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Aortic Augmentation Index is Associated with the Ankle Brachial Index; A Community Based Study

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Abstract

Background—Increased arterial stiffness has been associated with greater risk of cardiovascular events. We investigated whether aortic augmentation index (AIx), a measure of arterial stiffness and wave reflection, was associated with the ankle-brachial index (ABI), a measure of peripheral arterial disease (PAD).

Method—AIx and ABI were measured in a community-based sample of 475 adults without prior history of heart attack or stroke (mean age 59.3 years, 46.5% men). Radial artery pulse waveforms were obtained by applanation tonometry and an ascending aortic pressure waveform derived by a transfer function. AIx is the difference between the first and second systolic peak of the ascending aortic pressure waveform indexed to the central pulse pressure. ABI was measured using a standard protocol, and subjects with non-compressible vessels (ABI >1.5) were excluded from the analyses. Multivariable linear and logistic generalized estimating equations (GEE) analyses were used to assess whether AIx was associated with ABI and ABI <1.00 respectively, independent of conventional risk factors.

Results—Mean ($\pm$ SD) values were: AIx, 29.3 $\pm$ 11.6 %; ABI, 1.12 $\pm$ 0.13; 59 (12.4%) participants had an ABI <1.00. Variables associated with a lower ABI (and ABI <1.00) included older age, shorter height, female sex, higher total cholesterol, hypertension medication use, history of smoking, and higher AIx. After adjustment for mean arterial pressure and the above variables, higher AIx remained associated with a lower ABI ($P=0.015$) and ABI <1.00 ($P=0.002$). A significant interaction ($P=0.007$) was present between AIx and age in the prediction of ABI; the (inverse) association of AIx with ABI was stronger in older subjects (>65 years).

Conclusion—AIx, a measure of arterial stiffness and wave reflection, was independently associated with a lower ABI in asymptomatic subjects from the community, and this association was modified by age.

Keywords

arterial stiffness; ankle-brachial index; arteries

1. Introduction

Blood pressure increases with distance from the heart because of increased impedance resulting from tapering of arterial diameter [1]. Consequently, the systolic blood pressure

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(SBP) in the posterior tibial artery at the ankle is higher than in the brachial artery at the elbow. An ankle-brachial index (ABI) <1.00 is therefore abnormal, although a cut off <0.90 or <0.95 has greater specificity and is used to make the diagnosis of peripheral arterial disease (PAD) in the clinical setting. ABI is a simple, noninvasive method used to assess the presence and extent of PAD [2], and prospective studies have shown that a low ABI predicts fatal and non fatal coronary heart disease (CHD) and all cause mortality [3–9].

Increased arterial stiffness results in higher transmission velocities of both forward and reflected arterial pulse waves causing the reflected waves to arrive earlier in the central aorta and augment pressure in late systole [10]. The augmentation of central aortic systolic pressure is typically quantified as the increase of pressure from the first systolic shoulder to the systolic pressure peak of the aortic pressure waveform and is expressed as a percentage of central aortic pulse pressure (augmentation index (AIx)) [11]. A greater AIx is an indicator of the additional load imposed on the left ventricle by the reflected wave and is correlated with left ventricular mass [12, 13]. AIx has also been found to correlate with CHD risk factors [14–18], coronary atherosclerosis [19, 20], and cardiovascular outcomes [21, 22]. AIx, determined non-invasively, has been shown to be associated with angiographic coronary artery disease in men <60 years [20] and to be predictive of mortality in patients with end-stage renal disease even after adjustment for pulse wave velocity [21].

In the present study, we investigated the association of AIx with ABI and low ABI (<1.00), adjusting for conventional risk factors, in asymptomatic subjects drawn from the community and without prior history of CHD or stroke. We hypothesized that a higher AIx would be associated with lower ABI in these subjects.

2. Methods

2.1. Study population

Subjects were participants in the Functional Arterial Changes in Atherogenesis Study which is examining the relationship of arterial function measures to subclinical disease measures and cardiovascular risk factors in non-Hispanic white subjects participating in the community-based Epidemiology of Coronary Artery Calcification (ECAC) study [23]. The ECAC study is an ongoing study of the pathogenesis of coronary artery calcification in Rochester, Minnesota. Participants are not physician or self-referred and were recruited from the community-based Rochester Family Heart Study [24, 25] independent of risk factor and disease status except they did not have a history of previous bypass surgery, angioplasty, or coronary surgery [26]. Between September 2002 and December 2005, 622 subjects from the ECAC study had completed the Functional Arterial Changes in Atherogenesis Study protocol, and ABI had been measured in 513 participants. We excluded 25 subjects with technically inadequate or missing AIx, 11 subjects who reported a history of previous myocardial infarction or stroke, and 2 participants who had outlier values of total cholesterol (>4 standard deviation from the median). The study group included 221 men and 254 women. Study protocols were approved by the Mayo Clinic Institutional Review Board, and participants gave written informed consent.

Weight was measured by an electronic balance, height by a stadiometer, and body mass index (BMI) was calculated in units of kg/m^2 . Resting blood pressure (BP) levels were measured in the right arm with random zero sphygmomanometer (Hawksley and Sons, West Sussex, UK), and pulse pressure and mean arterial pressure (MAP) were calculated. Blood samples were obtained by venipuncture after an overnight fast. Standard enzymatic methods were used to measure total cholesterol, high density lipoprotein (HDL)-cholesterol, and plasma glucose.

Information about medication use including aspirin, antihypertensive medications, statins, oral hypoglycemic agents, and insulin, was obtained at the time of the study visit. Type 2 diabetes was considered present if a subject was being treated with insulin or oral agents or had a fasting glucose level >125 mg/dL. “Ever” smoking was defined as having smoked ≥ 100 cigarettes in the past. The diagnosis of hypertension was determined based on BP levels measured at the study visit (SBP ≥ 140 mm Hg or diastolic BP (DBP) ≥ 90 mm Hg) or report of a prior diagnosis of hypertension and current treatment with antihypertensive medications.

2.2 Ankle-Brachial Index

Measurement of ABI was performed with the patient in the supine position. Appropriately sized BP cuffs were placed over each brachial artery and above each malleolus, and SBP was measured using a hand-held 5-MHz Doppler probe (Meda Sonics, Fremont CA). The higher of the 2 brachial SBPs was used to calculate the ABI at the posterior tibial artery and the dorsalis pedis artery in each leg. The lowest of the 4 ABIs from the 2 legs was used in the analyses. Subjects with ABI >1.5 were considered to have non-compressible vessels

2.3 Aortic Augmentation Index

Measurement of AIx was performed noninvasively with the SphygmoCor system (AtCor Medical, Sydney, Australia) after an overnight fast and 24 h off of any antihypertensive medications. Subjects were asked to omit caffeine beverages, smoking, and alcohol for at least 12 h before the assessment. An ascending aortic pressure waveform was derived from the radial artery waveforms recorded at the wrist using applanation tonometry with a high-fidelity micromanometer (Millar Instruments, Houston, TX) and a previously validated generalized transfer function [27, 28]. Aortic augmentation pressure was calculated as the difference between the first and second systolic peaks of the ascending aortic waveform, and AIx was expressed as a percentage of the central pulse pressure (the difference between central systolic and diastolic pressure). We and others have shown that AIx is reproducible when measured by radial tonometry [29, 30].

2.4. Statistical Methods

Descriptive statistics are given as mean and standard deviation (as well as range) or frequency and percent. Because the study participants belonged to sibships, the association of AIx and conventional risk factors (age, male sex, BMI, diabetes, smoking history, total cholesterol, and HDL cholesterol), BP medication use, statin use, height, heart rate, and mean arterial pressure with ABI were assessed by simple and multivariable linear regression using generalized estimating equations (GEE). First, simple regression models were used to identify variables associated with ABI. Next, we checked interactions between AIx and cardiovascular risk factors in the prediction of ABI with significance level of $P < 0.01$. We then constructed multivariable regression models including all of the above variables and any significant interactions between conventional risk factors and AIx, and performed stepwise backward elimination to identify variables independently associated with ABI. Because heart rate and MAP are known to be associated with measures of arterial stiffness and wave reflection [10, 31], these variables were forced into the multivariable regression models. All predictors were standardized in GEE models.

We graphically depicted the ensemble-averaged central aortic waveforms in subjects with ABI <1.00 and in those with ABI ≥ 1.00 . These waveforms were obtained by exporting the central aortic waveform of each individual from SphygmoCor as a text file and then calculating average values at 10 ms intervals as described by Hirata et al [32]. We also performed multivariable logistic GEE analyses to assess whether AIx was associated with ABI <1.00 after adjustment for conventional risk factors. Statistical analyses were carried

out using SAS v 8.2 (SAS Institute, Cary NC) software package. A two sided P -value of <0.05 was deemed statistically significant.

3. Results

The study sample consisted of 475 subjects. The mean age was 59.3 ± 9.9 years, 46.5% of the subjects were men, 26.3% were on BP medications, 4.6% had diabetes, 19.4% of subjects were on statins, and 43.8% had a history of smoking (Table 1). Higher AIX was significantly associated with a lower ABI ($P < 0.001$) as well as $ABI < 1.00$ ($P = 0.001$) in univariable analyses (Table 2). A one-standard deviation increase in AIX was associated with an odds ratio of 1.79 (95% confidence interval: 1.27, 2.53; $P = 0.001$) for having an abnormal ABI in univariable logistic regression analysis. Other variables associated significantly with lower ABI included greater age, female sex, shorter height, higher total cholesterol, and BP medication use (Table 2).

We noted a significant ($P = 0.001$) interaction between AIX and age in the prediction of ABI. This interaction remained significant ($P = 0.007$) after adjustment for conventional risk factors in the multivariable linear regression analyses (Table 3). The interaction indicated that the effect of AIX on ABI varied with age, being positive in younger subjects (age < 45 years) and inverse in older subjects. The significant, inverse association between AIX and ABI was stronger as age increased (the absolute value of stratified regression coefficient increased from 0.016 in the lower quartile of age to 0.036 in the upper quartile, Figure 1). Other covariates independently associated with lower ABI were lower BMI, shorter height, higher total cholesterol, lower HDL cholesterol, history of smoking, and BP medication use (Table 3).

Ensemble averaged central aortic pressure waveforms in subjects with $ABI < 1.00$; those with $ABI \geq 1.00$ are shown in Figure 2. In a multivariable logistic regression model, AIX was significantly ($P = 0.002$) associated with $ABI < 1.00$ (Table 4). A one-standard deviation increase in AIX was associated with an odds ratio of 1.86 (95% confidence interval, 1.25–2.75) for having an abnormal ABI. Other significant predictors of $ABI < 1.00$ were higher total cholesterol, lower HDL cholesterol, history of smoking, and BP medication use.

4. Discussion

The present study is the first to report an independent association between AIX (a measure of arterial stiffness and wave reflection) and ABI (a non-invasive quantitative measure of peripheral arterial disease (PAD)) in participants drawn from the community and without a previous history of myocardial infarction or stroke. In a study of 184 patients with CHD, those with low ABI (< 0.94) had higher AIX than patients with $ABI \geq 0.94$ ($23 \pm 18\%$ vs. $18 \pm 13\%$, $P < 0.05$) after adjustment for confounding variables [33]. Eldrup et al [34] reported that in 4,159 individuals from the general population, AIX was associated with a lower ABI after adjustment for age. Additional adjustment for CHD risk factors, height, and heart rate was not reported. We extend the finding of these two studies by demonstrating an association between AIX and ABI in asymptomatic subjects drawn from the community, independent of CHD risk factors. In addition, we report that this association is modified by age, being stronger with older age.

Factors such as aortic pulse wave velocity, number and branching pattern of arterioles, and vasomotor tone are important determinants of the timing and amplitude of arterial wave reflection [10, 35, 36]. Arterial wave reflection may have implications for cardiovascular risk since AIX has been found to be associated with the presence and extent of angiographic coronary artery disease in men aged < 60 years [20] and with cardiovascular events in

patients with renal disease [21]. Prospective studies will be needed to assess whether AIx provides prognostic information incremental to ABI in asymptomatic subjects and in patients with symptomatic PAD.

The positive correlation of AIx and ABI in subjects <45 years in our study may be because, at a younger age, both measures are influenced predominantly by wave reflection properties rather than risk factors for vascular disease. Increasing arterial taper and impedance with greater distance from the heart results in the ankle SBP being higher than brachial SBP and an ABI >1.0 [1]. With older age and the cumulative effect of vascular risk factors, the presence of arterial stenosis in the lower extremities may overcome the effect of wave reflection properties and thereby lower the ABI [37]. Concomitantly, with increasing age and exposure to CHD risk factors, AIx increases, and therefore, an inverse association between AIx and ABI manifests.

Given the relatively small number of subjects with a low ABI (20, 33, and 59 subjects had ABIs <0.90, <0.95, and <1.00 respectively), we defined abnormal ABI as an ABI <1.0. Subjects with ABI between 0.9–1.0 have a higher burden of CHD risk factor, higher cardiovascular event rates than those who have an ABI >1.0, and lower cardiovascular event rates than those who have an ABI <0.9 [38, 39]. We found similar associations between AIx and ABI <0.95 ($P=0.019$) and ABI <0.90 ($P=0.017$) in separate multivariable logistic regression models (analyses not shown).

Since AIx is a percentage of pulse pressure, we investigated whether central pressure augmentation is associated with ABI independent of pulse pressure. In multivariable linear and logistic regression models, aortic augmentation pressure was significantly (inversely) associated with ABI ($P=0.001$) and with ABI <1.00 ($P<0.001$) respectively. A one-standard deviation increase in aortic augmentation pressure was associated with an odds ratio of 1.83 (95% confidence interval: 1.41, 2.36; $P<0.001$) and 2.13 (95% confidence interval: 1.50, 3.02; $P<0.001$) for having an abnormal ABI in univariable and multivariable logistic regression analysis, respectively; the area under the receiver operating characteristics curve when using AIx to predict ABI<1.0 was 0.66. (analyses not shown).

The association of a higher BMI with a higher ABI was unexpected; however, a similar association was noted in the Cardiovascular Health Study [40]. A possible explanation could be an artifactual elevation in the ankle systolic pressure due to “non-compliant” leg arteries in subjects with BMI >35. In the present study, participants with ABI >1.3 had a significantly higher mean BMI compared to those with ABI <1.0 or ABI = 1.0–1.3 (analyses not shown). In a recent study, Wattanakit et al [41] also reported a similar trend in association between BMI and ABI in 14,777 participants from the Atherosclerosis Risk in Communities (ARIC) Study.

The finding that a higher AIx is associated with lower ABI suggests a relationship between arterial stiffness/wave reflection and lower extremity atherosclerotic burden. Because of the cross sectional nature of the present study, the direction of possible causation is difficult to infer. The presence of lower extremity atherosclerosis vascular disease may increase wave reflection. Alternatively, increased arterial stiffness and wave reflection may increase the risk of developing lower extremity PAD. Lastly, because both ABI and arterial stiffness share common determinants (such as age, sex, height, and adiposity), increased arterial stiffness, wave reflection, and PAD may develop concomitantly. Aortic pulse wave velocity (aPWV) is considered the “gold standard” measure of arterial stiffness, and further investigation is needed to assess whether aPWV is associated with ABI.

A strength of the present study is that the sample consists of asymptomatic subjects without history of myocardial infarction or stroke. Although subjects were off BP medications for 24

h prior to measurement of AIx, we cannot exclude the possibility of non-BP related effects of these medications on indices of arterial stiffness. However, we adjusted for use of BP medications by including this variable in the regression models. In addition, when we repeated analyses in the normotensive subjects (n=350), the results were similar (analyses not shown). Although there was a time interval between measurement of ABI and measurement of AIx (median = 21 weeks), one would not expect significant change to occur in ABI over such a period of time. Furthermore, when we included time interval as a variable in regression models, the inferences did not change (analyses not shown).

5. Conclusion

In conclusion, higher AIx – a measure of arterial stiffness and wave reflection – is independently associated with a lower ABI in a community based sample. The results of this study add to the growing body of evidence linking measures of arterial stiffness/wave reflection to subclinical atherosclerotic vascular disease. These findings motivate further studies of AIx as a measure of cardiovascular risk in asymptomatic individuals.

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Figure 1.

Univariable regression coefficients of association between Aix and ABI in analyses stratified by quartiles of age. The magnitudes of the regression coefficients were larger in higher age quartiles indicating the existence of an interaction between Aix and age in the prediction of ABI.

Figure 2. Ensemble averaged aortic pressure waveforms for subjects with ABI ≥ 1.00 (dashed line) and subjects with ABI < 1.00 (solid line).

Table 1

Subject characteristics (n = 475)

	Mean $\pm$ SD or no. (%)	Range
Age, (y)	59.3 $\pm$ 9.9	32 – 82
Men, n (%)	221 (46.5%)	
Body mass index, (kg/m ²)	28.2 $\pm$ 5.0	15.9 – 49.4
Height, (cm)	169.5 $\pm$ 9.5	147.0 – 198.1
Heart rate, (beats/min)	61.3 $\pm$ 8.5	40 – 93
Total cholesterol, (mg/dL)	197.7 $\pm$ 33.8	114.0 – 301.0
HDL cholesterol, (mg/dL)	56.4 $\pm$ 16.8	21.2 – 127.2
Diabetes, n (%)	22 (4.6%)	
Ever smoker, n (%)	208 (43.8%)	
BP medication use, n (%)	125 (26.3%)	
Statin use, n (%)	92 (19.4%)	
Systolic BP, (mm Hg)	121.4 $\pm$ 16.8	82.0 – 176.0
Diastolic BP, (mm Hg)	74.7 $\pm$ 9.1	54.0 – 108.0
Aortic augmentation index, (%)	29.3 $\pm$ 11.6	–10.0 – 54.0
Aortic augmentation pressure, (mm Hg)	11.9 $\pm$ 7.1	–3.0 – 39.0
Ankle-brachial index	1.12 $\pm$ 0.12	0.61 – 1.49
Ankle-brachial index <1.00, n (%)	59 (12.5%)	

Continuous variables are presented as means $\pm$ standard deviation and range, whereas categorical variables are presented as counts and percentages.

BP, blood pressure; HDL, high density lipoprotein

Table 2

Variables associations with ankle-brachial index: univariable regression models

	ABI		ABI < 1.0	
	$\beta \pm \text{SE}$	<i>P</i>	$\beta \pm \text{SE}$	<i>P</i>
Age, (y)	-0.027 $\pm$ 0.006	< 0.001	0.491 $\pm$ 0.183	0.007
Male sex	0.041 $\pm$ 0.012	0.001	-0.687 $\pm$ 0.313	0.028
Body mass index, (mg/m ²)	0.007 $\pm$ 0.006	0.26	0.174 $\pm$ 0.132	0.19
Height, (cm)	0.025 $\pm$ 0.006	< 0.001	-0.436 $\pm$ 0.148	0.003
Heart rate, (beats/min)	-0.006 $\pm$ 0.006	0.26	0.008 $\pm$ 0.128	0.95
Mean arterial pressure, (mm Hg)	-0.008 $\pm$ 0.006	0.15	0.061 $\pm$ 0.143	0.67
Total cholesterol, (mg/dL)	-0.018 $\pm$ 0.005	0.001	0.451 $\pm$ 0.130	0.001
HDL cholesterol, (mg/dL)	-0.005 $\pm$ 0.006	0.35	0.035 $\pm$ 0.148	0.81
Diabetes	-0.034 $\pm$ 0.028	0.22	0.475 $\pm$ 0.563	0.40
Ever smoker	-0.035 $\pm$ 0.012	0.004	0.637 $\pm$ 0.281	0.023
Hypertension medication use,	-0.048 $\pm$ 0.014	< 0.001	0.676 $\pm$ 0.280	0.016
Statin use	-0.019 $\pm$ 0.016	0.23	-0.185 $\pm$ 0.368	0.62
Aortic augmentation index, (%)	-0.030 $\pm$ 0.005	< 0.001	0.585 $\pm$ 0.175	0.001

The β coefficients represent the predicted response (ABI and ABI < 1.0) for a one standard deviation change in continuous variables and the presence versus absence differences in the case of categorical variables.

HDL, high density lipoprotein

Table 3

Predictors of ABI: multivariable linear regression

	$\beta \pm SE$	<i>P</i>
Age, (year)	-0.015 ± 0.008	0.052
Body mass index, (kg/m ²)	0.015 ± 0.007	0.032
Height, (m)	0.015 ± 0.008	0.059
Heart rate, (beats/min)	-0.006 ± 0.006	0.31
Mean arterial pressure, (mm Hg)	-0.003 ± 0.006	0.60
Total cholesterol, (mg/dL)	-0.016 ± 0.006	0.006
HDL cholesterol, (mg/dL)	0.014 ± 0.007	0.028
Ever smoker	-0.035 ± 0.012	0.003
Hypertension medication use	-0.025 ± 0.014	0.079
Aortic augmentation index, (%)	-0.020 ± 0.008	0.015
Aortic augmentation index*age	-0.013 ± 0.005	0.007

Model was built from the following variables: AIX, age, sex, body mass index, height, resting heart rate, mean arterial pressure, total cholesterol, HDL cholesterol, diabetes, history of smoking, BP medication use, statin use, and AIX-age interaction. Variables, apart from resting heart rate, mean arterial pressure and age, were removed one-at-a-time until all remaining variables were significant at $P \leq 0.10$. See text for description of models. The β coefficients represent the amount of change in predicted response (ABI) for a one standard deviation change in continuous variables and the presence and absence difference in the case of a categorical variable.

HDL, high density lipoprotein

Table 4

Predictors of ABI < 1.00: multivariable logistic regression

	$\beta \pm SE$	<i>P</i>
Heart rate, (beats/min)	0.064 $\pm$ 0.261	0.68
Mean arterial pressure, (mm Hg)	-0.114 $\pm$ 0.154	0.46
Total cholesterol, (mg/dL)	0.524 $\pm$ 0.138	< 0.001
HDL cholesterol, (mg/dL)	-0.251 $\pm$ 0.142	0.077
Ever smoker	0.544 $\pm$ 0.289	0.060
Hypertension medication use	0.638 $\pm$ 0.320	0.046
Aortic augmentation index, (%)	0.619 $\pm$ 0.200	0.002

Model was built from the following variables: AIX, age, sex, body mass index, height, resting heart rate, mean arterial pressure, total cholesterol, HDL cholesterol, diabetes, history of smoking, BP medication use, and statin use. Variables, apart from resting heart rate and mean arterial pressure, were removed one-at-a-time until all remaining variables were significant at $P \leq 0.10$. See text for description of models. The β coefficients represent the amount of change in predicted response (ABI $\leq$ 1.00) for a one standard deviation change in continuous variables and the presence and absence difference in the case of a categorical variable.

HDL, high density lipoprotein