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EDITORIAL COMMENT

Primary and a Half Prevention

Can We Identify Asymptomatic Subjects With High Vascular Risk?*

David S. Celermajer, MB, BS, PHD, FRACP
Sydney, Australia

We should be able to detect atherosclerosis early, before clinical events occur. After all, it is a disease process that begins in childhood (1), takes many decades to progress in most subjects, and affects an organ (the vasculature) for which we have multiple diagnostic modalities available.

Nevertheless, we have not yet established a reliable methodology for seeing clearly through this long presymptomatic window of atherosclerotic disease. This failure is probably because the pathogenesis of the disease is very complex, involving a plethora of contributing moieties (lipoproteins, a variety of cells, extracellular matrix, oxidants, cytokines and thrombomodulators, among others) and because much of the disease processes occur inside the vessel wall, rather than adjacent to or within the lumen. Furthermore, there is only a loose association between the burden of plaque and the risk of an event, with factors such as vascular function, plaque composition, plaque geometry and remodeling, inflammation, and collateralization all confounding the relationships among plaque size, luminal narrowing, and clinical events.

See pages 1980 and 1987

Preventive strategies for atherosclerosis often are divided rather simplistically into "primary" and "secondary" prevention, on the basis of the presence or absence of a prior clinical event. This dichotomy, however, does not emphasize identification of those asymptomatic individuals with particularly high risk nor target such subjects for intensive preventive therapy, that is, those who require "primary and a half" prevention. In this regard, novel blood tests and imaging modalities have been developed for these high-risk asymptomatic subjects that now might improve our diagnostic capabilities and therapeutic targeting strategies.

With such developments, preventive cardiology efforts may now move beyond the identification of epiphenomenal "risk factors," to the measurement of processes more directly related to the pathology within the arterial wall (i.e., how the risk factors have impacted on atherogenesis in a particular individual).

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From the Department of Cardiology, Royal Prince Alfred Hospital and Faculty of Medicine, University of Sydney, Sydney, Australia.

INFLAMMATORY MARKERS

A number of large prospective population-based studies have established the potential importance of measuring serum inflammatory markers as a means of identifying high-risk asymptomatic subjects. Of these, the high-sensitivity C-reactive protein (hsCRP) measurement (2) is the best studied to date. However, not all researchers agree on the magnitude of risk conferred by an elevated hsCRP level (3), and further data are required concerning day-to-day variability in individual subjects as well as defining the clinical benefits that might accrue from treatment and risk stratification according to hsCRP results. Nevertheless, this is an exciting area in preventive medicine. Encouraging work also is now appearing about inflammatory markers that might be more specifically related to atherogenic processes, such as lipoprotein-associated phospholipase A2, a lipoprotein-associated enzyme implicated in the vascular inflammatory pathway leading to plaque formation (4).

CORONARY CALCIUM SCANNING

Vascular imaging is an even more appealing concept for identification for high-risk subjects because it might provide information about specific location of vulnerable plaque(s) in addition to identifying vulnerable patients. The detection of coronary artery calcium with fluoroscopy has long been recognized as valuable in predicting the presence of obstructive coronary artery disease, and it has been more than a decade since computed tomography scanning for quantification of coronary calcium was popularized (5). This promising technique does appear to add extra diagnostic information over and above the measurement of traditional risk factors (6), and the absence of coronary calcium appears to have a high negative predictive value for subsequent events. Nevertheless, some questions remain about lower specificity than sensitivity, particularly in low-risk subjects, reproducibility of measurements with serial studies, and aspects related to radiation and cost-effectiveness.

VASCULAR ULTRASONOGRAPHY

By contrast, ultrasonography is a very appealing technique for studying atherosclerosis because it is noninvasive, relatively inexpensive, widely available, simple, and generally reproducible. Although the coronary arteries cannot be well visualized by noninvasive ultrasonography, early changes in peripheral arteries have been widely studied in the hope and expectation that this might provide useful insights into presymptomatic atherosclerosis, given the systemic nature of this disease. Furthermore, it became apparent more than a decade ago that ultrasonography was useful for the detection of both early structural changes in the artery walls (such as thickening or minor plaque), as well as early functional changes (such as loss of endothelium-dependent dilatation, which precedes plaque formation in high-risk subjects).

Thus, in 1992, we first described the technique of ultrasonography-based measurement of flow-mediated dilatation (FMD) in children and young adults at risk of atherosclerosis (7), which was later shown to be mediated predominantly by endothelial nitric oxide release in response to increased shear stress. This technique has been used by many research groups, who have documented a relationship between FMD and most cardiovascular risk factors in both low-risk and high-risk subjects. Recently, several centers have demonstrated a relationship between decreased brachial FMD and a higher incidence of cardiovascular events during follow-up (e.g., reference 8). Nevertheless, long-term prognostic data in a large population of asymptomatic subjects remain lacking.

At around the same time, Salonen et al. (9) reviewed the data concerning the measurement of intima-media thickness (IMT) of the common carotid artery as an accurate and reproducible measure of atherosclerosis. Carotid IMT has been shown to correlate well with traditional risk factors and burden of atheroma elsewhere in the body, and it also appears to be predictive of subsequent cardiovascular events in large population studies. As with FMD, there is some variation in the protocols used for measurement carotid IMT, but most investigators have shown a significant relationship between ultrasonography-based measurement of this parameter and subsequent risk of events. Carotid IMT has now been used extensively as a surrogate endpoint in disease reversibility trials.

FMD, IMT, AND POPULATION SCREENING

Three recent studies have investigated the relationship between ultrasound-based measurements for vascular health using FMD and/or IMT and subsequent risk, two in this issue of the *Journal* (10,11) and one in a recent issue of *Circulation* (12).

In the larger of the two population-based ultrasound studies, Juonala et al. (12) studied the interrelations between brachial endothelial function and carotid IMT in 2,109 healthy adults ages 24 to 39 years, documenting a very strong inverse association between FMD and IMT ($p < 0.001$), in a multivariate model adjusted for traditional risk factors. Furthermore, this inverse relationship was strongest in subjects with intermediate or impaired FMD, suggesting that very good FMD might protect the vasculature from the propensity of risk factors to lead to structural wall thickening. This study encourages the use of both FMD and IMT, in appropriately expert hands, for the identification of high-risk asymptomatic individuals.

In sharp contrast, the publication by the Firefighters And Their Endothelium (FATE) investigators in this issue of the *Journal* (10) found no significant relationship at all between carotid IMT and brachial artery FMD in 1,578 middle-aged men without known cardiovascular disease. Although possible interpretations of these data include inaccuracies in the measurement techniques used or a lack of validity of carotid IMT and/or brachial FMD as good measures of early vascular disease, the authors argue convincingly that carotid IMT and brachial artery FMD probably provide complementary pathophysiologic insights into early atherosclerosis. Nevertheless, it is worrisome for the potential applicability of both techniques that two large population-based studies by highly experienced investigators have produced such strikingly discordant results.

In the third of these studies, Witte et al. (11) postulate, on the basis of meta-analysis, that the association between FMD and cardiovascular risk may be limited to low-risk populations, in whom they document a significant association between these parameters. However, it should be noted that the median sample size of the meta-analyzed studies was only 20 subjects, that many of the smaller studies recruited highly selected individuals rather than population-based samples, and that the resulting analysis will necessarily reflect the findings of the largest studies included, as well as being potentially confounded by publication bias and the combination of results from studies which used very different methodologies for the measurement of FMD. Thus, such findings could best be regarded as hypothesis-generating, rather as a definitive indication that FMD is best suited to risk stratification in low-risk populations.

There is little doubt that the measurement of both FMD and IMT has provided an extremely valuable insight into the relationship between risk factors and early arterial disease, as well as important data concerning the effects of treatment on early atherogenic processes. Large population studies support the predictive value of IMT, as do the only prospective studies of FMD and event rates that have been published to date, although as yet these have only been very small; thus, the final results of the FATE investigation concerning the predictive value of FMD for clinical events are anxiously awaited. However, at the moment, the measurement of FMD must be regarded as a valuable clinical research tool but certainly not ready for "prime time," for population screening, or clinical decision-making.

Therefore, the quest for "the Holy Grail" of identification of high-risk asymptomatic subjects continues. One feels, however, that the chalice is not far away, with blood tests and ultrasonography the most likely modalities to permit cost-effective identification of vulnerable patients and advanced imaging modalities more likely to allow localization of vulnerable plaques.

Reprint requests and correspondence: Dr. David S. Celermajer, Department of Cardiology, Royal Prince Alfred Hospital, Missenden Road, Camperdown NSW 2050, Australia. E-mail: david.celermajer@email.cs.nsw.gov.au.

REFERENCES

1. Malcom GT, Oalmann MC, Strong JP. Risk factors for atherosclerosis in young subjects: the PDAY Study. Pathobiological Determi-

nants of Atherosclerosis in Youth. Ann NY Acad Sci 1997;817: 179–88.
2. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation 2003;107:363–9.
3. Danesh J, Wheeler JG, Hirschfield GM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 2004;350:1387–97.
4. Packard CJ, O'Reilly DS, Caslake MJ, et al. Lipoprotein-associated phospholipase A2 as an independent predictor of coronary heart disease. West of Scotland Coronary Prevention Study Group. N Engl J Med 2000;343:1148–55.
5. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15;827–32.
6. Shaw LJ, Raggi P, Schisterman E, et al. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. Radiology 2003;228:826–33.
7. Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992;340:1111–5.
8. Gokce N, Keaney JF, Hunter LM, et al. Risk stratification for postoperative cardiovascular events via non-invasive assessment of endothelial function. A prospective study. Circulation 2002;105: 1567–72.
9. Salonen JT, Salonen R. Ultrasound B-mode imaging in observational studies of atherosclerosis progression. Circulation 1993;87 Suppl: II56–65.
10. Yan RT, Anderson TJ, Charbonneau F, Title L, Verma S, Lonn E, on behalf of the FATE Investigators. Relationship between carotid artery intima-media thickness and brachial artery flow-mediated dilation in middle-aged healthy men. J Am Coll Cardiol 2005;45:1980–6.
11. Witte DR, Westerink J, de Koning EJ, van der Graaf, Y, Grabbee DE, Bots ML. Is the association between flow-mediated dilation and cardiovascular risk limited to low risk populations? J Am Coll Cardiol 2005;45:1987–93.
12. Juonala M, Vikari JSA, Laitinen T, et al. Interrelations between brachial endothelial function and carotid intima-media thickness in young adults. The Cardiovascular Risk in Young Finns Study. Circulation 2004;110:2918–23.

2. Yan2005 (truncated)

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Relationship Between Carotid Artery Intima-Media Thickness and Brachial Artery Flow-Mediated Dilation in Middle-Aged Healthy Men

Raymond T. Yan, MD, MASc,* Todd J. Anderson, MD, FRCPC, FACC,†
Francois Charbonneau, MD, MSc, FRCPC, FACC,† Lawrence Title, MD, FRCPC, FACC,‡
Subodh Verma, MD, PhD,§ Eva Lonn, MD, MSc, FRCPC, FACC*., on behalf of the FATE Investigators
Hamilton, Calgary, Halifax, and Toronto, Canada

OBJECTIVES We aimed to determine the relationship between carotid intima-media thickness (IMT) and brachial artery flow-mediated dilation (FMD) in healthy middle-age men.

BACKGROUND Carotid IMT and brachial artery FMD are frequently used as surrogate measures of subclinical atherosclerosis. Whereas carotid IMT identifies early structural abnormalities, brachial artery FMD, considered a bioassay of endothelial function, measures functional vascular integrity. The relationship between carotid IMT and brachial artery FMD has not been well studied.

METHODS We measured traditional risk factors, carotid IMT, and brachial artery FMD in 1,578 middle-aged men without known cardiovascular disease and analyzed the relationship between carotid IMT and brachial FMD.

RESULTS Carotid IMT correlated with age, systolic blood pressure, body mass index, fasting glucose, total and low-density lipoprotein (LDL) cholesterol, and with the overall Framingham risk score ($p < 0.001$ for all), whereas impaired brachial artery FMD correlated with systolic and diastolic blood pressure ($p < 0.01$). No relationship was observed between carotid IMT and brachial artery FMD for the entire cohort ($r = -0.006$, $p = 0.82$) and in subgroups defined by traditional risk factors or by quintiles of carotid IMT and brachial FMD.

CONCLUSIONS In middle-aged healthy men, there is no significant correlation between carotid IMT and brachial artery FMD. This finding suggests that these are unique, independent surrogates that measure different aspects and stages of early atherosclerosis. Further studies are needed to define their role in clinical research and in cardiovascular risk assessment. (J Am Coll Cardiol 2005;45:1980–6) © 2005 by the American College of Cardiology Foundation

It has been suggested that "atherosclerosis imaging may enhance the detection and treatment of patients at risk for coronary heart disease" (1). Proposed noninvasive atherosclerosis imaging techniques that may improve current risk stratification include carotid ultrasound (US) and brachial artery reactivity testing. High-resolution US measurements of carotid artery intima-media thickness (IMT) identify and quantitate early *structural* vascular abnormalities (2,3). Increased carotid IMT correlates with cardiovascular (CV) risk factors (4–6) and is a potent independent predictor of myocardial infarction and stroke (6–8). Brachial artery flow-mediated dilation (FMD) is an in vivo indicator of vascular endothelial *function* (2,9,10) and was also shown to correlate with various CV risk factors (9–11) and to have prognostic significance (12–14), albeit in much smaller studies that require further confirmation.

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Several previous studies in patients with cardiovascular disease (CVD) or major risk factors have reported inverse correlations between carotid IMT and brachial artery FMD (15–19). These studies were small, however (ranging from 20 to 150 study participants), and need to be interpreted with caution. Moreover, the relationship between carotid IMT and brachial artery FMD has not been adequately evaluated in apparently healthy individuals without CVD. This relationship may be particularly relevant in those subjects considered to be at low and intermediate risk of future events based on current risk stratification algorithms, as they are expected to benefit most from early atherosclerosis detection.

The Firefighters And Their Endothelium (FATE) study is an ongoing prospective longitudinal cohort study designed to assess the relationship among endothelial function, emerging and traditional CV risk factors, and, ultimately, clinical events (20). The current report describes the determinants of carotid IMT and brachial artery FMD and examines the correlation between these two measures of subclinical atherosclerosis in the FATE study participants.

From the *Department of Medicine, Division of Cardiology, McMaster University, Hamilton, Canada; †Department of Medicine, Division of Cardiology, University of Calgary, Calgary, Canada; ‡Department of Medicine, Division of Cardiology, University of Dalhousie, Halifax, Canada; and §Division of Cardiovascular Surgery, University of Toronto, Toronto, Canada. Supported by grants from the Canadian Institute of Health Research, the Heart and Stroke Foundation of Canada, and Pfizer Canada.

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The two frames were averaged for each intervention. Endothelium-dependent FMD was defined as the maximal percent change in brachial artery diameter (between 60 and 90 s) after reactive hyperemia compared to baseline. The intraobserver and interobserver variability for repeat measurements at the Core Laboratory are 0 ± 0.07 mm and 0.05 ± 0.16 mm, respectively (24). To document scanning reproducibility, 50 subjects had repeat FMD testing 6 to 12 months after initial evaluation. The group mean was similar on both occasions, 8.2 ± 3.2% versus 8.3 ± 2.8%, and the mean of the absolute difference between determinations for each subject was a very favorable 1.8 ± 1.6%.

Statistical analysis. Continuous variables are expressed as means ± SD and discrete variables as counts and percentages. Because carotid IMT measurements were not normally distributed, logarithmic transformation was used. Means were compared using analysis of variance or the Student *t* test. Pearson's correlation was used to test bivariate correlations and results were verified using the nonparametric Spearman's rank correlation test. Multivariate linear regression analysis with backward elimination was used to determine the independent predictors of carotid IMT and of brachial FMD and to test the relationship between carotid IMT and brachial FMD (in this analysis carotid IMT was the dependent variable and brachial FMD was tested as an independent predictor) in models including classic risk factors. The relationship between carotid IMT and brachial FMD was tested for the entire cohort, in subgroups defined by traditional risk factors, and in subsets divided by quintiles of carotid IMT and by quintiles of brachial FMD (within each fifth, Pearson's and Spearman's rank bivariate correlation tests were performed). Statistical significance was defined as two-sided $p < 0.05$. All statistical analyses were performed using SPSS version 12.0 (SPSS Inc, Chicago, Illinois).

RESULTS

Study population. Demographic data, CV risk factors, carotid IMT, and brachial FMD measurements are shown in Table 1. By design, the cohort was predominantly male. Participants were commonly overweight. Relatively few study participants reported current smoking or a history of diabetes or hypertension. On average, blood pressure, cholesterol, and fasting plasma glucose levels were within target ranges for primary disease prevention. The average 10-year risk for coronary heart disease calculated according to the Framingham model (25) was 8.2%, consistent with a relatively low-risk population.

The average mean and maximum carotid IMT measurements were 0.72 ± 0.18 mm and 0.73 ± 0.19 mm, respectively, similar to previous published data in similar populations (26). Mean brachial artery FMD was 8.59 ± 4.05%, lower than 10%, which is the generally accepted normal lower range for this test. A significant number of subjects, 1,106 (70.1% of the study population), had attenuated FMD (<10%).

Table 1. Characteristics of the FATE Study Participants (n = 1,578)

Characteristic	Number (%)
Male gender	1,574 (99.7)
Hypertension	172 (10.9)
Diabetes	41 (2.6)
Current smoker	190 (12.0)

Characteristic	Mean ± SD	Median
Age (yrs)	49.37 ± 9.92	48.87
Systolic blood pressure (mm Hg)	128.15 ± 16.93	126.00
Diastolic blood pressure (mm Hg)	81.64 ± 10.00	80.00
BMI (kg/m^2)	28.48 ± 3.62	27.93
Total cholesterol (mg/dl)	203.40 ± 38.90	202.63
LDL cholesterol (mg/dl)	126.89 ± 32.60	126.83
HDL cholesterol (mg/dl)	48.29 ± 10.90	47.18
Triglycerides (mg/dl)	147.92 ± 105.40	120.46
Fasting glucose (mg/dl)	96.12 ± 17.38	93.60
Framingham risk score	3.99 ± 3.19	4.00
Framingham risk at 10 yrs (%)	8.17 ± 6.76	7.00
Mean carotid IMT (mm)	0.72 ± 0.18	0.70
Maximum carotid IMT (mm)	0.73 ± 0.19	0.76
Brachial artery FMD (%)	8.59 ± 4.05	8.20

BMI = body mass index; FMD = flow-mediated dilation; HDL = high-density lipoprotein; IMT = intima-media thickness; LDL = low-density lipoprotein.

Correlations between traditional cardiovascular risk factors and carotid IMT. Study participants with a history of hypertension had higher carotid IMT than those without (0.81 ± 0.20 mm vs. 0.70 ± 0.18 mm, $p < 0.0001$ for mean carotid IMT; and 0.82 ± 0.21 mm vs. 0.72 ± 0.18 mm, $p < 0.0001$ for maximum carotid IMT), as did those with a history of diabetes compared to those without (0.81 ± 0.22 mm vs. 0.71 ± 0.18 mm, $p = 0.001$ for mean carotid IMT; and 0.82 ± 0.22 mm vs. 0.73 ± 0.18 mm, $p = 0.002$ for maximum carotid IMT). Trends toward higher carotid IMT were observed for current smokers versus those who denied current smoking (0.72 ± 0.16 mm vs. 0.71 ± 0.18 mm for mean carotid IMT and 0.74 ± 0.17 mm vs. 0.72 ± 0.19 mm for maximum carotid IMT), although these differences did not reach statistical significance. Bivariate correlations between carotid IMT and measured traditional CV risk factors are summarized in Table 2. Both mean and maximum carotid IMT correlated with age, systolic blood pressure, body mass index, total and LDL cholesterol, and fasting plasma glucose ($p < 0.001$ for all). Similar results were obtained using nonparametric analyses (data not shown). Importantly, both mean and maximum carotid IMT had highly statistically significant correlations of moderate magnitude with the overall Framingham risk score ($r = 0.38$, $p < 0.001$; and $r = 0.37$, $p < 0.001$, respectively). In multivariate analyses, both mean and maximum carotid IMT were independently correlated with age and with systolic and diastolic blood pressure, and maximum carotid IMT also correlated with LDL cholesterol concentration.

Table 2. Bivariate Correlations (Pearson's Correlation Coefficients) Between Cardiovascular Risk Factors and Ultrasound Measures of Subclinical Atherosclerosis and Endothelial Dysfunction

Risk Factor	Mean Carotid IMT*	Maximum Carotid IMT*	Brachial Artery Flow-Mediated Dilation
Age (yrs)	+0.480†	+0.458†	−0.010
Systolic blood pressure	+0.187†	+0.179†	−0.078‡
Diastolic blood pressure	+0.012	+0.008	−0.077‡
BMI	+0.122†	+0.113†	−0.024
Total cholesterol	+0.097†	+0.102†	−0.015
LDL cholesterol	+0.093†	+0.102†	0.000
HDL cholesterol	0.000	−0.006	+0.012
Triglycerides	+0.036	+0.035	−0.017
Fasting glucose	+0.097†	+0.102†	−0.031
Framingham risk score	+0.379†	+0.367†	−0.019

*Log transformed; †$p < 0.001$; ‡$p < 0.01$.In multivariate analyses, age and systolic and diastolic blood pressure were significant independent predictors of both average and maximum carotid IMT ($p < 0.01$), and LDL cholesterol concentration was an independent predictor of maximum IMT ($p < 0.01$). Only systolic blood pressure was independently associated with brachial artery FMD ($p = 0.001$).
Abbreviations as in Table 1.

Correlations between traditional cardiovascular risk factors and brachial artery FMD. Brachial artery FMD did not differ significantly among study participants with or without a history of hypertension, diabetes, or current smoking. As shown in Table 2, there was a modest inverse correlation between brachial artery FMD and systolic and diastolic blood pressure in univariate analyses, suggesting that study participants with higher blood pressure had more abnormal endothelial function. However, there were no significant correlations between brachial artery FMD and other measured individual risk factors and the overall Framingham risk score ($r = -0.019$, p = NS). In multivariate analysis, only higher systolic blood pressure was independently predictive of lower brachial artery FMD ($p = 0.001$).

Relationship between carotid IMT and brachial artery FMD. Adequate measurements of both carotid IMT and brachial artery FMD were obtained in 1,557 study participants (98.7%). There was no significant correlation between brachial artery FMD and mean carotid IMT ($r = -0.006$, $p = 0.82$) or maximum carotid IMT ($r = -0.012$, $p = 0.65$) (Fig. 1). The lack of an overall correlation was consistent in nonparametric correlation analyses (Table 3). Because of the known impact of smoking on brachial artery FMD, these relationships were examined in analyses stratified by smoking status. No significant correlations were found. Subjects with and without abnormal endothelial response, defined as brachial artery FMD <10%, did not differ significantly in their measured mean or maximum carotid IMT (mean carotid IMT: 0.72 ± 0.18 mm vs. 0.71 ± 0.17 mm, $p = 0.59$; maximum carotid IMT: 0.73 ± 0.18 mm vs. 0.72 ± 0.18 mm, $p = 0.58$). No significant differences in brachial artery FMD were noted in those subjects with mean and/or maximum carotid IMT below and above the mean or the median value for the entire cohort. In multivariate regression models with mean and maximum carotid IMT, respectively, as dependent variables and brachial artery FMD and other variables identified in bivariate analysis to be significantly correlated with carotid IMT as predictors, brachial artery FMD was not an independent predictor of either mean (beta coefficient = −0.052; $p = 0.70$) or maximum carotid IMT (beta coefficient = −0.015; $p = 0.912$).

The impact of traditional CV risk factors on the relationship between carotid IMT and brachial artery FMD was evaluated in prespecified subgroup analyses. There was no significant correlation between carotid IMT (both mean and maximum IMT) and brachial artery FMD among current smokers or subjects with hypertension (history of hypertension or blood pressure >140/90 mm Hg) or diabetes (history of diabetes or fasting blood glucose >7.0 mmol/l).

We divided the study participants by quintiles of carotid IMT, i.e., in subsets defined by various degrees of structural vascular abnormalities (Table 3), and evaluated the correlation between carotid IMT and brachial artery FMD within each fifth. There were no significant correlations. We then divided the study population by quintiles of brachial artery FMD, i.e., in subsets defined by various degrees of functional vascular abnormalities (Table 3), and evaluated correlations between carotid IMT and brachial artery FMD within each fifth. No significant correlations were observed.

All correlation analyses between carotid IMT and brachial artery FMD were also evaluated in analyses stratified by study center. Results were similar, with lack of correlation between carotid IMT and brachial artery FMD for the entire cohort and within each of the four research centers.

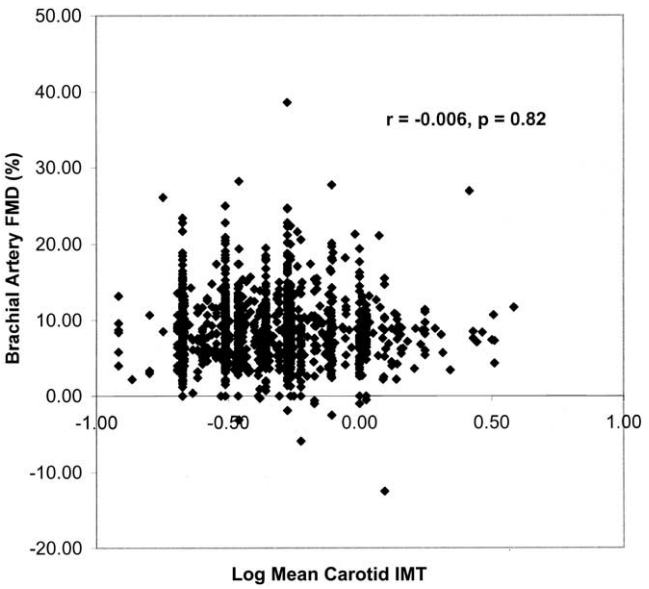

Figure 1. Correlation between mean carotid intima-media thickness (IMT) and brachial artery flow-mediated dilation (FMD).

Table 3. Relationship Between Carotid IMT and Brachial Artery FMD Across Quintiles of Carotid IMT and Brachial FMD

	Quintile of Mean Carotid IMT (mm)					
	1 0.51 ± 0.08	2 0.61 ± 0.09	3 0.69 ± 0.03	4 0.76 ± 0.01	5 0.98 ± 0.17	Spearman's Rho
Brachial artery FMD (%)	8.4 ± 3.7	8.7 ± 3.8	8.6 ± 4.0	8.9 ± 4.2	8.3 ± 4.3	−0.004; p = 0.885
	Quintile of Brachial Artery FMD (%)					
	1 3.8 ± 1.8	2 6.4 ± 0.6	3 8.2 ± 0.5	4 10.0 ± 0.6	5 14.6 ± 3.5	
Mean carotid IMT (mm)	0.71 ± 0.17	0.73 ± 0.19	0.73 ± 0.20	0.71 ± 0.16	0.71 ± 0.17	

The Spearman's rank correlation coefficient for mean carotid IMT and brachial artery FMD for the entire cohort was −0.004; p = 0.885; similarly, there was no significant correlation between mean carotid IMT and brachial FMD in study participants within any fifth of mean IMT and any fifth of brachial artery FMD.
Abbreviations as in Table 1.

DISCUSSION

The main finding of our study is the lack of correlation between measurements of carotid IMT and brachial artery FMD in a cohort of middle-aged men without CVD and with relatively few risk factors. This finding could have several explanations: 1) it is possible that, contrary to current prevalent beliefs, carotid IMT and/or brachial artery FMD are not valid measures of early vascular disease; 2) it is possible that the research techniques employed, specifically the US measurements, were not adequate and allowed for noise, which may have obscured an existent correlation; and finally, 3) carotid IMT and brachial artery FMD may provide *distinct* information identifying different stages in atherogenesis. We believe the latter to principally account for our findings, although we cannot exclude the possibility that brachial artery FMD may be less informative in this cohort than previously thought.

Thus, both carotid IMT and brachial artery FMD are well-validated techniques (2,3,9,23). Both are highly reproducible when performed by experienced technicians in a research environment (2–13,21–24). Carotid IMT was shown to correctly identify histologic abnormalities and to correlate with traditional and emerging cardiovascular risk factors (2–6). It correlates with prevalent CV disease (4,21) and, importantly, it was a potent independent predictor of incident myocardial infarction and of stroke in large cohort studies (6–8). Moreover, interventions known to decrease the atherosclerotic process and to prevent clinical events, such as statins, angiotensin-converting enzyme inhibitors, and other blood-pressure-lowering agents (2,3,22), were shown to retard the progression of carotid IMT. Several lines of evidence suggest that brachial artery FMD is a valid measure of vascular integrity. The vasomotor response of the brachial artery in response to hyperemia measured by high-resolution US was shown to be nitric-oxide-dependent and to correlate well with coronary endothelial-dependent vasomotor function (9,23,24). Interventions that improve vascular health and increase the bioavailability of nitric oxide, such as statins and angiotensin-converting enzyme inhibitors, were shown to improve brachial artery FMD (9,27,28). Finally, although examined to date only in relatively small studies that are often retrospective and requiring further confirmation, emerging evidence suggests that brachial artery FMD may be an independent predictor of outcomes (12–14). It is essential, however, to realize that the data correlating brachial artery FMD to coronary endothelial function and to CV outcomes are derived primarily from studies in individuals with manifest CV disease or at high risk for CV disease, with very limited information on low- and moderate-risk groups.

The notion that technical limitations in performing the US assessments may have obscured an existent correlation is not justified. Indeed, all US scans were performed at experienced research US laboratories, following common standardized protocols and using rigorous quality control measures; all measurements were obtained at the Core US Laboratories, which have extensive experience with these techniques. Scanning and measurement reproducibility were high. Moreover, analysis of the correlation between carotid IMT and brachial artery FMD within each center and for the entire cohort stratified by study center yielded similar results.

Therefore, we believe that our findings support the conclusion that in apparently healthy individuals with relatively few risk factors, carotid IMT and brachial artery FMD do indeed provide distinct, independent information about the complex atherosclerotic process. Such information may be temporarily dissociated, with abnormalities in endothelial function preceding anatomic lesion formation. However, we do recognize the possibility that brachial artery FMD, which is less well validated in prospective studies than carotid IMT and did not correlate with classic risk factors in our study, may be of limited value in a relatively healthy population, which, in the absence of major sustained alterations to vascular function imposed by the prolonged exposure to traditional risk factors, may be more susceptible to the impact of short-term (possibly transient) factors. Several previous small studies (some lacking methodologic details) have evaluated this relationship and do generally report significant correlations (15–19). We believe that a strong publication bias may have resulted in underreporting of negative studies. Moreover, with few exceptions (16), previous studies have focused on high-risk patients.

We also report associations between traditional CV risk factors and carotid IMT and brachial artery FMD, respectively. In univariate analysis, carotid IMT correlated with age, systolic blood pressure, body weight and body mass index, total and LDL cholesterol, fasting blood glucose, and a history of hypertension and of diabetes. Importantly, there was a significant correlation of moderate magnitude with the overall Framingham risk score. In multivariate analysis, age, blood pressure, and LDL cholesterol concentration were independent predictors of carotid IMT. Our observations are consistent with previous reports (2–7). Some risk factors appear only modestly correlated with carotid IMT, which may be related to overall good risk factor control in our population and the data for carotid IMT and for many risk factors clustering around average ("normal") population values.

By contradistinction, brachial artery FMD was correlated only with blood pressure. The poor correlation between brachial artery FMD and traditional risk factors is puzzling and may reflect the complexity of endothelial function, which is the result of the interplay of a wide range of systemic factors, including those acting for years or decades (CV risk factors), but also acute influences. Previous studies relating brachial FMD and risk factors have yielded mixed results and have suffered from small sample sizes, different methodologies, and heterogeneous populations. In one of the larger previous studies, Celermajer et al. (11) assessed brachial artery FMD in 500 healthy subjects. In multivariate analysis, the strongest determinants were age and cigarette smoking. However, no relationship between lipid parameters or blood pressure and brachial artery FMD was found. In a population of young adults (n = 326), Leeson et al. (29) demonstrated a weak relationship between n-3 fatty acids and FMD in certain subgroups, but no relationship with standard risk factors. In our study, a weak relationship between FMD and blood pressure is identified. However, there was no correlation with age, other risk factors, or Framingham risk scores. These findings suggest that brachial artery FMD could represent a unique measure of vascular health, which may be influenced significantly by parameters currently not measured. Such parameters may overwhelm the influences of traditional risk factors, especially in a generally healthy population with a low prevalence of traditional risk factors.

Our findings pertain solely to the population studied, middle-aged, apparently healthy men without CVD, and should not be generalized. Further studies in various populations are needed.

In conclusion, in a relatively healthy cohort of middle-aged men, no significant correlation exists between carotid IMT and brachial artery FMD. This finding may be related to a temporal dissociation between functional and structural vascular abnormalities in a low-risk population. However, we cannot exclude the possibility that brachial artery FMD, which did not correlate with most traditional CV risk factors in our study, may not be a good measure of the sustained effect of risk factors on endothelial function in a low-risk population and may register primarily the short-term impact of various factors. Although these noninvasive measures of early structural subclinical atherosclerosis and of endothelial dysfunction may provide unique and possibly complementary information about vascular health, our findings suggest that endothelial function testing is not yet ready for "prime time" clinical use and underscore the need for well-designed large prospective studies aimed at evaluating the value of brachial artery FMD in predicting CV events. Such studies are underway (20) and may represent the ultimate test of validity for this bioassay of endothelial function.

Reprint requests and correspondence: Dr. Eva Lonn, Hamilton General Hospital, 237 Barton Street East, Hamilton, Ontario L8L 2X2, Canada. E-mail: lonnem@mcmaster.ca

REFERENCES

1. Taylor AJ, Merz CNB, Udelson JE. Executive summary—can atherosclerosis imaging techniques improve the detection of patients at risk for ischemic heart disease? J Am Coll Cardiol 2003;41:1860–2.
2. Redberg RF, Vogel RA, Criqui MH, Herrington DM, Lima JAC, Roman MJ. 34th Bethesda Conference Task Force #3: what is the spectrum of current and emerging techniques for the noninvasive measurement of atherosclerosis? J Am Coll Cardiol 2003;41:1886–98.
3. Simon A, Gariepy J, Chironi G, Megnien JL, Levenson J. Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. J Hypertens 2002;20:159–69.
4. Chambless LE, Heiss G, Folsom AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk In Communities (ARIC) study, 1987–1993. Am J Epidemiol 1997;146:483–94.
5. Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age. The Muscatine Study. Circulation 2001;104:2815–9.
6. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991;11:1245–9.
7. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation 1997;96:1432–7.
8. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, Jr. Carotid artery intima and media thickness as a risk factor for myocardial infarction and stroke in elderly adults. N Engl J Med 1999;340:14–22.
9. Corretti MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery. J Am Coll Cardiol 2002;39:257–65.
10. Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of early endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992;340:1430–2.
11. Celermajer DS, Sorensen KE, Bull C, et al. Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction. J Am Coll Cardiol 1994;24:1468–74.
12. Gokce N, Keaney JF, Hunter LM, et al. Risk stratification for postoperative cardiovascular events via noninvasive assessment of endothelial function. A prospective study. Circulation 2002;105:1567–72.
13. Chan SY, Mancini GB, Kuramoto L, Schulzer M, Frohlich J, Ignaszewski A. The prognostic importance of endothelial dysfunction and carotid atheroma burden in patients with coronary artery disease. J Am Coll Cardiol 2003;42:1037–43.

Interrelations Between Brachial Endothelial Function and Carotid Intima-Media Thickness in Young Adults

The Cardiovascular Risk in Young Finns Study

Markus Juonala, MD; Jorma S.A. Viikari, MD, PhD; Tomi Laitinen, MD, PhD; Jukka Marniemi, PhD; Hans Helenius, MSc; Tapani Rönnemaa, MD, PhD; Olli T. Raitakari, MD, PhD

Background—Endothelial vasodilator dysfunction and carotid intima-media thickening (IMT) are 2 indicators of subclinical cardiovascular disease. We examined their correlation and interaction with risk factors in a large, community-based cohort of young adults.

Methods and Results—As part of the longitudinal Cardiovascular Risk in Young Finns Study, we measured endothelium-dependent brachial artery flow–mediated dilatation (FMD) and carotid artery IMT by ultrasound in 2109 healthy adults aged 24 to 39 years. FMD was inversely associated with IMT ($P \leq 0.001$) in a multivariate model adjusted for age, sex, brachial vessel size, and several risk variables. The subjects with age- and sex-specific FMD values in the extreme deciles were classified into groups of impaired (n=204, FMD=1.1±1.4%, mean±SD) and enhanced (n=204, FMD=16.3±2.9%) FMD response. The number of risk factors was correlated with increased IMT in subjects with an impaired FMD response ($P<0.05$) but not in subjects with an enhanced FMD response ($P>0.2$).

Conclusions—Brachial FMD is inversely associated with carotid IMT. The number of risk factors in young adults is correlated with increased IMT in subjects with evidence of endothelial dysfunction, but not in subjects with preserved endothelial function. These observations suggest that endothelial dysfunction is an early event in atherosclerosis and that the status of systemic endothelial function may modify the association between risk factors and atherosclerosis. (***Circulation*. 2004;110:2918-2923.**)

Key Words: endothelium ■ vasodilation ■ atherosclerosis

The endothelium controls vascular tone, coagulation, and inflammatory responses.[1] Endothelial dysfunction is an early event of atherosclerosis that precedes structural atherosclerotic changes in the vascular wall.[2] On the other hand, preserved endothelial function may offer protection against the development of future adverse cardiovascular events in subjects with atherosclerotic vascular disease.[3] The available evidence also suggests that an improvement in endothelium-dependent vasodilation in response to treatment is associated with a decreased risk of subsequent cardiovascular events.[4]

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A noninvasive ultrasound technique to evaluate brachial artery flow–mediated dilatation (FMD) has recently been much used in the study of arterial physiology.[5,6] The dilatation response with increased blood flow is mainly mediated by nitric oxide released from arterial endothelial cells.[7] Brachial FMD response is correlated with coronary endothelial function as tested by invasive methods.[8,9] Impaired brachial FMD is related to the prevalence and extent of coronary atherosclerosis[10] and predicts cardiovascular events.[3,11] The status of the vascular endothelium may therefore serve as a marker of inherent atherosclerotic risk in an individual. An impaired FMD response may reflect a vascular phenotype prone to atherosclerosis, whereas a preserved FMD response may be associated with a decreased risk to develop atherosclerosis.

The thickness of the common carotid intima-media (IMT) as measured by ultrasound represents a marker of structural atherosclerosis. Increased IMT is correlated with cardiovascular risk factors[12] and the severity of coronary atherosclerosis[13] and predicts cardiovascular events in population groups.[14] We have previously shown in the Young Finns cohort that risk factors identified in childhood predict increased IMT in adulthood,[12] emphasizing the importance of early risk factor exposure in the development of atherosclerosis. To gain insight about the role of the status of the vascular endothelium in the early stages of atherosclerosis, we have now analyzed the relation between brachial FMD and carotid IMT in this population of 2109 healthy young adults. We hypothesized that brachial FMD is a correlate of carotid IMT and that the status of brachial endothelial

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From the Centre of Applied and Preventive Cardiovascular Medicine (M.J.) and the Departments of Medicine (J.S.A.V., T.R.), Biostatistics (H.H.), and Clinical Physiology (O.T.R.), University of Turku, Turku; the Department of Clinical Physiology (T.L.), University of Kuopio, Kuopio; and the Department of Health and Functional Capacity (J.M.), National Public Health Institute, Turku, Finland.

Correspondence to Olli Raitakari, Department of Clinical Physiology, PO Box 52, 20521 Turku, Finland. E-mail olli.raitakari@utu.fi

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function would modify the association between risk factors and carotid atherosclerosis.

Methods

Subjects

The Cardiovascular Risk in Young Finns Study is an ongoing, 5-center, follow-up study of atherosclerosis precursors in Finnish children and adolescents. The first cross-sectional survey was conducted in 1980, when 3596 participants, aged 3, 6, 9, 12, 15, and 18 years, were randomly chosen in each area from the national population register.[15] In 2001, we reexamined 2283 of these individuals, then aged 24 to 39 years. Complete data on carotid and brachial artery ultrasound studies were available for 2109 subjects. Local ethics committees approved the study, and all subjects gave their written, informed consent.

Clinical Characteristics and Risk Factors

Height and weight were measured, and body mass index (BMI) was calculated.[16] Waist and hip circumference was measured with an accuracy of 0.1 cm. In 1980, blood pressure was measured in 3-year-olds with an ultrasound device (Arteriosonde 1020, Roche) and in others with a standard mercury sphygmomanometer. In 2001, a random-zero sphygmomanometer was used. The average of 3 measurements was used in the analysis. Smoking habits were assessed with a questionnaire in subjects aged 12 years or older. In 2001, a history of diabetes and a family history of premature coronary heart disease (CHD) were assessed by questionnaire. The family history was considered positive if either the study subject's father or mother had been diagnosed with CHD at or before the age of 55 years. For the determination of serum lipoprotein levels, venous blood samples were drawn after an overnight fast. All lipid determinations were done using standard methods.[16] LDL cholesterol concentration was calculated by the Friedewald formula. Fasting plasma highly sensitive C-reactive protein concentrations were analyzed by latex turbidometric immunoassay (Wako Chemicals GmbH). The lower detection limit reported for the assay was 0.06 mg/L, and the coefficient of variation (CV) in repeated measurements was 3.3%. Glucose concentrations were analyzed enzymatically (Olympus Diagnostica GmbH), and homocysteine concentrations were measured with use of a microparticle enzyme immunoassay kit (Imx assay, Abbott Laboratories).

Ultrasound Imaging

Carotid ultrasound studies were performed with Sequoia 512 ultrasound mainframes (Acuson) with a 13.0-MHz, linear-array transducer, as previously described.[12] In brief, the image was focused on the posterior (far) wall of the left carotid artery. A minimum of 4 measurements of the common carotid far wall were taken 10 mm proximal to the bifurcation to derive mean carotid IMT. The between-visit CV of IMT measurements was 6.4%.[12]

Brachial artery ultrasound studies were performed successfully for 2109 subjects. We excluded 146 scans because of poor image quality, and 9 subjects refused to participate in the test. To assess brachial FMD, the left brachial artery diameter was measured both at rest and during reactive hyperemia. Increased flow was induced by inflation of a pneumatic tourniquet placed around the forearm to a pressure of 250 mm Hg for 4.5 minutes, followed by release. Three measurements of arterial diameter were performed at end-diastole at a fixed distance from an anatomic marker at rest and at 40, 60, and 80 seconds after cuff release. The vessel diameter in scans after reactive hyperemia was expressed as the percentage relative to the resting scan. The average of 3 measurements at each time point was used to derive the maximum FMD (the greatest value between 40 and 80 seconds). All ultrasound scans were analyzed by a single reader blinded to the subject's details. We have previously reported a short-term (2-hour) between-study CV of 9% for FMD measurements.[17] In the present study, we assessed the long-term variation in brachial measurements by reexamining 57 subjects 3 months after the initial visit (2.5% random sample). The 3-month between-visit CV was 3.2% for brachial artery diameter measurements and 26.0% for FMD measurements.

Statistical Methods

In statistical analyses, the FMD response was first treated as a continuous variable and then as a categorized variable. When FMD was categorized, the subjects with age- and sex-specific FMD values in the extreme deciles were classified into groups of impaired (n=204, FMD=1.1±1.4%, mean±SD) and enhanced (n=204, FMD=16.3±2.9%) FMD response. Values between the 10th and 90th percentiles were considered intermediate (n=1701, FMD=7.8±3.0%). The correlates for IMT and FMD were studied by regression techniques. Variables in initial stepwise multivariate models included LDL cholesterol, HDL cholesterol, C-reactive protein, glucose, homocysteine, systolic blood pressure, BMI, waist circumference, waist-to-hip ratio, diabetes, family history of CHD, and smoking. Age and sex were forced into the models.

Subjects were defined to have a risk factor if they smoked or had smoked, had a positive family history of CHD, or if their childhood or current value of LDL cholesterol, systolic blood pressure, BMI (childhood), or waist circumference (adulthood) exceeded the age- and sex-specific 80th percentile.[12] To study how the FMD response modifies the association between risk factors and IMT, we studied the correlation between IMT and the number of risk factors in each FMD response category.

Correlation analysis suggested a direct relation between FMD and BMI. Because this was an unexpected finding,[18] we explored the possibility of a nonlinear relation between FMD and BMI with multivariate models that included FMD as the dependent variable and BMI, age, and higher-order BMI terms as independent variables.

Values for C-reactive protein were logarithmically (base 10) transformed before analyses owing to their skewed distribution. All analyses were repeated after excluding subjects who were taking lipid-lowering (n=7) or antihypertensive (n=47) medications, with essentially similar results. The statistical tests were performed with SAS version 8.1 software, and statistical significance was inferred at a 2-tailed probability value <0.05.

Results

The characteristics of study subjects and the correlations between risk variables and FMD/IMT are shown in Table 1. FMD was correlated inversely with male sex, blood pressure, glucose, and homocysteine (women only) and directly with HDL cholesterol, C-reactive protein, and BMI. Carotid IMT was correlated directly with male sex, age, LDL cholesterol, blood pressure, BMI, waist circumference, waist-to-hip ratio, glucose, smoking, and family risk of CHD and inversely with HDL cholesterol.

Because the direct correlation between FMD and BMI was unexpected, we examined the possibility of a nonlinear relation between FMD and BMI. A scatterplot of BMI and FMD values in the study population is shown in Figure 1 separately for men and women. Significant second-order terms for BMI×BMI supported a curvilinear relation between FMD and BMI, in both men ($P=0.047$) and women ($P=0.01$), as well as in smokers ($P\leq0.05$) and nonsmokers ($P=0.01$). To assess the possibility that the direct correlation in the nonobese range between BMI and FMD would result from a confounding effect of smoking potentially associated with a lower BMI, ie, linking lower weight to a lower FMD, we examined smoking patterns in more detail (daily smoking and number of cigarettes smoked per day). The distribution of daily smokers was statistically not different in subjects in BMI categories <20 kg/m^2 (26% daily smokers), between 20 and 25 kg/m^2 (21% daily smokers), 25 to 30 kg/m^2 (26% daily

TABLE 2. Multivariate Model of the Relations Between Risk Factors and Carotid IMT in 2011 Adults Aged 24 to 39 Years

	β±SE	P
FMD	−0.006±0.002	0.001
Age	0.029±0.002	<0.0001
Male sex	0.001±0.004	0.89
Systolic blood pressure	0.010±0.002	<0.0001
Waist circumference	0.013±0.002	<0.0001
Smoking	0.011±0.004	0.003
Positive family history of CHD	0.011±0.005	0.04

Values indicate the change in IMT (mm) per 1-SD change in risk variables. Abbreviations are as defined in text.

sure, carotid IMT, and male sex were inversely associated with FMD in multivariate analysis. The results remained similar when the second-order term for BMI was introduced into the model, which also emerged as a significant ($P=0.0006$) multivariate correlate of FMD.

Brachial FMD Response and Correlation Between Risk Factors and Carotid IMT

The correlation between the number of childhood and current risk factors and carotid IMT across the FMD groups is shown in Figure 2. The number of risk factors was correlated with IMT in subjects with impaired and intermediate FMD status, whereas there was no significant correlation between the number of risk factors and IMT in subjects with an enhanced FMD response.

Discussion

According to the response-to-injury model of atherosclerosis,[2] various factors can cause dysfunctional alterations in the overlying endothelium. This injury may then predispose arteries to the development of atherosclerosis, eg, by increasing the adhesiveness of the endothelium to leukocytes, by changing its permeability, and by inducing endothelial expression of vasoactive molecules favoring atherogenesis.[1] This model thus predicts that arterial endothelial damage or activation is required before risk factors can induce atherosclerotic changes in the arterial wall. Our findings support this hypothesis, as we found that the number of risk factors was associated with increased carotid IMT in subjects with impaired FMD but not among those with enhanced FMD. These data thus support the concept that systemic endothelial

TABLE 3. Multivariate Model of the Relations Between Risk Factors and Brachial FMD in 2021 Adults Aged 24 to 39 Years

	β±SE	P
Carotid IMT	−0.34±0.10	0.001
Age	0.15±0.10	0.14
Male sex	−1.58±0.22	<0.0001
BMI	0.76±0.11	<0.0001
Systolic blood pressure	−0.33±0.10	0.002
HDL cholesterol	0.22±0.11	0.04

Values indicate the change in FMD (%) per 1-SD change in risk variables. Abbreviations are as defined in text.

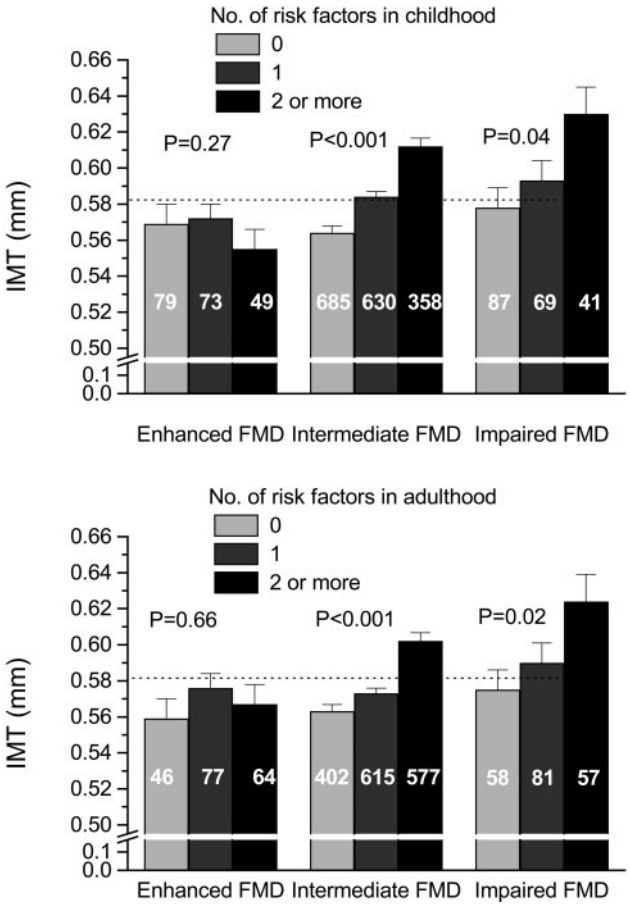

Figure 2. Association between number of risk factors and carotid IMT (mean±SEM) in young adults with enhanced, intermediate, and impaired FMD response (probability values are from linear regression models adjusted for age and sex, testing correlation between number of risk factors and IMT). Subjects were defined to have risk factor if they smoked or had smoked, had positive family history of CHD, or if their childhood or current values of LDL cholesterol, systolic blood pressure, body mass index (childhood), or waist circumference (adulthood) exceeded age- and sex-specific 80th percentile. Dashed line indicates population mean for IMT. Number of subjects is shown in columns. Abbreviations are as defined in text.

function reflects the propensity of arteries to develop atherosclerosis in response to exposure to cardiovascular risk factors.[19]

Consistent with the idea that impaired systemic endothelial function is an early event in atherosclerosis,[2] we found that impaired brachial FMD was related to increased carotid IMT. Our data from a population of >2000 subjects thus confirm observations from previous small-scale studies that have suggested an inverse relation between brachial FMD response and carotid IMT.[20,21] In concert with this idea, we have recently reported that children with type 1 diabetes who have endothelial dysfunction may be especially prone to develop increased carotid IMT.[22]

Several risk factors related to atherosclerosis have also been linked to endothelial dysfunction, presumably because of increased oxidative stress.[23] However, recent studies have also shown that individuals with normal endothelial function and various stages of endothelial dysfunction do not neces-

sarily differ in their risk factor profiles.[3,19,24] Al Suwaidi et al[24] observed among 157 patients with mildly diseased coronary arteries that the proportion of hyperlipidemic, hypertensive, or smoking subjects did not differ across the groups with or without endothelial dysfunction. Similarly, Gokce et al[3] found no difference in the proportion of these 3 main risk factors for CHD among 187 patients undergoing vascular surgery between subjects with normal endothelial function and mild or severe dysfunction. In the present study, FMD was significantly related to carotid IMT but surprisingly, not with serum LDL cholesterol or smoking. In a multivariate model controlling for the effects of age, sex, and BMI, we found that FMD was correlated significantly, albeit weakly, with systolic blood pressure (inverse association) and with HDL cholesterol concentration (direct association). Together these observations suggest that endothelial status may not be determined solely by the individual risk factor burden.

Previously we[12] and others[25,26] have shown that childhood risk factors predict increased carotid IMT in adulthood. This association seems to be independent of current risk factors,[12] ie, suggesting that exposure to risk factors in childhood may induce permanent effects on arteries that contribute to the development of future atherosclerosis.[12,27] In the present study, the number of risk factors identified in childhood was associated with increased carotid IMT measured in adulthood in subjects with impaired FMD but not in subjects with enhanced FMD. Therefore, these prospective data suggest that enhanced vascular endothelium function in adulthood may offer some protection for arteries against the development of atherosclerosis in response to early-life exposure to risk factors.

Brachial artery size is an important determinant of the FMD response. Smaller vessels dilate relatively more then larger ones. Body size is directly related to brachial artery diameter. In our population, there was a direct correlation ($r=0.28$) between vessel size and BMI. Thus, one would expect to observe smaller FMD responses in subjects with higher BMIs, because they have larger brachial arteries and presumably, an increased amount of systemic oxidative stress.[28] However, we found that BMI was directly associated with FMD. This was unexpected, because in previous studies, obesity had been linked to impaired coronary and peripheral endothelial function.[18,29–31] We have no plausible explanation for this observation, but it suggests that an increase in body size within the nonobese range in a population of healthy young adults is associated with physiological changes that lead to enhanced FMD responses and overcomes the opposing influences of larger vessel size and increased oxidative stress associated with higher BMIs. One possibility is that the relation between body size and endothelial function is curvilinear and that we are observing the upward slope of this relation in our population of healthy adults. Significant second-degree terms in the regression models for BMI in both men and women gave support for a curvilinear association between BMI and IMT. A curvilinear relation between body size and endothelial function is also supported in a previous study by Higashi et al,[32] linking lower BMIs to reduced endothelium-dependent, acetylcholine-induced forearm flow responses. Despite the unexpected association between BMI and FMD, we have demonstrated that a higher BMI was strongly associated with increased IMT in our population.[12]

We found a relatively large, long-term variation in FMD measurements, larger than we have reported for the short-term variation,[17] but comparable to that in some earlier reports.[33,34] Several factors, including physiological and technical issues, may affect FMD variation.[6] However, the long-term reproducibility of the brachial artery diameter measurements was excellent. This suggests that much of the long-term variation in FMD is due to physiological fluctuations and not to measurement error. To simplify the FMD test, we did not perform flow measurements to quantify the hyperemia stimulus after cuff release. This was justified by our earlier findings showing that the flow stimulus is not correlated with the FMD response.[35] We measured carotid IMT in the far wall of the distal part of the common carotid artery. A more complex carotid IMT score involving both the internal and common carotid arteries might have a better predictive value than either measure alone. However, the association between carotid and coronary atherosclerosis is only marginally increased when information about IMT in the internal carotid artery and carotid bulb is added to that of the common carotid IMT.[36] Finally, we examined the relation between FMD and IMT in a cross-sectional study, which cannot prove a causal relation between these variables.

We conclude that brachial FMD is inversely associated with carotid IMT. Our data also indicate that young adults presenting with risk factors are at increased risk of having thickened carotid IMTs, especially when they have evidence of endothelial dysfunction. These results are in line with the concepts that impaired systemic endothelial function is an early event in atherosclerosis and that the status of systemic endothelial function may modify the association between risk factors and atherosclerosis. Thus, in addition to the evaluation of conventional cardiovascular risk factors, noninvasive evaluation of endothelial dysfunction might be helpful to discriminate individuals at risk for atherosclerosis.

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References

1. Ross R. Atherosclerosis: an inflammatory disease. *N Engl J Med*. 1999; 340:115–126.
2. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature*. 1993;362:801–809.
3. Gokce N, Keaney JF, Hunter LM, et al. Risk stratification for postoperative cardiovascular events via noninvasive assessment of endothelial function: a prospective study. *Circulation*. 2002;105:1567–1572.
4. Modena MG, Bonetti L, Coppi F, et al. Prognostic role of reversible endothelial dysfunction in hypertensive postmenopausal women. *J Am Coll Cardiol*. 2002;40:505–510.
5. Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet*. 1992;340:1111–1115.

6. Corretti MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilatation of the brachial artery: report of the international brachial artery reactivity task force. *J Am Coll Cardiol*. 2002;39:257–265.
7. Mullen MJ, Kharbanda RK, Cross J, et al. Heterogenous nature of flow-mediated dilatation in human conduit arteries in vivo: relevance to endothelial dysfunction in hypercholesterolemia. *Circ Res*. 2001;88:145–151.
8. Anderson TJ, Uehata A, Gerhard MD, et al. Close relation of endothelial function in the human coronary and peripheral circulations. *J Am Coll Cardiol*. 1995;26:1235–1241.
9. Takase B, Uehata A, Akima T, et al. Endothelium-dependent flow-mediated vasodilatation in coronary and brachial arteries in suspected coronary disease. *Am J Cardiol*. 1998;82:1535–1539.
10. Neunteufl T, Katzenschlager R, Hassan A, et al. Systemic endothelial dysfunction is related to the extent and severity of coronary artery disease. *Atherosclerosis*. 1997;129:111–118.
11. Chan SY, Mancini GBJ, Kuramoto L, et al. The prognostic importance of endothelial dysfunction and carotid atheroma burden in patients with coronary artery disease. *J Am Coll Cardiol*. 2003;42:1037–1043.
12. Raitakari OT, Juonala M, Kähönen M, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA*. 2003;290:2277–2283.
13. Burke GL, Evans GW, Riley WA, et al. Arterial wall thickness is associated with prevalent cardiovascular disease in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Stroke*. 1995;26:386–391.
14. O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults: Cardiovascular Health Study Collaborative Research Group. *N Engl J Med*. 1999;340:14–22.
15. Åkerblom HK, Viikari J, Uhari M, et al. Atherosclerosis precursors in Finnish children and adolescents, I: general description of the cross-sectional study of 1980, and an account of the children's and families' state of health. *Acta Paediatr Scand Suppl*. 1985;318:49–63.
16. Juonala M, Viikari JSA, Hutri-Kähönen N, et al. The 21-year follow-up of the Cardiovascular Risk in Young Finns Study: risk factor levels, secular trends and east-west difference. *J Intern Med*. 2004;255:457–468.
17. Järvisalo MJ, Jartti L, Karvonen MK, et al. Enhanced endothelium-dependent vasodilation in subjects with proline 7 substitution in the signal peptide of neuropeptide Y. *Atherosclerosis*. 2003;167:319–326.
18. Benjamin EJ, Larson MG, Keyes MJ, et al. Clinical correlates and heritability of flow-mediated dilation in the community: the Framingham Study. *Circulation*. 2004;109:613–619.
19. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. *Arterioscler Thromb Vasc Biol*. 2003;23:168–175.
20. Hashimoto M, Eto M, Akishita M, et al. Correlation between flow-mediated vasodilatation of the brachial artery and intima-media thickness in the carotid artery in men. *Arterioscler Thromb Vasc Biol*. 1999;19:2795–2800.
21. Ravikumar R, Deepa R, Shanthirani C, et al. Comparison of carotid intima-media thickness, arterial stiffness, and brachial artery flow mediated dilatation in diabetic and nondiabetic subjects (The Chennai Urban Poulation Study [CUPS-9]). *Am J Cardiol*. 2002;90:702–707.
22. Järvisalo MJ, Raitakari M, Toikka JO, et al. Endothelial dysfunction and increased arterial intima-media thickness in children with type 1 diabetes. *Circulation*. 2004;109:1750–1755.
23. Raitakari OT, Celermajer DS. Testing for endothelial dysfunction. *Ann Med*. 2000;32:293–304.
24. Al Suwaidi J, Hamasaki S, Higano ST, et al. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation*. 2000;101:948–954.
25. Davis PH, Dawson JD, Riley WA, et al. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: the Muscatine Study. *Circulation*. 2001;104:2815–2819.
26. Li S, Chen W, Srinivasan SR, et al. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *JAMA*. 2003;290:2271–2276.
27. McGill HC, McMahan CA. Starting earlier to prevent heart disease. *JAMA*. 2003;290:2320–2322.
28. Keaney JF, Larson MG, Vasan RS, et al. Obesity and systemic oxidative stress: clinical correlates of oxidative stress in the Framingham Study. *Arterioscler Thromb Vasc Biol*. 2003;23:434–439.
29. Steinberg HO, Chaker H, Leaming R, et al. Obesity/insulin resistance is associated with endothelial dysfunction. *J Clin Invest*. 1996;97:2601–2610.
30. Suwaidi JA, Higano ST, Holmes DRJ, et al. Obesity is independently associated with coronary endothelial dysfunction in patients with normal or mildly diseased coronary arteries. *J Am Coll Cardiol*. 2001;37:1523–1528.
31. Raitakari M, Ilvonen T, Ahotupa M, et al. Weight reduction with very-low-caloric diet and endothelial function in overweight adults: role of plasma glucose. *Arterioscler Thromb Vasc Biol*. 2004;24:124–128.
32. Higashi Y, Sasaki S, Nakagawa K, et al. Low body mass index is a risk factor for impaired endothelium-dependent vasodilatation in humans: role of nitric oxide and oxidative stress. *J Am Coll Cardiol*. 2003;42:256–263.
33. Lind L, Hall J, Larsson A, et al. Evaluation of endothelium-dependent vasodilation in the human peripheral circulation. *Clin Physiol*. 2000;20:440–448.
34. De Roos NM, Bots ML, Schouten EG, et al. Within-subject variability of flow-mediated vasodilatation of the brachial artery in healthy men and women: implications for experimental studies. *Ultrasound Med Biol*. 2003;29:401–406.
35. Järvisalo MJ, Rönnemaa T, Volanen I, et al. Brachial artery dilatation responses in healthy children and adolescents. *Am J Physiol*. 2002;282:H87–H92.
36. Crouse JR III, Craven TE, Hagaman AP, et al. Association of coronary disease with segment-specific intimal-medial thickening of the extracranial carotid artery. *Circulation*. 1995;92:1141–1147.