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

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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 6814 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 ($\leq$0.90, 0.91–1.29; $\geq$1.30) with analyses adjusted for cardiovascular risk factors and subclinical atherosclerosis.

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 $\leq$0.9 ($p < 0.01$ vs. all), but were not reduced in subjects with an ankle-brachial index $\geq$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.

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1. Introduction

A high ankle-brachial index (ABI) is associated with increased cardiovascular disease (CVD) risk and mortality in population cohort studies [1–4]. 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 [7–9]. Moreover, although a high ABI is thought to reflect stiff, non-compressible infrageniculate arteries [10,11], it may not reflect

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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

2.1. 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.

2.2. 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 min. 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 antihypertensive 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].

2.3. 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 denominator [18]. 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 and 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.

2.4. 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-T scanners, with low inter-observer variability as previously described [22]. Brachial pulse pressure was recorded at commencement of magnetic resonance imaging. Sample size for total arterial compliance (TAC) analyses was limited to the 4903 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 procedure. [21]

2.5. Carotid and aortic distensibilty

Carotid distensibility was calculated from a 20-s 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.

2.6. 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