Published in final edited form as:

J Am Soc Hypertens. 2008 April ; 2(2): 70–79.

Association between Endothelial Biomarkers and Arterial Elasticity in Young Adults – The CARDIA Study

Narayanan I. Valappil, PhD, MPH^a, David R. Jacobs Jr., PhD^b, Daniel A. Duprez, MD, PhD^c, Myron D. Gross, PhD^d, Donna K. Arnett, PhD^e, and Stephen Glasser, MD^f

^aHealth Resources and Services Administration, 5600 Fishers Lane, Room 7A-42, Rockville, MD 20857

^bDivision of Epidemiology, School of Public Health University of Minnesota, 1300 South Second Street, Minneapolis, Minnesota 55454; also affiliated with the Department of Nutrition, University of Oslo, Oslo, Norway

^cCardiovascular Division, Medical School, University of Minnesota, MMC 508, 420 Delaware Street Southeast, Minneapolis, Minnesota 55455

^dDepartment of Laboratory Medicine and Pathology, School of Medicine, University of Minnesota, Mayo Mail Code 609, 420 Delaware Street Southeast, Minneapolis, Minnesota 55455

^eDepartment of Epidemiology, UAB School of Public Health, 1665 University Blvd. Birmingham, AL 35294

^fDivision of Preventive Medicine, Department of Medicine, University of Alabama at Birmingham, 1717 11th Ave S., Birmingham, AL 35205

Abstract

Background—Reduced arterial elasticity and endothelial dysfunction both may indicate early cardiovascular (CV) disease in young adults. Pulse waveform analysis estimates large (LAE) and small (SAE) artery elasticity noninvasively. We assessed the associations between LAE and SAE and markers of endothelial dysfunction and CV risk factors.

Methods—The Coronary Artery Risk Development in Young Adults (CARDIA) assessed arterial elasticity and other characteristics cross-sectionally in 389 men and 381 women aged 27–42 years in 1995 (CARDIA year 10) and circulating levels of P-selectin and soluble intercellular adhesion molecule 1 (sICAM-1) in 2000. We adjusted for variables included in the estimation of arterial elasticity (year 10 height, body mass index, age, heart rate, and blood pressure) and other year 10 characteristics.

Results—Mean adjusted SAE was 8.5 vs. 7.6 ml/mmHg ×100 in those with urine albumin/creatinine ratio ≤4 vs. microalbuminuria (ratio > 25; $p_{\text{trend}}=0.008$). Mean LAE was 25.6 vs. 24.2 ml/mmHg ×10 in the lowest vs. highest quintile of P-selectin ($p_{\text{trend}}=0.004$). sICAM-1 was unrelated to either LAE or SAE. Plasma triglycerides were inversely related to LAE ($p_{\text{trend}}=0.029$). Cigarette smokers had lower SAE than nonsmokers ($p_{\text{trend}}=0.009$).

Conclusion—In addition to smoking and triglycerides, biomarkers for endothelial dysfunction were associated with impaired LAE and SAE in young adults.

Corresponding author: David R. Jacobs, Jr., PhD, Professor of Epidemiology, School of Public Health, University of Minnesota, 1300 S 2nd St, Suite 300, Minneapolis MN 55454, jacobs@epi.umn.edu Phone 1 612 624 4196, Fax 1 612 624 0315.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

Blood lipids; smoking; albuminuria; endothelial dysfunction

Introduction

The abnormalities of the arterial vasculature that precede atherosclerotic events are likely to occur in temporal sequence.¹ This disease begins at an early age, probably initially with a defect or injury of arterial endothelial protective function and progresses with structural remodeling in the microcirculation. The rate of progression of atherosclerosis is highly variable and is strongly influenced by risk contributors such as blood lipids, blood pressure, smoking, diabetes, and aging.²

Pulse pressure, the difference between the systolic and diastolic blood pressure has been considered in the past to be one of the simplest measures of arterial elasticity.³ However, pulse pressure alone is inadequate to assess arterial elasticity accurately, because the “normal” amplification of the pressure wave as it travels from the aorta to the periphery is not well estimated by pulse pressure. The arterial pressure wave has two principal components: the wave generated by the heart, which travels away from the heart, and the reflected wave, which returns to the heart from peripheral sites, predominantly in the lower part of the body.

Noninvasive measurement of arterial elasticity entails measurement of surrogate parameters that are intrinsically associated with elasticity. This involves three main methodologies: 1) pulse transit time or pulse wave velocity; 2) analysis of the arterial pressure pulse and its wave contour, and 3) direct elasticity estimation using measurements of diameter and distending pressure.^{4–8} These surrogate parameters are related to the functional effects of arterial elasticity, and as such can be used to quantify changes. A number of computerized devices are now available that enable quantification of global indices of elasticity. Diastolic pulse contour analysis based on the Windkessel model⁹ can provide separate information regarding elasticity of the pool of large arteries and also of the medium and small arteries.

Endothelial dysfunction is an established risk factor for morbid events. Recently, measurement of endothelial function in patients has emerged as a useful tool for early atherosclerotic disease.¹⁰ Risk factors are associated with impaired endothelial function, and clinical syndromes relate, in part, to a loss of endothelial control of vascular homeostasis. Recent studies have shown that the severity of endothelial dysfunction relates to cardiovascular risk.^{11, 12}

Limited information is available, especially in young adults, about the association of arterial elasticity with biomarkers that are known generally to reflect endothelial dysfunction and with cardiovascular disease (CVD) risk factors. In this study, we examined these associations in the Coronary Artery Risk Development in Young Adults (CARDIA) study. We hypothesized that arterial elasticity covaries inversely with biomarkers that generally reflect endothelial dysfunction (albuminuria, soluble P-selectin, and soluble intercellular adhesion molecule 1 (sICAM1)) and with unfavorable CVD risk factors such as dyslipidemia and cigarette smoking. Because albuminuria occurs due to dysfunction in small arteries, we anticipated that albuminuria would relate more strongly to small than to large artery elasticity.

Methods

Study Sample

CARDIA is a multi-center longitudinal cohort study designed to investigate the development of coronary artery disease risk factors in young adults. The CARDIA cohort initially included

5115 black and white men and women aged 18–30 years old in 1985–1986 recruited from 4 geographic areas (Birmingham, Alabama; Chicago, Illinois; Oakland, California; Minneapolis, Minnesota). The methods of recruitment and study design have been published.¹³

Radial artery pulse registration and determination of LAE and SAE were offered as an ancillary procedure in the Minneapolis and Chicago clinics in 1995 at year 10. These measurements were completed in 1251 participants. Urinary albumin and creatinine were obtained in 1097 of these participants. After accounting for missing information on other variables, further restriction to those in whom circulating sICAM1 and P-selectin were measured 5 years later left 770 participants. The latter two measures were provided by another ancillary study, the Young Adult Longitudinal Trends in Antioxidants study, which has been described elsewhere¹⁴, and whose goals were separate from the ancillary study to measure LAE and SAE. There were no qualitative differences in the findings reported herein when all available data were used rather than restricting to the 1097 participants or the 770 in whom sICAM1 and P-selectin were also measured; for simplicity of presentation, we restricted all analyses to the 770 participants.

Data Collection

Participant age, race, sex and educational attainment were self-reported during the recruitment phase and verified during the baseline clinic visit. Body mass index (BMI) was calculated as weight in kg/m². Resting seated blood pressure was assessed using the average of the second and third random zero sphygmomanometric measures; 30 second heart rate was assessed during the BP measurement. Tobacco use was obtained from a CARDIA-specific tobacco questionnaire and was used to classify participants as never smokers, former smokers, or current smokers. Number of cigarettes smoked per day also was queried in current smokers. The alcohol consumption (in drinks of beer, wine, and liquor per week, translated to ml/day of alcohol) and the average hours of leisure time TV viewing, and hours of physical activities were also collected using specific questionnaires administered during the year 10 visit.

Biochemical Measurements

Following an overnight fast of at least 8 hours, blood samples were collected in EDTA-containing and serum vacutainer tubes. Plasma total cholesterol, HDL-cholesterol and triglycerides were measured enzymatically within six weeks of collection¹⁵ at the Northwest Lipid Research Laboratory at the University of Washington, Seattle, WA. High-density lipoprotein cholesterol (HDL-C) was determined after precipitation of low-density lipoprotein (LDL)-containing lipoproteins with dextran sulfate/magnesium chloride.¹⁶ LDL-cholesterol (LDL-C) was calculated using the Friedewald equation.¹⁷ A single untimed urine sample was collected during the clinic visit in 1995. Concentrations of albumin (A) and creatinine (C) were assayed (Regional Kidney Disease Program, Renal Laboratory at Hennepin County Medical Center, Minneapolis, MN; nephelometry based on monoclonal antibodies to human albumin (assay sensitivity, 0.45 mg/liter). Degree of albuminuria, a marker of albumin excretion rate, was estimated by A/kC as mg of albumin per g of creatinine, where k corrects for the relatively greater average daily creatinine excretion in men and blacks than in women and whites. $k = 0.68$ in white men, 0.68×0.88 in black men, 0.88 in black women, and 1 in white women;¹⁸ Warram et al. showed that there is a high correlation between a single untimed urine and the value obtained in 24 hour urine collection.¹⁹

Using samples obtained at CARDIA year 15, sICAM-1 was measured by ELISA, using kits supplied by R & D systems, Inc. catalog number DY720; and pipetted using the ELISA by Biomek- robotic automation manufactured by Beckman. The dilution of samples was performed at 1:400. Soluble P-selectin was also measured by ELISA using kits supplied by R

& D systems, Inc. catalog number BBE 6 and robotic pipetting. The sample was performed at 1:5 dilution.

Large (LAE) and Small Artery (SAE) Elasticity

LAE and SAE were derived from the radial diastolic pulse contour analysis using a Nellcor NCAT-500 (HDI, Inc., Eagan MN)^{8, 9}. A solid-state pressure transducer array (a tonometer sensor) was placed over the radial artery of the dominant arm to record the pulse contour. The waveform was calibrated by the oscillometric method. Once a stable measurement was achieved, a 30 second analog tracing of the radial waveform, excluding the dicrotic notch, was digitized at 200 samples per second. Before, during and after the waveform assessment, an automated, oscillatory blood pressure measurement (oscillatory device built into the NCAT-500) was also taken on the contra-lateral arm, and systolic and diastolic pressure were recorded and computer stored.²⁰

Data Analysis

LAE and SAE were treated as separate dependent variables and the selected risk factors for heart disease as independent variables. The associations between LAE and SAE and the selected cardiovascular risk factors and markers of endothelial function were examined using linear regression models (SAS PROC GLM). We first examined a base model including those variables that are unchangeable (race, sex, age, clinical center, and education) as well as correlates of arterial elasticity that are part of the estimation formulae (height, BMI, heart rate, and blood pressure). Other potential correlates of LAE and SAE, namely blood pressure medication, smoking status, plasma triglycerides, total cholesterol, HDL-C, LDL-C, circulating glucose, circulating insulin, alcohol intake, hours of TV viewing, physical activity, ln(albuminuria), sICAM1 and P-selectin, were added one at a time to the base model to form a series of partial models. Statin use was rare and was ignored (2 participants were taking lipid lowering drugs at year 10 and 14 at year 15). All variables were added simultaneously to the base model to form the full model. The continuous independent variables were divided into equal sized categories (quintiles) or categories based on meaningful cut points that allowed us to show gradations over important biological ranges and examined in the fully adjusted model. Statistical significance to predict arterial elasticity was declared at $P < 0.05$. All analyses were performed using the SAS statistical software, version 9.0 (SAS Institute, Cary, NC).

Results

Table 1 summarizes the Characteristics of study participants by gender at Year 10 of the CARDIA study.

Arterial elasticity, demographics, and variables in the arterial elasticity equation

The unadjusted mean LAE was 25.1 ± 6.7 ml/mmHg $\times 10$ and SAE was 8.3 ± 2.5 ml/mmHg $\times 100$. The Pearson correlation coefficient for LAE and SAE was 0.24. The LAE and SAE increased significantly with height (as expected given that it is used in the estimate of body surface area) from 20.1 ml/mmHg $\times 10$ and 7.3 ml/mmHg $\times 100$, respectively, in the shortest women (median height 157 cm) to 30.1 ml/mmHg $\times 10$ and 9.9 ml/mmHg $\times 100$, respectively, in the tallest men (median height 187 cm). Although the unadjusted LAE and SAE were lower for women (LAE = 23.4 ± 6.1 ml/mmHg $\times 10$; SAE = 7.6 ± 2.2 ml/mmHg $\times 100$) compared to men (LAE = 26.8 ± 6.7 ml/mmHg $\times 10$; SAE = 9.1 ± 2.6 ml/mmHg $\times 100$), the elasticity values were similar for men and women in the quintiles in which height overlapped; thus the sex difference appeared to be explained by the difference in height between men and women (Figure 1 and Figure 2). Given the limited overlap of height in men and women, the height adjusted test for sex difference in arterial elasticity may be imprecise. With this caution, we note that height adjustment reversed the sex ordering for LAE (height adjusted levels means

25.7 and 24.6 ml/mmHg $\times 10$, $p = 0.06$) and attenuated the SAE means by 50% to 8.0 and 8.7 ml/mmHg $\times 100$ ($p = 0.005$).

The participants examined in the Chicago clinical center had LAE 24.2 ml/mmHg $\times 10$, 2.1 ml/mmHg $\times 10$ lower than those examined in the Minneapolis center ($p < 0.001$ in the fully adjusted model), but the difference in SAE was 0.03 ml/mmHg $\times 100$ and not significant between the two centers ($p = 0.85$).

Comment on Table 2–Table 4 is restricted to the full models; partial models are also presented in the tables. Table 2 displays the association between arterial elasticity, demographic variables and other variables used in estimation of arterial elasticity. The LAE was 1.0 ml/mmHg $\times 10$ lower in participants age 38–42 than in those aged 27–33 ($p = 0.06$) and correspondingly the SAE was 0.5 ml/mmHg $\times 100$ lower ($p = 0.007$). African Americans had lower LAE and SAE compared to whites, although the difference was only significant for SAE. There was a positive association between the years of education attained and LAE ($p < 0.001$), but the level of education did not associate with SAE.

Blood pressure was inversely related to both LAE and SAE ($P < 0.001$), as expected as it is in the denominator of the estimate of both LAE and SAE. After adjustment for blood pressure, taking antihypertensive medication was not a significant predictor of either large or small vessel elasticity (data not shown) and the variable was omitted from the full model. Resting heart rate was also inversely related to LAE, but, despite being directly proportional to the estimate of arterial elasticity, was unrelated to SAE.

BMI was strongly positively related to SAE, but was not significantly related to large artery elasticity, despite the fact that BMI is highly correlated with body weight and therefore involved directly in the estimation of LAE.

Arterial elasticity, biomarkers of endothelial dysfunction, and CVD risk factors

Table 3, describes LAE and SAE and biochemical factors that are not used in estimation of arterial elasticity. Among the blood lipids, triglycerides had an inverse relation to LAE, but were not related to SAE. HDL cholesterol showed an inverse relation with SAE. Total cholesterol and LDL cholesterol (data not shown) were not associated with LAE and SAE. Similarly, there was no significant association between arterial elasticity and blood glucose or insulin levels, with the exception of an apparently reduced value of SAE in the highest insulin quintile.

Albumin excretion rate was not significantly associated with LAE, but showed a strong and graded inverse association with SAE. Soluble P-selectin was inversely associated with LAE ($p < 0.001$) whereas sICAM1 was unrelated to either LAE or SAE (Table 3).

Among health behaviors, cigarette smoking was unrelated to LAE but current smokers had significantly lower SAE than did nonsmokers (Table 4). There was no relationship between the number of cigarettes smoked and arterial elasticity among current smokers (data not shown). Alcohol consumption was inversely related to LAE, but not significantly related to SAE. Neither physical activity nor the hours of TV viewing per week were significantly associated with arterial elasticity.

Discussion

In this mostly cross sectional analysis of LAE and SAE, we found graded inverse associations of two biomarkers generally related to endothelial dysfunction in young adults with relatively limited atherosclerosis: albuminuria with SAE and soluble P-selectin with LAE. Differences

in LAE across the range of the predictor variables were typically 1 to 2 ml/mmHg*10 and for SAE was 0.5 to 1 ml/mmHg*100. While the exact clinical implications of a 1 unit change in LAE or SAE is not known, such a change is a substantial part of the population variability. For example, 1 unit is 15% of the LAE population standard deviation and 40% of the SAE population standard deviation. This level of difference is worth noting. The rate of urinary albumin excretion is an important risk factor for kidney failure, coronary heart disease, and stroke. Higher albumin excretion reflects dysfunction in small arteries, probably in part due to endothelial dysfunction.^{21–23} This concept is consistent with our observed association between albumin excretion rate and SAE, but not LAE. Similarly, cell adhesion molecules play an important role in the pathogenesis of atherosclerosis by mediating the binding of leukocytes to the endothelium.²⁴ Soluble P-selectin is produced by platelets and is correlated with similar molecules produced by endothelial cells; higher P-selectin levels in serum may reflect activation of platelets during the formation of atherosclerotic lesions.²⁵ This process might be specific to larger arteries, consistent with our observation that P-selectin was correlated with LAE, but not SAE. sICAM1 is another molecule produced by the endothelium, but which did not relate to arterial elasticity. The linkages between arterial elasticity and both albuminuria and P-selectin are further consistent with the observation that albuminuria is a known risk factor for the development of CVD.^{21, 26–31} that P-selectin is higher in CVD patients, and that there is reduced LAE and SAE in CVD.^{32–35}

We observed an inverse relation between triglycerides and LAE, but total and LDL cholesterol were not associated with arterial elasticity in either arterial bed; and HDL cholesterol was unexpectedly inversely associated with SAE. The Bogalusa study^{36, 37} found inverse associations of triglycerides with SAE only. Another study in elderly hypertensives reported that there were no significant associations between arterial stiffness parameters and either total or HDL cholesterol.³⁸ Like the study in Minneapolis Children³⁹ we saw inverse associations of SAE with insulin; the study in Bogalusa^{36, 37} found an association with LAE with insulin. The same study demonstrated lower SAE in cigarette smokers.³⁷ McVeigh et al. demonstrated reduced SAE in smokers compared to nonsmokers.⁴⁰ In the CARDIA study our relatively young participants did not have many pack years of smoking, compared to older long term smokers, which may explain the relatively poor relation with cigarette smoking. The mechanisms by which smoking accelerates blood vessel damage remain poorly understood, but it has been shown to adversely affect endothelial function.

We observed a significant difference in LAE between the Chicago and Minneapolis measurement centers, independent of all other factors studied, despite the common measurement protocol. On the other hand, SAE was similar in those studies^{36, 37, 39} and in our study, with a mean of about 8 ml/mmHg*100. The mathematical underpinnings for estimating LAE and SAE are provided in the CR-2000 operator's manual; the mathematical method did not change between the Nellcor NCAT-500 and newer CR-2000 device (personal communication, G. Guettler, HDI, Inc.). Differences in elasticity estimates between studies and between centers in our study seem to us most likely to be due to an operator dependent factor, such as different tension on the study subject's radial artery or difference in the sensitivity of the tonometric probes used at different clinical sites.

This study also reported lower arterial elasticities for African Americans compared to whites of similar ages, in agreement with the study in Bogalusa.³⁶ This finding was independent of other factors studied and its cause is not known. Although women had lower arterial elasticity than did men, this observed difference appeared to be explained by difference in height, similar to the findings reported by Arnett et al.³⁹

Relatively modest correlations have been shown among a variety of subclinical markers of cardiovascular disease, even though each predict subsequent occurrence of clinical disease.

⁴¹ In the same sense, different ways of assessing and interpreting the pulse waveform may yield complementary information. In common with all cross-sectional studies, our study is limited in the inferences it can make. The fact that P-selectin and sICAM1 were measured five years after the arterial elasticity measurement may have resulted in an underestimation of the true associations. It is alternatively possible that sustained higher blood pressure, a consequence of decreased elasticity, has an adverse effect on endothelial function, raising P selectin and urinary albumin excretion rate.

Others have pointed out limitations in the Windkessel model as a technique to estimate arterial elasticity (42,⁴³). Several methodologically independent measures of arterial stiffness derived from either the systolic or diastolic segments of the arterial pulse have been proposed (7,⁹). Different ways of assessing and interpreting the pulse waveform correlate poorly across methods. The biologic information that each method provides is intrinsically different across methods. There have been controversial claims in the literature relating to the theory of systolic and diastolic waveform analysis (42,⁴³). Manning et al. (42) described that the lumped-parameter Windkessel models yield different results if the pulse waveform is derived from the upper vs. the lower limb. These differences probably represent the influences of regional circulatory properties and suggested that a simple "systemic measurement" of whole-body, proximal or distal compliance cannot be reliably obtained from peripheral tonography. Systolic blood pressure wave analysis has been criticized as well (5).

A comparative study was performed between systolic and diastolic pulse contour analysis in normotensive and hypertensive subjects (43). This was a study long in need of performance because of the controversial claims in the literature relating to the theory of systolic and diastolic waveform analysis. As earlier studies had anticipated and predicted, a reasonably good correlation was observed between the SAE measured by diastolic pulse wave analysis using a modified Windkessel analysis and late systolic augmentation index assessed using a transfer function previously described (44). The values from both of these techniques apparently related at least in part to reflected waves from the peripheral small arteries (43). The augmentation index is also critically dependent on large artery pulse wave velocity that accounts for appearance of the reflected wave at the root of the aorta in late systole. SAE also may have some dependency on large artery elasticity, but fortunately an independent assessment of this large artery elasticity is also available from the calculation of LAE in the modified Windkessel model.

Zimlichman et al. (45) determined the reliability and repeatability of measurements of LAE and SAE and gender- and age-specific normal ranges for a healthy European population. Both intravisit and intervisit estimates of reliability indicate good repeatability of measure and were significant. Measurement of the radial artery waveform system and using diastolic pulse contour analysis is highly reproducible in healthy subjects.

In addition to smoking and triglycerides, biomarkers for endothelial dysfunction are associated with impaired LAE and SAE in young adults. As the parent CARDIA study is still ongoing, long-term follow up for CVD events and eventual reevaluation of arterial elasticity in the participants would add to our knowledge of these measures as predictors.

Acknowledgement

The CARDIA study is supported by contracts N01-HC-48047, N01-HC-48048, N01-HC-48049, N01-HC-48050, and N01-HC-95095 from the National Heart, Lung, and Blood Institute. The YALTA study is supported by R01 HL 53560. This work was performed while Narayanan Valappil was a student at the University of Minnesota. The information presented in this article does not necessarily represent the views of the Department of Health and Human Services, nor the Health Resources and Services Administration. All research was carried out with the approval of the University of Minnesota Institutional Review Board, study number 9402M07801. There are no directly related manuscripts or

abstract, published or unpublished, by any author of this paper. There are no financial or other relations that could lead to conflict of interest.

References

1. Duprez DA, Somasundaram PE, Sigurdsson G, Hoke L, Florea N, Cohn JN. Relationship between C-reactive protein and arterial stiffness in an asymptomatic population. *J Hum Hypertens* 2005;19:515–519. [PubMed: 15905893]
2. Cobb FR, Kraus WE, Root M, Allen JD. Assessing risk for coronary heart disease: beyond Framingham. *Am Heart J* 2003;146:679–685. [PubMed: 14564323]
3. Duprez DA, Cohn JN. Monitoring vascular health beyond blood pressure. *Curr Hypertens Rep* 2006;8:287–291. [PubMed: 16884658]
4. Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular disease. *Hypertension* 2003;107:2864–2869.
5. Davies JI, Struthers AD. Pulse wave analysis and pulse wave velocity: a critical review of their strengths and weakness. *J Hypertens* 2003;21:463–472. [PubMed: 12640232]
6. McVeigh GE. Pulse waveform analysis and arterial wall properties. *Hypertension* 2003;41:1010–1011. [PubMed: 12682083]
7. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE. Clinical applications of arterial stiffness, definitions and reference values. *Am J Hyperten* 2002;15:426–444.
8. Duprez DA, Kaiser DR, Whitwam W, Finkelstein S, Belalcazar A, Patterson R, et al. Determinants of radial artery pulse wave analysis in asymptomatic individuals. *Am J Hypertens* 2004;17:647–653. [PubMed: 15288881]
9. Finkelstein SM, Cohn JN. First- and third-order models for determining arterial compliance. *J Hypertens Suppl* 1992;10:S11–S14. [PubMed: 1432309]
10. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA. The clinical implications of endothelial dysfunction. *J Am Coll Cardiol* 2003;42:1149–1160. [PubMed: 14522472]
11. Cox DA, Vita JA, Treasure CB, Fish RD, Alexander RW, Ganz P, et al. Atherosclerosis impairs flow-mediated dilation of coronary arteries in humans. *Circulation* 1989;80:458–465. [PubMed: 2527643]
12. Nigam A, Mitchell GF, Lambert J, Tardif JC. Relation between conduit vessel stiffness (assessed by tonometry) and endothelial function (assessed by flow-mediated dilatation) in patients with and without coronary heart disease. *Am J Cardiol* 2003;92:395–399. [PubMed: 12914868]
13. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR Jr, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol* 1988;41:1105–1116. [PubMed: 3204420]
14. Gross M, Yu X, Hannan P, Prouty C, Jacobs DR Jr. Lipid standardization of serum fat-soluble antioxidant concentrations: the YALTA study. *Am J Clin Nutr* 2003;77:458–466. [PubMed: 12540408]
15. Warnick G. Enzymatic methods for quantification of lipoprotein lipids. *Methods Enzymol* 1986;129:101–123. [PubMed: 3724535]
16. Warnick G, Benderson J, Albers J. Dextran sulphate -Mg²⁺ precipitation procedure for quantification of high-density-lipoprotein cholesterol. *Clin Chem* 1982;28:1379–1388. [PubMed: 7074948]
17. Friedewald W, RI L, Friederickson D. Estimation of the concentration of low density lipoprotein cholesterol in plasma, without the use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–502. [PubMed: 4337382]
18. Jacobs DR, Murtaugh M, Steffes M, Yu X, Roseman J, Goetz F. Gender- and race-specific determination of albumin excretion rate using albumin-to-creatinine ratio in 18 single, untimed urine specimens: the Coronary Artery Risk Development in Young Adults Study. *Am J Epidemiol* 2002;155:1114–1119. [PubMed: 12048225]
19. Warram JH, Gearin G, Laffel L, Krolewski AS. Effect of duration of type I diabetes on the prevalence of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio. *J Am Soc Nephrol* 1996;7:930–937. [PubMed: 8793803]

20. Cohn JN, Finkelstein S, McVeigh G, Morgan D, LeMay L, Robinson J, et al. Noninvasive pulse wave analysis for the early detection of vascular disease. *Hypertension* 1995;26:503–508. [PubMed: 7649589]
21. Murtaugh MA, Jacobs DR Jr, Yu X, Gross MD, Steffes M. Correlates of urinary albumin excretion in young adult blacks and whites: the Coronary Artery Risk Development in Young Adults Study. *Am J Epidemiol* 2003;158:676–686. [PubMed: 14507604]
22. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A. Albuminuria reflects widespread vascular damage. The Steno hypothesis. *Diabetologia* 1989;32:219–226. [PubMed: 2668076]
23. Karalliedde J, Viberti G. Microalbuminuria and cardiovascular risk. *Am J Hypertens* 2004;17:986–993. [PubMed: 15485765]
24. Marschang P, Friedrich GJ, Dittlacher H, Stoeger A, Nedden DZ, Kirchmair R, et al. Reduction of soluble P-selectin by statins is inversely correlated with the progression of coronary artery disease. *Int J Cardiol* 2006;106:183–190. [PubMed: 16321690]
25. Demerath E, Towne B, Blangero J, Siervogel RM. The relationship of soluble ICAM-1, VCAM-1, P-selectin and E-selectin to cardiovascular disease risk factors in healthy men and women. *Ann Hum Biol* 2001;28:664–678. [PubMed: 11726042]
26. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001;286:421–426. [PubMed: 11466120]
27. Beamer NB, Coull BM, Clark WM, Wynn M. Microalbuminuria in ischemic stroke. *Arch Neurol* 1999;56:699–702. [PubMed: 10369309]
28. Winocour PH, Harland JO, Millar JP, Laker MF, Alberti KG. Microalbuminuria and associated cardiovascular risk factors in the community. *Atherosclerosis* 1992;93:71–81. [PubMed: 1596306]
29. Jager A, Kostense PJ, Ruhe HG, Heine RJ, Nijpels G, Dekker JM, et al. Microalbuminuria and peripheral arterial disease are independent predictors of cardiovascular and all-cause mortality, especially among hypertensive subjects: five-year follow-up of the Hoorn Study. *Arterioscler Thromb Vasc Biol* 1999;19:617–624. [PubMed: 10073965]
30. Borch-Johnsen K, Feldt-Rasmussen B, Strandgaard S, Schroll M, Jensen JS. Urinary albumin excretion. An independent predictor of ischemic heart disease. *Arterioscler Thromb Vasc Biol* 1999;19:1992–1997. [PubMed: 10446083]
31. Haffner SM, Stern MP, Gruber MK, Hazuda HP, Mitchell BD, Patterson JK. Microalbuminuria. Potential marker for increased cardiovascular risk factors in nondiabetic subjects? *Arteriosclerosis* 1990;10:727–731. [PubMed: 2403300]
32. de Simone G, Roman MJ, Koren MJ, Mensah GA, Ganau A, Devereux RB. Stroke volume/pulse pressure ratio and cardiovascular risk in arterial hypertension. *Hypertension* 1999;33:800–805. [PubMed: 10082490]
33. Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. *Hypertension* 1999;33:1111–1117. [PubMed: 10334796]
34. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001;37:1236–1241. [PubMed: 11358934]
35. Safar ME, Henry O, Meaume S. Aortic pulse wave velocity: an independent marker of cardiovascular risk. *Am J Geriatr Cardiol* 2002;11:295–298. [PubMed: 12214167]
36. Bhuiyan AR, Li S, Li H, Chen W, Srinivasan SR, Berenson GS. Distribution and correlates of arterial compliance measures in asymptomatic young adults: the Bogalusa Heart Study. *Am J Hypertens* 2005;18:684–691. [PubMed: 15882552]
37. Bhuiyan AR, Srinivasan SR, Chen W, Paul TK, Berenson GS. Correlates of vascular structure and function measures in asymptomatic young adults: the Bogalusa Heart Study. *Atherosclerosis* 2006;189:1–7. [PubMed: 16569409]
38. Dart AM, Gatzka CD, Cameron JD, Kingwell BA, Liang YL, Berry KL, et al. Large artery stiffness is not related to plasma cholesterol in older subjects with hypertension. *Arterioscler Thromb Vasc Biol* 2004;24(9):62–68.

39. Arnett DK, Glasser SP, McVeigh G, Prineas R, Finklestein S, Donahue R, et al. Blood pressure and arterial compliance in young adults: the Minnesota Children's Blood Pressure Study. *Am J Hypertens* 2001;14:200–205. [PubMed: 11281229]
40. McVeigh GE, Morgan DJ, Finkelstein SM, Lemay LA, Cohn JN. Vascular abnormalities associated with long-term cigarette smoking identified by arterial waveform analysis. *Am J Med* 1997;102:227–231. [PubMed: 9217589]
41. Jacobs DR, Crow RS. Subclinical Cardiovascular Disease Markers Applicable to Studies of Oral Health: Multiethnic Study of Atherosclerosis. *Ann NY Acad Sci* 2007;1098:269–287. [PubMed: 17435135]
42. Manning TS, Shykoff BE, Izzo JL Jr. Validity and reliability of diastolic pulse contour analysis (windkessel model) in humans. *Hypertension* 2002;39:963–968. [PubMed: 12019277]
43. Rietzschel ER, Boeykens E, De Buyzere ML, Duprez DA, Clement DL. A comparison between systolic and diastolic pulse contour analysis in the evaluation of arterial stiffness. *Hypertension* 2001;37:E15–E22. [PubMed: 11408401]
44. Cohn JN. Pathophysiologic and prognostic implications of measuring arterial compliance in hypertensive disease. *Prog Cardiovasc Dis* 1999;41:441–450. [PubMed: 10445868]
45. Zimlichman R, Shargorodsky M, Boaz M, Duprez D, Rahn KH, Rizzoni D, Payeras AC, Hamm C, McVeigh G. Determination of arterial compliance using blood pressure waveform analysis with the CR-2000 system: Reliability, repeatability, and establishment of normal values for healthy European population--the seven European sites study (SESS). *Am J Hypertension* 2005;18:65–71.

Figure 1.
Unadjusted mean large artery elasticity (LAE) by height within sex.

Figure 2.
Unadjusted mean small artery elasticity (SAE) by height within sex.

Table 1

Year 10 - Characteristics of study participants by sex: The CARDIA study 1995–96.

	Male (n = 389)		Female (n = 381)	
	Mean	Std. Dev	Mean	Std. Dev
Age (yrs)	35.1	3.6	35.3	3.6
Height (cm)	178.3	6.8	165.1	6.4
BMI (kg/m ²)	27.1	4.3	27.4	6.4
Systolic blood pressure (mm/Hg)	112.1	9.9	105.2	11.6
Diastolic blood pressure (mm/Hg)	73.4	9.0	68.2	9.9
Heart rate (beats/min)	65.2	9.3	68.2	10.0
Total Cholesterol (mg/dL)	182.1	37.8	177.3	32.7
LDL Cholesterol (mg/dL)*	115.3	34.8	107.3	30.2
HDL cholesterol (mg/dL)	45.5	13.3	54.8	14.0
Triglycerides (mg/dL)	109.6	101.3	73.8	43.4
Glucose (mg/dL)	88.9	17.6	84.8	11.5
Insulin (mg/dL)	13.0	8.2	12.7	7.7
Alcohol Consumption (ml/d)	16.2	26.0	7.3	17.7
Physical Activity(Intensity Score)	434.1	282.6	295.5	239.2
TV Watching (hours/wk)	7.4	10.2	6.7	9.6
	%	Geometric mean	%	Geometric mean
Urine Albumin to Creatinine Ratio (% with A/kC ≥ 25, geometric mean)**	6.2	6.4	5.8	5.5
Smoking Status (%)				
Never smokers	61.2		56.2	
Ex-smokers	15.9		21.3	
Current smokers	22.9		22.6	
Educational Level (%)				
Less than 12 years	5.9		5.8	
12 years	23.1		18.1	
13– 15 years	28.0		31.2	
16 years	22.6		24.2	
17 years or more	20.3		20.7	

* LDL cholesterol was not estimated for 6 men with triglycerides ≥ 400 mg/dL

** k = 1 in white women, 0.88 in black women, 0.68 in white men, and 0.68*0.88 in black men

Table 2

Partial and full linear regression models with large or small artery elasticity as dependent variables; demographic variables and variables that are used in estimation of arterial elasticity.

Independent Variable	Class	n	Large Artery Elasticity (LAE) (ml/mmHg×10)				Small Artery Elasticity (SAE) (ml/mmHg×100)			
			Partial Model		Full model		Partial Model		Full model	
			LAE	p	LAE	p	SAE	p	SAE	p
Age classes	27 – 33	237	25.6	0.04	25.5	0.02	8.6	0.010	8.6	0.047
	34 – 37	280	25.3		25.2		8.3		8.4	
	38 – 42	253	24.6		24.6		8.1		8.0	
Race	Blacks	287	24.7	0.18	24.6	0.14	7.9	<0.001	7.9	0.007
	Whites	483	25.4		25.4		8.6		8.6	
Education (years)	0 – 11	45	24.1	<0.001	24.8	0.10	7.9	0.56	8.5	0.83
	12	159	24.0		24.3		8.1		8.3	
	13 – 15	228	24.6		24.7		8.5		8.4	
	16	180	24.5		25.3		8.4		8.3	
	17 or higher	158	26.8		26.4		8.4		8.3	
Blood pressure (mm/Hg)	<100/75	385	26.5	<0.001	26.1	<0.001	8.6	0.001	8.7	<0.001
	<120/80	199	24.8		25.1		8.4		8.3	
	<130/85	114	23.4		23.6		8.0		7.7	
	<140/90	42	21.9		22.8		7.2		6.8	
	≥140/90	30	20.3		22.6		7.7		7.6	
Heart rate beats/min	40 – 59	157	28.2	<0.001	27.8	<0.001	7.9	0.72	7.9	0.08
	60 – 65	177	26.6		26.5		8.5		8.4	
	66– 69	145	25.2		25.0		8.6		8.5	
	70 – 75	165	23.9		24.0		8.6		8.6	
	76 – 132	126	20.8		21.4		8.0		8.3	
BMI (kg/m ²)	17 – 22.9	171	25.0	0.35	24.4	0.13	7.4	<0.001	7.3	<0.001
	23 – 24.9	126	26.2		25.2		8.1		7.8	
	25 – 29.9	290	25.1		25.0		8.6		8.5	
	30 – 34.9	110	24.4		25.6		9.0		9.3	
	35 – 54.4	73	24.6		26.4		9.1		9.6	

Note: The blood pressure category <130/85 means that systolic blood pressure was <130 mmHg and diastolic blood pressure was <85 mmHg, but systolic blood pressure was at least 120 mmHg and diastolic blood pressure was at least 80 mmHg. The other categories are defined analogously.

The partial models include the base model (race, sex, age, clinical center, and education) and the indicated variable.

The full models were adjusted for all variables listed in Table 2–Table 4.

Variance explained in the base model (including age, race, sex, center, education, and height) was $r^2 = 24\%$ for LAE and $r^2 = 15\%$ for SAE. Variance explained in the full model was $r^2 = 40\%$ for LAE and $r^2 = 28\%$ for SAE.

Table 3

Partial and full linear regression models with large or small artery elasticity as dependent variables: biochemical factors that are not used in estimation of arterial elasticity.

Independent Variable	Class	N	Large Artery Elasticity (LAE) (ml/mmHg×10)			Small Artery Elasticity (SAE) (ml/mmHg×100)		
			Partial Model		Full model	Partial Model		Full model
			LAE	p	LAEE	SAE	p	SAEE
Triglycerides (mg/dL)	16–46	154	26.3	<0.001	25.8	8.7	0.03	8.6
	47–62	150	25.6		25.4	8.3		8.2
	63–81	170	25.2		25.1	8.5		8.5
	82–117	143	24.7		24.5	8.3		8.3
	118–1314	153	23.8		24.7	7.9		8.0
HDL Cholesterol (mg/dL)	22–35/23–42*	154	25.0	0.17	25.2	9.0	<0.001	8.9
	36–40/43–48	134	26.0		25.5	8.9		8.6
	41–46/49–55	172	25.0		25.0	8.3		8.2
	47–54/56–64	159	25.3		25.2	7.8		7.9
	55–122/65–123	151	24.5		24.7	7.8		8.0
Total Cholesterol (mg/dL)	89–149	140	24.7	0.96	24.7	8.0	0.15	8.2
	150–167	153	25.6		25.2	8.3		8.2
	168–182	155	25.6		25.7	8.4		8.5
	183–204	167	24.8		25.1	8.6		8.6
	205–358	155	24.9		24.9	8.3		8.1
Glucose (mg/dL)	51–79	148	24.7	0.09	24.6	8.2	0.53	8.3
	80–83	153	25.9		25.8	8.5		8.7
	84–87	157	25.8		25.2	8.2		8.2
	88–92	158	24.4		24.4	8.5		8.3
	93–393	154	24.8		25.5	8.3		8.2
Insulin (μ U/mL)	2–7	103	25.6	0.07	25.5	7.9	0.74	8.5
	8–9	176	26.2		26.9	8.2		8.6
	10–12	211	25.3		25.3	8.3		8.4
	13–16	126	24.5		24.5	8.7		8.4
	17–103	154	23.9		24.3	8.4		7.8
Urine albumin/creatinine (mg/g)**	0.8–4	273	25.2	0.10	24.8	8.6	<0.002	8.5
	4.01–6	204	25.7		25.8	8.3		8.4
	6.01–10	146	24.7		24.7	8.2		8.2
	10.01–25	101	24.7		25.6	8.1		8.3
	25.01–1975	46	24.1		24.7	7.6		7.6
P-selectin (ng/mL)	10.1–28.4	155	26.1	0.002	25.6	8.2	0.14	8.3
	28.5–33.3	143	25.8		25.7	8.2		8.1
	33.4–38.5	158	24.9		25.4	8.3		8.4
	38.6–44.5	157	24.7		24.8	8.4		8.4
	44.6–85.7	157	24.2		24.2	8.5		8.4
Intercellular adhesion molecule 1 (ng/mL)	67.5–120.2	158	25.3	0.01	24.4	8.1	0.29	8.2
	120.3–135.4	161	25.8		25.6	8.4		8.4
	135.5–152.1	154	25.7		25.5	8.6		8.5
	152.2–178.9	147	24.7		25.1	8.6		8.6
	178.9–368.9	150	24.1		25.0	8.0		8.0

Notes: The partial models include the base model and the indicated variable; except the partial lipid model includes the base model and all 3 lipid variables. The full models were adjusted for all variables listed in Table 2–Table 4.

*
cupoints for males/females

**
Estimated from a single untimed urine; creatinine adjusted for race and sex as indicated in the text.

Table 4

Partial and full linear regression models with large or small artery elasticity as dependent variables: lifestyle factors that are not used in estimation of arterial elasticity.

Independent Variable	Class	N	Large Artery Elasticity (LAE) (ml/mmHg×10)			Small Artery Elasticity (SAE) (ml/mmHg×100)		
			Partial Model		Full model	Partial Model		Full model
			LAE	p		SAE	p	
Smoking status	Current	175	24.8	0.41	25.8	7.8	0.002	7.9
	Former	143	24.7		24.8	8.6		8.6
	Never	452	25.4		24.9	8.5		8.4
Alcohol intake (ml/day)	None	337	25.7	0.002	25.8	8.5	0.44	8.2
	0-10	172	25.5		25.2	8.4		8.5
	10-20	126	24.9		24.9	8.2		8.4
	20-30	55	23.7		23.6	8.4		8.7
	30-237	80	23.4		23.3	7.7		8.0
TV viewing (Hours/week)	0-2	351	25.2	0.23	25.0	8.2	0.78	8.3
	3-7	168	26.2		26.0	8.5		8.4
	8-14	144	24.0		24.3	8.5		8.3
	15-21	49	24.5		25.2	8.5		8.6
	22-63	58	24.8		25.3	8.3		8.4
Physical Activity (Exercise units)	0-100	106	25.3	0.13	25.2	8.5	0.07	8.4
	101-300	264	24.9		25.3	8.4		8.3
	301-500	199	24.6		24.9	8.4		8.5
	501-800	146	25.9		25.9	8.3		8.4
	801-2072	55	25.6		24.9	7.8		7.9