



Associations of cardiovascular risk factors, carotid intima-media thickness and left ventricular mass with inter-adventitial diameters of the common carotid artery: The Multi-Ethnic Study of Atherosclerosis (MESA)

Joseph F. Polak^{a,*}, Quenna Wong^b, W. Craig Johnson^b, David A. Bluemke^c, Anita Harrington^a, Daniel H. O'Leary^a, N. David Yanez^b

^a Department of Radiology, Tufts Medical Center, 800 Washington Street, Boston, MA 02111, United States

^b Collaborative Health Studies Coordinating Center University of Washington Collaborative Health Studies Coordinating Center, Building 29, Suite 310, 6200 NE 74th Street, Seattle, WA 98115, United States

^c Radiology and Imaging Sciences, National Institutes of Health, 10 Center Drive, Rm. 1C355, Bethesda, MD 20892, United States

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ABSTRACT

Background: Common carotid artery inter-adventitial diameter (IAD) and intima-media thickness (IMT) are measurable by ultrasound. IAD may be associated with left ventricular mass (LV mass) while IMT is a marker of subclinical atherosclerosis. It is not clear if IAD is associated with LV mass after accounting for IMT and traditional cardiovascular risk factors.

Methods: IAD and IMT were measured on participants of the Multi-Ethnic Study of Atherosclerosis (MESA) IMT progression study. A total of 5641 of the originally enrolled 6814 MESA participants were studied. LV mass was measured by magnetic resonance imaging. Multivariable linear regression was used with IAD as the outcome and adjustment for risk factors, as well as IMT and LV mass.

Results: Traditional cardiovascular risk factors, height, weight and ethnicity were significantly associated with IAD. After adjustment for risk factors, a 1 mm difference in IMT was associated with a 1.802 mm (95% CI: 1.553, 2.051) higher mean IAD. A 1 g difference in LV mass was associated with a 0.006 mm (95% CI: 0.005, 0.007) higher mean IAD. After adjusting for cardiovascular risk factors and IMT, a 1 g difference in LV mass was associated with a 0.006 mm (95% CI: 0.005, 0.008) higher mean IAD for women and 0.004 mm (95% CI: 0.003, 0.005) higher IAD for men.

Conclusions: Inter-adventitial diameters are associated with left ventricular mass after adjusting for cardiovascular risk factors and IMT. IAD might serve as a surrogate for left ventricular mass and have predictive value for cardiovascular outcomes.

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1. Introduction

The increase in diameter of the coronary and carotid arteries that occurs in response to the deposition of atherosclerotic plaque is referred to as the Glagov phenomenon [1]. This adaptive response is therefore directly linked to the atherosclerotic process.

Arterial diameters also increase as blood pressure increases [2–5]. Increases in left ventricular mass (LV mass) are associated with chronic blood pressure elevation [6] and with larger common

carotid artery lumen diameters as well as external (adventitia to adventitia) diameters [7,8].

Inter-adventitial diameter (IAD) of the carotid artery is non-invasively measured with ultrasound. IAD is a combination of the lumen diameter and of IMT and has been shown to be associated with carotid artery intima-media thickness (IMT) and blood pressure [2–4,9,10] while there are no data confirming an association with LV mass. If present, the association between IAD and LV mass might be weakened by taking into consideration traditional cardiovascular risk factors, height, weight given the presence of subclinical disease measured as carotid artery IMT since IMT is implicitly part of the IAD measurement.

We hypothesize that IAD is independently associated with LV mass and that IAD might be a marker of elevated LV mass after accounting for IMT and traditional risk factors. We study these

* Corresponding author at: Department of Radiology, Tufts Medical Center, 800 Washington Street, Box 299, Boston, MA 02111, United States. Tel.: +1 617 636 0036; fax: +1 617 636 0067.

E-mail address: jpolak@tuftsmedicalcenter.org (J.F. Polak).

possibilities in participants of a multi-ethnic cohort: the Multi-Ethnic Study of Atherosclerosis (MESA).

2. Materials and methods

2.1. Population

MESA recruited and examined a multiethnic population of 6814 men and women aged 45–84 with no history of clinical cardiovascular disease [11]. The MESA cohort is composed of white, African-American, Hispanic-American, and Chinese participants. Participants were excluded if they had physician diagnosis of myocardial infarction, stroke, transient ischemic attack, heart failure, angina, atrial fibrillation or history of any cardiovascular procedure, weight above 300 lbs, pregnancy, or any medical conditions that would prevent long-term participation. MESA protocols and all studies described herein have been approved by the Institutional Review Boards of all collaborating institutions and are HIPAA compliant.

2.2. Risk factors and anthropomorphic variables

Weight was measured after an overnight fast in pounds (lbs) and height measurements in centimeters (cm). Age, gender, race/ethnicity, and medical history were self-reported. Use of lipid-lowering and anti-hypertensive medications was also recorded.

Current smoking was defined as self-report of one or more cigarettes in the last 30 days. Resting systolic and diastolic blood pressures (BP) were measured three times in the seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida). The average of the last two measurements was used in the analyses. Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg, a diastolic blood pressure ≥ 90 mm Hg, or currently taking anti-hypertensive medications.

Glucose and lipids were measured after a 12-h fast. Diabetes mellitus was determined using the 2003 ADA fasting criteria algorithm [12]. Total cholesterol was measured using a cholesterol oxidase method (Roche Diagnostics), as was HDL after precipitation of non-HDL cholesterol with magnesium/dextran, triglycerides using Triglyceride GB reagent (Roche Diagnostics).

2.3. Carotid artery measures

Participants were examined supine with the head rotated 45° towards the left side. Imaging was done parallel to the right common carotid artery with the jugular vein above (or at 45° from the vertical if the internal jugular vein was not present). The image was centered on a 10 mm segment of the right common carotid artery at least 5 mm below (caudad to) the right common carotid artery bulb. A matrix array probe (M12L, General Electric, Milwaukee, WI) was used, with the frequency set at 13 MHz. Images acquired for 20 s at 32 frames-per-second were digitized and automated inter-adventitial diameter measurements (near wall inter-adventitial interface to far wall inter-adventitial interface) made. The end-diastolic diameter was obtained from the smallest diameter of the inter-adventitial diameter-versus-time curve.

The reproducibility of the measurements was assessed by replicate readings of the same series of images on 139 participants giving an overall intra-class correlation coefficient (ICC) of 0.990 (95% CI: 0.987, 0.993). The intra-reader ICC was 0.997 (95% CI 0.991, 0.999) while the inter-reader ICC was 0.989 (95% CI 0.985, 0.993).

Images selected at end-diastole were used for measurements of the mean far wall common carotid IMT [13].

2.4. Left ventricular mass

The six MESA field centers used 1.5-Tesla magnets for their evaluation of LV mass according to a standard protocol [14].

All images were acquired during a 12–15 s breath hold at resting lung volume. Short-axis cine images were acquired from the end-diastolic image and image data were analyzed using MASS software (version 4.2; Medis, The Netherlands). The papillary muscles were excluded from the LV mass measurement. LV mass was determined by the sum of the myocardial area (the difference between endocardial and epicardial contours) times slice thickness plus image gap multiplied by the specific gravity of myocardium (1.05 g/mL).

2.5. Statistical analysis

Descriptive and summary statistics are reported as mean and standard deviation for continuous variables and count and percent for categorical variables.

We used linear regression with robust standard errors to investigate associations between IAD and traditional cardiovascular risk factors. We considered unadjusted models and fully adjusted models (including age, gender, race, height, weight, HDL and total cholesterol with lipid-lowering medications, diabetes status, blood pressures and anti-hypertensive medication use, and cigarette smoking status with pack-years of cigarette smoking). Height and weight were included to adjust for confounding due to body size.

To investigate associations between IAD and subclinical disease measures, we considered the same set of models as described for the risk factors. Specifically, we looked at left ventricular end-diastolic mass and far wall mean carotid IMT at diastole. Models including IMT were corrected for measurement error by regression calibration [15]. Replicate reads of single ultrasound scans [15,16] were used to estimate the variance of the measurement error.

All analyses were performed using Intercooled STATA 10.0 (StataCorp, College Station, TX).

3. Results

Baseline demographics are summarized in Table 1. Of the 5641 subjects studied, 52% were female, while African-Americans formed 26% of the group, Chinese 12%, Hispanic 22% and the rest were Caucasian (40%).

Key associations between IAD and cardiovascular risk factors are shown in Table 2. For unadjusted analyses, positive associations with IAD were seen for age, male gender, height and weight, lipid-lowering medication use, all diabetes categories (treated diabetes, untreated diabetes, impaired fasting glucose compared to normal), systolic blood pressure and anti-hypertensive medication use, former cigarette smoking and pack-years smoked and for Chinese as well as African-Americans as compared to Caucasians. Negative associations were seen for HDL-cholesterol and for total cholesterol.

The associations of total cholesterol, IFG and untreated diabetes, and former cigarette smoking status with IAD seen in unadjusted analyses were not significant after full adjustment. IAD was associated with all other cardiovascular risk factors.

Both common carotid IMT and LV mass were associated with IAD in all unadjusted and fully adjusted analyses (Figs. 1 and 2). After adjustment for all risk factors, a 1 mm difference in IMT was associated with a 1.802 mm (95% CI: 1.553, 2.051) higher mean IAD and a 1 g difference in LV mass was associated with a 0.006 mm (95% CI: 0.005, 0.007) higher mean IAD. When IMT and LV mass were both included in the model, a 1 mm difference in IMT was associated with a 1.623 mm (95% CI: 1.372, 1.874) higher mean IAD

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