

The Prognostic Importance of Endothelial Dysfunction and Carotid Atheroma Burden in Patients With Coronary Artery Disease

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- OBJECTIVES** The goal of this study was to determine the relative prognostic importance of noninvasive measures of endothelial function and atheroma burden in patients with coronary artery disease (CAD).
- BACKGROUND** Direct measurement of atherosclerosis by carotid ultrasound and endothelial function assessment by brachial artery flow-mediated dilation (FMD) have both been shown to predict vascular events. The combined prognostic utility of carotid ultrasound and FMD relative to traditional risk markers and cardiovascular fitness has not been evaluated.
- METHODS** A total of 152 patients with CAD underwent metabolic testing, exercise stress tests, carotid ultrasound, and endothelial function measurements.
- RESULTS** Patients were followed for 34 ± 10 months during which 22 vascular events occurred. Peak FMD ($p = 0.012$) and FMD/nitroglycerin-mediated dilation (NMD) ratio ($p = 0.008$) were lower in subjects with events. Univariate analysis with Cox proportional hazards modeling identified plaque area ($p = 0.0047$), total area ($p = 0.0085$), peak FMD ($p = 0.01$), FMD/NMD ratio ($p = 0.008$), stress test workload ($p = 0.027$), long-acting nitroglycerin (NTG) ($p = 0.0071$), and calcium blockers ($p = 0.0057$) as predictors of adverse events. Multivariate analysis showed that FMD/NMD ratio ($p < 0.0001$), carotid plaque area ($p = 0.06$), and NTG ($p = 0.005$) were independent predictors. Based on median values, subjects were divided into high and low "plaque burden" groups and into high and low FMD/NMD subgroups. Patients with high FMD/NMD had low event rates irrespective of the degree of carotid atheroma. Patients with low FMD/NMD and high "plaque burden" had the highest event rate ($p < 0.05$).
- CONCLUSIONS** The structural and functional status of the vasculature are independent predictors of coronary events as shown by noninvasive measurement of endothelial function and carotid atheroma burden in patients with CAD. Preserved endothelial function attenuates the risk of future events associated with a high plaque burden. (J Am Coll Cardiol 2003;42:1037-43) © 2003 by the American College of Cardiology Foundation
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Risk stratification for the development of cardiovascular disease or the occurrence of vascular events is a complex process made even more complex by the steady and rapid emergence of new biochemical markers and imaging methods. Endothelial dysfunction is both an early marker of vascular disease and a facilitative process in the development of atherosclerosis (1,2). Some evidence indicates that the presence and degree of endothelial dysfunction are of prognostic importance (3-11). But these early results are tempered by the paucity of studies utilizing noninvasive methods (4,6,9). Moreover, one of these studies failed to show that noninvasively measured endothelial dysfunction was of independent prognostic importance when considered in a multivariate model that included the extent of angiographic coronary vessel disease (9). In the other two studies, no alternative imaging methods were considered, and so the independent value of risk stratification based on noninvasive

endothelial function assessment could not be determined (4,6). One of the studies focused solely on hypertensive postmenopausal women and excluded women without depressed endothelial function (6). And finally, one study was limited to a follow-up period of only 30 days after elective vascular surgery (4).

The purpose of this investigation was to assess the prognostic value of noninvasive endothelial function measurement in a broader population of patients with coronary artery disease (CAD). Our main goal was to assess the additional value of this potential method of risk stratification within a context of alternative, noninvasive methods, particularly exercise stress testing or carotid ultrasound measures of atheroma burden.

METHODS

Patient population. Subjects were recruited from consecutive patients enrolled in a lifestyle modification program who were able to exercise and willing to undergo extensive biochemical and imaging assessment. All subjects had known CAD as defined by one of history of myocardial infarction (MI), previous percutaneous coronary angioplasty

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Manuscript received January 15, 2003; revised manuscript received May 16, 2003, accepted May 21, 2003.

Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CAD	= coronary artery disease
EST	= exercise stress test
FMD	= flow-mediated dilation
HDL	= high-density lipoprotein
IMT	= intima medial thickness
LDL	= low-density lipoprotein
MI	= myocardial infarction
NMD	= nitroglycerin-mediated dilation
NTG	= nitroglycerin
PTCA	= percutaneous coronary angioplasty

(PTCA), previous coronary artery bypass grafting (CABG), positive myocardial perfusion scan, or positive exercise stress test (EST).

Baseline assessment. All subjects underwent metabolic testing including lipids, glucose, and homocysteine. Lipids and apolipoprotein B were measured by enzymatic and apolipoprotein B by a nephelometric method on fasting samples. Lipoprotein (a) concentration was measured with an immunoassay (Mercodia AB, Uppsala, Sweden) of apolipoprotein (a). Glucose was measured by a standard enzymatic method. Total homocysteine was measured by enzyme immunoassay (Abbott Diagnostics, Abbott Park, Illinois). All subjects underwent an EST using the Bruce protocol.

Carotid ultrasound studies. All subjects underwent carotid ultrasound for evaluation of intima medial thickness (IMT) and plaques. Carotid scans were acquired using high-resolution ultrasound (Sonos 5500, Agilent Technologies, Palo Alto, California) and a 10-MHz linear array transducer as described previously (12,13). Longitudinal views of the left and right common carotid, carotid bifurcations, internal and external carotid arteries were obtained and recorded on super VHS tapes. All ultrasound studies (carotid and brachial flow-mediated dilation [FMD]) were analyzed off-line by specially trained technicians blinded to other study variables using the Prosound system (13); IMT was measured over 10 mm in the far wall of the common carotid within 2 cm proximal to the bulb. The region with the thickest IMT without focal lesions was measured. Left and right carotid IMT were averaged. Intima medial area was defined as: $(\text{IMT mm}) \times (\text{length over which IMT was measured [20 mm]}) = \text{intima medial area in mm}^2$. Plaques were quantified in all carotid segments (common, internal, and external carotid arteries). Plaque was defined as any focal protrusion above the intima. Plaque thickness was defined as the sum of the maximal thickness of all plaques. Plaque area was calculated as the sum of the total area of all plaques. We also integrated IMT and plaque measurements as follows: 1) total area was defined as the sum of all plaque areas and the areas of IMT measured in both left and right carotid arteries (i.e., over 10 mm in each), and 2) total thickness was defined as the total area divided by the total length of plaques plus the length of the regions used to

measure IMT (i.e., 20 mm). The intra- and interobserver variations in our laboratory have been published (12). For intraobserver measurements, the accuracy was between -0.019 and 0.014 mm with a precision of 0.049 to 0.089 mm. For interobserver measurements, the accuracy was between -0.003 to 0.000 mm with a precision of 0.040 to 0.051 mm. Plaque length and average plaque thickness are measured with a precision of 1.37 mm and 0.4 mm, respectively.

Endothelial function studies. Endothelial function was assessed with brachial artery FMD as modified from Celermajer et al. (14). This assessment was not available in the first 28 patients enrolled in the program but was performed in the subsequent 124 patients. Studies were carried out after an overnight fast. Vasoactive medications were withheld on the day of the study. The brachial artery was imaged using the same equipment as carotid studies and imaged in the mid-upper arm. Baseline diameter was measured; FMD was induced by occlusion of the vessel just below the elbow by inflation of a sphygmomanometer to 300 mm Hg for 5 min. The cuff was then released. Imaging was initiated 30 s before release and continued for 5 min. The brachial artery was allowed to return to baseline when a new baseline diameter was measured. Then 0.3 mg of nitroglycerin (NTG) was given sublingually, and the artery was imaged for the next 6 min to measure endothelium-independent nitroglycerin-mediated dilation (NMD). Ultrasound images were recorded on Super-VHS videotapes and analyzed off-line. A 1-cm linear segment of the artery was selected for analysis; FMD (%) was defined as: $100 \times (\text{peak post-cuff deflation diameter} - \text{resting diameter})/\text{resting diameter}$. Nitroglycerin-mediated dilation (%) was defined as: $100 \times (\text{peak diameter post-NTG} - \text{resting diameter})/\text{resting diameter}$; FMD/NMD ratio was calculated by dividing peak FMD by NMD. The variability of FMD and NMD measurements from our laboratory have been reported (15). For FMD, the intraobserver accuracies are -0.31% to 0.57% with precision of 1.50% to 1.97% . The interobserver accuracy is 0.50% with a precision of 0.83% . For NMD, the intraobserver accuracies are -1.27% to 0.16% with precision of 2.45% to 3.97% . The interobserver accuracy is -1.41% with a precision of 3.68% .

Follow-up. Major adverse cardiovascular events were defined as death from vascular cause, acute vascular events including cerebrovascular, cardiovascular (MI and unstable angina requiring hospitalization), peripheral vascular events (new onset of claudication), and symptom-driven revascularization procedures (carotid endarterectomy, PTCA, or CABG). Revascularization was recommended at the discretion of the patients' personal physician, without knowledge of carotid or endothelial dysfunction measurements or other input from the risk reduction clinic and based on clinically significant worsening of symptoms or new onset of significant symptoms of ischemia. Cerebrovascular events were defined as transient or permanent neurological dysfunction verified by a neurologist. Acute MI was defined as elevation

in creatine kinase or troponin I >2 times the upper limit of normal with or without electrocardiogram changes (ST-segment elevations >0.1 mV in >2 contiguous leads or new left bundle branch block).

Statistical analysis. Results were expressed as mean \pm SD or interquartile range. Mann-Whitney *U* test was used for comparison between variables. Correlations were defined using Pearson correlation coefficient. Univariate and multivariate analyses using Cox stepwise forward regression techniques were used to examine the associations between variables and vascular events during follow-up. The continuous variables included in the model were age, ejection fraction, carotid IMT, total thickness, total area, plaque thickness, plaque area, brachial FMD and NMD, FMD/NMD ratio, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, total cholesterol/HDL ratio, LDL/HDL ratio, non-HDL-cholesterol, apolipoprotein B, homocysteine, lipoprotein (a), fasting glucose, creatinine, resting systolic and diastolic blood pressure, maximal workload on stress test, peak exercise heart rate and blood pressure, weight, body mass index, waist circumference, and waist-to-hip ratio. High sensitivity C-reactive protein analyses were not being performed at the time of initiation of enrollment of this cohort. Categorical variables were gender, presence of angina, use of statin, other lipid-lowering drugs, beta-blockers, long-acting NTG, acetylsalicylic acid, calcium channel blockers, angiotensin-converting enzyme inhibitors, vitamin E, vitamin C, other multivitamins, folic acid, other supplements. The interaction between carotid ultrasound and brachial endothelial function variables was examined with a chi-square contingency table. A value of $p < 0.05$ was considered significant for comparison between means and chi-square contingency testing. A p value of 0.15 with univariate analysis was required for entry into the multivariate model with a final p value of < 0.1 indicating significance in consideration of the large number of variables and the overall sample size (16). Correlation coefficients with $p < 0.01$ were considered significant in identifying associations between variables. A Cox proportional hazards model was used to address whether changes in endothelial dysfunction or carotid ultrasound measurements predicted an adverse cardiac event. The percent changes, from measurements taken at baseline, were considered for each covariate. For those patients who experienced a cardiac event, only covariate values before the event were considered.

RESULTS

Patient characteristics. A total of 152 subjects were recruited. Demographic and other features are summarized in Table 1. Carotid ultrasound and brachial endothelial function results are shown in Table 2. Focal carotid plaques were found in 118 subjects (77.6%).

Relationship between variables. Relationships among different parameters of carotid ultrasound and endothelial

Table 1. Baseline Subject Characteristics

Age (yrs)	55.9 \pm 6.2
Gender (male/female)	131/21
Previous MI (%)	53.3
Previous PTCA (%)	48.0
Previous CABG (%)	25.7
Ejection fraction (%)	56 \pm 10
Risk factors	
Smoker	
Current (%)	1.3
Previous	64.7
Never	34.0
History of hypertension (%)	42.3
History of diabetes mellitus	11.5
Laboratory analysis	
Total cholesterol (mmol/l)	4.67 \pm 0.97
LDL (mmol/l)	2.72 \pm 0.83
HDL (mmol/l)	1.17 \pm 0.33
Triglycerides (mmol/l)	1.69 \pm 0.95
Apolipoprotein B (mg/l)	0.95 \pm 0.24
Glucose (mmol/l)	5.5 \pm 1.1
Creatinine (mmol/l)	88 \pm 17
Lipoprotein (a) (mg/l)	480 \pm 499
Homocysteine (mmol/l)	8.5 \pm 2.5
Blood pressure	
Systolic (mm Hg)	128 \pm 16
Diastolic (mm Hg)	80 \pm 7
Maximal workload on stress test (METS)	11.7 \pm 2.9
Weight (kg)	84.1 \pm 14.9
Body mass index	28.0 \pm 4.1
Waist circumference (cm)	94.1 \pm 11.4
Medications	
Angiotensin-converting enzyme inhibitor (%)	29.5
Aspirin (%)	91.0
Beta-blocker (%)	48.1
Calcium channel blocker (%)	28.2
Statin (%)	76.3
Nitrate (%)	7.7

CABG = coronary artery bypass grafting; HDL = high-density lipoprotein; LDL = low-density lipoprotein; METS = metabolic equivalent; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

function are presented in Table 3. Carotid IMT did not correlate with plaque thickness or area. There was no correlation between peak FMD, NMD, or FMD/NMD ratio with IMT or plaque measurements. There was also no correlation between IMT, plaques, brachial FMD, NMD, FMD/NMD ratio with any biochemical, anthropometric, blood pressure, or stress test variable (data not shown).

Predictors of adverse vascular events. During 34 ± 10 months of follow-up, 22 major, adverse cardiac events were identified in 22 patients. There were 1 death, 8 acute coronary syndromes (7 MI, 1 unstable angina), 2 neurological events (1 transient ischemic attack, 1 cerebrovascular accident), and 11 revascularization procedures (5 coronary angioplasties, 5 coronary bypass surgeries, 1 carotid endarterectomy). Peak brachial FMD and FMD/NMD ratio were lower in subjects with events ($p = 0.012$ and $p = 0.008$, respectively) (Fig. 1). None of the carotid ultrasound variables was significantly different between subjects with and without events.

Univariate analysis with Cox proportion hazard modeling

Table 2. Carotid Atherosclerosis and Brachial Artery Endothelial Function Studies

	Range	Mean ± SD	Median	IQR
Carotid artery				
IMT (mm)	0.632-1.268	0.865 ± 0.135	0.865	0.773-0.956
Plaque thickness (mm)	0.00-17.38	3.22 ± 3.02	2.42	1.15-4.88
Plaque area (mm ²)	0.00-92.09	6.13 ± 10.68	6.59	0.24-7.79
Total thickness (mm)	0.64-2.05	1.06 ± 0.25	1.03	0.89-1.20
Total area (mm ²)	12.76-159.77	28.48 ± 16.68	25.14	19.26-32.09
Brachial artery				
Peak FMD (%)	-0.4-27.1	5.93 ± 3.80	5.25	3.35-8.13
NMD (%)	1.0-37.9	15.98 ± 6.70	15.65	11.9-19.5
FMD/NMD ratio	-0.04-1.54	0.40 ± 0.24	0.34	0.25-0.53

FMD = flow-mediated dilation; IMT = intima medial thickness; IQR = interquartile range; NMD = nitroglycerin-mediated thickness.

selected peak FMD (p = 0.03), FMD/NMD ratio (p = 0.005), plaque area (p = 0.09), total area (p = 0.09), plaque thickness (p = 0.11), diastolic blood pressure (p = 0.13), EST workload (p = 0.027), NTG (p = 0.03), and calcium channel blockers (p = 0.06) for entry into a multivariate model. Multivariate analysis identified FMD/NMD ratio (p < 0.0001), plaque area (p = 0.06), and use of long-acting NTG (p = 0.005) as independent predictors of events. Figures 2 and 3 show the survival curves using tertiles for FMD/NMD and plaque area. Figure 4 shows outcomes stratified with respect to the median values of these two measurements. Event rates of less than 5 per 100 patient-years were seen in patients with high FMD/NMD (>0.34), irrespective of atheroma burden. The highest event rate (9.4 per 100 patient-years) was seen in patients with poor FMD/NMD (≤0.34) and a high plaque area (≥6.59 mm²). This high rate was significantly greater than in the subgroup with high plaque area and preserved endothelial function (p < 0.05). Analysis of changes in endothelial dysfunction or carotid ultrasound measurements during follow-up was undertaken in patients who had at least one reassessment before an event. Endothelial function and carotid ultrasound results obtained after an event could not be included in this analysis of change. Based on 106 patients and 8 events, we found that deterioration of endothelial dysfunction was predictive of adverse cardiac events (p = 0.05 for change in FMD, p = 0.071 for change in FMD/NMD), whereas changes in carotid ultrasound measurements were

not (p = 0.53 for change in IMT and p = 0.73 for change in plaque).

DISCUSSION

The main finding in this investigation is the demonstration of the concomitant prognostic importance of vasodilatory endothelial dysfunction and atheroma burden, both measured noninvasively in coronary patients. The degree of endothelial dysfunction at baseline and its change during follow-up was more discriminating than carotid measures regarding outcome. The prognostic value of atheroma burden was also modulated by the degree of endothelial dysfunction. The results support the concept that both structural and functional properties of the vasculature are key co-determinants of cardiovascular outcome.

The prognostic importance of endothelial dysfunction noted in this study is in keeping with the results of several other studies (3-11). However, this paper provides information not previously available. No study to date has examined the independent value of noninvasive endothelial function assessment in comparison with stress testing and carotid ultrasound for risk stratification. Even more importantly, the prognostic importance of endothelial dysfunction measurements and carotid ultrasound analyses were evaluated while taking into account multiple biochemical and physical measurements in a group of patients at high risk on the basis of established CAD.

Table 3. Pearson Correlation Coefficients Between Carotid Artery Ultrasound and Brachial Artery Endothelial Function Variables

	IMT	Plaque Thickness	Plaque Area	Total Thickness	Total Area	Peak FMD	NMD
IMT							
Plaque thickness	0.057						
Plaque area	0.021	0.807					
Total thickness	0.513	0.760	0.783				
Total area	0.233	0.841	0.968	0.875			
Peak FMD	-0.195	-0.145	-0.140	-0.218	-0.175		
NMD	-0.078	-0.120	-0.100	-0.138	-0.115	0.437	
FMD/NMD ratio	-0.163	0.002	-0.074	-0.110	-0.099	0.588	-0.319

Values in **bold** indicate significant correlation.
Abbreviations as in Table 2.

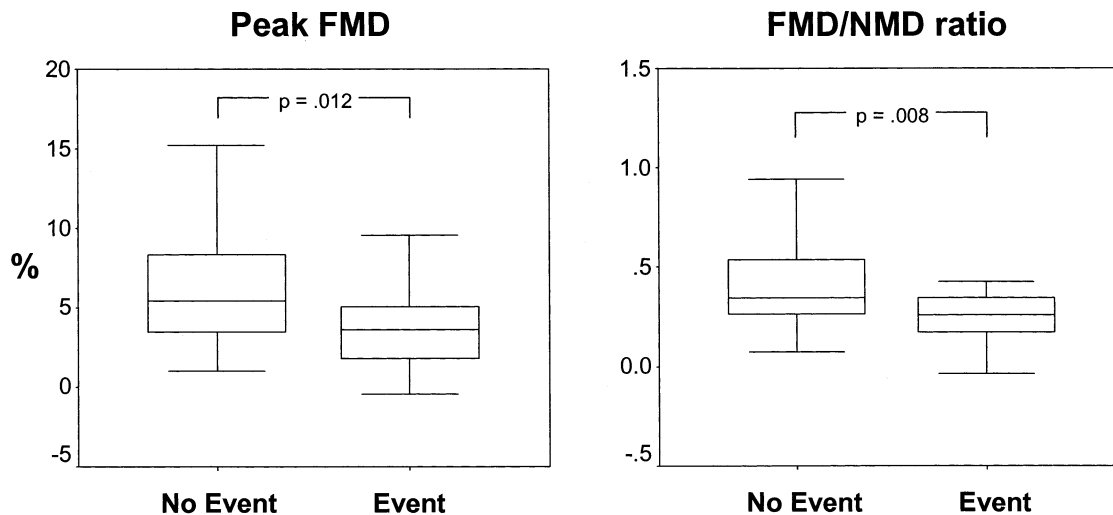


Figure 1. Box plots (median and 25th to 75th interquartile range) of brachial artery endothelial function variables between subjects with and without vascular events. Peak flow-mediated dilation (FMD) and FMD/nitroglycerin-mediated dilation (NMD) ratio were significantly lower in subjects with events compared with subjects without events. There was no difference in NMD between subjects with and without events.

The FMD/NMD ratio at baseline was a more powerful predictor of vascular events than baseline FMD, whereas during follow-up, both change in FMD and change in FMD/NMD were significant predictors, and FMD deterioration was slightly more significantly associated with adverse events than FMD/NMD. These results may have occurred because the parameters were significantly correlated with each other (Table 3), and so the slight differences do not represent a difference in concept. However, we believe that the baseline results are more robust than those during follow-up because only measurements made before events could be considered in the statistical model of changes detected during follow-up, thereby diminishing statistical power. We do suggest that the FMD/NMD ratio has some advantages; NMD may be slightly impaired in

subjects with endothelial dysfunction, but this may not be evident except in very large groups (17). We did not find a difference between the NMD of patients suffering or not suffering events during follow-up, but we did note a significant correlation between NMD and FMD (Table 3). In contrast, there was no correlation between NMD and FMD/NMD, suggesting that this ratio is a convenient way to express specifically endothelium-dependent vasodilation. Thus, the link between reduced FMD/NMD ratio and future vascular events suggests that the portion of vascular dilation specifically related to an endothelial mechanism and not a smooth muscle (endothelium-independent) mechanism is most important. Our results are also consistent with

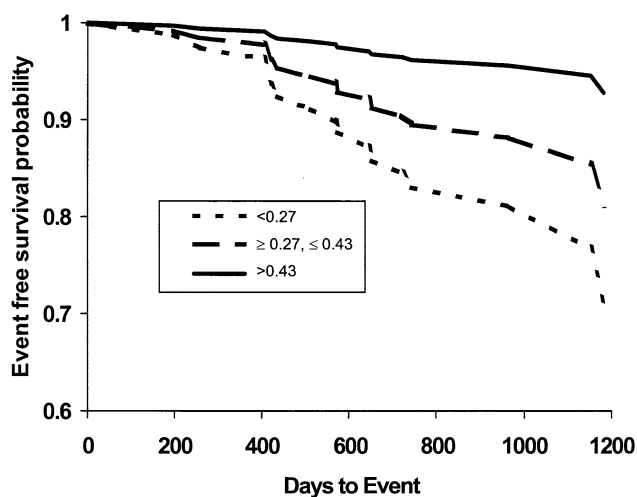


Figure 2. Event-free survival curves for tertiles of flow-mediated dilation (FMD)/nitroglycerin-mediated dilation (NMD) ratio. There is a graded response between FMD/NMD ratio tertiles and risk of adverse vascular events. Lower FMD/NMD ratio is associated with higher risk of adverse events.

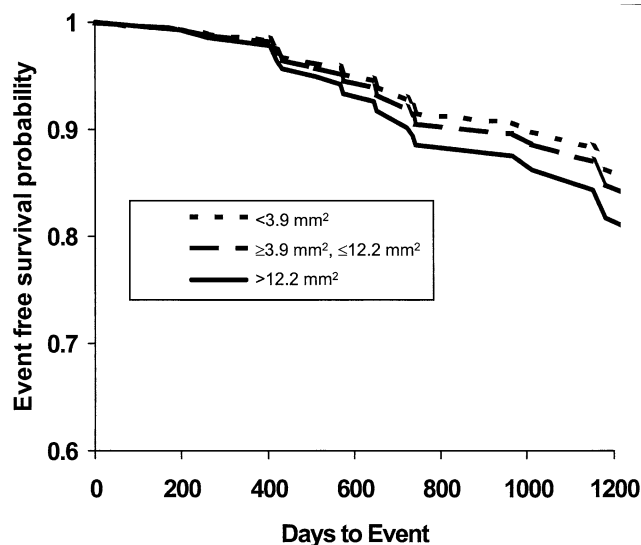


Figure 3. Event-free survival curves for tertiles of carotid plaque area. There is a graded response between carotid plaque area tertiles and risk of adverse vascular events. Higher carotid plaque areas are associated with increased risk of adverse events.

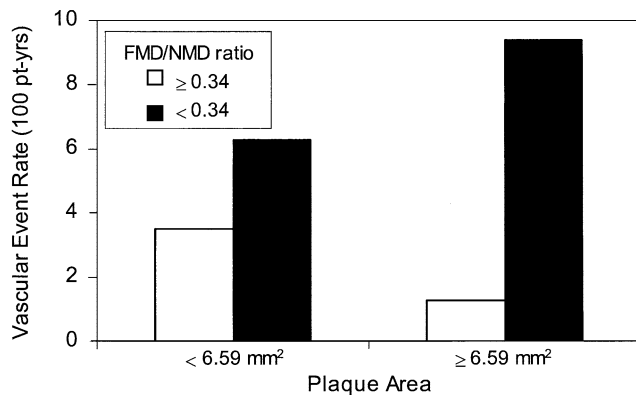


Figure 4. Interaction between plaque burden and endothelial function in prediction of future adverse vascular events. Patients with high flow-mediated dilation (FMD)/nitroglycerin-mediated dilation (NMD) (≥ 0.34) had low event rates irrespective of the plaque area. The highest event rate was seen in patients with a high plaque burden ($\geq 6.59 \text{ mm}^2$) and low FMD/NMD (< 0.34) ($p < 0.05$).

previous literature demonstrating the utility of the FMD/NMD ratio (18–20).

The prognostic importance of carotid ultrasound measures of atherosclerosis is well recognized (21,22), and correlative analyses between endothelial dysfunction tests and IMT have been published (23,24). There are, however, no prior studies that compare the relative prognostic importance of carotid analysis and endothelial function in the same study. We showed that both were independent predictors, but endothelial dysfunction was statistically more strongly related to outcome; it provided better discriminatory information with respect to event-free survival (Fig. 2), and it modulated the outcome for any degree of atheroma burden (Fig. 4) in patients with coronary disease. Our results also suggest that plaque formation, and not IMT per se, is the most important feature of carotid ultrasound that is associated with risk factors and a poor outcome (12,25). Our method of IMT measurement specifically excludes focal plaques, thereby allowing an evaluation of which ultrasound feature is contributing most to the predictive model; IMT alone was not predictive of future adverse events. The parameters that integrated IMT and plaque measurements did not provide further prognostic value than plaque assessment alone. These results are concordant with the conclusions of other groups (22,25). The lack of a significant relationship between carotid changes during follow-up should be interpreted cautiously due to the decreased number of patients and events upon which these analyses were based, the protracted period of time required to induce structural changes, and the fact that all patients were receiving treatment that could have impeded plaque progression.

We found that long-acting NTG at enrollment was an independent predictor of future adverse events. The Fourth International Study of Infarct Survival (ISIS-4) study showed that use of nitrates post-MI had no short-term benefit (26). Long-term usage was associated with increased

MI, death from heart failure, and sudden death (27). Although it is possible that long-acting NTG was a surrogate of more symptomatic disease in our patients, we do not think that this is likely, as the presence of angina was not predictive of adverse cardiac events. Finally, this finding should be interpreted with caution, as the use of long-acting NTG was not randomized, and there were only 12 subjects using it.

We should emphasize that the majority of our subjects were treated for hyperlipidemia and hypertension and were physically fit (Table 1). This probably contributes to the apparent lack of association of traditional risk factors (e.g., lipids and blood pressure values, waist circumference, etc.), other assays (e.g., apolipoprotein B, lipoprotein [a]), or medications associated with improved prognosis (e.g., statins, angiotensin-converting enzyme inhibitors) with adverse events in the multivariate model, or with carotid and endothelial measurements. This may also account for the low-event rate, a rate that is similar, however, to that noted in another study of patients with stable coronary disease evaluated with carotid ultrasound (28). This study did not assess coronary angiographic burden of disease but only carotid atheroma burden. Whether coronary angiographic assessment would negate the prognostic value of endothelial dysfunction measurement is not clear. For example, Heitzer et al. (3), using intrabrachial infusion of acetylcholine, Schachinger et al. (7), using several different methods applied at the time of coronary angiography, and Halcox et al. (5), using coronary infusions of acetylcholine at the time of catheterization, all reported that endothelial dysfunction measures were of independent prognostic importance in patients with coronary disease even when considered with respect to the number of coronary vessels with angiographic stenosis. The only study that came to a different conclusion was that of Neunteufl et al. (9).

Carotid plaque formation reflects the propensity for atherosclerosis development in response to previous, long-standing exposure to risk factors. In contrast, endothelial dysfunction may give a better reflection of on-going processes affecting the functional status of the vasculature. Acute intervention studies of risk factors show that endothelial function is dynamic and responds quickly to changes in the internal milieu of the artery (29,30). The therapeutic importance of this was recently underscored by Modena et al. (6) who showed that, in patients treated equally well with respect to hypertension, the status of endothelial function at six months after initiation of treatment was predictive of future events. Our finding that deterioration of endothelial function correlated with adverse events in spite of treatment during follow-up are consistent with their observations.

In conclusion, the noninvasive measurement of endothelial dysfunction is an important and independent predictor of the outcome of patients with CAD. This aspect of vascular function modulates the impact of atheroma burden as measured noninvasively by carotid ultrasound. These

structural and functional measurements are fundamental determinants of the prognosis of patients with CAD.

Acknowledgments

We would like to thank Susanne Burns, BSN, Frances F. Johnson, BHEC, MSc, Anka P. Brozic, BPHE, Kori Kingsbury, BSN, MN, and Sandra Barr, BSN, for their invaluable assistance in following this cohort of patients. We would also like to acknowledge the computer analyses of carotid and brachial ultrasound studies by Eunice Yeoh, BSc, and Craig Kamimura, BSc.

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