Brachial Artery Distensibility as A Cardiovascular Risk Marker in Asymptomatic Individuals

Meng-Cheng Chiang, Wei-Hsian Yin, Yeu-Tyng Lin², Hsu-Lung Jen, Jiann-Jong Wang, Wen-Pin Huang, An-Ning Feng, Yung-Nien Yang, and Mason Shing Young¹

Division of Cardiology, ¹Department of Internal Medicine, ²Division of Physical Examination, Cheng-Hsin General Hospital, Taipei, Taiwan

Abstract

Previous studies have shown that brachial arterial distensibility (BD) is a measure of arterial stiffness and may be used in risk assessment for cardiovascular disease (CVD). The aim of this study was to explore the predictive value of BD for CVD risk levels and to seek cardiovascular risk factors influencing BD. In this study, BD data were obtained using the DynaPulse 2000A instrument (Pulse Metric, Inc, USA) in 300 asymptomatic, apparently healthy subjects (M/F=152/148; aged 52 ± 13 years) who were admitted for routine physical check-up. Family history, serum lipids and lipoproteins, glucose levels and mercury sphygmomanometer blood pressure measurements were obtained. The risk for CVD in each individual was assessed using the Framingham Risk Score system. Significant correlations were found between unadjusted BD and age, measures of blood pressure, height, body mass index, total cholesterol levels, LDL-cholesterol levels, and glucose levels. Multivariate regression analyses showed that age, systolic and diastolic blood pressures and glucose levels independently predicted changes in BD. There was a significantly negative correlation between BD and the Framingham risk scores (r = -0.45, P < 0.0001). Subjects with a 10-year risk for a future coronary heart disease events of <10% had significantly higher BD than those whose risk for coronary heart disease was \geq 10% (6.12 \pm 1.25 %/mmHg vs. 4.94 \pm 1.2 %/mmHg, P= 0.0001). These findings indicate that non-invasive measures of BD are effective in assessing CVD risk. (J Intern Med Taiwan 2005; 16: 1-10)

Key Words : Arterial stiffness, Brachial artery distensibility, Cardiovascular risk factors

Introduction

Atherosclerosis, hypertension and diabetes produce vascular changes that are reflected in arterial function and vascular physical properties before the development of clinical disease¹⁻⁴. Measurement of these changes may therefore prove useful for identifying subjects at particular risk of cardiovascular complications.

A reproducible, noninvasive method for measuring atherosclerotic and hypertensive vascular changes in living subjects was used in this study. The new device records a brachial artery pressure waveform from a cuff sphygmomanometer and estimates brachial artery distensibility (BD), systemic vascular compliance and left ventricular work using proprietary pulse waveform analysis algorithms^{2.5}. As both hypertension and atherosclerosis are associated with structural and functional vascular changes, it has been suggested that this method of compliance and distensibility measurement could be of value in the early detection and management of those diseases^{2,4,6}.

Although stiffer vessels with decreased distensibility have been seen in subjects with higher levels of cardiovascular risk factors^{4,6,7}, the predictive relationship of BD to future risk of cardiovascular events in asymptomatic apparently healthy subjects has not been well studied. The aims of this study were to establish the relationship between noninvasive measures of BD and ten-year estimated absolute risk of a cardiovascular event using the Framingham risk score system. Additionally, the relation between BD and other cardiovascular risk factors and the determinants of BD were investigated.

Materials and Methods

Study Population

A sample of 300 apparently healthy subjects (152 men and 148 women, mean age 52 \pm 13 years) was selected. All of them were asymptomatic, free of angina pectoris and cardiac dysfunction, and were ad-

mitted for routine physical check-ups. Subjects were excluded from the study if they had a history of cardiovascular disease, such as coronary artery disease, cerebrovascular disease, and peripheral vascular disease; or if they had abnormal resting electrocardiograms. The Institutional Review Board of Cheng-Hsin General Hospital approved the study protocol. Subject Evaluation

After obtaining informed consent, measured blood pressure and anthropometric data were collected by trained observers. Height and weight for each subject were included in the model of BD measurements. Two measurements, each of height to the nearest 0.1 cm and weight to the nearest 0.1 kg, were obtained. Direct measurement of blood pressure (BP) and pulse was also obtained using a mercury sphygmomanometer at the time of study. For BP cuff selection, measurements of right upper arm length (using anthropometric calipers) and circumference were obtained.

Cardiovascular risk status was established on the basis of physical examination and responses to standardized questionnaires, and electrocardiograms were obtained and blood samples taken for measurement of serum lipids and lipoproteins and of glucose. Brachial Artery Distensibility Measures

Brachial artery distensibility measures, including validation studies, as well as the method to derive arterial compliance, have been published previously^{5,8}. This noninvasive instrument derives BD using waveform analysis of the arterial pressure signals obtained from a standard cuff sphygmomanometer. For BD measurements, subjects had a special BP cuff placed around their upper arm with the subject in a sitting position after resting for 5 minutes. Three recordings were performed sequentially, and measurements were obtained for systolic, diastolic and mean arterial BPs as well as heart rate at 20-msec sampling intervals by oscillometric cuff signal pattern recognition. Subject data were entered into a personal computer interfaced to the DynaPulse 2000A noninvasive BP and hemodynamic monitoring instrument (Pulse Metric, Inc., San Diego, CA, USA). Off-line analyses of brachial artery pressure curve data were performed by Pulse Metric, Inc. using an automated system to derive parameters from the pulse curves to calculate BD.

In brief, the pressure waveform was calibrated and incorporated into a physical model of the cardiovascular system assuming a straight tube brachial artery and T-tube aortic system. The method assumed that the systolic phase of the suprasystolic cuff signal and the diastolic phase of the subdiastolic cuff signal most closely approximate systolic and diastolic aortic pressures, respectively. Brachial artery compliance was derived from waveform parameters as:

Arterial Compliance (Cp) =
$$\frac{\pi^2 \cdot D_0^2 \cdot [D_0 + L_c]}{dP/dt_{pp} \cdot t_{pp}}$$

where dP/dt_{PP} was the amplitude from the peak positive pressure derivative to the peak negative pressure derivative and t_{PP} was the time interval between the peak positive and peak negative pressure derivatives. The effective cuff width (L_c) is defined as the cuff width divided by the square root of 2. Brachial artery diameter (D_0) was estimated using an empirically derived model based on sex, height, weight, and mean arterial BP, and has been validated using Bmode ultrasound^{4,6}. Brachial artery distensibility was then calculated as the percent volume change per pressure change using the formula:

BD = Cp / [
$$\pi$$
 (D₀²/4) · L_c] $\approx 4 \pi / (dP/dt_{pp} \cdot t_{pp})$

Estimation of Risk of Future Cardiovascular Evenst using Framingham Risk Score System

Data on risk factors for coronary artery disease were collected by a study physician or nurse. Risk factors included the following: current cigarette smoking, history of premature coronary disease in a first degree relative, diabetes mellitus, hypertension and hypercholesterolemia. Cigarette smoking was defined as use of > 10 cigarettes/day. Subjects currently using insulin, oral hypoglycemic agents or diet-controlled diabetes were classified as diabetic. Hypertension was defined by current use of antihypertensive medication or known and untreated hypertension (systolic blood pressure \geq 140 mmHg or diastolic blood pressure \geq 90 mmHg). Hypercholesterolemia was similarly defined by use of cholesterol lowering medication or known but untreated high cholesterol (total cholesterol \geq 200 mg/dL or lowdensity lipoprotein \geq 130 mg/dL).

Investigators with the Framingham Heart Study have developed a useful tool to assess risk of a first cardiovascular event based on age, gender, total or low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, systolic and diastolic BP, and history of diabetes and cigarette smoking⁹. Point-based weights are assigned to the presence and/or level of each risk factor. Once the points have been assigned and summed, the total score can be translated to an estimated absolute risk of a cardiovascular event occurring within the next ten years. The risk for cardiovascular disease in each individual was assessed using this score system. Statistical Analysis

Continuous variables were presented as medians or means \pm SD. All statistical tests were two tailed, with significance defined as P <0.05. Patient demographics and BD for men and women were presented. Comparison of demographics and BD in men and women were made with the Students' t-test for quantitative data and with the Fisher exact test or chi-square test for categorical data.

Linear regression analyses were performed to determine the correlation of BD to cardiovascular risk factor levels. The analyses were performed using all demographic variables including age and gender, current smoking status, as well as systolic BP, diastolic BP, pulse pressure, height, weight, body mass index, total cholesterol levels, LDL cholesterol levels, HDL cholesterol levels, triglyceride levels and glucose levels. Multiple linear regression analysis of BD on selected variables was performed to determine the influencing factors of BD.

By using linear regression analysis, the correlation between BD and the Framingham risk scores was also determined. Finally, we divided the subjects into two risk groups, based on their 10-year risk for a future cardiovascular event: the low risk group was composed of subjects with a 10-year risk for a future coronary heart disease event of < 10%; the intermediate risk group contained those whose risk was \ge 10%. The BD of both groups was compared with the Students' t-test.

Results

Patient Characteristics

Characteristics of the study population by gender group are displayed in Table 1. Men were taller (P < 0.0001), heavier (P < 0.0001) and had significantly higher body mass indices (P = 0.009) than women. Men had significantly higher diastolic BP (P = 0.0001) and mean BP (P = 0.0009) than women, although pulse pressure was similar in both gender groups. Men had higher values for triglycerides (P = 0.0006) and lower values for HDL cholesterol (P < 0.0001) then did women. The prevalence of smoking in women was significantly lower (P = 0.0001) than in men. No other risk factors or demographic data were statistically different. Men had larger BD than women (6.0 ± 1.2 vs. 5.7 ± 1.4 , P = 0.0166).

The subjects who participated in this study were relatively healthy and only very few of them were taking anti-hypertensive drugs, statins or antiplatelets. The medications used in both gender groups were similar. The Framingham risk score were similar in

Table 1. Characteristics of the study bobulation i	by dende	r aroup
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Variable	Total(n=300)	Men(n=152)	Women(n=148)	p value
Age (years)	52 ± 13	51 ± 14	52 ± 12	NS
Diabetes mellitus	19 (6%)	9 (6%)	10 (7%)	NS
Smoking	74 (25%)	63 (41%)	11 (7%)	0.0001
Height (cm)	163 ± 9	169 ± 7	156 ± 6	< 0.0001
Weight (kg)	64 ± 12	70 ± 11	57 ± 10	< 0.0001
Body mass index (kg/m ²)	24 ± 4	24 ± 3	23 ± 4	0.009
Fasting blood sugar (mg/dl)	100 ± 33	99 ± 19	100 ± 42	NS
Triglyceride (mg/dl)	129 ± 79	144 ± 86	113 ± 69	0.0006
Total cholesterol (mg/dl)	212 ± 42	209 ± 38	215 ± 45	NS
High-density lipoprotein cholesterol (mg/dl)	59 ± 16	52 ± 13	66 ± 17	< 0.0001
Low-density lipoprotein cholesterol (mg/dl)	128 ± 35	129 ± 33	126 ± 36	NS
Systolic blood pressure (mmHg)	143 ± 20	145 ± 16	141 ± 23	NS
Diastolic blood pressure (mmHg)	79 ± 10	82 ± 9	76 ± 11	0.0001
Mean arterial blood pressure (mmHg)	98 ± 13	100 ± 11	96 ± 14	0.0009
Pulse pressure (mmHg)	64 ± 14	64 ± 11	65 ± 16	NS
Heart rate (beats/min)	69 ± 12	69 ± 12	70 ± 11	NS
Medication				
Statin	3 (1%)	2 (1%)	1 (0.7%)	NS
β -blocker	8 (2.7%)	2 (1%)	6 (4%)	NS
CCB	6 (2%)	3 (2%)	3 (2%)	NS
ACEI/ARB	2 (0.7%)	1 (0.7%)	1 (0.7%)	NS
Aspirin	12 (4%)	8 (5%)	4 (3%)	NS
Brachial Artery Distensibility (%mmHg ⁻¹)	6.0 ± 1.0	6.0 ± 1.2	5.7 ± 1.4	0.016
Framingham risk score	10.1 ± 5.8	10.3 ± 5.5	10 ± 6.1	NS

CCB = calcium channel blocker; ACEI/ARB = angiotensin converting enzyme inhibitors or angiotensin II receptor blockers Table 2. Simple linear regression analysis of the relationship between brachial artery distensibility and other

associated variables in the study population					
Variable	<i>r</i> value	<i>p</i> value			
Age	-0.506	<0.0001			
Systolic blood pressure	-0.718	< 0.0001			
Diastolic blood pressure	-0.228	< 0.0001			
Pulse pressure	-0.846	< 0.0001			
Height	0.226	< 0.0001			
Weight	-0.001	0.986			
Body mass index	-0.189	0.001			
Total cholesterol	-0.147	0.011			
Low-density lipoprotein cholesterol	-0.116	0.044			
High-density lipoprotein cholesterol	-0.054	0.384			
Triglyceride	-0.066	0.257			
Fasting blood sugar	-0.255	< 0.0001			



Fig.1. Brachial artery distensibility displayed by age and gender. Brachial artery distensibility decreased with age in both men and women.

men and in women (10.3 ± 5.5 and $10.0 \pm 6.1\%$, respectively).

Relation of BD to other Cardiovascular Risk Factors

Correlation coefficients were derived between BD and selected cardiovascular risk factors (Table 2). With all subjects pooled, significant correlations were found between unadjusted BD and age (Figure 1), measures of BP (Figure 2), height, body mass index, total cholesterol levels, LDL-cholesterol levels and fasting glucose levels.

Results for multiple linear regression of BD on selected associated variables are included in Table 3.



Fig.2. Significant negative correlation between brachial artery distensibility and systolic blood pressure (A), diastolic blood pressure (B), mean arterial blood pressure (C) and pulse pressure (D).

The model includes age, gender, cigarette smoking, systolic BP, diastolic BP, height, weight, body mass index, triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol and glucose levels. Multivariate regression analyses showed that age, systolic and diastolic BP and glucose levels independently predicted changes in BD.

Correlation between BD Values and the Framingham Risk Scores

Linear regression analysis revealed a significantly negative correlation between BD and the

	Regression coefficient	Standard error	Standardized coefficient	t value	<i>p</i> value
Age	-0.015	0.004	-0.153	-4.209	< 0.0001
Gender	-0.169	0.125	-0.064	-1.351	0.178
Smoking	0.027	0.099	0.009	0.270	0.787
SBP	-0.078	0.003	-1.153	-22.674	< 0.0001
DBP	0.075	0.006	0.584	12.728	< 0.0001
FBS	0.005	0.001	0.121	3.489	0.001
Triglyceride	0.004	0.005	0.233	0.812	0.417
Total cholesterol	-0.019	0.024	-0.609	-0.808	0.420
HDL	0.021	0.024	0.258	0.862	0.389
LDL	0.021	0.024	0.538	0.861	0.390
BMI	0.001	0.096	0.002	0.009	0.993
Height	0.010	0.029	0.068	0.342	0.733
Weight	-0.001	0.036	-0.008	-0.025	0.980

Table 3. Multiple linear regression analysis of the relationship between brachial artery distensibility and other associated variables in the study population

SBP = systolic blood pressure; DBP = diastolic blood pressure; FBS = Fasting blood sugar;

HDL = High-density lipoprotein cholesterol; LDL = Low-density lipoprotein cholesterol;

BMI = Body mass index



Fig.3. The correlation between brachial artery distensibility values and the Framingham risk scores.

Framingham risk scores (r = -0.458, P < 0.0001) (Figure 3).

We then divided the subjects into two risk groups, based on their ten-year risk for a future coronary heart disease event. The low risk group (n= 235) was composed of subjects with a 10-year risk for a future coronary heart disease event of < 10%; those whose risk was $\ge 10\%$ formed the intermediate risk group (n= 65). As shown in Figure 4, subjects in the intermediate to high risk group had a mean BD that was significantly lower than those in the low risk





group (6.12 \pm 1.25 %/mmHg vs. 4.94 \pm 1.2 %/mmHg, P= 0.0001).

Discussion

Increased arterial stiffness has recently been proposed as a powerful and independent risk factor for cardiovascular disease¹⁰⁻¹². Reduced arterial compliance and distensibility can contribute to the development and progression of hypertension, left ventricular afterload, left ventricular hypertrophy and dysfunction, and to decreased myocardial perfusion and vasculopathy^{10,13}. Since increased arterial stiffness is a dysfunctional property of the arterial circulation that precedes the development of clinical cardiovascular disease¹⁻⁴, the study of this early change is of interest. Noninvasive devices to measure vascular stiffness. such as arterial compliance and distensibility, to reflect these changes have been developed and are commercially available. These new techniques, which utilize different aspects of the pulse pressure waveform, are simple, reliable, correlate with development of atherosclerosis in nonhuman primates and human beings^{7,14-15} and may identify patients at increased risk of developing cardiovascular complications^{3-5,16-20}. However, these changes in the arterial pulse wave and distensibility need to be explored for their relation to other cardiovascular risk factors and for their predictive value for future cardiovascular events in asymptomatic, apparently healthy subjects.

In this study, we observe the clinical utility of one of these methods for estimating BD by recording a brachial artery pressure waveform from a cuff sphygmomanometer and using proprietary pulse waveform analysis algorithms^{2,5}. This method has been suggested as a screening tool for coronary artery disease, particularly in asymptomatic individuals with coronary risk factors^{2,4,6}. Our data did demonstrate the ability to relate noninvasive measures of BD to cardiovascular risk factors. Correlations were found between BD and BP, body mass index, total cholesterol levels, LDL-cholesterol levels and glucose levels.

In previous investigations, the strongest determinants of BD were measures of BP, with age and body size also contributing^{4,27,28}. However, multivariate regression analyses in our study showed that only age, systolic and diastolic BP and glucose levels independently predicted changes in BD. As shown in Figure 1 and Figure 2, BD decreased with age and increasing blood pressure measures. Increased arterial stiffening and decreased arterial compliance and distensibility have been demonstrated in both type 1 and type 2 diabetes²¹⁻²⁴, and insulin may have an effect on distensibility^{25,26}. Our results showed that fasting glucose levels independently predicted changes in non-invasive measures of BD, which were consistent with these findings.

Although other researchers have demonstrated gender differences with lower BD seen in men²⁹, we found that men had higher BD. However, these gender differences were abolished when adjustments were made for body size (Table 2). Differences in these results may be multifactorial²⁵⁻²⁹ and it is known that measures of body size, such as height and weight, may influence arterial compliance through various mechanisms²⁶⁻²⁸.

The relatively weak association of BD with lipids may be related to the mild elevations in lipids seen in this relatively healthy population. Furthermore, oxidized low-density lipoprotein, not measured in the present study, may be a better measure of risk of abnormal BD because it has been found to relate more strongly to aortic elasticity than standard lipid variables³⁰. However, even though the contribution of an individual risk factor to abnormalities in vascular function may be small, multiple risk factors may act in concert to exert an even greater influence on blood vessels as suggested by the rather high amount of variance explained by our multivariate model. This evidence points to the value of modifying multiple risk factor levels in asymptomatic persons in an attempt to improve BD.

Finally, we demonstrated a significantly negative correlation between BD and the Framingham risk scores using linear regression analysis (Figure 3). As shown in figure 4, subjects with higher levels of cardiovascular risk factors and higher risk of developing future cardiovascular events demonstrate stiffer vessels and lower BD. Our findings indicate that this relatively cheap and simple technique delivers not only systolic and diastolic arterial pressures, but also can derive vascular distensibility, and is effective in assessing cardiovascular risk. However, larger longitudinal prospective studies are required to confirm these findings. Furthermore, whether identifying arterial stiffness in high risk individuals at a pre-symptomatic phase allows earlier use of therapeutic interventions, e.g. statins etc., that decrease the development of clinical cardiovascular events also remains to be determined. If future studies do provide such confirmation then measurement of arterial stiffness may become a routine test to help assess cardiovascular risk and the efficacy of therapeutic interventions.

Study Limitations

The present study has several limitations. The study participants were volunteers who were admitted to the hospital for routine physical check-ups. Although they were relatively healthy and asymptomatic, they may not be truly representative of the general population and our results may not extrapolate to the entire population. Secondly, not all risk factors were measured in this study, and thus were not entered into the model. Measures of oxidized lowdensity lipoprotein, inflammatory markers such as Creactive protein and homocysteine were not obtained in the current study. Whether BD provides additional predictive value to these conventional and novel cardiovascular risk factors remains to be determined. Finally, we used estimated absolute ten-year risks for future coronary heart disease events based on the Framingham Coronary Risk Score instead of solid end-points, such as long-term adverse cardiovascular event rates etc., to determine the individual cardiovascular risks in this study. It is known that traditional risk factors do not fully account for the occurrence of disease, so the extent to which BD will correlate with future risks for cardiovascular events may not be fully established in the present study. Conclusions

Our findings indicate that noninvasive measures of BD are effective in assessing cardiovascular risk. Further and larger prospective studies are needed to determine whether they may provide clinicians and research scientists with another diagnostic tool in addition to standard cardiovascular disease risk factors.

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以手臂動脈擴張度評估無症狀接受健康檢查者 之心血管病風險

江孟橙 殷偉賢 林雨亭² 任勗龍 王鑑忠 黃文彬 馮安寧 楊永年 楊茂勳¹

财團法人振興復健醫學中心附設醫院 心臟内科 1 内科部 2 健檢科

摘 要

過去的研究已知手臂動脈擴張度(brachial arterial distensibility)可反映動脈血管硬度(arterial stiffness),因此被建議使用於心血管病風險的評估。但針對外表健康的無症狀族群,使用 手臂動脈擴張度來評估心血管病風險的研究則不多。本研究之目的即在探討以手臂動脈擴 張度預測此一族群未來發生心血管病風險的能力,同時探討手臂動脈擴張度與各種心血管 病危險因子間的關聯性與影響測定手臂動脈擴張度的因素。本研究選取300位(男性152 位,女性148位,平均年龄52±13歲)自願來院做健康檢查,外觀正常且無臨床症狀者,詳 細記錄其血壓、身高、體重、家族病史、各種心血管病危險因子、抽血測定血脂肪、血脂 蛋白及空腹血糖、並使用DynaPulse 2000A 型機器測量其手臂動脈擴張度。最後吾人使用 Framingham 心血管病風險評估計分表來計算每人未來十年發生心血管病的風險,並統計分 析手臂動脈擴張度是否能預測此風險。本研究發現手臂動脈擴張度與各種心血管病危險因 子,包括:年龄、血壓、身高、體質量指數(body mass index)、總膽固醇、低密度脂蛋白膽 固醇及空腹血糖等之间確有顯著之相關性。多變項分析則顯示影響手臂動脈擴張度測量值 的主要決定因素是年齡、血壓及空腹血糖值。手臂動脈擴張度與參加者依Framingham 心血 管病風險評估表計算所得的分數間成明顯負相關(r=-0.45, P<0.0001)。吾人進一步將參加 者依换算所得的十年内心血管病風險分爲低風險組(其十年内心血管病風險 < 10%)及中等 風險組(其十年内心血管病風險 ≥10%),結果前組之手臂動脈擴張度數值明顯高於後組 (6.12±1.25%/mmHg vs. 4.94±1.2%/mmHg, P=0.0001)。以非侵入方式測量手臂動脈擴張度應 有助於評估此族群將來發生心血管病之風險。