Association between Carotid-Femoral Pulse Wave Velocity with Cardiovascular Disease Risk Factors and Framingham Coronary Disease Risk Prediction Score among Hypertensive Patients in Primary Health Care

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Abstract

Introduction: Pulse wave velocity, an index of arterial stiffness, is a standard tool for screening and stratification of cardiovascular risk and act as a surrogate endpoint for clinical management of patients.

Objectives: This study aims to describe the 10-year cardiovascular disease (CVD) risk and to determine the association between Carotid-Femoral Pulse Wave Velocity (cfPWV) with CVD risk factors and Framingham Risk Score (FRS).

Methods: A cross-sectional study was conducted from January to December 2012 in Out-Patient Clinic, Universiti Sains Malaysia Hospital. The CVD risk and arterial stiffness were assessed by Framingham Coronary Disease Risk Prediction Score (FRS) and cfPWV respectively. Simple and General Linear Regression confirmatory analyses were performed using SPSS version 19.0.

Results: A total of 197 hypertensive patients were involved. The mean (SD) of FRS was 13.3 (3.66). The 10-year CVD risk of <10%, 10-20% and >20% was 71.1%, 25.4% and 3.6% respectively. The cfPWV was significantly associated with CVD risk factors of age (<0.001), waist-hip ratio (0.003) and systolic blood pressure (0.002). cfPWV was also significantly associated with FRS ($P=$0.002).

Conclusion: Carotid-femoral PWV provides a measure of early changes in arterial function. Strong association with cfPWV allows estimation of CVD risk via FRS to act as a surrogate for monitoring and evaluating the severity of target organ damage.

Key words: vascular stiffness, risk, risk factors, cardiovascular diseases, hypertension
Introduction

Accurately assessing cardiovascular (CV) risk in individuals remains a challenge. Cardiovascular risk prediction relies on classical risk factors such as age, gender, lipids, hypertension, smoking and diabetes. Although the value of such scales of risk is high for populations, its value for individuals is reduced and influenced by non-modifiable risk factors such as age and sex. Pulse wave velocity (PWV), an index of arterial stiffness, has been widely validated as providing additional risk prediction above and beyond classical risk factors and is included in the latest guidelines for hypertension of the European Society of Hypertension / European Society of Cardiology. The Artery Society and the European Society of Hypertension is aiming to promote arterial stiffness as a standard tool for screening and stratification of CV risk and as a surrogate endpoint for clinical management of patients.

Carotid-femoral (cf) PWV is a marker of central arterial stiffness that can be measured non-invasively. Pulse wave velocity is an independent predictor of coronary heart disease and stroke in healthy subjects and an independent predictor of mortality in general population, older community, hospitalized individuals, hypertensive, chronic kidney disease and chronic obstructive pulmonary disease patients. Based on prospective observational cohort studies, cfPWV is highly predictive of cardiovascular events. A meta-analysis of 17 longitudinal studies showed that a slight increase in aortic PWV of 1 m/s was associated with an increase of 14%, 15% and 15% in total CV events, CV mortality and all-cause mortality, respectively.

Hypertension, a lifestyle-related disease, was shown to strongly alter the arterial stiffness compared to diabetes and dyslipidemia. All stages of hypertension are associated with increased risk of non-fatal and fatal cardiovascular diseases (CVD) events. The higher the blood pressure, the greater is the risk. Even small increment of 2 mmHg in systolic blood pressure (SBP) was shown to be associated with a 7% increase in mortality from coronary artery disease (CHD) and 10% increase in stroke mortality.

Although arterial stiffness was related to many CVD risk factors, the strength of association of each CVD risk factor to cfPWV is unclear. This is because individual risk factors may fluctuate over time and secondly, the cumulative of genetic, epigenetic, lifestyle, CV risk and environmental factors may have impact on the arterial wall. Thus, their measurement at the time of risk assessment may be unreliable and do not reflect their true impact on the arterial wall. Furthermore, there is no study on these associations based on Malaysian hypertensive population has been reported.

Although a wider clinical use of PWV measurement could add further precision to the assessment of organ damage, the availability of techniques for PWV measurement is limited to research centers. Therefore, identifying the strength of association between the 10-year CVD risk and the target organ damage parameter may act as a surrogate for identifying the severity of the damage. Presence of target organ damage identifies a condition of high risk of future cardiovascular events and thus, prompts initiation of pharmacological treatment.

Aims

This study aims (1) to determine the association between cfPWV and CVD risk factors and (2) to determine the association between cfPWV and 10-year CVD risk among hypertensive patients. Carotid-femoral PWV, an index of arterial stiffness, refers to the velocity of pulse wave along the carotid femoral segment measured using the Sphygmocor device. A 10-year cardiovascular disease risk is defined as the probability of an individual experiencing a cardiovascular event over a 10-year period based on Framingham Coronary Disease Risk Prediction Score (FRS).
Methods

Study participants. A cross-sectional study was conducted among hypertensive patients attending Out-Patient Clinic, Universiti Sains Malaysia (USM) Hospital, Kota Bharu, Kelantan. Patients diagnosed with essential hypertension based on World Health Organization - International Society of Hypertension (WHO-ISH) guidelines aged at or above 20 years old on pharmacological or non-pharmacological intervention were invited. Those with established coronary heart disease (CHD) as diagnosed by physicians and previous history of stroke were excluded.

Sample size was calculated using sample, power and precision calculator for single sample correlation. The biggest sample size obtained was for the risk factor total cholesterol. With correlation coefficient between PWV and total cholesterol of 0.20, precision of 0.05, power of 0.8 and 10% non-response, the sample size calculated was 213.17 Systematic random sampling in the ratio of 1:2 based on attendance list in the Out-Patient Clinic was used. All participants provided written informed consent in order to participate in the study. The Human Research Ethics Committee, USM (USM KK/PPP/JEPeM [244.3.(8)]) approved this study.

Basic profile, physical and laboratory assessment. The researcher obtained information by questionnaire, physical examination and laboratory assessment. Demographic, social, family and medical information including personal history of CVD, diabetes mellitus (DM), family history of CHD and information on tobacco use i.e. smoking within the past one month were obtained.16 Physical examination included anthropology and measurement of blood pressure. The body mass index (BMI) [weight (kg) / height (m²)] and waist-to-hip ratio (WHR) were calculated. Blood pressure was measured when the patient was relaxed and seated with arm outstretched and supported. The measurement of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken using a calibrated desktop sphygmomanometer. Blood samples were obtained from a peripheral vein in the morning after an 8-hour overnight fast. Fasting blood sugar (FBS) and fasting lipid profile of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) were collected in fluoride bottles and plain bottles, respectively and were sent to laboratory.

Cardiovascular risk assessment. Cardiovascular risk of each participant was assessed based on Framingham scoring system. Separate score sheets were used for men and women. Points associated with age, cholesterol and smoking status, which depend on age, HDL and SBP either treated or untreated were summed and the 10-year coronary risk was determined.

Carotid-femoral PWV measurement. Participants underwent measurement of arterial stiffness in Pharmacology Laboratory in the morning following at least 3-hour fast from food, caffeine, cigarettes and alcohol. The participants were studied in a supine position after a 10-minute rest. The distance between carotid and femoral arteries was measured with a tape over the surface of the body. Arterial tonometry of the right carotid and femoral arteries was measured with a validated non-invasive SphygmoCor device (AtCor Medical, Sydney, Australia) and simultaneous electrocardiography (ECG) recording. The transit time between the onset of carotid and femoral waveforms was determined as the mean of 10 consecutive cardiac cycles against a simultaneously measured QRS complex from the ECG. Carotid-femoral PWV was calculated from the distance between measurement points and the measured time delay as follows: cfPWV = distance (m) / transit time (s).

Carotid-femoral PWV was chosen to evaluate aortic distensibility for several reasons: first, because pressure waveforms can be easily recorded on these two sites; second, because the distance between these
two sites is large enough to allow an accurate calculation of the time interval between the two waves and thirdly, because cfPWV reflects arterial wall elasticity, which is widely related to the aorta.

**Statistical analyses.** Data entry and analysis were performed using Statistical Package for the Social Sciences, (SPSS Inc, Chicago, Illinois) version 19.0. Descriptive analysis was used to evaluate the 10-year CVD risk based on FRS. Simple Linear Regression and $R^2$ were used to determine the association between pulse wave velocity and CVD risk factors (age, BMI, WHR, SBP, DBP, FBS, TC, HDL-C, LDL-C, TG). Simple and General Linear Regression confirmatory analysis were used to determine the association between cfPWV and FRS. Dependent variable is cfPWV and fixed factor is FRS after adjusting for BMI, WHR, duration of HPT, education, family history of CHD and DM.

**Results**

A total of 213 hypertensive patients were recruited. However, only data from 197 (92.4%) were used in analysis. Those not included were due to abnormal pulse wave and difficulty to detect pulse due to obesity. The socio-demographic and medical characteristics of participants were described elsewhere. The arterial stiffness as determined by cfPWF was skewed to the right with median (IQR) of 11.5 (2.3) m/s ranging from 7.9 to 33.0 m/s. The cfPWV was significantly associated with age, WHR and SBP (Table 1). There was significant association between cfPWV and FRS ($P=0.002$) when BMI, WHR, duration of HPT, education, family history of CHD, DM were included in the model (Table 2). For every one score increase in FRS, there will be 0.2 m/s increase in cfPWV.

**Discussions**

We have shown that in patients with essential hypertension, arterial stiffness is associated with CVD risk factors i.e. age, SBP and WHR with $R^2$ values of 6.7%, 5.0% and 4.3% respectively. There was significant association between cfPWV and FRS, in which for every one score increase in FRS, there will be 0.2 m/s increase in cfPWV.

**Association between cfPWV and CVD risk factors.** Carotid- femoral PWV is widely used as a measure of aortic stiffness and is recognized as the gold standard for evaluating arterial stiffness. It represents the velocity of the pressure wave from the descending aorta to the femoral artery, thus, reflecting the stiffness of the descending aorta. Our findings confirm the well-established association between cfPWV with age that accounts for 24% of the cfPWV variance in hypertensive patients. In fact, the most important factor contributing to increased PWV in human populations is age because of increased arterial stiffness caused by medial calcification and loss of elasticity, suggesting that increase in PWV could be an early indicator of atherosclerosis development.

The different arterial segments may further explain the association between age and arterial stiffness. Age was significantly associated with central (aortic) stiffness (i.e., heart-femoral (hf) PWV), rather than peripheral (leg) stiffness (i.e., femoral-ankle (fa) PWV). Large elastic arteries near the heart stiffen with age due to a decrease in elastin content. However, peripheral muscular arteries may be less or not affected by age because of their more vascular smooth muscle cells and less elastin, although there have been some controversies. Choo et al. (2014) reported lack of significant association between cfPWV and age that was explained by small variability in cfPWV index in the group studied.

Pulse wave velocity also depends on SBP level in which, the higher the pressure, the faster the speed of wave travels. As the arterial wall stiffens, there are greater swings in blood pressure,
pulse pressure increases, cardiac function impaired and end-organ damage ensues.\textsuperscript{35} Since PWV is related to wall elasticity, it becomes directly related to distending pressure. A systematic review\textsuperscript{36} proved that age and blood pressure have greater influence on PWV while other CVD risk factors showed inconsistent findings.

In the current study, we also found that WHR is positively associated with arterial stiffness, which parallels with another study.\textsuperscript{37} Obesity is associated with increased arterial stiffness. Endothelial dysfunction, impaired smooth muscle cell function, insulin resistance, hypercholesterolemia and hyperleptinaemia were the possible contributory factors for obesity-related impaired arterial compliance.\textsuperscript{38}

However, BMI failed to show any relationship with cfPWV which were also reported in other studies.\textsuperscript{25, 39} Obesity is associated with increased CVD risk especially when the excess body fat is distributed preferentially within the abdominal region.\textsuperscript{38} Nevertheless, several studies reported positive association between increased BMI and cfPWV.\textsuperscript{8, 40-42} Choo \textit{et al.} reported significant association between BMI and cfPWV but not with faPWV.\textsuperscript{20}

Similar to other studies, we do not demonstrate any association between PWV and TC.\textsuperscript{12, 25, 28, 29} Even with different fractions of lipoproteins i.e. HDL-C and non-HDL, cfPWV was not a significant predictor of CV mortality.\textsuperscript{22, 25, 39, 43} On the contrary, significant relationship was found between TC,\textsuperscript{20, 24} HDL-C,\textsuperscript{44-46} TG\textsuperscript{20} levels and arterial stiffness.

Lack of association between cfPWV and lipids contradicts with the reported association of cfPWV with atherosclerotic plaque.\textsuperscript{47-50} However, it is possible that this is due to the lack of effect of lipid fractions on early stages of atherosclerosis compared to advanced plaque, particularly calcified plaque on the arterial wall stiffness.\textsuperscript{49} Hence, it is possible that, in participants with advanced plaque, the association between PWV and lipid may differ.\textsuperscript{51}

We also found no significant relationship between cfPWV and fasting blood sugar. This is consistent with a systematic review\textsuperscript{52} and a subsequent newer study\textsuperscript{20} regarding PWV and CVD risk factors.

\textit{Association between cfPWV and FRS.} Measured index of arterial stiffness in this study was within the range of 8.0 -17.2 m/s as in other hypertensive population.\textsuperscript{27, 53, 54} However, different methods and locations of measurement and different demographic characteristics of the studied patients have contributed to the varying results.\textsuperscript{25}

In this study, we have shown that cfPWV was strongly associated with FRS in hypertensive patients, an association that has previously been shown with cfPWV\textsuperscript{26, 27} and brachial-ankle (ba) PWV\textsuperscript{25, 54, 55} in general populations. Our group of hypertensive patients showed that for every one score increase in FRS corresponds to 0.2 m/s increase in cfPWV. A recent meta-analysis predicted that for 1 m/s increase in aortic PWV, there was a 7% increased risk of a CV events occurring for a 60-year-old man who is non-smoker, not diabetic, not on any blood pressure medication, with SBP of 120 mmHg, TC of 5.5 mmol/l and HDL of 1.3 mmol/l\textsuperscript{10}.

Framingham Coronary Disease Risk Prediction Score was developed to predict the 10-year risk of CVD,\textsuperscript{56} whereas, cfPWV was to indicate alterations at the site of arteries that has a real pathophysiological link with the clinical outcome. Arterial thickening is related to atherosclerosis, arterial stiffening to arteriosclerosis and endothelial dysfunction is believed to be a basic phenomenon of CVD.\textsuperscript{2} As FRS is positively associated with cfPWV, it may act as a surrogate for identifying the severity of cardiac target organ damage especially in most health centres where instrument for assessing arterial stiffness is unavailable.
This study has several limitations. This was a cross-sectional study, and, as such, the associations do not necessarily imply causality and not powered to predict CVD events. Reported $R^2$ values for individual contributions of variables may have been underestimated, because some variability may be explained by interactions with age and blood pressure. However, the strength of this study is that it focuses on a traditionally at risk population for CVD. Evaluating the vulnerable subjects serves to broaden the applicability of research findings.

Conclusions

Carotid-femoral PWV provides a measure of early changes in arterial function. Our results demonstrated that cfPWV is strongly associated with older age, higher systolic blood pressure, greater WHR and FRS. Strong association with cfPWV allows estimation of CVD risk via FRS to act as a surrogate for monitoring and evaluating the severity of target organ damage.

Recommendations

The measurement of cfPWV is limited to research centers. Strong association with cfPWV allows estimation of CVD risk via FRS to act as a surrogate for monitoring and evaluating the severity of target organ damage.

Consent

Informed consent was obtained.

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgement

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References


Table 1: Association between cfPWV and CVD risk factors

<table>
<thead>
<tr>
<th>CVD risk factors</th>
<th>$R^2$</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>0.066</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>0.000</td>
<td>0.984</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.043</td>
<td>0.003</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>0.050</td>
<td>0.002</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>0.003</td>
<td>0.429</td>
</tr>
<tr>
<td>Fasting blood sugar (mmol/L)</td>
<td>0.017</td>
<td>0.068</td>
</tr>
<tr>
<td>Total-cholesterol (mmol/L)</td>
<td>0.018</td>
<td>0.059</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mmol/L)</td>
<td>0.000</td>
<td>0.813</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol (mmol/L)</td>
<td>0.005</td>
<td>0.330</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>0.006</td>
<td>0.265</td>
</tr>
</tbody>
</table>

Table 2: Association between cfPWV and Framingham risk score

<table>
<thead>
<tr>
<th>Variables</th>
<th>SLR$^a$</th>
<th>GLR$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b (95% CI)</td>
<td>t stat</td>
</tr>
<tr>
<td>Framingham point total</td>
<td>0.21 (0.09, 0.34)</td>
<td>3.47</td>
</tr>
</tbody>
</table>

$^a$ Simple Linear Regression ($R^2=0.058$)
$^b$ General Linear Regression ($R^2=0.163$); There was no interaction between fixed factor and the controlled variables and no multicollinearity problem; model assumptions met). Adjusted for BMI, WHR, duration of HPT, education, family history of CHD, DM.
$^c$ Crude regression coefficient
$^d$ t statistic
$^e$ Adjusted regression coefficient