A COMPARISON OF ARTERIAL STIFFNESS IN HYPERTENSIVE PATIENTS WITH CONTROLLED AND UNCONTROLLED SYSTOLIC BLOOD PRESSURE USING PULSE WAVE VELOCITY MEASUREMENT.

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TABLE OF CONTENTS PAGE

LIST OF FIGURES **PAGE**

LIST OF TABLES PAGE

LIST OF ABBREVIATIONS

ACE	: Angiotensin converting enzyme
AGE	: Advanced glycation end products
ALLHAT	: Antihypertensive and Lipid Lowering treatment to prevent Heart ATtack
AMBP	: Ambulatory blood pressure
ANCOVA	: Analysis of covariance
ARB	: Angiotensin receptor blocker
BP	: Blood pressure
BRFSS	: Behavioural Risk Factor Surveillance System
CDC	: Centre for Disease Control
CO	: Cardiac output
CONVINCE	: Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints.
DBP	: Diastolic blood pressure
DM	: Diabetes mellitus
ECG	: Electrocardiogram
ESRF	: End-stage renal failure
FBS	: Fasting blood sugar
HbA1C	: Glycosylated haemoglobin
HDL	: High density lipoprotein
HMG CoA	: 3, Hydroxy-3,methyl glutaryl Co enzyme A
HOPE	: Heart Outcomes Prevention Evaluation
HOT	: Hypertension Optimal Treatment
HUSM	: Hospital Unversiti Sains Malaysia
IHD	: Ischaemic heart disease

IMT	: Intima media thickness
JNC	: Joint National Committee
LDL	: Low density lipoprotein
LIFE	: Losartan Intervention For Endpoints
MBP	: Mean blood pressure
MRC	: Medical Research Council
MRFIT	: Multtiple Risk Factor InTervention
NCEP ATP III	: National Cholesterol Education Program Adult Treatment Panel III
P III NP	: N terminal propeptide of type III collagen
PP	: Pulse pressure
PWV	: Pulse wave velocity
REASON	: pREterax in regression of Arterial Stiffness in a cONtrolled double bliNd study
SBP	: systolic blood pressure
SD	: Standard deviation
SHEP	: Systolic Hypertension in the Elderly Program
SHIPAS	: Shiga Pravastatin Atherosclerosis Study
Syst Eur	: Systolic hypertension In Europe
TG	: Triglycerides

Abstrak

Latar belakang: Kekakuan arteri merupakan penyumbang penting bagi peningkatan kes kardiovaskular. Ia menunjukkan korelasi positif dengan tekanan darah sistolik. Halaju Gelombang Denyut (PWV), digunakan untuk mengukur kekakuan arteri secara tidak invasif dan mampu menganggarkan tahap kekakuan arteri bagi pesakit hipertensi yang tidak mempunyai gejala namun berisiko tinggi untuk penyakit jantung iskemik.. Bagi pesakit darah tinggi , tekanan darah yang tidak terkawal berkait terus dengan halaju gelombang denyut yang tinggi ,dan seterusnya kekakuan arteri yang lebih tinggi berbanding dengan pesakit darah tinggi dengan tekanan darah sistolik yang terkawal. Oleh itu, pesakit yang mempunyai tekanan darah sistolik yang tidak terkawal adalah berisiko tinggi untuk mendapat masalah kardiovaskular.

Objektif :Objektif utama kajian ini adalah untuk mendemonstrasikan sebarang perbezaan PMV pesakit darah tinggi yang mempunyai tekanan darah sistolik terkawal dan tidak terkawal di Hospital Universiti Sains Malaysia (HUSM). Objektif kedua adalah untuk mengenalpasti ubat-ubatan yang digunakan oleh kedua-dua kumpulan pesakit yang mempunyai tekanan darah terkawal dan sebaliknya.

Kaedah: Kajian ini merupakan kajian 'cross sectional' dengan persampelan mudah ('convenient') . 84 orang pesakit darah tinggi telah dipilih dan dibahagikan sama rata kepada 2 kumpulan (tekanan darah terkawal dan tidak terkawal) berdasarkan kepada pemerhatian bacaan tekanan darah sistolik 6 bulan terdahulu. Halaju gelombang denyut diukur menggunakan mesin Sphygmocor, sejenis 'automated tonometer' dan merupakan kaedah piawai pengukuran . Gelombang karotid dan femoral sebelah kanan dirakamkan.

Keputusan:. Tidak ada perbezaan signifikan ciri-ciri umum antara kedua-dua kumpulan, kecuali tekanan darah sistolik. Berdasarkan pemerhatian, terdapat perbezaan statistik yang signifikan bagi halaju gelombang denyut (PMV) bagi kumpulan tekanan darah yang tidak terkawal berbanding kumpulan darah yang terkawal ($p<0.001$).

Kesimpulan: : Kajian ini membuktikan bahawa halaju gelombang denyut adalah lebih tinggi dalam pesakit darah tinggi dengan tekanan darah sistolik yang tidak terkawal. Oleh itu, halaju gelombang denyut boleh dipertimbangkan sebagai kaedah tidak invasif bagi saringan penyakit kardiovaskular dalam pesakit darah tinggi, memandangkan kekakuan arteri telah terbukti sebagai penanda aras untuk masalah kardiovaskular pada masa akan datang.

Abstract

Background: Arterial stiffness is an important predictor of increased cardiovascular events. It has been shown to be strongly positively correlated with systolic blood pressure. The pulse wave velocity (PWV) is a non invasive measure of arterial stiffness and can reliably predict the degree of arterial stiffness in hypertensive patients who are asymptomatic of cardiovascular disease but who are at risk of developing ischemic heart disease. In hypertensive patients, uncontrolled systolic blood pressure is associated with a higher pulse wave velocity, which corresponds to a greater degree of arterial stiffness compared to hypertensive subjects with well controlled systolic blood pressure. Therefore those patients with uncontrolled systolic blood pressure and increased arterial stiffness are at higher risk of developing cardiovascular events.

Objectives: The objective of this study was to determine a difference in the pulse wave velocity (PWV) between controlled and uncontrolled systolic blood pressure (SBP) in hypertensive subjects at Hospital Universiti Sains Malaysia (HUSM).

Methods: This is a cross sectional study. 84 hypertensive patients were recruited. They were equally divided into 2 groups (controlled and uncontrolled systolic blood pressure) based upon the systolic blood pressure readings observed over the previous 6 months. The pulse wave velocity was determined using standard methods, using the Sphygmocor ® machine, which is an automated tonometer. The right carotid and right femoral pulse waves were the sites used in this study to determine the pulse wave velocity.(W-C Yu *et al.*, 2008)

Result: There was no significant difference in the baseline characteristics between the two groups, except for the systolic blood pressure. It was observed that there was a statistically significant difference in the PWV in the uncontrolled SBP group (12.9 m/s) compared to the PWV in the controlled SBP group((9.9m/s, $p<0.001$).

Conclusion: This study has shown that pulse wave velocity is higher in hypertensive patients with an uncontrolled systolic blood pressure. Hence pulse wave velocity may be considered to be a useful non invasive tool for early screening of cardiovascular disease in hypertensive patients, since arterial stiffness is a proven surrogate marker for future cardiovascular events.

Chapter 1

1.1. Introduction

Cardiovascular disease remains a major cause of mortality and morbidity in Malaysia (Ministry Of Health, Malaysia, 2004).According to latest statistics; it was the leading cause of death in 2006, totalling 24.2% of all deaths recorded in the government hospitals (Ministry Of Health, Putrajaya, 2008). Despite significant progress in terms of treatment of the ischaemic heart disease (IHD), strategies for early recognition are a major tool in order to potentially reduce the incidence of cardiovascular morbidity and mortality.

Current recommendations for prevention of IHD focus on controlling the level of reversible risk factors, such as hypertension, smoking, dyslipidemia and diabetes mellitus. Hypertension remains an important and modifiable risk factor in the development of IHD. Quantitative risk assessment is expected to improve outcome in patients at high risk of developing IHD (Anderson KM, 1991). Cardiovascular risk scores differ considerably from one individual to the next. Hence, it is more beneficial for individualized risk assessment and reduction strategies.(Blacher J et al, 2005). Past clinical researches have proposed measurement of endothelial dysfunction, left ventricular mass, vessel calcification, or echographic findings of arteries as an early means of detecting atherosclerosis in patients at increased risk of developing cardiovascular disease. These tests must ideally be safe, accurate and affordable to patients. They must also be fast and easy to perform. The results of these tests should correctly give an estimate of the severity of atherosclerotic disease and should not be influenced by genetic and environmental factors (Celermajer, DS et al; 1998)

Arterial stiffness has been identified as an important predictor of increased cardiovascular events (Cecelja et al, 2009). Pulse wave velocity (PWV), which is a non invasive measure of arterial stiffness is strongly correlated with systolic blood pressure (SBP) (Staessen JA et al, 2000). This marker of arterial stiffness has also been found to be beneficial in predicting cardiovascular events according to severity of hypertension grading.(Munakata M et al, 2003). Increased aortic stiffness correlates with reduced arterial compliance and has been associated with atherosclerosis in the aorta, and the coronary arteries. Patients who have hypertension show increase in arterial stiffness.(Nicole M. van Popele et al, 2001). This hastens the aging of the arteries, which is characterised by progressive dilatation of the vessels and a gradual increase in the thickness of the arterial wall. (Guerin AP et al, 1996). Blacher et al performed a cross-sectional study involving 710 essential hypertensive patients in order to determine the factors influencing aortic PWV and the potential predictor for atherosclerosis. Atherosclerosis alterations were defined on the basis of clinical events. It was shown that in these patients, PWV was the first determinant of extent of atherosclerosis, assessed as a sum of atherosclerotic sites.

1.1.1. Hypertension- a risk factor for IHD

Hypertension is rapidly becoming an important medical and public health concern. According to studies conducted by Burt VL et al, the prevalence of hypertension rises with increase in age of an individual, especially as from the age bracket of 60-69 years, where more than fifty percent of people are affected with hypertension. At the age of 70 years, approximately three fourths of people may be suffering from hypertension. The rise in blood pressure in this age group is primarily seen in the

systolic blood pressure (SBP). Therefore the main cause of increasing prevalence and incidence of hypertension is age related increase in SBP.

Several observational studies conducted by Lewington et al involving large populations have demonstrated that there is a linear increase in death due to IHD in those subjects whose diastolic blood pressure is 75 mmHg and beyond, and systolic blood pressure is 115mmHg and more. In fact there is a doubling of mortality for every 20 mmHg rise in systolic BP. Data from the Framingham Heart Study have shown that the relative risk for cardiovascular disease increased two fold with a SBP ranging from 130 to 139mmHg, compared to those with a BP of 120/80 mmHg or lower. (Vasan RS et al, 2002)

The new classification of hypertension is based on the JNC VII report (Aram V. Chobanian et al, 2003) and can be summarised as follows:

Blood Pressure (mmHg)	Disease
>140/90	Hypertension
140-159/90-99	Stage I hypertension
160-179/100-109 >180/110	Stage II hypertension

Table1: Stages of hypertension

1.1.2. Cardiovascular disease risk.

Hypertension is considered an independent risk factor for the development of cardiovascular disease (JNC VII, 2003). There is a continuous and consistent relationship

between high blood pressure and the occurrence of a cardiovascular event. This risk is compounded by several other risk factors, such as deranged lipid profile, diabetes mellitus, active smoking and presence of left ventricular hypertrophy. (Aram V. Chobanian et al, 2003)

There is compelling evidence to ascertain that systolic blood pressure is a major risk factor in the development of cardiovascular disease. According to data published in The Framingham Heart Study blood pressure increases with advancing age. (Vasan RS et al, 2002). Both the systolic and diastolic blood pressure increase to the same degree until about the age of 50 years. In individuals older than 50 years of age, the diastolic blood pressure has a tendency to remain the same. However the systolic blood pressure keeps increasing regardless of the age of the individual. Hence most elderly patients aged 50 years or more suffer predominantly from systolic hypertension. At this point in time systolic blood pressure represents a major risk factor for the development of cardiovascular disease, as opposed to younger individuals, in which diastolic blood pressure is considered the major cardiovascular risk factor. (Vasan RS et al, 2002)

Several trials have shown that controlling isolated systolic hypertension reduces death from cardiovascular causes and reduces all cause mortality. In the Systolic Hypertension in the Elderly (SHEP) trial, active systolic blood pressure reduction led to significant reduction in cardiovascular events, as well as clinical non fatal myocardial infarction and coronary death ($p < 0.001$) (Perry HM Jr et al, 2000). Other placebo-controlled interventional trials like the Systolic Hypertension in Europe (Syst-EUR) (Tuomilehto J et al, 1999) and The Systolic Hypertension in China (Liu L et al, 1999) also demonstrated that controlling systolic hypertension was associated with significant reduction in the occurrence of cardiovascular events. In the Multiple Risk Factor Intervention (MRFIT)

trial, results showed that in patients aged 45 years or older, systolic blood pressure becomes a more important cardiovascular risk factor compared to diastolic blood pressure. In the Losartan Intervention For Endpoint Reduction (LIFE) Trial a subset of the subjects had isolated systolic hypertension and also had left ventricular hypertrophy. These patients showed reduced incidence of cardiovascular events with adequate systolic BP reduction, particularly so with the use of angiotensin II receptor blocker (ARB) compared to beta blocker therapy. (de Simone el al, 2005)

Overall blood pressure reduction (both systolic and diastolic) is nevertheless associated with reduction of all cause mortality and cardiovascular events. In the Heart Outcomes Prevention Evaluation (HOPE) Trial, a proportion of patients were also hypertensive with other risk factors like diabetes mellitus. This subset of patients demonstrated significant reduction in cardiovascular events with adequate blood pressure control. (Peter Sleight et al, 2000)

In clinical practice, diastolic blood pressure is given more importance than systolic blood pressure, when in fact systolic hypertension is a major risk factor in the development of cardiovascular disease in the elderly patients.

Several data from clinical trials have demonstrated that ineffective control of systolic blood pressure is largely responsible for overall poor blood pressure control. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT)(Cushman WC et al, 2002) and Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) Trials(Black HR et al, 2003), there was significant diastolic blood pressure control as opposed to systolic blood pressure, which had poor control rates (90% versus 60-70%). The CONVINCE trial also demonstrated

that adequate blood pressure control using single drug therapy was rarely sufficient. In the Hypertension Optimal Treatment (HOT) trial, drug monotherapy was not effective in significant lowering of blood pressure, and also favours the use of two or more antihypertensive drugs to achieve adequate blood pressure reduction. (Zanchetti et al, 2001)

1.1.3. Increasing Arterial stiffness- a risk factor for IHD.

Arterial stiffness has been described as an independent predictor of cardiovascular events in patients with hypertension. (Laurent S et al, 2001). There are several mechanisms which are responsible for this association. Arterial stiffness causes a premature return of the backward wave towards the end of systole. This increases the pulse pressure (PP) in the central arteries and increases ventricular load. The ejection fraction subsequently decreases and myocardial oxygen demand rises. The rise in oxygen demand will result in cardiovascular events. (Nichols WW et al, 1991). Left ventricular hypertrophy, which is a well known risk factor for IHD in both normotensive and hypertensive patients, is caused by increasing arterial stiffness. The rise in systolic blood pressure (SBP) increases afterload on the left ventricle and increases workload on the heart. Reduction in DBP reduces coronary perfusion and causes subendocardial ischemia. (Nichols WW et al, 1991). There is an association between atherosclerosis and arterial stiffness, presumably due to shear stresses borne by the arteries during the cardiac cycle. This leads to thickening of the arterial walls. (Farrar DJ et al, 1991).

Arterial stiffness, assessed using PWV, has been shown to correlate with the severity of coronary artery disease in patients suffering from Ischemic heart Disease. (Ahmed Yahya Alarhabi et al, 2009).

Recently, a longitudinal study was performed on 1045 patients with essential hypertension but with no overt cardiovascular symptoms or disease (Pierre Boutouyrie et al, 2002). These patients had a baseline measurement of arterial stiffness using pulse wave velocity, and their baseline blood pressure was recorded. They were followed up for a period of 5.7 years and the risk assessment was calculated based on the Framingham Risk Score. The results showed that arterial stiffness, assessed by PWV, predicted cardiovascular disease beyond that assessed by the Framingham algorithm. This proves that arterial stiffness has a significant predictive value on cardiovascular events in patients with essential hypertension only, and no other symptom to suggest cardiovascular disease. Hence arterial stiffness is able to identify that subset of hypertensive patients at increased risk of developing cardiovascular disease but who are otherwise asymptomatic.

In the MRC Mild Hypertension Trial, which was conducted in males with untreated hypertension, pulse pressure (corresponding to arterial stiffness) was associated with increased incidence of adverse cardiovascular events compared to systolic, diastolic and even mean arterial pressure. (Millar et al, 1999)

In a follow up study of The Multiple Risk Factor Intervention Trial (MRFIT), it was shown that subjects with a higher pulse pressure were not only at greater risk of adverse cardiovascular events, but were also at increased risk of developing end organ damage. This in itself is a risk factor for cardiovascular disease. (Michael Domanski et al, 2002)

The higher is the systolic blood pressure, the higher is the pulse wave velocity, and the greater is the degree of arterial stiffness. It could be inferred that a reduction in blood pressure will reduce the degree of arterial stiffness in a given artery by lowering the PWV measurement. The Complior Study which was a large scale intervention trial

demonstrated that significant blood pressure reduction was associated with reduction of pulse wave velocity. (Roland Asmar et al, 2001)

In a recent prospective randomised trial, patients with essential hypertension and left ventricular hypertrophy were treated with a combination of 2 antihypertensives ACE Inhibitor perindopril and ARB valsartan versus each drug alone, for a period of 40 weeks. Their baseline readings of 24 hour ambulatory BP(AMBP), PWV were recorded and compared after treatment with the antihypertensives, either alone or in combination. It was seen that the reduction in 24 hour AMBP resulted in significant reduction in reduction of aortic stiffness in all the groups. However the reduction was most pronounced in the group of patients who were given combination therapy. (N. et al, 2005)

In a recent cross over randomised study, hypertensive patients randomised to monotherapy of ACE inhibitor captopril or ARB valsartan for a total period of 4 weeks efficiently reduced the blood pressure as well as the PWV. (Mahmud A et al, 2002)

In the multicentre trial POEMA 237 patients with arterial hypertension were treated with ACE inhibitor enalapril. A subset of these patients was treated with a combination of enalapril with a diuretic (indapamide). They were followed up for a period of 6 months. Results of this study demonstrated that this treatment reduced the stiffness of the major arteries by reducing the PWV which was associated with BP lowering. (Belenkov IuN, 2007)

A randomised double blinded crossover study conducted in hypertensive diabetics investigated the effect of the diuretic spironolactone on systolic blood pressure, N terminal propeptide of type III procollagen (PIIINP) and pulse wave velocity. In these patients it was seen that spironolactone effectively reduced the systolic blood pressure and

arterial stiffness by a reduction in the PWV. It also reduced the PIIINP levels. (Davies J et al, 2005)

This study aims to compare PWV in patients with uncontrolled v/s controlled systolic BP. Patients with a higher pulse wave velocity have a greater degree of arterial stiffness and are prone to developing cardiovascular phenomena earlier than those with a lower pulse wave velocity. These patients are however, asymptomatic of heart disease. PWV may be a useful non invasive tool for early screening of cardiovascular risk in these patients.

1.2. Arterial Stiffness

1.2.1 Anatomy of an artery.

The arterial system of the human body is a complex array of major blood vessels originating from the heart. These vessels further break down into arterioles and capillaries, and at the same time their calibre gets reduced accordingly. The latter are the main contributors to resistance to blood flow. Arteries form part of the "higher pressure" portion of the body's circulatory system and as a result are subject to higher shear stresses. (Glagov et al., 92)

Arteries can be classified based upon their calibre. In decreasing order of thickness and size, there are 3 main arterial vessels in the human body; the large elastic or conducting arteries, the medium and small arteries, which can also be called the distributing arteries, and the arterioles. Examples of conducting arteries are the aorta and its main branches, and the pulmonary arteries. The luminal diameter is roughly around 2.5 cm in the aorta, 0.4 cm in the artery and around 30 um in the arterioles. (Paulsen, 1996)

Histologically, arteries are divided into 3 layers, and from within outwards, consist of the tunica intima (innermost layer), the tunica media (intermediate layer), and the tunica adventitia (outermost layer). The tunica intima is made up of an endothelial cell layer, a subendothelial connective tissue layer and an elastic tissue layer, which is the internal elastic membrane. The tunica media has smooth fibres, collagen in varying amounts and elastic tissue. The tunica adventitia is mostly composed of loose collagenous connective tissue. (Glagov et al., 92)