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Predictive Value of Reactive Hyperemia for Cardiovascular Events in Patients With Peripheral Arterial Disease Undergoing Vascular Surgery

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Abstract

Objective—Reactive hyperemia is the compensatory increase in blood flow that occurs after a period of tissue ischemia, and this response is blunted in patients with cardiovascular risk factors. The predictive value of reactive hyperemia for cardiovascular events in patients with atherosclerosis and the relative importance of reactive hyperemia compared with other measures of vascular function have not been previously studied.

Methods and Results—We prospectively measured reactive hyperemia and brachial artery flow-mediated dilation by ultrasound in 267 patients with peripheral arterial disease referred for vascular surgery (age 66±11 years, 26% female). Median follow-up was 309 days (range 1 to 730 days). Fifty patients (19%) had an event, including cardiac death (15), myocardial infarction (18), unstable angina (8), congestive heart failure (6), and nonhemorrhagic stroke (3). Patients with an event were older and had lower hyperemic flow velocity (75±39 versus 95±50 cm/s, P=0.009). Patients with an event also had lower flow-mediated dilation (4.5±3.0 versus 6.9±4.6%, P<0.001), and when these 2 measures of vascular function were included in the same Cox proportional hazards model, lower hyperemic flow (OR 2.7, 95% CI 1.2 to 5.9, P=0.018) and lower flow-mediated dilation (OR 4.2, 95% CI: 1.8 to 9.8, P=0.001) both predicted cardiovascular events while adjusting for other risk factors.

Conclusions—Thus, lower reactive hyperemia is associated with increased cardiovascular risk in patients with peripheral arterial disease. Furthermore, flow-mediated dilation and reactive hyperemia incrementally relate to cardiovascular risk, although impaired flow-mediated dilation was the stronger predictor in this population. These findings further support the clinical relevance of vascular function measured in the microvasculature and conduit arteries in the upper extremity.

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Disclosures
None.

Keywords

endothelium; cardiovascular risk; surrogate markers; reactive hyperemia; flow-mediated dilation

Reactive hyperemia is a complex response that occurs after a period of tissue ischemia and primarily depends on local production of adenosine and other non–endothelium-dependent vasodilators that dilate tissue microvessels.[1] Studies in humans have shown that endothelium-derived nitric oxide also contributes to reactive hyperemia.[2,3] Peak brachial artery hyperemic flow velocity after 5-minute cuff occlusion of the arm relates inversely to traditional cardiovascular disease risk factors[4] and to markers of inflammation[5] in the Framingham Heart Study. Smaller scale mechanistic studies suggest that the nitric oxide–dependent component of reactive hyperemia may be particularly affected by risk factors.[3] The relation of reactive hyperemia to the incidence of cardiovascular disease events in atherosclerosis has not been previously studied.

We previously demonstrated that brachial artery flow-mediated dilation, a measure of conduit artery endothelial vasodilator function, relates inversely to cardiovascular disease events in a high-risk cohort of patients with peripheral arterial disease.[6] In the present study, we related peak hyperemic flow velocity in the brachial artery, a measure of microvascular function, to cardiovascular events in a larger cohort that included subjects from our previous study. Because reactive hyperemia is the stimulus for flow-mediated dilation and has been suggested to explain in large part the relationship between flow-mediated dilation and cardiovascular disease,[4,7] we examined the relative predictive value of both of these measures of vascular function for cardiovascular events.

Methods

Study Subjects

Patients with peripheral artery disease undergoing nonemergent vascular surgery between November 1998 and May 2006 were eligible for participation. Patients were excluded if they had recent (up to 1 month) history of unstable angina, myocardial infarction, coronary revascularization, stroke, or decompensated heart failure. We previously reported the relation between flow-mediated dilation and long-term outcomes in 185 patients from this cohort.[6] Since that time, we consecutively recruited an additional 82 subjects yielding a total of 267 patients in the present report, which examined the relation between reactive hyperemia and cardiovascular events. All participants provided written informed consent as approved by Boston Medical Center Institutional Review Board.

Preoperative Assessment

Study personnel prospectively reviewed medical records and interviewed each subject to determine clinical characteristics including age, gender, and ethnicity, and clinical history of coronary artery disease, congestive heart failure, cigarette smoking, diabetes mellitus, hypertension, and hypercholesterolemia. We also recorded lipid values, complete blood count, and serum creatinine when available from the medical record.

Up to 1 month before surgery, brachial artery flow-mediated dilation and reactive hyperemia were assessed by ultrasound using an established and standardized method.[8,9] Briefly, patients were studied after at least a 6-hour fast and were asked to refrain from smoking overnight before study. Two-dimension ultrasound images of the conduit brachial artery were recorded before and 1 minute after induction of reactive hyperemia by 5-minute cuff occlusion of the upper arm. Doppler flow signals were recorded at baseline and for 15 seconds after cuff release to identify peak reactive hyperemia. After a 10-minute rest to allow return of brachial diameter

and flow to the basal state, 2-dimensional images of the brachial artery were recorded before and 3 minutes after a 0.4 mg sublingual dose of nitroglycerin in a subset of patients. The nitroglycerin portion of the study was omitted if the patient declined or had previous adverse reactions to nitroglycerin, history of migraine headache, critical carotid stenosis, systolic blood pressure less than 100 mm Hg, or use of a sildenafil, tadalafil, or vardenafil within 1 week of the study. All images were digitized online and analyzed using customized software (Medical Imaging Applications Inc) in a blinded manner. Baseline and hyperemic flows were expressed as flow velocity measured by ultrasound and as flow volume calculated from peak flow velocity and vessel cross-sectional area. Flow-mediated dilation was expressed as percentage change from baseline and as the actual change from baseline expressed in millimeters. Brachial artery shear stress was calculated as $8\mu V$/diameter, where μ is blood viscosity (assumed to be 0.035 dyne-sec/cm^2) and V is brachial velocity at baseline or at peak hyperemia.

Reproducibility for measurement of flow-mediated dilation is well established and has been previously reported for our laboratory.[10] To assess reproducibility of the primary end point of this study, the same ultrasonographer analyzed hyperemic flow velocity 5 separate times in 64 patients, and the intraobserver coefficient of variation was 2.8%. When hyperemic flow was measured on 2 separate occasions in a group of 65 patients with coronary artery disease, the coefficient of variation was 15.5%.

Follow-Up and Assessment of Cardiovascular Events

Patients were monitored for cardiovascular events beginning the day of surgery for up to 2 years. We prospectively measured serum troponin and obtained an ECG after surgery to ascertain postoperative myocardial infarction. After hospital discharge, patients were then contacted by telephone 30 days and every 6 months after surgery to obtain event information. If an event had occurred, medical records were obtained and the presence or absence of a cardiovascular event was adjudicated by a committee of 3 cardiologists, as previously described.[6,11] The events included cardiovascular death, myocardial infarction, unstable angina, decompensated heart failure, and nonhemorrhagic stroke. The first event in each patient was included in the analysis.

Statistical Analysis

We grouped the study subjects according to the presence or absence of a cardiovascular event and compared clinical characteristics and vascular function for the 2 groups using the chi-square test for categorical variables and the Student *t* test or the Mann–Whitney test for continuous variables that had a normal or skewed distribution, respectively.

We completed Kaplan–Meier analysis to examine the relation between reactive hyperemia or flow-mediated dilation and event-free survival. When a subject had more than 1 event, we considered only the time to the first event. In these analyses, we categorized hyperemia as tertile of peak hyperemic flow velocity and flow-mediated dilation as tertile of flow-mediated dilation expressed as percent of baseline.[6,11] We also completed forward conditional Cox regression analyses to determine whether reactive hyperemia and flow-mediated dilation were multivariable predictors of events while adjusting for baseline variables that had a probability value less than 0.10 in the univariable analysis (Table 1), including age, gender, diabetes mellitus, serum creatinine, hypertension, current smoking, and more invasive surgery (surgery other than carotid endarterectomy). We completed the same analysis including both flow-mediated dilation and reactive hyperemia in the model.

Analysis was completed using SPSS for Windows version 12.0.1 (SPSS Inc). Data were presented as mean±SD, and a probability value <0.05 was considered statistically significant.

Results

Study Subjects

A total of 267 patients enrolled in the study. All underwent a vascular surgical operation after enrollment, including carotid endarterectomy (n=63), peripheral bypasses (n=132), abdominal aortic aneurysm repair (n=46), limb amputation (n=19), or other surgery, including femoral endarterectomy or wound exploration and debridement (n=7). The median follow-up time was 309 days (ranging from 1 to 730 days). An event occurred in 50 patients (19%) during the follow-up period, including cardiovascular death (n=15), myocardial infarction (n=18), unstable angina (n=8), heart failure (n=6), and nonhemorrhagic stroke (n=3).

The clinical characteristics of patients with and without an event are listed in Table 1. As shown, patients with an event were older, and were more likely to have diabetes mellitus. Patients with an event were less likely to have undergone carotid endarterectomy. Unexpectedly, LDL cholesterol was lower in patients with an event, possibly reflecting indication bias.

Brachial Artery Ultrasound Results

For the group as a whole, mean hyperemic flow velocity was 91±48 cm/s (n=267), mean flow-mediated dilation was 6.4±4.5% (n=267), and mean nitroglycerin-mediated dilation was 10.6 ±6.6% (n=86). The vascular function variables for patients with and without an event are listed in Table 2. As shown, the subjects with an event had lower hyperemic flow velocity and flow-mediated dilation. They also had lower nitroglycerin-mediated dilation and lower hyperemic shear stress. In contrast, there were no group differences in mean baseline brachial diameter, flow volume, flow velocity, or shear stress. There also were no differences in hyperemic flow volume or percent change in flow volume.

Predictive Value of Hyperemic Flow Velocity and Flow-Mediated Dilation

Kaplan–Meier plots according to tertiles of hyperemic flow velocity and flow-mediated dilation are shown in Figure 1 and Figure 2, respectively. As shown, subjects with hyperemic flow velocity in the highest tertile (≥ 105 cm/sec) had better event-free survival compared with subjects in the middle and lower tertiles (P=0.01 for both). Similarly, subjects with the highest flow-mediated dilation (≥7.9%) had better event-free survival compared with subjects in the lower and middle tertiles (P<0.001 and P=0.002, respectively). Because the middle and lower tertiles had comparable event-free survival for both measures of vascular function, these tertiles were grouped together in subsequent analyses.

We further explored the relation between hyperemic flow velocity and events by examining the incidence of specific events according to hyperemic flow velocity. As shown in Table 3, the incidence of death and the combined primary end point of any event were significantly higher in subjects with lower hyperemic flow velocity. There was a trend for a higher incidence of unstable angina in patients with lower hyperemic flow. The incidence of myocardial infarction was numerically higher and the incidence of stroke was numerically lower in patients with lower hyperemic flow, but these differences did not reach statistical significance, possible reflecting type 2 statistical error due to the relatively low number of individual events. We also considered the possibility that the relationship between cardiovascular events and hyperemic flow might be different for events in the immediate post-operative period compared with more chronic events. As shown in Table 3, reactive hyperemia predicted events in both periods.

Multivariable Analyses

Table 4 displays the results of multivariable analyses of the relation between vascular function and the primary endpoint of any cardiovascular event. As shown (Model 1), lower hyperemic flow velocity, older age, and more invasive surgical procedure were significant predictors in

an analysis that also included gender, diabetes mellitus, hypertension, current smoking, and serum creatinine as candidate variables. As previously reported in a subset of the present cohort,[6] flow-mediated dilation was also a significant multivariable predictor of events (Model 2).

To assess the relative strength of hyperemic flow velocity and flow-mediated dilation as predictors of events, we repeated the Cox regression analysis including both measures of vascular function as candidate variables. As shown in Table 4 (Model 3), hyperemic flow velocity and flow-mediated dilation were both significant predictors of events, suggesting that these measures of vascular function provide incremental information about cardiovascular risk. The concept that hyperemic flow velocity and flow-mediated dilation provide distinct information about risk is further supported by the finding that there was no significant correlation between the 2 variables (r=0.12, P=0.053). There also was no significant a correlation between hyperemic flow volume and flow-mediated dilation (r=0.12, P=0.06). There was, however, a significant correlation between hyperemic shear stress and flow-mediated dilation (r=0.24, P<0.001). The study had 80% power (alpha=0.05) to detect an r value of 0.17.

Discussion

In this prospective study, older age, more invasive (noncarotid) surgery, and lower hyperemic flow velocity in the brachial artery predicted cardiovascular events in a high risk group of patients with peripheral arterial disease referred for surgery. When hyperemic flow velocity, a measure of microvascular function, flow-mediated dilation, a measure of conduit artery function, and other risk factors were included in the same multivariable model, both measures of vascular function were significant predictors, although flow-mediated dilation was the stronger predictor of risk. These findings suggest that microvascular and conduit artery vasodilator function provide incremental information about cardiovascular risk, and that both may relate to the pathogenesis of cardiovascular events.

Reactive hyperemia is a fundamental homeostatic response of the vasculature that serves to accelerate oxygen delivery to tissues following a period of ischemia. Hyperemic blood flow peaks within a few seconds after restoration of flow and flow then declines in an exponential fashion to basal levels over a period of 2 to 3 minutes. Early studies by Rubio and Berne suggested that this response depends on increased tissue level of adenosine, which dilates resistance vessels and increases blood flow.[12] Reactive hyperemia has been shown to depend on several other factors, including prostaglandins, potassium, pH,[13] and hydrogen peroxide.[14] Studies in animal models[15] have shown that reactive hyperemia also depends, in part, on endothelium-derived nitric oxide, which may be produced as a secondary response to increased flow and local shear stress.

Reactive hyperemia after 5-minute cuff occlusion has frequently been examined in humans by measuring hyperemic flow velocity or volume flow by ultrasound, as was done in the present study, or by measuring hyperemic volume flow using venous occlusion plethysmography. Using the latter methodology, several groups have shown that reactive hyperemia in healthy volunteers depends, in part, on endothelium-derived nitric oxide.[2,3,16] Human studies have also demonstrated that reactive hyperemic is blunted in patients with atherosclerosis[17,18] or cardiovascular disease risk factors.[3–5] For example, recent studies from the Framingham Heart Study demonstrated inverse correlations between hyperemic flow velocity and traditional coronary risk factors[4] and systemic markers of inflammation.[5]

A number of studies have examined the mechanisms of blunted reactive hyperemia in patients with risk factors. Higashi and colleagues observed that the nitric oxide synthase inhibitor mono-methyl-L-arginine reduces reactive hyperemia in healthy subjects, but not hypertensive

subjects, suggesting that blunted reactive hyperemia reflects, in part, a loss of endothelium-derived nitric oxide.[3] On the other hand, histological examination of microvessels in skeletal muscle from hypertensive patients reveals increased medial thickness and other structural changes that might impair vasodilator capacity.[19] Thus, it appears likely that multiple mechanisms contribute to blunted reactive hyperemia in the setting of hypertension and other forms of cardiovascular disease.

Impairment of reactive hyperemia in the coronary circulation has the potential to worsen myocardial ischemia, and, thus, could contribute to the pathogenesis of cardiovascular events. Our study provides support for this possibility. Two prior studies examined this issue in patients with end-stage renal disease and demonstrated associations between cardiovascular events and postocclusive hyperemia in the forearm[20] and in the skin.[21] Those studies involved relatively small numbers of patients (n=78 and n=70, respectively), and in the latter study the investigators did not perform a multivariable analysis. The present study had a larger sample size and greater statistical power to adjust for potential confounders, and thus provides additional and stronger support for hypothesis that impaired reactive hyperemia contributes to cardiovascular risk. Our findings with a noninvasive method also fit well with prior studies that used intraarterial infusion of specific endothelium-dependent vasodilators to show that endothelial dysfunction in forearm microvessels predicts cardiovascular events.[22,23]

It is notable that we observed a relationship between events and hyperemic flow velocity, but the relationship was not statistically significant with hyperemic flow volume. This observation is consistent with our prior study showing no relationship with events when hyperemia was expressed as percent change in flow volume.[11] The study by Mitchell and colleagues from the Framingham Heart Study also demonstrated a weaker relationship between percent change in hyperemic flow volume and cardiovascular risk factors, whereas hyperemic flow velocity and hyperemic shear stress both correlated much more strongly with risk factors.[4] The explanation for the stronger relationship with hyperemic flow velocity is not entirely clear but may reflect greater variability in the volume results, which is calculated as the product of velocity and the square of the arterial diameter, compounding the measurement variability associated with each variable. Alternatively, brachial diameter is larger whereas velocity is lower in patients with risk factors, and these opposing trends may confound the volume flow analysis. In the present study, we have focused on flow velocity based on our prior studies at the Framingham Heart Study that examined the cross-sectional relation of hyperemic flow velocity with risk factors.[4,5] The present prospective study provides new evidence that hyperemic flow velocity provides prognostic information in patients with atherosclerosis.

In addition to presenting new data on hyperemic flow, which reflects microvascular function, we also reexamined the relationship between conduit artery vasodilator function and cardiovascular events in this somewhat larger cohort. As we previously reported in a subset of the patients used in the present study, patients with an event had lower brachial artery flow-mediated dilation.[6] In our prior report, we observed no significant relationship between nitroglycerin-mediated dilation and events in the subset of 65 patients that received nitroglycerin. In the present study, 86 patients received nitroglycerin and the vasodilator response was significantly lower in the group of patients with an event. We attribute these apparently discrepant results to the larger sample size of the present study. Although the nitroglycerin findings are limited by the small sample size, they are consistent with prior work by other investigators.[22,24]

Recently, there has been controversy about the relative clinical utility of reactive hyperemia and brachial artery flow-mediated dilation, which also has been shown to predict cardiovascular events.[6,11,25–27] Investigators have suggested that reactive hyperemia might be a better predictor, because Mitchell and colleagues observed that reactive hyperemic

velocity and hyperemic shear stress correlated more strongly with risk factors than flow-mediated dilation in the Framingham Heart Study.[4,7] Furthermore, adjusting for hyperemic velocity in multivariable models greatly attenuated the inverse correlation between flow-mediated dilation and risk factors.[4] Because reactive hyperemia is the stimulus for flow-mediated dilation, investigators interpreted these findings to suggest that the previously reported relationship between flow-mediated dilation and cardiovascular disease might be attributable to reactive hyperemia.[7]

The present study directly compared the relative predictive values of these 2 measures of vascular function. If diminished reactive hyperemia accounted for the observed relation between impaired flow-mediated dilation and events, we would have expected that inclusion of both variables in the multivariable model would have decreased the odds ratio and lessened the degree of statistical significance. In our study, both variables were retained in the model (Table 4, Model 3) and the odds ratios were actually increased, suggesting that both measures of vascular function provide distinct and incremental information about cardiovascular risk.

Our study has several limitations. First, we examined a relatively select population of patients with advanced atherosclerosis referred for surgery and the findings may not be more generally applicable. Second, we did not control medications or time of vascular study. We previously demonstrated, however, that withholding medications does not alter the results of our studies of vascular function,[28] and such factors would be expected to bias the study toward a null result. Third, it is likely that a larger study would have allowed us to identify other predictors of cardiovascular risk that approached significance in our study such as prevalent coronary artery disease, hypertension, white blood cell count, and hyperemic volume flow.[29–31] Finally, we were only able to administer nitroglycerin to a minority of patients and could not administer an inhibitor of nitric oxide synthase, so we cannot categorically conclude that the relation between flow-mediated dilation and events reflects endothelial function. Balancing these limitations are the prospective study design and simultaneous comparison of hyperemic flow velocity and flow-mediated dilation in the same patients.

In conclusion, our study demonstrated for the first time that both hyperemic flow velocity and conduit artery flow-mediated dilation predicted long-term cardiovascular events in patients with peripheral artery disease referred for vascular surgery. These findings support the relevance of conduit artery dysfunction and microvascular dysfunction in the pathogenesis of cardiovascular events and support the possibility that such testing might have clinical utility for patient management.

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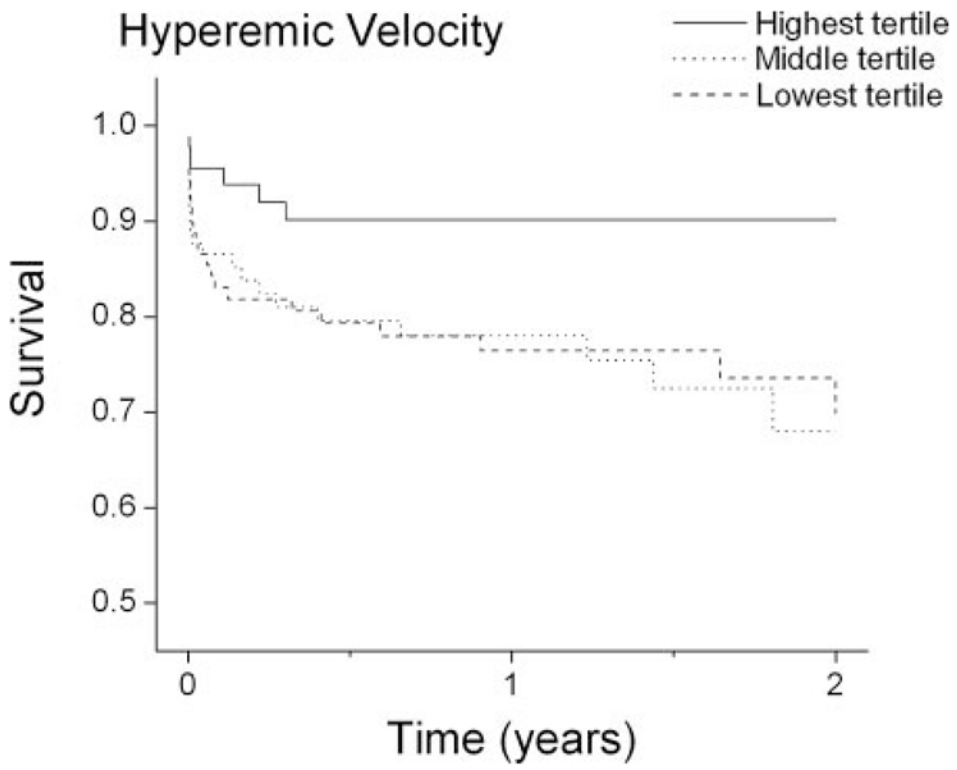

Figure 1.

Kaplan–Meier plots showing survival according to tertile of hyperemic velocity. Overall, survival differed according to tertile of hyperemic velocity by log-rank test (*P*=0.03). By pairwise comparison, the survival curves for the lower (8 to 61 cm/sec, n=89) and middle (63 to 105 cm/sec, n=89) tertiles did not differ (*P*=0.91), but both differed from the highest tertile (105 to 269 cm/sec, n=89) by log-rank test (*P*=0.01 for both).

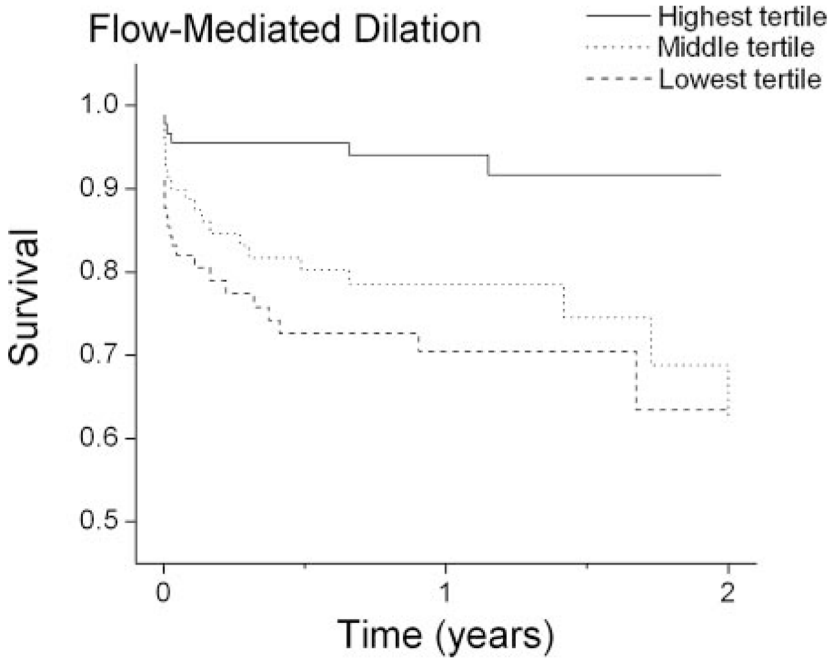

Figure 2.

Kaplan–Meier plots showing survival according to tertile of flow-mediated dilation. Overall, survival differed according to tertile of flow-mediated dilation by log-rank test ($P<0.001$). By pairwise comparison, the survival curves for the lower (−2.3 to 4.1%, n=89) and middle (4.2 to 7.9%, n=89) tertiles did not differ ($P=0.34$), but both differed from the highest tertile (8.0% to 25%, n=89) by log-rank test ($P<0.001$ and $P=0.002$, respectively).

Table 1

Baseline Characteristics

Characteristic	No Event (n=217)	Event (n=50)	*P*
Age, years	64±11	71±9	<0.001
Gender, % female	53 (24%)	17 (34%)	0.17
Race, % Black	45 (21%)	8 (16%)	0.45
Diabetes mellitus, %	85 (39%)	29 (58%)	0.02
Hypertension, %	154 (71%)	42 (84%)	0.06
Coronary artery disease, %	78 (36%)	24 (48%)	0.11
History of heart failure, %	16 (7%)	6 (12%)	0.28
History of smoking, %	165 (76%)	33 (66%)	0.14
Ex-smoker (%)	72 (33%)	20 (40%)	0.36
Current Smoker (%)	93 (43%)	13 (26%)	0.03
History of hypercholesterolemia, %	132 (61%)	30 (63%)	0.86
Total cholesterol, mg/dL (n=194)	175±40	166±55	0.23
LDL cholesterol, mg/dL (n=182)	100±35	84±35	0.02
HDL cholesterol, mg/dL (n=191)	42±12	40±13	0.30
Triglyceride, mg/dL (n=186)	172±103	200±227	0.48
Creatinine, mg/dL (n=267)	1.2±1.4	1.6±1.6	0.06
White blood cell count, 1000/μL (n=259)	8.3±2.8	9.0±3.0	0.15
Hematocrit, % (n=167)	38.6±6.5	38.5±5.5	0.92
Carotid endarterectomy, %	59 (27%)	4 (8%)	0.004
ACE inhibitor or ARB therapy, %	90 (42%)	27 (54%)	0.11
Lipid lowering therapy, % (n=257)	111 (53%)	23 (48%)	0.52
Beta-blocker therapy, %	117 (54%)	33 (66%)	0.12
Calcium channel blocker, %	40 (18%)	11 (22%)	0.56
Nitrate, %	12 (6%)	3 (6%)	0.90
Aspirin and/or clopidogrel, %	126 (58%)	31 (62%)	0.61
Ascorbic acid therapy, % (n=226)	8 (4%)	3 (7%)	0.48

Data are mean±SD or No. and percentage as indicated. Sample size is 267 unless otherwise indicated. ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blocker.

Table 2

Brachial Ultrasound Results

	No Event (n=217)	Event (n=50)	*P*
Baseline			
Brachial diameter, mm	4.06±0.87	4.11±0.91	0.72
Flow volume, mL/min	156±114	142±108	0.45
Flow velocity, cm/s	20±14	17±10	0.18
Shear stress, dyne/cm^2	14±11	12±7	0.13
Hyperemic			
Flow volume, mL/min	788±562	650±490	0.11
Flow velocity, cm/s	95±50	75±39	0.004
Shear stress, dyne/cm^2	68±39	53±30	0.004
Change from baseline			
Flow-mediated dilation, %	6.9±4.6	4.5±3.0	<0.001
Flow-mediated dilation, mm	0.27±0.17	0.18±0.11	<0.001
Nitroglycerin-mediated dilation, %*	11.5±6.7	7.6±5.3	0.02
Change in flow volume, %	472±330	438±319	0.52

* n=86 for nitroglycerin-mediated dilation. The remainder of subjects had a contra-indication or declined to take nitroglycerin.

Table 3

Cardiovascular Events According to Hyperemic Response

	Hyperemic Velocity		
	Lower Two Tertiles <105 cm/ sec (n=178)	**Upper Tertile ≥105 cm/sec (n=89)**	***P* Value***
Death	14 (7.9%)	1 (1.1%)	0.02
Myocardial infarction	15 (8.4%)	3 (3.4%)	0.12
Unstable angina	8 (4.5%)	0	0.06
Heart failure	5 (2.8%)	1 (1.1%)	0.67
Ischemic stroke	1 (0.6%)	2 (2.2%)	0.26
Any event	43 (24%)	7 (7.9%)	0.001
Early events (<30 days)†	25 (14%)	4 (5.5%)	0.02
Late events (30 days to 2 years)	22 (12%)	3 (3.4%)	0.02

* Chi Square test. n=267;

† Four subjects had an event in both the early and late periods.

Table 4
Stepwise Models for Predictors of Cardiovascular Events

	Odds Ratio	95.0% CI	*P*
Model 1			
Low hyperemic flow velocity	2.6	1.2–5.9	0.019
Age (per decade)	1.9	1.4–2.5	<0.001
More invasive surgery	3.8	1.4–11	0.01
Model 2			
Low flow-mediated dilation	4.1	1.8–9.7	0.001
Age (per decade)	1.8	1.3–2.3	<0.001
More invasive surgery	4.3	1.5–12	0.005
Model 3			
Low hyperemic flow velocity	2.7	1.2–5.9	0.018
Low flow-mediated dilation	4.2	1.8–9.8	0.001
Age (per decade)	1.8	1.3–2.4	<0.001
More invasive surgery	3.9	1.4–11	0.01

Candidate variables for all models included age, gender, serum creatinine, more invasive (noncarotid) surgery, diabetes mellitus, hypertension, and current cigarette smoking. Model 1 also included hyperemic flow, Model 2 also included flow-mediated dilation, and Model 3 also included both vascular function variables.