Title

Arterial compliance across the spectrum of ankle-brachial index: The multiethnic study of atherosclerosis

Journal

Atherosclerosis, 233(2)

ISSN

0021-9150

Authors

Lilly, Scott M
Jacobs, David R
Kronmal, Richard
et al.

Publication Date

2014-04-01

DOI

10.1016/j.atherosclerosis.2014.01.029

Peer reviewed

HHS Public Access

Author manuscript

Atherosclerosis. Author manuscript; available in PMC 2018 July 12.

Published in final edited form as:

Atherosclerosis. 2014 April ; 233(2): 691–696. doi:10.1016/j.atherosclerosis.2014.01.029.

Arterial Compliance Across the Spectrum of Ankle-Brachial Index: The Multiethnic Study of Atherosclerosis

Scott M. Lilly, MD, PhD[a], **David R. Jacobs Jr., PhD**[b], **Richard Kronmal, PhD**[c], **David A. Bluemke, MD**[d], **Michael Criqui, MD MPH**[e], **Joao Lima, MD**[d], **Matthew Allison, MD MPH**[e], **Daniel Duprez, MD PhD**[f], **Patrick Segers, PhD**[g], and **Julio A. Chirinos, MD, PhD**[h]

[a]Division of Cardiovascular Medicine, Ohio State University Heart and Vascular Center, Columbus OH

[b]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, MN

[c]Department of Biostatistics, University of Washington, Seattle, WA

[d]Departments of Radiology and Medicine, John Hopkins University School of Medicine, Baltimore, MD

[e]Division of Preventive Medicine, University of California, San Diego, San Diego, CA

[f]Cardiovascular Division, University of Minnesota, MN

[g]Institute Biomedical Technology, Ghent University, Gent, Belgium

[h]Hospital of the University of Pennsylvania, Philadelphia, PA

Abstract

Objective—A low ankle-brachial index is associated with cardiovascular disease and reduced arterial compliance. A high ankle-brachial index is also associated with an increased risk of cardiovascular events. We tested the hypothesis that subjects with a high ankle-brachial index demonstrate a lower arterial compliance. In addition, we assessed whether pulse pressure amplification is increased among subjects with a high ankle-brachial index.

Methods—We studied 6,814 adults enrolled in the multiethnic study of atherosclerosis who were, by definition, free of clinical cardiovascular disease at baseline. Differences in total arterial compliance (ratio of stroke volume to pulse pressure), aortic and carotid distensibility (measured with magnetic resonance imaging and duplex ultrasound, respectively) were compared across ankle-brachial index subclasses (≤0.90, 0.91–1.29; ≥1.30) with analyses adjusted for cardiovascular risk factors and subclinical atherosclerosis.

Correspondence. Julio A. Chirinos, MD, PhD, Room 8B111, 5800 Woodland Ave, Philadelphia, PA. 19104, Phone: 215-823-5800, julio.chirinos@uphs.upenn.edu.

Conflict(s) of Interest/Disclosure(s): None declared

Results—Peripheral arterial disease was detected in 230 (3.4%) and high ABI in 648 (9.6%) of subjects. Those with high ankle-brachial index demonstrated greater aortic-radial pulse pressure amplification than those with a normal ankle-brachial index. In adjusted models aortic and carotid distensibility as well as total arterial compliance, were lowest among those with ankle-brachial index ≤ 0.9 ($p < 0.01$ vs. all), but were not reduced in subjects with an ankle-brachial index ≥1.3.

Conclusion—Lower aortic, carotid and total arterial compliance is not present in subjects free of overt cardiovascular disease and with a high ankle-brachial index. However, increased pulse pressure amplification contributes to a greater ankle-brachial index in the general population and may allow better characterization of individuals with this phenotype.

Keywords

Cardiovascular disease; medial artery calcification; vascular compliance; atherosclerosis

1. Introduction

A high ankle-brachial index (ABI) is associated with increased cardiovascular disease (CVD) risk and mortality in population cohort studies[1,2,3,4]. A high ABI has been associated with increased left ventricular mass, chronic kidney disease, stroke and microvascular disease among healthy populations and diabetics, in some cases independently of atherosclerosis[3,5–6]. These patterns of end-organ damage differ from those associated with lower extremity atherosclerosis, and in many cases are associated with arterial stiffness and abnormal central (aortic) hemodynamics[7,8,9]. Moreover, although a high ABI is thought to reflect stiff, non-compressible infrageniculate arteries[10,11], it may not reflect similar changes in large artery stiffness. Indeed, differential changes in the stiffness of muscular and large arteries occur with aging and with various risk factors[12].

An additional important question regarding the phenotype of high ABI is the mechanism that leads to a greater systolic blood pressure in the ankle than in the arm. Although in clinical populations with a high prevalence of vascular disease calcification and incompressibility of infrageniculate arteries has been implicated[10,11], this is probably less likely in the general population. Normally, the pulse pressure amplifies (and systolic blood pressure increases) as the energy wave generated by the heart travels to the periphery with summation of forward and reflected waves. Accordingly, higher ankle systolic pressures may simply reflect exaggerated amplification of the pressure pulse in some individuals, which increases ankle pressure relative to brachial pressure due to the comparably longer traveling paths[13,14]. Whether a high ABI is related to exaggerated pulse pressure amplification (PPA) has not been investigated.

Given the incomplete understanding of the underlying phenotypes among adults with a high ABI in the general population, we aimed to assess whether a high ABI is associated with: (1) A reduction in the compliance of central arteries; (2) Exaggerated PPA; (3) Evidence of calcification or atherosclerosis in coronary and non-coronary vascular beds.

2. Materials and Methods

MESA Study Design

The MESA study design has been previously described[15]. Briefly, MESA is a prospective observational cohort study designed to identify the prevalence, risk factors, and progression of subclinical atherosclerosis in a diverse population. Individuals from different ethnic groups (white, Chinese, black, Hispanic) were recruited between July 2000 and August 2002 from 6 geographical centers across the United States. All participants provided informed consent, and MESA was approved by the institutional review boards of each recruiting center.

Definition of Variables

Demographic and clinical variables (medical history, ethnicity, medication use) were obtained from standardized questionnaires. Smoking was determined by patient history, and categorized as current, former or never. Brachial blood pressures were collected in the seated position, after a subject had been resting for at least 5 minutes. Fasting blood samples were collected for determination of total, high-density lipoprotein cholesterol and triglyceride levels, as well as serum glucose and creatinine. Low-density lipoprotein cholesterol concentration was calculated by the Friedewald equation. Hypertension was defined according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (>140/90 or current anti-hypertensive medication use)[16], and diabetes mellitus was defined as elevated fasting glucose (>126 mg/dl) or the use of oral or subcutaneous hypoglycemic. Estimated glomerular filtration rate was determined by the abbreviated Modification of Diet in Renal Disease formula[17].

Ankle Brachial Index

For ankle-brachial index, a hand-held Doppler and with the participant in the supine position, systolic blood pressure measurements were collected in bilateral arms, posterior tibial and dorsalis pedis arteries. The ABI was defined as the higher of two ankle pressures divided by the mean of two brachial artery pressures, unless right and left brachial systolic pressures differed by >10 mmHg, in which case the higher value was used in the denominator18. Individuals with ABI values >1.3 or <0.9 in either limb comprise the high and low subgroups, respectively, while those with ABI values between 0.91–1.29 in both limbs comprise the normal ABI subgroup. The cutpoint of 1.3 for defining a high ABI has been used previously[19,20] and was chosen over a cutpoint of 1.4 given the limited number of subjects with ABI >1.4. When the ABI was analyzed by 5 subgroups (<0.90, 0.90–1.00, 1.01–1.30, 1.31–1.40, >1.40), the mean ABI was used for individuals between 1.0 and 1.29, and those with individuals with opposing limbs < 0.9 and > 1.3 were excluded.

Total Arterial Compliance, Pulse Pressure and Pulse Pressure Amplification

Central aortic pressure waveforms were derived using a generalized transfer function applied to the radial pressure waveform acquired using arterial tonometry as previously described[21]. Aortic-radial pulse pressure amplification was computed as radial/aortic pulse pressure. Total arterial compliance was estimated using the left ventricular stroke volume divided by

the average brachial pulse pressure (collected before and after magnetic resonance imaging), and was expressed as ml/mmHg. Left ventricular stroke volume was assessed by magnetic resonance imaging using 1.5-Tesla scanners, with low inter-observer variability as previously described22. Brachial pulse pressure was recorded at commencement of magnetic resonance imaging. Sample size for total arterial compliance (TAC) analyses was limited to the 4,903 participants from whom magnetic resonance imaging data was available. TAC is more closely related to aortic, rather than brachial pulse pressure and therefore our TAC computations may have been affected by the variability in PPA. Therefore, comparisons were adjusted for PPA. Rather than attempting to compute a central pulse pressure value at the time of stroke volume measurements used for TAC computations, we elected to adjust for the population variability in PPA, which was assessed at a different time during the arterial tonometry procedure21.

Carotid and Aortic Distensibilty

Carotid distensibility was calculated from a 20-second acquisition of longitudinal images from the right distal common carotid artery. Carotid distensibility is defined as 2*(systolic – diastolic diameter)/(brachial pulse pressure × systolic diameter) as previously described[24,25]. Aortic distensibility was calculated by magnetic resonance imaging as previously described[26], and defined as [(Maximum area — Minimum area) / (Minimum area × brachial pulse pressure)]*1000. Electrocardiogram-gated cross-sectional images were obtained at the level of the right pulmonary artery. Brachial pulse pressure was the average systolic – diastolic pressure from brachial blood pressures collected immediately before and after imaging. All images were interpreted at a central reading center by readers blinded to clinical information. Because distensibility is related to central, rather than brachial pulse pressure and our computations may have been affected by the variability in PPA. Therefore, comparisons were adjusted for PPA.

Subclinical Atherosclerosis

Indices of subclinical atherosclerosis, including coronary artery calcification (CAC), common (CcIMT) and internal carotid intima medial thickness (IcIMT), and aortic wall calcification (AWC) were collected at baseline, and methods for the measurement of these quantitative phenotypes in MESA have been previously described[26,27,28]. Coronary artery calcification was evaluated by multi-detector CT or a gated electron-beam CT scanner, and indexed to a known calcium concentration placed in the field of view. The mean Agatston score was determined from consecutive scans by a radiologist or cardiologist at a central reading center (Harbor-UCLA Medical Center). Aortic wall calcification refers to calcification existing from the lower border of the pulmonary artery bifurcation to the cardiac apex, in both the ascending and descending aorta. These regions were imaged in tandem with every coronary calcium scan, and scored using the same definitions as coronary artery calcium28. For the analysis of intimamedial thickness, the right and left carotid arteries were analyzed with high-resolution B-mode ultrasonography and interpreted at a central center (Tufts-New England Medical Center)[28]. Carotid intima-media thickness is expressed as the mean maximum thickness of the anterior and posterior walls of the right and left common (CcIMT) and internal (IcIMT) carotid arteries.

Statistical Analysis

For statistical analysis, demographic and clinical features were compared across low (<0.9), normal (0.91–1.29) and high (>1.3) ABI subgroups. Categorical variables were expressed as percentages and continuous variables as medians with the inter-quartile range (25th and 75 percentiles) or means (standard deviation) as appropriate. For categorical variables, differences in demographic and clinical features between the ABI groups were compared with the chi-square test unless the expected value for any one cell was <10 in which case the Fisher's exact test was applied. For continuous variables, differences were analyzed using analysis of variance. *Post-hoc* testing for continuous variables was performed via least-standard difference. Analysis of covariance was used to test the relationship between ABI subgroups with TAC. Sequential models were as follows: Model 1 (age, sex, race/ethnicity, height and weight); model 2 additionally incorporated cardiovascular disease risk factors (LDL-C, HDL-C, hypertension, diabetes, heart rate, mean arterial pressure, anti-hypertensive medication use, smoking status, and estimated glomerular filtration rate); model 3 additionally incorporated subclinical atherosclerosis (CAC, AWC, CcIMT, IcIMT); and model 4 additionally incorporated PPA. CAC and AWC were rightward skewed, and were log-transformed for incorporation into the statistical models. SPSS 17.0 was used for all statistical analyses.

3. Results

There were 6,795 participants in MESA with ABI and compliance data (Table 1). Among these, the mean age was 62 years and 53% were female while 38% were Caucasian, 28% African American, 22% Hispanic and 12% Chinese. Two-hundred thirty participants had an ABI < 0.90 (3.4%) and 648 were found to have ABI > 1.3 (9.6%). Compared to those with normal ABI values (0.91 – 1.29), those with low ABI (<0.90) were older, more commonly African-American, and had a greater incidence of hypertension, diabetes, and current tobacco use. Those with elevated ABI values (>1.3) were more likely to be male, Caucasian, demonstrated a higher BMI and a lower incidence of hypertension and LDL-C levels. Systolic blood pressure, brachial pulse pressure and central pulse pressure had a graded and inverse relationship with ABI subclasses (Table 1). After adjustment for gender, subjects with a high ABI demonstrated a greater body height compared to those with a normal ABI (P<0.01), without significant differences in body height between subjects with normal vs. low ABI (P=0.49). Subjects with a high ABI demonstrated greater PPA than those with normal ABI (1.15 ± 0.11 vs 1.12 ± 0.10; p < 0.01; Table 1).

Subclinical coronary and carotid atherosclerosis across the ABI spectrum has been formerly reported in elegant detail[19]. The patterns of atherosclerotic calcification differed between ABI subclasses (Table 2). The prevalence of CAC was greater among those with either low (83.0%) or high ABI (56.6%) compared to those with normal ABI (47.5%, p<0.01 for both). However, the prevalence of AWC was higher only among those with low ABI (64.3%) but not high ABI (24.4%) compared to subjects with a normal ABI (26.7%; low vs normal p< 0.01; high vs normal p = 0.42). The severity of CAC and AWC showed similar relationships to ABI subclasses. With respect to indices of carotid atherosclerosis, CcIMT was greater among those with low ABI (1.05 ± 0.27 mm) compared to those with a normal ABI (0.86

± 0.19 mm; p< 0.01) but did not differ between those with normal and high ABI (high ABI 0.87 ± 0.22; p = 0.67). IcIMT showed had a similar relationship to ABI subclasses.

Total arterial compliance for the entire cohort was 1.64 ± 0.60 ml/mmHg, and varied by ABI subclass on unadjusted analysis (Table 3). A low ABI was associated with reduced TAC compared to those with normal ABI on unadjusted analysis (low ABI: 1.19 ± 0.04; normal ABI: 1.63 ± 0.59 ml/mm Hg, p < 0.01) and in models adjusted for age, sex, ethnicity, anthropomorphic features and cardiovascular risk factors. Upon adjustment for subclinical atherosclerosis, the association between low ABI and reduced TAC was no longer significant (low ABI 1.58 + 0.04, normal ABI 1.64 + 0.01 ml/mm Hg). A high ABI was associated with increased TAC in unadjusted models (high ABI 1.89 + 0.60; normal ABI 1.63 + 0.59 ml/mm Hg; p < 0.01), although this relationship was attenuated to non-significance with the incorporation of PPA (high ABI 1.70 + 0.02, normal ABI 1.65 + 0.01; p = 0.17).

On unadjusted analysis aortic (1.40 + 0.13/mm Hg × 10^3) and carotid distensibilty (1.96 + 0.93/mm Hg × 103) were lower among those with low ABI compared to normal ABI (1.87 + 0.013 and 2.53 + 1.1, respectively; p <0.01). However, these differences did not persist upon incorporation of age, gender, race and anthropomorphic variables (Tables 4 and 5). There were no differences in aortic or carotid distensibility among those with high compared to normal ABI on unadjusted analysis.

4. Discussion

We have identified reduced arterial compliance among individuals with low ABI, but not high ABI in a large sample of adults without overt cardiovascular disease from the general population. Individuals with low ABI (< 0.9) demonstrate increased incident CVD event rates and mortality[3,29] in tandem with reduced TAC[30,31,32,33]. Increased CVD events have also been observed in the high ABI phenotype both in healthy populations and those referred for evaluation of vascular disease[34,35,36] and in at-risk populations in whom ABI is preferentially performed[33]. Our findings suggest that the increased mortality and CVD event rates in this subgroup are not attributable to a reduction in aortic, carotid or total arterial compliance in a healthy population, an observation with important mechanistic and therapeutic implications.

TAC is primarily determined by large arteries, and has predictive value for CVD event and mortality rates in at-risk populations[37,38,39]. The relationship between lower extremity PAD and lower TAC identified herein is consistent with former studies[30,31,32,33], and illustrates both the systemic nature of arterial disease and a mechanism distinct from luminal narrowing by which end-organ damage might occur[40]. The absence of considerable differences in aortic and carotid distensibility among the ABI subclasses likely reflects native heterogeneity in muscular and elastic arteries composition and the risk factors associated with altered compliance.

An elevated ABI in populations at risk for vascular disease is thought to represent poorly compressible vessels that are histologically characterized by medial arterial calcification[10,11,41], a process associated with reduced arterial compliance and end-organ

damage in human and animal studies[8,42]. However, atherosclerosis and reduced arterial compliance often occur together, and discrimination is difficult due to the prevalence of CVD risk factors and the frequent overlap between atherosclerosis and medial arterial degeneration in the existing epidemiologic studies[6,35,41]. In the present cohort, a high ABI was not associated with extra-coronary subclinical atherosclerotic disease manifest by cIMT or aortic calcification[19]. Moreover, a notable finding of this study is that TAC was not reduced among subjects with an elevated ABI, even at cut-points where left ventricular hypertrophy or increases in aggregate CVD events have been reported[1,34]. Collectively, these findings suggest that although a high ABI is associated with increased CVD risk in populations with known or suspected vascular disease, this relationship is not generalizable to the healthy population represented herein.

The ABI was originally designed to detect an intra-arterial pressure drop across stenoses in the lower extremities that would non-invasively identify obstructive peripheral arterial disease. A high ABI was subsequently noted to occur in subjects with diabetes and calcified noncompressible vessels, leading to an artifactual measurement of lower extremity SBP[10,11,41]. However, a potentially overlooked mechanism for a high ABI is exaggerated amplification of the pulse pressure as the wave travels from the aorta to the periphery. An important finding of the present study is the presence of increased aortic to radial PPA in subjects with high ABI. PPA describes the amplification of pulse pressure from the aorta to peripheral arteries, owing to gradual reductions in vessel compliance and lumen size from the central aorta to the periphery, as well as the summation of forward and reflected waves[13,14]. Accordingly, exaggerated PPA would favor a higher ABI due to differences in traveling distance between the brachial and ankle vessels, particularly in taller subjects. This mechanism of a high PPA is in principle, independent of peripheral arterial incompressibility. Therefore, the group with a high ABI may represent a mixed population with different hemodynamic mechanisms (greater PPA and peripheral arterial stiffness / calcification with incompressibility). Interestingly, lower (not higher) PPA has been associated with an increased cardiovascular risk[43]. Therefore, although a high PPA does not explain the increased CVD risk in populations with a high ABI, it is possible that this measure may allow the distinction of subjects with a more benign phenotype of—artificially greater ABI purely on the basis of greater PPA from the aorta to the periphery (who may presumably have a lower CVD risk) from those with stiff, incompressible peripheral arteries (who may presumably have greater CVD risk). This hypothesis should be tested in future studies. Thus, the findings and methods applied herein may allow a better evaluation of the mechanisms of increased CVD events in subjects with this incompletely understood phenotype.

The strengths of the present study include its ethnic and geographic diversity, as well as the availability of temporally proximate assessments of subclinical atherosclerosis, ABI, and measures of arterial compliance. There are also limitations to this study, including its cross-sectional and observational nature, which precludes conclusions regarding temporality. Although we report differences in the prevalence of high and low ABI between ethnic groups and we adjusted for race in our multivariable models, the number of participants that had low- or high-ABI, when stratified specifically by race was small, precluding a meaningful race-specific analysis of arterial compliance across the ABI spectrum or

adequately powered interaction analyses to assess whether race moderates the differences seen. Other limitations include the absence of compliance data for all participants within ABI subgroups, necessitating the evaluation ABI strata with the upper cut-point of 1.3, for which less observational and outcome data have been formerly published.

Acknowledgments

The authors would like to thank the staff and investigators of the Multi-Ethnic Study of Atherosclerosis (MESA) for the support and contributions.

Source(s) of Funding: None declared

References

1. Aboyans V, Ho E, Denenberg JO, Ho LA, Natarajan L, Criqui MH. The association between elevated ankle systolic pressures and peripheral occlusive arterial disease in diabetic and nondiabetic subjects. Journal of Vascular Surgery. 2008; 48:1197–1203. [PubMed: 18692981]
2. Signorelli SS, Fiore V, Catanzaro S, Simili M, Torrisi B, Anzaldi M. Prevalence of high ankle-brachial index (abi) in general population of southern italy, risk factor profiles and systemic cardiovascular co-morbidity: An epidemiological study. Archives of Gerontology and Geriatrics. 2011; 53:55–59. [PubMed: 20591512]
3. Ix JH, Katz R, Peralta CA, de Boer IH, Allison MA, Bluemke DA, Siscovick DS, Lima JAC, Criqui MH. A high ankle brachial index is associated with greater left ventricular mass: Mesa (multi-ethnic study of atherosclerosis). Journal of the American College of Cardiology. 2010; 55:342–349. [PubMed: 20117440]
4. Allison MA, Hiatt WR, Hirsch AT, Coll JR, Criqui MH. A high ankle-brachial index is associated with increased cardiovascular disease morbidity and lower quality of life. Journal of the American College of Cardiology. 2008; 51:1292–1298. [PubMed: 18371562]
5. Ix JH, Katz R, De Boer IH, Kestenbaum BR, Allison MA, Siscovick DS, Newman AB, Sarnak MJ, Shlipak MG, Criqui MH. Association of chronic kidney disease with the spectrum of ankle brachial index the chs (cardiovascular health study). J Am Coll Cardiol. 2009; 54:1176–1184. [PubMed: 19761940]
6. Sutton-Tyrrell K, Venkitachalam L, Kanaya AM, Boudreau R, Harris T, Thompson T, Mackey RH, Visser M, Vaidean GD, Newman AB. Study HABC. Relationship of ankle blood pressures to cardiovascular events in older adults. Stroke. 2008; 39:863–869. [PubMed: 18258843]
7. Toussaint ND, Lau KK, Strauss BJ, Polkinghorne KR, Kerr PG. Associations between vascular calcification, arterial stiffness and bone mineral density in chronic kidney disease. Nephrol Dial Transplant. 2008; 23:586–593. [PubMed: 17933842]
8. Sutliff RL, Walp ER, El-Ali AM, Elkhatib S, Lomashvili KA, O'Neill WC. Effect of medial calcification on vascular function in uremia. Am J Physiol Renal Physiol. 2011; 301:F78–83. [PubMed: 21478480]
9. Wohlfahrt P, Palous D, Ingrischova M, Krajcoviechova A, Seidlerova J, Galovcova M, Bruthans J, Jozifova M, Adamkova V, Filipovsky J, Cifkova R. A high ankle-brachial index is associated with increased aortic pulse wave velocity: The czech post-monica study. Eur J Cardiovasc Prev Rehabil. 2011; 18:790–796. [PubMed: 21450589]
10. Everhart JE, Pettitt DJ, Knowler WC, Rose FA, Bennett PH. Medial arterial calcification and its association with mortality and complications of diabetes. Diabetologia. 1988; 31:16–23. [PubMed: 3350219]
11. Young MJ, Adams JE, Anderson GF, Boulton AJ, Cavanagh PR. Medial arterial calcification in the feet of diabetic patients and matched non-diabetic control subjects. Diabetologia. 36:615–621. 993.
12. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: The framingham heart study. Hypertension. 2004; 43:1239–1245. [PubMed: 15123572]

13. Agnoletti D, Zhang Y, Salvi P, Borghi C, Topouchian J, Safar ME, Blacher J. Pulse pressure amplification, pressure waveform calibration and clinical applications. Atherosclerosis. 2012; 224:08–12.

14. London GM, Guerin AP, Pannier B, Marchais SJ, Stimpel M. Influence of sex on arterial hemodynamics and blood pressure. Role of body height. Hypertension. 1995; 26:514–519. [PubMed: 7649591]

15. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-ethnic study of atherosclerosis: Objectives and design. Am J Epidemiol. 2002; 156:871–881. [PubMed: 12397006]

16. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The jnc 7 report. JAMA. 2003; 289:2560–2572. [PubMed: 12748199]

17. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006; 145:247–254. [PubMed: 16908915]

18. Adam DJ, Bradbury AW. Tasc ii document on the management of peripheral arterial disease. Eur J Vasc Endovasc Surg. 2007; 33:1–2. [PubMed: 17161778]

19. McDermott MM, Liu K, Criqui MH, Ruth K, Goff D, Saad MF, Wu C, Homma S, Sharrett AR. Ankle-brachial index and subclinical cardiac and carotid disease: The multiethnic study of atherosclerosis. Am J Epidemiol. 2005; 162:33–41. [PubMed: 15961584]

20. Allison MA, Laughlin GA, Barrett-Connor E, Langer R. Association between the ankle-brachial index and future coronary calcium (the rancho bernardo study). Am J Cardiol. 2006; 97:181–186. [PubMed: 16442359]

21. Chirinos JA, Kips JG, Jacobs DR Jr, Brumback L, Duprez DA, Kronmal R, Bluemke DA, Townsend RR, Vermeersch S, Segers P. Arterial wave reflections and incident cardiovascular events and heart failure: Mesa (multiethnic study of atherosclerosis). J Am Coll Cardiol. 2012; 60:2170–2177. [PubMed: 23103044]

22. Natori S, Lai S, Finn JP, Gomes AS, Hundley WG, Jerosch-Herold M, Pearson G, Sinha S, Arai A, Lima JA, Bluemke DA. Cardiovascular function in multi-ethnic study of atherosclerosis: Normal values by age, sex, and ethnicity. AJR Am J Roentgenol. 2006; 186:S357–365. [PubMed: 16714609]

23. Blaha MJ, Budoff MJ, Rivera JJ, Katz R, O'Leary DH, Polak JF, Takasu J, Blumenthal RS, Nasir K. Relationship of carotid distensibility and thoracic aorta calcification: Multiethnic study of atherosclerosis. Hypertension. 2009; 54:1408–1415. [PubMed: 19805639]

24. Gamble G, Zorn J, Sanders G, MacMahon S, Sharpe N. Estimation of arterial stiffness, compliance, and distensibility from m-mode ultrasound measurements of the common carotid artery. Stroke. 1994; 25:11–16. [PubMed: 8266356]

25. Malayeri AA, Natori S, Bahrami H, Bertoni AG, Kronmal R, Lima JA, Bluemke DA. Relation of aortic wall thickness and distensibility to cardiovascular risk factors (from the multi-ethnic study of atherosclerosis [mesa]). Am J Cardiol. 2008; 102:491–496. [PubMed: 18678312]

26. Carr JJ, Nelson JC, Wong ND, McNitt-Gray M, Arad Y, Jacobs DR Jr, Sidney S, Bild DE, Williams OD, Detrano RC. Calcified coronary artery plaque measurement with cardiac ct in population-based studies: Standardized protocol of multi-ethnic study of atherosclerosis (mesa) and coronary artery risk development in young adults (cardia) study. Radiology. 2005; 234:35–43. [PubMed: 15618373]

27. Folsom AR, Kronmal RA, Detrano RC, O'Leary DH, Bild DE, Bluemke DA, Budoff MJ, Liu K, Shea S, Szklo M, Tracy RP, Watson KE, Burke GL. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: The multi-ethnic study of atherosclerosis (mesa). Arch Intern Med. 2008; 168:1333–1339. [PubMed: 18574091]

28. Al-Mallah MH, Nasir K, Katz R, Takasu J, Lima JA, Bluemke DA, Hundley G, Blumenthal RS, Budoff MJ. Thoracic aortic distensibility and thoracic aortic calcium (from the multi-ethnic study of atherosclerosis [mesa]). Am J Cardiol. 2010; 106:575–580. [PubMed: 20691319]
29. Zheng ZJ, Sharrett AR, Chambless LE, Rosamond WD, Nieto FJ, Sheps DS, Dobs A, Evans GW, Heiss G. Associations of ankle-brachial index with clinical coronary heart disease, stroke and preclinical carotid and popliteal atherosclerosis: The atherosclerosis risk in communities (aric) study. Atherosclerosis. 1997; 131:115–125. [PubMed: 9180252]
30. Duprez DA, De Buyzere MM, De Bruyne L, Clement DL, Cohn JN. Small and large artery elasticity indices in peripheral arterial occlusive disease (paod). Vasc Med. 2001; 6:211–214. [PubMed: 11958385]
31. Brewer LC, Chai HS, Bailey KR, Kullo IJ. Measures of arterial stiffness and wave reflection are associated with walking distance in patients with peripheral arterial disease. Atherosclerosis. 2007; 191:384–390. [PubMed: 16730015]
32. Li B, Gao H, Li X, Liu Y, Wang M. Correlation between brachial-ankle pulse wave velocity and arterial compliance and cardiovascular risk factors in elderly patients with arteriosclerosis. Hypertens Res. 2006; 29:309–314. [PubMed: 16832150]
33. Wilkins JT, McDermott MM, Liu K, Chan C, Criqui MH, Lloyd-Jones DM. Associations of noninvasive measures of arterial compliance and ankle-brachial index: The multiethnic study of atherosclerosis (mesa). Am J Hypertens. 2012; 25:535–541. [PubMed: 22357412]
34. Criqui MH, McClelland RL, McDermott MM, Allison MA, Blumenthal RS, Aboyans V, Ix JH, Burke GL, Liu K, Shea S. The ankle-brachial index and incident cardiovascular events in the mesa (multi-ethnic study of atherosclerosis). J Am Coll Cardiol. 2010; 56:1506–1512. [PubMed: 20951328]
35. Resnick HE, Lindsay RS, McDermott MM, Devereux RB, Jones KL, Fabsitz RR, Howard BV. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: The strong heart study. Circulation. 2004; 109:733–739. [PubMed: 14970108]
36. O'Hare AM, Katz R, Shlipak MG, Cushman M, Newman AB. Mortality and cardiovascular risk across the ankle-arm index spectrum: Results from the cardiovascular health study. Circulation. 2006; 113:388–393. [PubMed: 16432070]
37. Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, Laurent S. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: A longitudinal study. Hypertension. 2002; 39:10–15. [PubMed: 11799071]
38. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension. 2001; 37:1236–1241. [PubMed: 11358934]
39. Lind L, Andren B, Sundstrom J. The stroke volume/pulse pressure ratio predicts coronary heart disease mortality in a population of elderly men. J Hypertens. 2004; 22:899–905. [PubMed: 15097228]
40. Cavalcante JL, Lima JA, Redheuil A, Al-Mallah MH. Aortic stiffness: Current understanding and future directions. J Am Coll Cardiol. 2011; 57:1511–1522. [PubMed: 21453829]
41. Suominen V, Uurto I, Saarinen J, Venermo M, Salenius J. Pad as a risk factor for mortality among patients with elevated abi--a clinical study. Eur J Vasc Endovasc Surg. 2010; 39:316–322. [PubMed: 20089422]
42. Niederhoffer N, Lartaud-Idjouadiene I, Giummelly P, Duvivier C, Peslin R, Atkinson J. Calcification of medial elastic fibers and aortic elasticity. Hypertension. 1997; 29:999–1006. [PubMed: 9095090]
43. Chirinos JA, Townsend R. Pulse pressure amplification as a predictor of cardiovascular risk. J Am Coll Cardiol. 2010; 56:744. author reply 744–745. [PubMed: 20723810]

Highlights

- We compared arterial compliance across the ankle-brachial index (ABI) spectrum.
- A low, but not high ABI was associated with reduced arterial compliance.
- Increased pulse pressure amplitude was observed in those with high ABI.
- Exaggerated pulse pressure amplification may account for high-ABI in healthy individuals.

Table 1

Demographics and Clinical Characteristics Across ABI Subclasses

	ABI ≤ 0.9	ABI 0.91 – 1.29	ABI ≥ 1.30	*P value*
	n = 230	n = 5856	n = 648	
Age (yrs)	72 (67,78)	62 (53,70)	61 (52,69)	<0.01 *‡
Female (%)	50.9%	55.3%	27.8%	<0.01 †‡
Race (%)				
White	30.9	37.6	49.1	<0.01 *†‡
Black	50.0	27.8	19.9	
Hispanic	13.5	22.1	24.1	
Chinese	5.65	12.64	6.94	
Height, cm	165 ± 9.9	165.9 ± 10.0	171.1 ± 8.8	<0.01 †‡
Weight, lbs	168.0 ± 36.9	171.6 ± 37.7	192.1 ± 38.0	<0.01 †‡
BMI, kg/m^2 (%)	27.7 ± 5.4	28.2 ± 5.4	29.7 ± 5.7	<0.01 †‡
Hypertension (%)	74.4	44.3	37.2	<0.01 *†‡
Diabetes (%)	28.3	11.8	13.5	<0.01 *‡
Fasting Glucose (mg/dl)	105.5 ± 31.8	96.7 ± 29.3	100.1± 36.9	<0.01 *†‡
Smoking (%)				
Never	35.5	50.8	51.6	<0.01 *
Former	39.5	36.2	39.0	
Current	25.0	13.0	9.4	<0.01 *†‡
Systolic blood pressure (mm Hg)	140.9 ± 27.4	126.5 ± 21.3	122 ± 18.7	<0.01 *†‡
Diastolic blood pressure (mm Hg)	72 ± 11.4	72 ± 10.3	71.6 ± 9.8	0.65
Mean arterial pressure (mm Hg)	99.5 ± 16.3	93.8 ± 13.2	91.8 ± 12.1	<0.01 *†‡
Brachial pulse pressure	69 ± 21.7	54.5 ± 17	50.4 ± 14.5	<0.01 *†‡
Central pulse pressure	65.9 ± 19.4	53.1 ± 14.6	49.4 ± 13.0	<0.01 *†‡
Pulse pressure amplification≠	1.12 ± 0.11	1.12 ± 0.1	1.15 ± 0.11	<0.01 †‡
Heart rate, bpm	64.2 ± 11.1	63.1 ± 9.5	62.6 ± 9.8	0.085
HDL cholesterol (mg/dl)	49.5 ± 14.7	51.2 ± 14.8	48.5 ± 14.2	<0.01 †
Triglycerides (mg/dl)	127.6 ± 72.9	131.8 ± 90.8	130.5 ± 75.3	0.75
LDL cholesterol (mg/dl)	118.7 ± 33.9	117.5 ± 31.5	114.5 ± 30.2	0.05 †
eGFR < 60 ml/min/1.73 m^2	20.0	9.1	8.6	<0.01 *‡
Urine albumin/creatinine (mg/g)	46.34 ± 146.55	22.6 ± 107.45	26.71 ± 155.31	0.02 *‡

Values are mean + SD or percentages, or median (inter-quartile range);

*low vs normal ABI group;

†high vs normal ABI group;

‡high vs low ABI group;

BMI = body mass index; HDL = high density lipoprotein; LDL = low density lipoprotein; eGFR = estimated glomerular filtration rate; CAC = coronary artery calcium.

≠ radial/aortic pulse pressure.

TABLE 2

Subclinical Atherosclerosis Across ABI Subclasses

	ABI ≤ 0.9	**ABI 0.91 – 1.29**	**ABI ≥ 1.30**	***P value***
	n = 230	n = 5856	n = 648	
CcIMT(mm)	1.05 ± 0.27	0.86 ± 0.19	0.87 ± 0.21	<0.01 *‡
IcIMT(mm)	1.65 ± 0.81	1.05 ± 0.59	1.04 ± 0.56	<0.01 *‡
Coronary Artery Calcium Prevalence	83.0%	47.5%	56.6%	<0.01 *‡
Total Coronary Artery Calcium	458.6 ± 769.56	127.37 ± 374.28	194.41 ± 541.35	<0.01 *†‡
Aortic Calcium Prevalence	64.3%	26.7%	24.4%	<0.01 *‡
Total Aortic Calcium	980.99 ± 2226.03	201.84 ± 792.68	167.6 ± 780.97	<0.01 *‡

Values represent means ±standard deviation;

*low vs normal ABI group;

†high vs normal ABI group;

‡high vs low ABI group.

TABLE 3

Association of ABI with Total Arterial Compliance

	ABI < 0.9	**ABI 0.91 – 1.29**	**ABI > 1.30**	***P value***
	n = 157	n =4288	n =456	
Unadjusted	1.19 ± 0.4	1.63 ± 0.59	1.89 ± 0.6	<0.01 *†≠
Model 1	1.46 ± 0.04	1.64 ± 0.01	1.73 ± 0.02	<0.01 *†≠
Model 2	1.53 ± 0.04	1.64 ± 0.01	1.70 ± 0.02	<0.01 *†≠
Model 3	1.58 ± 0.04	1.64 ± 0.01	1.70 ± 0.02	0.01 †≠
Model 4	1.58 ± 0.04	1.65 ± 0.01	1.70 ± 0.02	0.03 ≠

Values represent estimated marginal means (± S.E.M.) adjusted for indicated covariates; units are ml/mm Hg.

Model 1 is corrected for age, gender, race, height and weight; Model 2 additionally incorporates hypertension, total and HDL cholesterol, smoking status, eGFR, hypertension therapy, statin use, mean arterial pressure and heart rate; Model 3 additionally incorporates coronary and aortic wall calcification, along with maximum common carotid and internal carotid intima-medial thickness; Model 4 additionally incorporates PPA.

* low vs normal ABI group;

† high vs normal ABI group;

≠ high vs low ABI group. Analyzed subpopulation limited to those with that underwent magnetic resonance imaging.

TABLE 4

Association of ABI with Aortic Distensibility

	ABI ≤ 0.9	**ABI 0.91 – 1.29**	**ABI ≥ 1.30**	***P value***
	n = 117	n = 3200	n = 326	
Unadjusted	1.40 ± 0.13	1.87 ± 0.13	1.99 ± 0.11	<0.01 *ǂ
Model 1	1.87 + 0.11	1.86 + 0.02	1.93 + 0.07	0.64
Model 2	2.00 + 0.11	1.86 + 0.02	1.88 + 0.07	0.49
Model 3	2.01 + 0.11	1.85 + 0.20	1.88 + 0.06	0.35
Model 4	2.01 + 0.12	1.87 + 0.02	1.90 + 0.07	0.49

Values represent estimated marginal means (± S.E.M.) adjusted for indicated covariates; units are 1/mm Hg × 10^3.

Model 1 is corrected for age, gender, race, height and weight; Model 2 additionally incorporates hypertension, total and HDL cholesterol, smoking status, eGFR, hypertension therapy, statin use, mean arterial pressure and heart rate; Model 3 additionally incorporates coronary and aortic wall calcification, along with maximum common carotid and internal carotid intima-medial thickness; Model 4 additionally incorporates PPA.

* low vs normal ABI group;

† high vs normal ABI group;

ǂ high vs low ABI group. Analyzed subpopulation limited to those with that underwent magnetic resonance imaging.

TABLE 5

Association of ABI with Carotid Distensibility

	ABI ≤ 0.9	**ABI 0.91 – 1.29**	**ABI ≥ 1.30**	***P value***
	n = 217	n =5637	n =638	
Unadjusted	1.96 ± 0.93	2.53 ± 1.1	2.60 ± 0.11	<0.01 *ǂ
Model 1	2.38 + 0.07	2.51 + 0.01	2.55 + 0.04	0.10
Model 2	2.45 + 0.06	2.51 + 0.01	2.49 + 0.04	0.49
Model 3	2.45 + 0.07	2.53 + 0.01	2.48 + 0.04	0.39
Model 4	2.47 + 0.07	2.52 + 0.01	2.50 + 0.04	0.59

Values represent estimated marginal means (± S.E.M.) adjusted for indicated covariates; units are 1/mm Hg × 10^3.

Model 1 is corrected for age, gender, race, height and weight; Model 2 additionally incorporates hypertension, total and HDL cholesterol, smoking status, eGFR, hypertension therapy, statin use, mean arterial pressure and heart rate; Model 3 additionally incorporates coronary and aortic wall calcification, along with maximum common carotid and internal carotid intima-medial thickness; Model 4 additionally incorporates PPA. Results were similar when Young's Modulus was employed as the dependent variable.

*low vs normal ABI group;

†high vs normal ABI group;

ǂhigh vs low ABI group