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Relationship Between Brachial Flow - Mediated Dilation and Carotid Intima- Media Thickness in an Elderly Cohort: The Cardiovascular Health Study

Joseph Yeboah, MD, MS, Gregory L Burke, MD, MS, FAHA, John R Crouse III, MD, FAHA, and David M Herrington, MD, MHS, FAHA

From Departments of Internal Medicine/Cardiology and Public Health Sciences, Wake Forest University School of Medicine Winston- Salem North Carolina

Abstract

Objective—The aim of this study was to determine the relationship between brachial flow-mediated dilation (FMD) and carotid intima-media thickness (IMT) in a large multi-ethnic elderly cohort.

Background—Brachial flow-mediated dilation (FMD) is a physiologic measure and Carotid IMT is an anatomic structural measure of subclinical atherosclerosis. Both brachial FMD and carotid IMT have been associated with cardiovascular risk factors and cardiovascular events. The relationship between brachial FMD and carotid IMT is less clear especially in older adults.

Methods—Brachial FMD, carotid IMT and traditional cardiovascular risk factors were measured in 2338 adults, age 72–98 years who were participants in the Cardiovascular Health Study. The relationship between FMD and IMT was assessed both unadjusted and also after adjusting for age, gender, race/ethnicity. BMI, HDL, LDL, systolic and diastolic blood pressure, serum creatinine, current smoking, diabetes mellitus, hormone therapy and prior CVD.

Results—Both brachial FMD and carotid IMT correlated significantly with age, HDL levels, waist/hip ratio, serum cholesterol and number of CV risk factors. Brachial FMD was not associated with CCA IMT in this elderly cohort (Pearson partial correlation coefficient= -0.0252 , $p=0.222$). In the adjusted linear regression model with CCA IMT as the dependent variable, brachial FMD was also not associated with CCA IMT (beta coefficient= -0.006 , $p=0.470$)

Conclusion—Brachial FMD and CCA IMT are not related in population-based older adults. Brachial FMD and CCA IMT may be distinct and independent stages in the complex atherosclerotic process.

Address Correspondence and reprints request to: Joseph Yeboah MD, Department of Internal Medicine/Cardiology, Wake Forest University School of Medicine, Medical Center Boulevard. Winston- Salem NC 27157 Phone: 336 716 7253, Fax: 336 716 9188., Email: jyeboah@wfubmc.edu.

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Keywords

Brachial flow-mediated dilation; carotid intima-media thickness; endothelial function; atherosclerosis; elderly

INTRODUCTION

Subclinical cardiovascular disease (CVD) has both physiologic and anatomic components. Non-invasive measurement techniques allow for the characterization of both physiologic as well as anatomic structural changes in the arterial wall due to cardiovascular disease. Brachial flow-mediated dilation (FMD) is a validated non-invasive physiologic measure of endothelial dysfunction (a marker of subclinical CVD) (1). Carotid intima-media thickness (IMT) however, is a non-invasive anatomic structural measure of subclinical CVD (2). Brachial FMD has been associated with both cardiovascular risk factors (3) and future CVD morbidity and mortality (4–7). Similarly, Carotid IMT has also been associated with both cardiovascular risk factors (8) and with CVD morbidity and mortality (8–11).

The data on the relationship between brachial FMD (a physiologic measure of early CVD) and carotid IMT (an anatomic measure of early CVD) are somewhat limited. Some studies have shown an inverse association between brachial FMD and carotid IMT (12–17); however other studies did not observe an association (18, 19). The difference in the number of publications for and against such an association may be due to publication bias (18). Most of the previously published studies were conducted in small number of participants from relatively young single - gender or single - race/ethnic cohorts. The relationship between brachial FMD and CCA IMT in multi-ethnic cohorts and also in older adults is unclear.

To address some of the limitations in current literature, we assessed the association between brachial FMD and carotid IMT in a large multi-ethnic population- based sample of older adults who were participants in the Cardiovascular Health Study (CHS).

METHODS

Study Participants

The CHS population has been previously described (20). Briefly, CHS was a longitudinal multicenter study of 5888 adults aged ≥ 65 years designed to be representative of the US population. Recruitment of 5201 adults into the study began between May 1989 and May 1990 at four clinic sites (University of California Davis-Sacramento county CA, The Johns Hopkins University- Baltimore MD, Wake Forest University- Forsyth county NC and University of Pittsburgh- Pittsburgh PA) with the coordinating center at University of Washington Seattle, WA. Between 1992 and 1993, an additional 687 African American participants were recruited from three out of the four clinic sites (Sacramento county, Forsyth county and Pittsburgh). All participants were either medicare beneficiaries or medicare-eligible during recruitment. The Cardiovascular Health Study was approved by the institutional review boards of each study site and informed consent was obtained from all participants.

Eight years into the study (1997–1998), the 3032 participants who returned for their yearly visit were approached for participation in a brachial FMD ancillary study. Of the 3032 subjects, 130 were excluded (74- history of mastectomy, 20- history of Raynaud's disease and 36- other miscellaneous reasons). Sixty-one (61) participants refused the ultrasound examination and an additional 49 discontinued the scan {19- discomfort during the exam, 9- equipment problems and 21- other reasons}. In all 2792 participants, 666 with prior history of cardiovascular disease, age 72–98 years had the brachial artery ultrasound measurements performed. This ancillary study was approved by the institutional review boards of each study site and informed consent was obtained from all participants.

For the analyses, the 2338 out of the 2792 participants, who had both the brachial ultrasound measurement and carotid intima-media thickness measured in the subsequent CHS clinic visit (1998–1999 CHS clinic visit) were included.

Clinical Evaluation and Biochemical Analysis

All participants provided a medical history and underwent a clinical examination at baseline and then yearly thereafter. As previously described by Fried et al, standardized questionnaires were used to determine medical history, medication use and cardiovascular risk assessment at baseline and then at yearly visits. Participants were contacted biannually to ascertain interim hospitalizations, medical diagnosis or morbidity/mortality. Health Care Financing Administration records were reviewed to supplement information provided by participants. Event ascertainment and adjudication of clinical events in the CHS was done using standard criteria, by a formal adjudication committee as previously published (21–23). For the purpose of these analyses cardiovascular event were defined as any of the following adjudicated events: CVD death, myocardial infarction, stroke, congestive heart failure, claudication, angioplasty or cardiac bypass graft surgery.

Hypertension in CHS was defined as systolic blood pressure > 140 mmHg or diastolic blood pressure >90 mmHg, history of hypertension or antihypertensive medication usage. Diabetes mellitus was defined as fasting blood glucose ≥ 126 mg/dl, history of diabetes mellitus or use of insulin/oral hypoglycemics. Race was defined by self-report with the following 5 choices: white, black, American Indian/Alaskan Native, Asian/Pacific Islanders or other. For the sake of simplicity, race was re-categorized into three categories: whites, blacks and others.

Blood for biochemical analysis was obtained from fasting venous samples and total cholesterol was determined using standard enzymatic methods (24). All the covariates used in this analysis were collected at the eight CHS clinic visit except data on body mass index which was collected during the seventh CHS clinic visit and high density lipoprotein and low density lipoprotein which were measure on the fourth CHS clinic visit.

Carotid Ultrasound Measurement

Carotid artery ultrasound was performed during the 1998–99 CHS clinic visit with Toshiba SSA-270A imaging units (Toshiba America Medical Systems). Details of the scanning and reading protocols, as well as reproducibility results, have been published (25). All machines were identically equipped with a phased-array imaging probe with a characteristic –3-dB cutoff point of 6.7 MHz and a pulsed Doppler frequency of 4.0 MHz.

To quantify the degree of thickening of the carotid artery walls, the many measures of IMT were summarized into two variables: one for the CCA and one for the ICA. The maximum wall thickness of the CCA was defined as the mean of the maximum wall thicknesses for near and far wall on both the left and right sides: $(mLNW+mLFW+mRNW+mRFW)/4$. The maximum wall-thickness variable of the ICA was defined in the same way; the results from the three scans were averaged. The number of measurements available for averaging thus ranged from 1 to 4 for the CCA and 1 to 12 for the ICA.

Flow-Mediated Brachial Artery Vasodilation

A detailed description of the scanning and reading protocol has been previously published (26). Briefly, sonographers underwent centralized training in brachial FMD measurement at Wake Forest University School of Medicine and were certified after performing at least 20 acceptable scans on volunteers. Participants were instructed to refrain from caffeine, cigarettes or food at least eight hours prior to the examination. All the examinations took place at approximately the same time (morning) in a room with an ambient temperature of 72°F. Participants underwent examination after 15 minutes rest in the fasting state. With each participant supine and using an automated sphygmomanometer, the left arm was used to monitor blood pressure and pulse at five minute intervals throughout the exam. A standard pediatric cuff was positioned around the right arm, 2 inches below the antecubital fossa. A 10 MHz Biosound Phase 2 ultrasound system (BiosoundEsaote, Indianapolis Ind.) was used to acquire images of the right brachial artery. After obtaining baseline images of the right brachial artery for 2 minutes, the pediatric cuff was inflated to 50mmHg above the participant's systolic blood pressure to occlude the right brachial artery. The pediatric cuff was kept inflated for 4 minutes. Images of the right brachial artery were captured continuously for 2 minutes after cuff deflation. Video tapes of the acquired images of the brachial artery were analyzed at the Wake Forest University Cardiology Image Processing Laboratory using a previously validated semi-automated system. All brachial diameter images were captured in diastole (ECG gated R-wave). The semi-automated readings of these digitized images generated the baseline and maximum diameters of the brachial artery from which the absolute change in baseline diameter and % brachial FMD was computed.

Correlations for repeated measures of baseline diameter, maximum diameter and %FMD using 80 CHS participants scanned on two separate days more than 2 weeks apart, were 0.94, 0.94 and 0.67 respectively (26). The reproducibility of the method including cuff placement below the antecubital fossa and the automated analysis was tested with repeated examinations less than one week apart among 127 CHS participants. The mean $\pm$ SD difference in percent change in diameter (brachial FMD) was $0.02 \pm 1.54\%$ and R^2 was 0.7(27).

Statistical Analysis

Data are presented as mean $\pm$ SD for continuous variables and frequencies for categorical variables. Both brachial FMD and CCA IMT were highly skewed and were log transformed prior to the analyses. Pearson correlations between traditional CV risk factors and brachial FMD/carotid IMT were evaluated. Both brachial FMD and CCA IMT are heavily influenced by age and gender. Therefore Partial Pearson correlations were used to evaluate the

relationship between brachial FMD and CCA IMT (adjusting for age and gender) in the entire cohort and also in subgroups. Multiple linear regression analysis was also used to evaluate the association between carotid IMT (dependent variable) and brachial FMD (%) adjusting for covariates known to be associated with carotid IMT in prior studies or significantly associated with carotid IMT in the univariate analysis including age, gender, race/ethnicity, BMI, HDLc, LDLc, systolic blood pressure, diastolic blood pressure, serum creatinine, cigarette smoking, diabetes mellitus, hormone replacement therapy and prevalent CVD status. Analysis was done using SAS version 9.1 (SAS institute, Cary NC).

RESULTS

Study population

The characteristics of the 2338 participants included in the analyses are shown in Table 1. The participants were elderly with a mean age of about 78 years. The study population was 58.7% female and 83.7% Caucasians. Participants were mostly overweight with mean systolic blood pressure above normal. Very few of the female participants were on hormone replacement therapy (12.9% of females) and only 14% of the participants were taking HMG CoA reductase inhibitors. Four hundred and seventy-nine (20.5%) of the participants had prevalent cardiovascular disease.

The mean maximum CCA IMT and ICA IMT were 1.06 mm and 1.54 mm respectively while the mean brachial FMD was 2.43 %.

As previously published by O'Leary et al (23), carotid IMT was significant associated with CV risk factors in this elderly cohort (Tables 2).

Correlations between traditional cardiovascular risk factors and FMD

Participants age, HDLc, waist/hip ratio, serum creatinine and number of CV risk factors showed significant correlations (Pearson's) with brachial FMD ($P < 0.001$ for all). Participants BMI and systolic blood pressure also correlated with brachial FMD ($P < 0.05$ for both) (Table 2). Participants with history of hypertension had lower brachial FMD compared with those without history of hypertension [2.36(2.31–2.41) vs 2.61(2.55–2.67) %, $p < 0.001$]. Females had higher brachial FMD compared with males [2.72(2.25–3.29) vs 2.18(2.13–2.24) %, $p < 0.0001$]. Caucasians had higher brachial FMD compared with blacks [2.57(2.53–2.61) vs 2.12(2.03–2.20) %, $p < 0.001$]. Participants with diabetes mellitus have lower brachial FMD compared with those without diabetes mellitus [2.27(2.18–2.36) vs 2.54(2.49–2.58) %, $p < 0.01$]. Participants with history of CVD events had a lower brachial FMD compared with those without prevalent CVD events [2.27(2.20–2.34) vs 2.53(2.16–2.97) %, $p < 0.01$].

Relationship between CCA IMT and brachial FMD

Brachial FMD did not correlate with CCA IMT in neither the entire cohort [Pearson partial correlation coefficient (r) = -0.025 , $p = 0.222$] (Figure 1) nor in all the subgroups defined by CV risk factors such as diabetes (yes/no), hypertension (Yes/no), cigarettes smoking (Yes/no), prior CVD (Yes/no), gender and Race (Caucasian/Black) (data not shown).

Exploration for a possible curvilinear (quadratic) association or a threshold above (or below) which there may be an association also proved futile.

In the univariate linear regression model (age and gender adjusted), brachial FMD was not associated with CCA IMT (beta coefficient = -0.0075 , $p=0.222$). Brachial FMD was also not associated with CCA IMT in the fully adjusted model (beta coefficient = -0.006 , $p=0.470$) (Table 3). A significant interaction term for brachial FMD (continuous variable) and diabetes status (yes/no) was observed in our multivariable model ($p=0.01$). Brachial FMD was not significantly associated with CCA IMT in any of the subgroups defined by CV risk factors and also gender after adjusting for covariates (data not shown). Similar findings were observed using internal carotid IMT as the dependent variable.

Discussion

Our study which included 2338 population-based older adults, with or without prevalent cardiovascular disease, showed no relationship between brachial FMD, a physiologic measure of early atherosclerosis and common carotid IMT, a structural measure of early atherosclerosis. Our findings buttresses earlier studies such as the study by Yan et al, that suggested that brachial FMD and CCA IMT may be distinct and independent stages in the complex atherosclerosis process.

The data on the relationship between brachial FMD and CCA IMT are mixed. Majority of earlier studies showed an association between brachial FMD and CCA IMT (12–17). However other studies which were mostly conducted either in healthy cohorts or cohorts with minimal CV risk factors did not show an association (18, 19). The inference that one may draw from these studies is that brachial FMD is not related to CCA IMT only in middle-aged healthy men. Our study which has the largest sample size so far studied on this topic and was conducted in older adults with a very high atherosclerotic burden/CV risk factors also showed that brachial FMD is not related to CCA IMT. Our study adds substantially to the brachial FMD – CCA IMT association data by showing that even in the elderly/high CV risk cohorts, there is no association between brachial FMD and CCA IMT.

Brachial FMD is the most widely studied measure of endothelial function. Even though brachial FMD is variable, it has been associated with both CV risk factors and CV events mostly in subjects with cardiovascular risk factors/history of CV events. In this study, brachial FMD was modestly associated with age, systolic blood pressure, high density lipoprotein levels, waist/hip ratio, creatinine levels and the number of CV risk factors; all of which are recognized cardiovascular risk factors. Even though the strength of association is not as strong as in other relatively young cohorts, this finding suggests that the association between brachial FMD and CV risk factors persist into older adulthood. We have also shown that brachial FMD is an independent predictor of CV events in this cohort (7). These findings are consistent with the fact that brachial FMD (endothelial dysfunction) may be a stage in the pathogenesis of atherosclerosis/cardiovascular disease.

Intima-media thickness is a measure of the early structural changes that occurs in the wall of blood vessels due to atherosclerosis. Carotid IMT has also been widely associated with

CV risk factors and has also been shown to be predictive of CV events. In this study CCA IMT showed a stronger association with CV risk factors compared with brachial FMD and CV risk factors. This was probable due to the fact that IMT is a more precise measure than brachial FMD (which is derived). O'leary et al showed in this cohort that carotid IMT is predictive of cardiovascular events such as myocardial infarction and stroke (11). These findings are also consistent with Intima-media thickness as a stage in the pathogenesis of atherosclerosis/cardiovascular disease.

Even though current data suggest that both brachial FMD and CCA IMT are stages in the complex atherosclerosis process, our study and a few that preceded it have shown that they are not related (18,19). Atherosclerosis is a complex disease and may have complex/multiple pathways. Thus endothelial dysfunction and intima-media thickness may both be stages in the pathogenesis of atherosclerosis/cardiovascular disease but may be in different pathways all of which leads to clinical atherosclerosis/cardiovascular disease.

Our study has the following limitations. Endothelial- independent vasodilation with nitroglycerin was not examined in our cohort due to the age of our study participants (72–98 years) and the risk-benefit considerations of nitroglycerin administration in a population-based cohort study. Thus, although brachial FMD was not associated with carotid IMT in this study, we are uncertain the effect that smooth muscle dysfunction may have on the brachial FMD that was obtained. However studies which evaluated endothelial-independent vasodilation showed no significant effect on the relationship between brachial FMD and carotid IMT (13).

Although brachial FMD and most of the covariates were measured on the same CHS clinic visit, carotid IMT was measured one year later and other covariates such as HDL, LDL and triglycerides about 4 years earlier. Our results should therefore be interpreted within this background. Finally, our study was in older adults and therefore our results may not hold true in other age groups. However studies in other age-groups have made similar observations.

Conclusion

Our study found no relationship between brachial FMD and CCA IMT in population-based older adults. Atherosclerosis is a complex disease and may have multiple pathways. Brachial FMD and CCA IMT may be distinct and independent stages in these pathways.

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Figure 1.
Association between brachial FMD and Common carotid IMT in the elderly.

Table 1

Demographics of the study sample (N=2338).

Variable	Mean± sd
Age (years)	78.3 ± 4.2
Females (%)	1373 (58.7)
Race (%)	
Caucasians	1956 (83.7)
Blacks	374 (16.0)
others	8 (0.3)
BMI (Kg/m ²)	27.1 ± 4.5
Total cholesterol (mg/dl)	201.8 ± 38.8
HDL cholesterol (mg/dl)	54.4 ± 14.3
LDL cholesterol (mg/dl)	127.8 ± 32.0
Triglycerides (mg/dl)	142.9 ± 87.6
Systolic blood pressure (mmHg)	145.2 ± 22.6
Diastolic blood pressure (mmHg)	74.0 ± 10.5
Serum Creatinine (mg/dl)	1.01± 0.3
Current smoking	154(6.7)
Females on HRT (%)	177(12.9)
HMG CoA reductase inhibitor use	328 (14.0)
Prior cardiovascular event	479 (20.5)
Number of CV risk factors	4.2 ± 1.4
Common carotid IMT (mm)*	1.06(0.86–1.31)
Internal carotid IMT(mm)*	1.54(0.97–2.44)
Brachial FMD (%)*	2.48(1.22–5.05)

* Common carotid IMT, Internal carotid IMT and brachial FMD values obtained by back transformation.

Table 2

Bivariate correlations (Pearson coefficients) between cardiovascular risk factors and common carotid IMT/brachial FMD.

Risk Factors	Common Carotid IMT*	Brachial artery FMD*
Age (years)	+ 0.115 [†]	−0.07 [†]
Systolic BP	+0.154 [†]	−0.047 [‡]
Diastolic BP	+0.051 [‡]	−0.032
BMI	+0.073 [†]	−0.043 [‡]
Total Cholesterol	+0.013	+0.035
LDLc	+0.090 [†]	+0.004
HDLc	−0.142 [†]	+0.010 [†]
Triglycerides	+0.062 [†]	−0.021
Waist/Hip Ratio	+0.151 [†]	−0.080 [†]
Creatinine (mg/dl)	+0.144 [†]	−0.116 [†]
Number of CV risk factors	+0.260 [†]	−0.130 [†]
Cigarette smoking	+0.114 [†]	−0.030

* Log transformed;

[†] p < 0.001,

[‡] p < 0.05

Table 3

Relationship between carotid IMT (dependent variable) and brachial FMD in multiple linear regression models.

	Beta coefficient	Standard error	P value
Model 1 (Unadjusted)	−0.016	0.006	0.008
Model 2 (Adjusted for age and gender)	−0.007	0.006	0.222
Model 3 (Full model*)	−0.006	0.008	0.470

Full model was adjusted for age, gender, race/ethnicity, BMI, HDL, LDL, systolic and diastolic blood pressure, serum creatinine, current smoking, diabetes mellitus, hormone therapy and prior CVD.