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Interrelations Between Brachial Endothelial Function and Carotid Intima-Media Thickness in Young Adults The Cardiovascular Risk in Young Finns Study

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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 ($n=204$, $FMD=1.1 \pm 1.4\%$, mean \pm SD) and enhanced ($n=204$, $FMD=16.3 \pm 2.9\%$) 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 atherosclerosis¹⁰ 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 factors¹² and the severity of coronary atherosclerosis¹³ 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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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 ($n=204$, $FMD=1.1\pm 1.4\%$, mean \pm SD) and enhanced ($n=204$, $FMD=16.3\pm 2.9\%$) FMD response. Values between the 10th and 90th percentiles were considered intermediate ($n=1701$, $FMD=7.8\pm 3.0\%$). 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 \times 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 ($P\leq 0.05$) 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/m² (26% daily smokers), between 20 and 25 kg/m² (21% daily smokers), 25 to 30 kg/m² (26% daily

TABLE 1. Clinical Characteristics and Relations Between Risk Variables and FMD/IMT in 2109 Young Adults

Variable	Mean	SD	Regression Coefficients and SE§	
			Correlation With FMD	Correlation With IMT
Age, y	31.6	5.0	0.14±0.10	0.029±0.002‡
Male sex, %	44.2		-1.88±0.19†	0.022±0.004‡
LDL cholesterol, mmol/L	3.27	0.84	0.08±0.10	0.013±0.002‡
HDL cholesterol, mmol/L	1.29	0.32	0.41±0.10‡	-0.006±0.002†
Systolic blood pressure, mm Hg	116	13	-0.40±0.10‡	0.018±0.002‡
Diastolic blood pressure, mm Hg	71	11	-0.23±0.10*	0.020±0.002‡
BMI, kg/m ²	25	4	0.41±0.10‡	0.019±0.002‡
Waist circumference, cm	84	12	0.10±0.10	0.022±0.002‡
Waist-to-hip ratio	0.84	0.08	-0.15±0.10	0.021±0.002‡
C-reactive protein, mg/L	1.9	3.9	0.49±0.10‡	0.004±0.002
Glucose, mmol/L	5.04	0.83	-0.22±0.10*	0.009±0.002‡
Homocysteine, μmol/L	9.80	3.85	-0.30±0.10†	0.002±0.002
Smoking				
Ever smoking, %	46.6		-0.033±0.196	0.014±0.004‡
Current daily smoking, %	23.6		-0.186±0.230	0.006±0.005
No. of cigarettes per day	5.1	7.8	-0.017±0.012	0.0006±0.0003*
Pack-years of smoking	2.8	5.4	-0.016±0.019	0.002±0.0004‡
Family history of CHD, %	15.4		0.089±0.267	0.026±0.006‡

The correlations were similar between sexes, except for FMD and homocysteine (homocysteine×sex interaction term $P<0.05$; correlation significant in females only) and for IMT and obesity indices (BMI×sex, waist×sex, and waist-to-hip ratio×sex interaction terms, $P<0.05$). The correlations between obesity indices and IMT were highly significant in both sexes but were consistently stronger in males with ≈2-times higher regression coefficients in men vs women. Abbreviations are as defined in text.

* $P<0.05$, † $P<0.01$, ‡ $P<0.001$.

§Values are regression coefficients for 1-SD change in continuous variables.

smokers), and >30 kg/m² (23% daily smokers) ($P=0.10$). Furthermore, the distribution of daily smoking was similar (21% versus 24% versus 18%, $P=0.12$) across the groups with impaired (lowest decile), intermediate (between the 10th and 90th percentile), and enhanced (highest decile) FMD responses, respectively. Also, the average number of ciga-

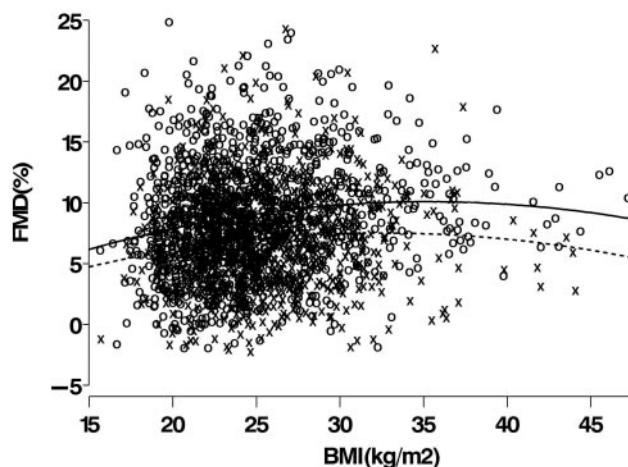


Figure 1. Scatterplot of BMI and FMD values in 2109 study subjects. Lines indicate curvilinear relation between BMI and FMD, which was observed in both men (×) ($P=0.047$) and women (○) ($P=0.01$). Abbreviations are as defined in text.

rettes smoked per day did not differ across the FMD groups ($P=0.13$). In addition, the relation between BMI and FMD remained significant ($P<0.0001$) in a multivariate model adjusted for daily smoking and the number of cigarettes (in addition to age and sex). We also assessed weight distribution in the FMD groups to examine the possibility that the increased BMI in the enhanced-FMD group would be associated with a pattern of weight distribution less likely to be associated with atherosclerosis. This was done by comparing waist circumferences and waist-to-hip ratios in subjects with a BMI >25 kg/m² across the FMD groups. In these analyses, no evidence of differences in weight distribution could be observed in overweight or obese subjects across the FMD categories (data not shown).

Multivariate Correlates of Carotid IMT

Brachial FMD (treated as a continuous variable) was correlated inversely with carotid IMT in a multivariate model (Table 2). Systolic blood pressure, waist circumference, smoking, a family history of CHD, and age were directly correlated with IMT.

Multivariate Correlates of FMD

Age- and sex-adjusted correlates of FMD (treated as a continuous variable) are shown in Table 3. BMI and HDL cholesterol were directly associated and systolic blood pres-

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

	$\beta \pm SE$	<i>P</i>
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

	$\beta \pm SE$	<i>P</i>
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.

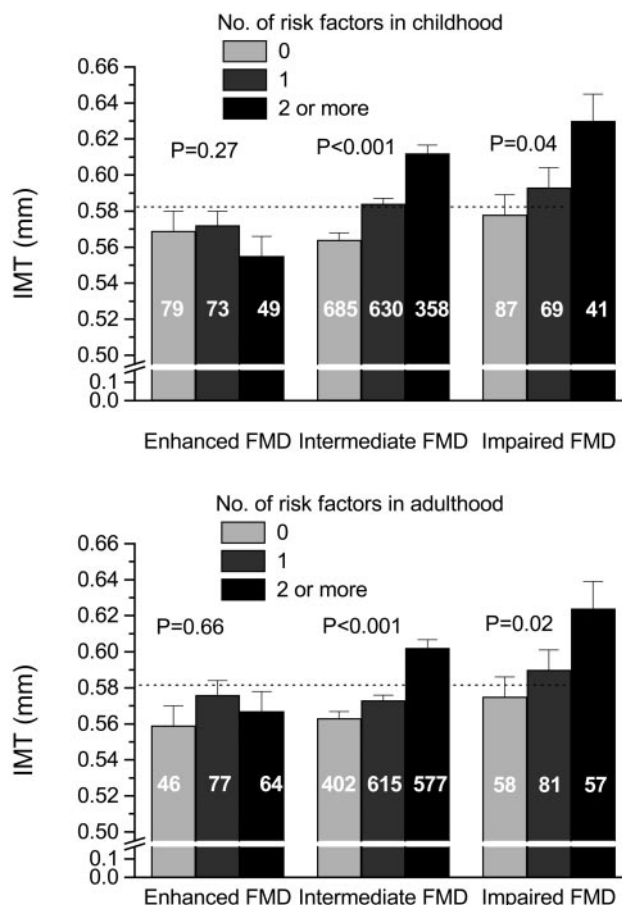


Figure 2. Association between number of risk factors and carotid IMT (mean ± SEM) in young adults with enhanced, intermediate, and impaired FMD response (probability values are from linear regression models adjusted for age and sex, testing correlation between number of risk factors and IMT). Subjects 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 al²⁴ 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 al³ 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 we¹² 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 than 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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