Original Article

Ankle Brachial Index as a Marker of Atherosclerosis in Chinese Patients with High Cardiovascular Risk

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To obtain reliable data on the epidemiology, co-morbidities and risk factor profile of peripheral arterial disease (PAD), we evaluated the clinical significance of the ankle brachial index (ABI) as an indicator of PAD in Chinese patients at high cardiovascular (CV) risk. ABI was measured in 5,646 Chinese patients at high CV risk, and PAD was defined as an ABI<0.9 in either leg. Multivariable logistic regression analyses were performed to identify factors associated with PAD. A total of 5,263 patients were analyzed, 52.9% male, mean age 67.3 years, mean body mass index (BMI) 24.2 kg/m^2, mean systolic/diastolic blood pressure (SBP/DBP) 139/80.7 mmHg. The prevalence of PAD in the total group of patients was 25.4%, and the prevalence was higher in females than in males (27.1% *vs.* 23.9%; odds ratio [OR]: 1.64). Patients with PAD were older than those without PAD (72.3±9.9 years *vs.* 65.6±11.7 years; OR: 1.06), and more frequently had diabetes (43.3% *vs.* 31.3%; OR: 2.02), coronary heart disease (CHD) (27.0% *vs.* 18.8%; OR: 1.67), stroke (44.4% *vs.* 28.3%; OR: 1.78), lipid disorders (57.2% *vs.* 50.7%; OR: 1.3) and a smoking habit (42.7% *vs.* 38.6%; OR: 1.52). The ORs for the PAD group compared with the non-PAD group demonstrated that these conditions were inversely related to ABI. Statin, angiotensin-converting enzyme-inhibitors and antiplatelet agents were only used in 40.5%, 53.6% and 69.1% of PAD patients, respectively. The data demonstrated the high prevalence and low treatment of PAD in Chinese patients at high CV risk. A lower ABI was associated with generalized atherosclerosis. Based on these findings, ABI should be a routine measurement in high risk patients. Aggressive medication was required in these patients. (*Hypertens Res* 2006; 29: 23–28)

***Key Words*: ankle brachial index, atherosclerosis, peripheral artery disease, risk factors**

Introduction

Atherosclerotic diseases are the main cause of mortality worldwide. Peripheral arterial disease (PAD) is an important manifestation of systemic atherosclerosis. In this context, the importance of the early identification and treatment of PAD has been increasingly acknowledged recently (*1–12*). Limb loss due to necrosis is very rare in PAD patients, and more importantly, PAD is a powerful predictor of future cerebrovascular and cardiovascular (CV) events such as myocardial infarction and stroke, and of increased mortality. A recent

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Table 1. Baseline Characteristics and Univariate Analysis of Patients

Risk factors	ABI≥0.9 (*N*=3,927)	ABI<0.9 (*N*=1,336)	Total (*N*=5,263)	*p* value
ABI	1.09±0.10	0.86±0.19	1.03±0.16	<0.0001
Age (years)	65.6±11.7	72.3±9.9	67.3±11.7	<0.0001
Gender				
M	2,120 (54.0%)	665 (49.8%)	2,785 (52.9%)	0.0077
F	1,807 (46.0%)	671 (50.2%)	2,478 (47.1%)	
SBP (mmHg)	138±22.27	143±24.59	139±22.95	<0.0001
DBP (mmHg)	80.9±12.26	80.3±12.98	80.7±12.45	0.1618
PP (mmHg)	57.5±17.35	62.3±19.76	58.7± 18.11	<0.0001
TC (mmol/l)	4.56±1.07	4.60±1.08	4.57±1.07	0.2302
TG (mmol/l)	1.58±0.87	1.61±0.90	1.59±0.88	0.2816
HDL-C (mmol/l)	1.19±0.35	1.16±0.34	1.18±0.35	0.0288
LDL-C (mmol/l)	2.70±0.81	2.72±0.83	2.71±0.82	0.6592
BUN (μmol/l)	6.34±4.85	7.25±4.75	6.57±4.84	<0.0001
CRE (μmol/l)	92.20±69.26	106.28±80.93	95.77±72.65	<0.0001
UA (mmol/l)	316.35±112.06	339.35±125.01	322.19±115.91	<0.0001
BG (mmol/l)	6.22±2.61	6.52±2.75	6.30±2.65	0.0004
BMI (kg/m^2)	24.33±3.577	23.76±3.781	24.18±3.64	<0.0001
Diabetes history	1,229 (31.3%)	578 (43.3%)	1,807 (34.3%)	<0.0001
Hypertension history	2,749 (70%)	1,057 (79.1%)	3,806 (72.3%)	<0.0001
Stroke history	1,111 (28.3%)	593 (44.4%)	1,704 (32.4%)	<0.0001
PAD history	78 (2.0%)	76 (5.7%)	154 (2.9%)	<0.0001
Lipid disorder	1,312 (33.4%)	462 (34.6%)	1,774 (33.7%)	0.1457
CHD history	738 (18.8%)	361 (27.0%)	1,099 (20.9%)	<0.0001
Smoke habits	1,517 (38.6%)	570 (42.7%)	2,087 (39.7%)	0.0248
Statin use	1,403 (35.7%)	541 (40.5%)	1,944 (36.9%)	0.0077
ACEI use	1,753 (44.6%)	716 (53.6%)	2,469 (46.9%)	<0.0001
Antiplatelet use	2,518 (64.1%)	923 (69.1%)	3,441 (65.4%)	0.0041

ABI, ankle-brachial index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; CRE, creatinine; UA, uric acid; BG, blood glucose; BMI, body mass index; PAD, peripheral arterial disease; CHD, coronary heart disease; ACEI, angiotensin-converting enzyme-inhibitor.

publication by the Prevention of Atherothrombotic Disease Network (*10*) highlighted the need for improving detection and treatment of PAD as a largely underdiagnosed and undertreated deleterious disease.

Patient history and physical examination are limited by a lack of consistent sensitivity and specificity for diagnosing PAD (*2*). Ankle brachial index (ABI) can be used as a noninvasive method of assessing PAD (*1–8*). When compared to angiography, the sensitivity of ABI for detecting PAD is about 90%, and the specificity is about 98% (*3*). It is already known that an inverse relationship exists between ABI and cardiovascular diseases (CVDs) and that ABI can be a marker for generalized atherosclerotic disease (*4–10*, *13–15*). However, this correlation has not been thoroughly investigated in Chinese patients with CVD or high CV risk factors.

The aims of the present study were to evaluate the relationship between ABI and CVD, and to determine whether noninvasive measurement of ABI can be a useful approach to screening Chinese patients with high risk for generalized atherosclerosis.

Methods

Subjects

This investigation is based on a large-scale epidemiological study in China with cross-sectional and longitudinal parts. 5,646 Chinese patients over 50 years of age with two or more CV risk factors who attended the inpatient department in Tongji University Hospitals (Shanghai) and Beijing University Hospitals (Beijing) were sequentially enrolled in the study. All subjects were inpatients from the Departments of Cardiology, Coronary Care Unit, Intensive Care Unit, Endocrinology, Renal Disease, Neurology, Vascular Disease, *etc.*, and were admitted to the hospital because of hypertension, hyperlipidemia, diabetes, stroke, acute coronary syndrome, renal disease, and so on. ABI was measured between October 2004 and January 2005. Informed consent was obtained from all subjects and the clinical data were collected cross-sectionally from medical records.

Risk factors included obesity, smoking, diabetes, hypertension, and lipid disorders. The weight and height of subjects were measured while they were wearing light clothes and no shoes. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Obesity was defined as BMI over 30 kg/m^2. Smoking habits were recorded, and smokers were considered those who smoked at least 10 cigarettes a day. Total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were determined using standard laboratory techniques.

Lipid disorder was defined as TC>5.7 mmol/l, TG>1.7 mmol/l, LDL-C>3.6 mmol/l, or HDL-C<0.9 mmol/l or treatment with antihyperlipidemic agents.

Type 2 diabetes was defined as 1) a fasting plasma glucose concentration of >7.0 mmol/l in the absence of treatment; 2) a plasma glucose concentration of ≥11.0 mmol/l, 2 h after a 75 g oral glucose load; or 3) current treatment with glucose-lowering drugs. All selected subjects had no history of ketoacidosis.

The presence of underlying coronary heart disease (CHD) was defined as a history of a physician-diagnosed heart attack, evidence of prior myocardial infarction by electrocardiogram or self-reporting of a prior coronary revascularization procedure (percutaneous coronary artery intervention [PCI] or coronary-artery bypass surgery [CABG]).

Hypertension was defined as a systolic blood pressure (SBP) of ≥140 mmHg, a diastolic blood pressure (DBP) of ≥90 mmHg or the current use of antihypertensive drugs to control hypertension (according to WHO criteria).

Prior peripheral arterial disease was defined as intermittent claudication (IC; *i.e.*, pain in the calf muscles while walking or during other exertion and disappearing within 10 min at rest), revascularization procedures on the peripheral arteries, previous abnormal ABI, previous vascular laboratory diagnosis of PAD or previous lower-limb arterial revascularization.

Ankle Brachial Index at Rest

The investigators were specifically trained to perform ABI measurements under standardized conditions. A standardized Doppler ultrasonic device was used (5 MHz; Nicolet Vascular, Elite100R, USA).

Measurements were carried out after a 5-min rest in the supine position with the upper body as flat as possible. The ABI was calculated as the ratio of the higher of the two systolic pressures (tibial posterior and anterior artery) above the ankle to the average of the right and left brachial artery pressures, unless there was a discrepancy ≥10 mmHg in blood pressure values between the two arms. In such cases, the higher reading was used for ABI. Pressures in each leg were measured and ABIs were calculated separately for each leg. In the case of a missing ABI value in one leg, the value from the other was used, and the missing brachial artery pressure values in one arm were dealt with in the same manner. Accordingly, in the case of a missing artery pressure value (tibial posterior or anterior) above the ankle in one leg, the other was used for the calculation of the side-specific ABI.

All patients had ankle and arm blood pressures recorded using a blood pressure cuff and a Nicolet handheld Doppler; and the ABI was calculated. PAD was defined as an ABI of <0.9 in at least one leg (*7*). The lower ABI between the two legs was used as the index ABI. Subjects were assigned to one of two groups according to their ABI level as follows: ABI≥0.9 and ABI<0.9.

Statistical Analysis

Continuous variables were given as the mean±SD. The variables included in the analysis were age, gender, BMI, smoking habits, the presence of hypertension, diabetes and hyperlipidemia. Stepwise logistic regression analysis, which included variables that identified as statistically significant in the univariate analysis, was used to assess the independence of the association with PAD, and the corresponding odds ratios (ORs) and/or their 95% confidence intervals (CI) were calculated. The results were compared between the ABI<0.9 group and the ABI≥0.9 group. Statistical analysis was performed using SAS version 8.02 software, and values of $p<0.05$ were considered to indicate statistical significance.

Results

Peripheral Arterial Disease Prevalence

Table 1 lists the baseline characteristics of patients with and without a decreased ABI, the results of the univariate analysis of comorbidity and treatment, and the levels of statistical significance. 5,646 patients were included in the study; those with an ABI>1.4 ($n=192$) were excluded because of the possibility that rigidity and calcium in the peripheral arteries could falsely elevate ABI in the elderly, and 191 patients were excluded due to missing data. Thus a total of 5,263 patients were included in the statistical analysis. 47.1% of the 5,236 patients were female, and the mean age and mean BMI were 67.3±11.7 years and 24.18±3.64 kg/m^2, respectively. 39.7% of the patients were smokers, 25.4% were diabetics, 64.5% had hypertension, 33.7% had lipid disorders, and 1,336 (25.4%) of patients had PAD according to the study definition (ABI<0.90). The prevalence of PAD was higher in females (27.1%) than in males (23.9%). 17.9% of PAD patients were symptomatic according to the ROSE questionnaire.

The mean value of ABI was 1.03±0.16 in all patients, 1.09±0.10 in the non-PAD group, and 0.86±0.19 in the PAD group. The difference was significant between the PAD and non-PAD group.

Table 2. Risk Factors and Comorbidities Associated with PAD in Multiple Logistic Regression Analysis

Risk factors	OR	95% CI	*p* value
Women	1.64	1.39–1.93	<0.001
Age	1.06	1.05–1.06	<0.001
BMI	0.96	0.94–0.98	<0.001
CHD	1.67	1.42–1.95	<0.001
Stroke	1.78	1.55–2.04	<0.001
Diabetes	1.76	1.53–2.02	<0.001
Smoking	1.52	1.29–1.79	<0.001
TC	1.11	1.04–1.19	0.0017
HDL-C	0.77	0.62–0.95	0.016
Creatinine	1.002	1.001–1.003	0.0013
BUN	1.008	0.992–1.024	0.3294
Uric acid	1.001	1.001–1.002	<0.001

PAD, peripheral arterial disease; OR, odds ratio; CI, confidence interval; BMI, body mass index; CHD, coronary heart disease; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; BUN, blood urea nitrogen.

There were also significant differences in SBP, pulse pressure, HDL-C, blood urea nitrogen (BUN), creatinine (CRE), uric acid and fasting blood glucose between the PAD and non-PAD group.

Patients with PAD were older, had a higher mean SBP (but not DBP) and pulse pressure, and comprised a higher proportion of smokers. The proportion of patients in the PAD group with concomitant diabetes mellitus, clinical hypertension, and lipid disorders was also higher (Table 1).

Risk Factors and Co-Morbidity

Table 2 shows the adjusted ORs of CV risk factors and comorbidity. After adjusting for other risk factors, female sex, age, BMI, CHD, stroke, diabetes, smoking, TC, HDL-C, CRE and uric acid were significantly associated with PAD. The prevalence of PAD was higher in females than in males (27.1% *vs*. 23.9%; OR: 1.64). Patients with PAD were older than those without PAD (72.3±9.9 years *vs*. 65.6±11.7 years; OR: 1.06), and more frequently had diabetes (43.3% *vs*. 31.3%; OR: 2.02), CHD (27.0% *vs*. 18.8%; OR: 1.67), stroke (44.4% *vs*. 28.3%; OR: 1.78), lipid disorders (57.2% *vs*. 50.7%; OR: 1.3), a smoking habit (42.7% *vs*. 38.6%; OR: 1.52) and BMI (23.7±3.8 *vs*. 24.3±3.6; OR: 0.96). The comparison between the ORs for the PAD group and those for the non-PAD group demonstrated that these conditions were inversely related to ABI.

As shown in Table 1, CHD was present in 27% of PAD patients and 18.8% of non-PAD patients ($p<0.001$); for stroke, these values were 44.4% *vs*. 28.3% ($p=0.035$); for diabetes, 43.3% *vs*. 31.3% ($p<0.001$); and for hypertension, 79.1% *vs*. 70% ($p<0.001$). Conversely, no group difference was observed for lipid disorder (33.4% *vs*. 34.6%, $p=0.1457$). After multiple logistic regression analysis, female sex, older age, BMI, TC, HDL-C, CRE, uric acid, CHD, stroke, diabetes, and smoking were related with PAD. Among these, HDL-C and BMI were protective factors.

Treatments

As shown in Table 1, compared with those of the ABI≥0.9 group, a higher number of patients in the ABI<0.9 group took antiplatelet medication (64.1% *vs*. 69.1%, $p<0.005$), statins (35.7% *vs.* 40.5%, $p=0.007$) and angiotensin-converting enzyme-inhibitors (ACEIs) (44.6% *vs*. 53.6%, $p<0.001$). It is noteworthy that among all high risk patients, only 65.4%, 36.9%, and 46.9% received antiplatelet, statin and ACEI treatment, respectively.

Discussion

This is the first large-scale study on Chinese patients with high CV risk. We demonstrated that a lower ABI was associated with age, female sex, stroke, CHD, diabetes, smoking, TC, HDL-C and renal function. Our data suggest that measurements of ABI might be useful indicators of systemic atherosclerosis in Chinese patients with cardiovascular risk factors. Previous studies (*4–9*) reported that ABI could be used to diagnose atherosclerotic PAD, which was associated with CV events and risk factors. The present report is consistent with these observations.

Because our study population consisted only of relatively old hospitalized patients, it is not fully generalizable to the population at large. Nonetheless, our results clearly showed that the prevalence of PAD in patients at high risk for CVD is substantial. On average, about every fourth patient (25.4%) had an ABI<0.9. Other studies (*4*, *16–20*) have investigated different populations, but have consistently confirmed the high and underestimated prevalence of PAD. For example, in the Rotterdam study (*16*) on 7,715 individuals ≥55 years old, who were identified from a registry, the prevalence of PAD was 19.1%; in the Limburg PAOD study (*17*) employing

3,171 primary-care patients aged 45–74 years old, the prevalence was 6.9%; and in the Cardiovascular Health Study (*18*) with 5,888 Medicare patients ≥65 years old the prevalence was 13.4%. The PARTNERS program (*19*) investigated a considerably more selective patient group, namely, GP patients aged >70 years old as well as high risk patients (*e.g.*, patients with diabetes) aged 50–69 years old, and reported a PAD prevalence of 29%. Stavros *et al*. (*21*) reported a prevalence as high as 36% in 990 Greek hospitalized patients aged 50 years or older; however, their sample size was far smaller than that of our study, and thus the results of our study might be more convincing.

Smoking is considered to be one of the most significant risk factors for CVD; in our study, smokers appeared to have a 1.52-fold higher risk of developing PAD than non-smokers.

According to Framingham data, hypertension increases the risk of PAD by a factor of 2.5 in males and 3.9 in females. In our study, univariate regression analysis showed that SBP was associated with PAD, but logistic regression analysis showed that there were no significant difference between two groups. We will continue to observe the relationship between blood pressure and PAD during follow-up.

In the present study, the prevalence of PAD was higher in females (27.1%) than in males (23.9%), which was inconsistent with other studies (*17–27*). A possible explanation for this finding is that the patients in our study were older (mean age, 67.3 years old), and the postmenopausal females probably had a higher risk of atherosclerosis than the males had. We will examine the gender difference in ABI and its associations with CV risk factors and manifestations in a further longitudinal part of our study.

Only 65.4%, 36.9% and 46.9% of high risk patients and 69.1%, 40.5%, and 53.6% of PAD patients were receiving antiplatelet, statin and ACEI treatment, respectively, and only 5.7% of PAD patients had been diagnosed. 17.9% of the PAD patients were symptomatic, and 60% of these patients were unaware of their condition despite being symptomatic, confirming that in China PAD is also an under-recognized and under-treated condition, as observed in other countries (*10*, *13–19*). As outlined by the Prevention of Atherothrombotic Diseases Network, patient and physician education are needed to improve the identification of patients with symptomatic PAD and increase the awareness of its consequences. Such a policy will contribute to improving the prognosis of a group of patients at elevated CV risk.

There are certain limitations to our study. Because this was the cross-sectional part of our investigation, we could not determine whether ABI could predict CV events. Further longitudinal studies will reveal the clinical significance of the ABI. ABI may be normal at rest despite hemodynamically significant arterial stenosis, yet decline following calf muscle exercise. For this reason, ABI should be measured following exercise.

Our study suggests that ABI might be a marker of atherosclerosis. Furthermore, non-invasive measurements of ABI can provide an accurate indication of CV abnormality and might be used to screen for atherosclerotic diseases in Chinese patients with risk factors. The numbers of patients with CVD has been increasing in China due to recent changes in diet and lifestyle. Therefore, the screening tests for atherosclerosis described in the present report might be particularly useful in the future.

Because PAD is an under-diagnosed and under-treated condition in China, ABI measurement should be a routine part of the clinical evaluation of high risk patients. Atherosclerotic risk factors such as diabetes, hypercholesterolemia and hypertension can and should be treated adequately, and smoking should be strongly discouraged.

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