resistant.

SECTION THREE

OBJECTIVES

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3.1   Significant of the Study

Ultrasonographic measurement of brachial artery IMT, PSV and RI is a fast and non-invasive screening tool for risk stratification for CAD. The graphic evidence can be shown to convince smokers of the atherosclerotic changes. Early identification of smokers at of high cardiovascular risk can help in successful prevention treatment.

3.2   Hypothesis of the Study

1. There is no significant difference of brachial artery sonographic parameters between smokers and non-smokers. [Null hypothesis]

2. There is no significant association between brachial artery sonographic parameters with duration of smoking among smoker. [Null hypothesis]

3. There is no significant association between brachial artery sonographic parameters with amount of smoking among smoker. [Null hypothesis]

3.3   Objectives of the Study

3.3.1   General Objective

1. To assess the relationship between sonographic parameters of brachial artery and smoking

3.3.2   Specific Objectives

1. To compare the mean difference of brachial artery intimal media thickness between smokers and non-smokers