Risk Stratification for Postoperative Cardiovascular Events via Noninvasive Assessment of Endothelial Function
A Prospective Study

Noyan Gokce, MD; John F. Keaney, Jr, MD; Liza M. Hunter, ANP; Michael T. Watkins, MD; James O. Menzoian, MD; Joseph A. Vita, MD

Background—Brachial artery endothelial function is impaired in individuals with atherosclerosis and coronary risk factors and improves with risk reduction therapy. However, the predictive value of brachial artery endothelial dysfunction for future cardiovascular events is unknown.

Methods and Results—We preoperatively examined brachial artery vasodilation using ultrasound in 187 patients undergoing vascular surgery. Patients were prospectively followed for 30 days after surgery. Forty-five patients had a postoperative event, including cardiac death (3), myocardial infarction (12), unstable angina/ischemic ventricular fibrillation (2), stroke (3), or elevated troponin I, reflecting myocardial necrosis (25). Preoperative endothelium-dependent flow-mediated dilation was significantly lower in patients with an event (4.9±3.1%) than in those without an event (7.3±5%; \( P<0.001 \)), whereas endothelium-independent vasodilation to nitroglycerin was similar in both groups. In a Cox proportional-hazards model, the independent predictors of events were age \( (P=0.001) \), renal insufficiency \( (P=0.03) \), noncarotid surgery \( (P=0.05) \), and lower brachial artery flow-mediated dilation \( (P=0.007) \). If troponin I elevation was not considered an event, low flow-mediated dilation remained an independent predictor of risk \( \text{odds ratio} 9.0, 95\% \text{ CI} 1.2 \text{ to } 68; P=0.003 \). When a flow-mediated dilation cutpoint of 8.1% was used, endothelial function had a sensitivity of 95%, specificity of 37%, and negative predictive value of 98% for events.

Conclusions—Impaired brachial artery endothelial function independently predicts postoperative cardiac events, which supports a role for endothelial dysfunction in the pathogenesis of cardiovascular disease. The strong negative predictive value of preserved endothelial function raises the possibility that assessment of brachial artery flow-mediated dilation will be useful in the management of patients undergoing vascular surgery. (Circulation. 2002;105:1567-1572.)

Key Words: endothelium • surgery • risk factors

The vascular endothelium plays a central role in the regulation of vascular tone, thrombosis, and inflammation through elaboration of a number of paracrine factors, including nitric oxide. Impaired endothelium-dependent dilation in the coronary circulation is associated with coronary atherosclerosis and coronary risk factors and improves with risk reduction therapies. Several previous studies using invasive methodology have suggested a link between endothelial dysfunction in the coronary and peripheral circulations and cardiovascular risk.

Ultrasound assessment of brachial artery flow-mediated dilation during reactive hyperemia has recently emerged as a noninvasive and broadly applicable method for examination of endothelial function. The dilator response depends on nitric oxide synthesis, is impaired in patients with coronary disease and risk factors, and improves in response to interventions known to reduce cardiovascular disease risk. Furthermore, impaired flow-mediated dilation in the brachial artery predicts endothelial dysfunction in the coronary circulation. On the basis of these observations, investigators have speculated that endothelial function in the brachial artery may reflect the integrated effects of systemic risk factors on the entire vasculature. Thus, brachial artery flow-mediated dilation might prove useful to assess cardiovascular risk, guide therapy, and judge the potential utility of new interventions for cardiovascular disease. To date, however, no study has shown that the presence of endothelial dysfunction detected noninvasively in the brachial artery provides independent prognostic information.

To investigate this issue, we sought a population with high short-term cardiovascular risk. Patients undergoing vascular surgery frequently have subclinical or overt coronary artery disease, and 7% to 19% of patients have been reported to have cardiovascular events within 30 days of surgery.
The purpose of the present study was to determine the relation between brachial artery endothelial function and cardiovascular risk in patients undergoing vascular surgery.

Methods

Patient Population

Patients undergoing nonemergent vascular surgery between November 1998 and March 2001 at Boston Medical Center and the VA Boston Healthcare System were eligible for participation in the study. Operations included thoracic or abdominal aortic aneurysm repair, carotid endarterectomy, aortofemoral or femoral-distal vessel bypass, axillary-femoral bypass, and amputations. Approximately 500 vascular surgical procedures were performed during this time period in both institutions. Patients with recent (within 1 month) unstable angina, myocardial infarction, stroke, decompensated heart failure, or malignant cardiac arrhythmias were excluded. All patients provided written informed consent as approved by the institutional review boards.

Study Protocol

Up to 1 month before surgery, endothelium-dependent flow-mediated dilation of the brachial artery was examined noninvasively by an established method. Briefly, 2D images of the brachial artery and pulsed-Doppler flow velocity signals were obtained above the antecubital crease at baseline and during a period of reactive hyperemia induced by 5-minute cuff occlusion of the upper arm. Images were obtained at baseline and 60 seconds after cuff release with a Toshiba 140A ultrasound system equipped with a 7.5-MHz linear array transducer (Toshiba Medical, Inc). After a 10-minute rest period to allow restoration of baseline conditions, we assessed the extent of non–endothelium-dependent brachial artery dilation by obtaining 2D images before and 3 minutes after administration of sublingual nitroglycerin (0.4 mg). Nitroglycerin was omitted if the patient refused or if the patient had a history of migraine headaches, sublingual nitroglycerin (0.4 mg). Nitroglycerin was omitted if the patient refused or if the patient had a history of migraine headaches, sublingual nitroglycerin (0.4 mg). Nitroglycerin was omitted if the patient refused or if the patient had a history of migraine headaches, sublingual nitroglycerin (0.4 mg). Nitroglycerin was omitted if the patient refused or if the patient had a history of migraine headaches, sublingual nitroglycerin (0.4 mg). Nitroglycerin was omitted if the patient refused or if the patient had a history of migraine headaches, sublingual nitroglycerin (0.4 mg). Nitroglycerin was omitted if the patient refused or if the patient had a history of migraine headaches, sublingual nitroglycerin (0.4 mg). Nitroglycerin was omitted if the patient refused or if the patient had a history of migraine headaches, sublingual nitroglycerin (0.4 mg). Nitroglycerin was omitted if the patient refused or if the patient had a history of migraine headaches, sublingual nitroglycerin (0.4 mg). Nitroglycerin was omitted if the patient refused or if the patient had a history of migraine headaches, sublingual nitroglycerin (0.4 mg). Nitroglycerin was omitted if the patient refused or if the patient had a history of migraine headaches.

Assessment of Cardiovascular Events

Starting on the day of surgery and continuing throughout hospitalization, a cardiologist monitored the patient’s course for cardiovascular events. In addition, an ECG, serum troponin I levels, and creatine kinase with MB fractionation were obtained on postoperative days 1 and 3. Cardiovascular events were prospectively defined by univariate analysis (including criterion P<0.10). Because the Kaplan-Meier curves for the lowest and middle tertiles of flow-mediated dilation overlapped and differed from the highest tertile, patients were dichotomized in this multivariate analysis as having high (upper tertile) or low (lower 2 tertiles) flow-mediated dilation. By the same approach, a separate analysis was completed after exclusion of elevated troponin I as a postoperative event. The analyses were completed with SPSS for Windows version 10.1 (SPSS Inc). Data are presented as means±SD.

Statistical Analysis

The prospectively determined primary end point was any postoperative cardiovascular event, as defined above. Kaplan-Meier analysis with the log-rank test was used to plot and compare event-free survival distributions according to tertile of brachial artery flow-mediated dilation. Two patients died of noncardiac causes before 30 days and were censored in the survival analysis. Relations among potential confounders, events, and flow-mediated dilation were examined with the Student t test, 1-way ANOVA, χ² test, or Fisher exact test, as appropriate. Potential confounders included age, sex, race, diabetes mellitus, hypertension, chronic renal insufficiency (creatinine >1.2 mg/dL), known coronary disease, history of smoking, history of hypercholesterolemia, white blood cell count, hematocrit, ACE-inhibitor therapy, β-blocker therapy, nitroglycerin-mediated dilation, and baseline brachial artery diameter. A Cox proportional-hazards model was used to control for the confounders identified by univariate analysis (inclusion criterion P<0.10).21

Results

Study Patients

A total of 187 patients were enrolled in the study and underwent a vascular operation, including carotid endarterectomy (47 patients), femoral-popliteal or other peripheral bypass (100), aortic aneurysm repair (24), and limb amputation (16). Thirty-day follow-up was obtained for all patients. Forty-five patients had a cardiovascular event, including cardiac death (3 patients), myocardial infarction (12), unstable angina (1), ischemic ventricular fibrillation (1), stroke (3), and elevated troponin I (25). Two patients died of noncardiac causes (1 of sepsis on postoperative day 26 and 1 with a ruptured abdominal aortic aneurysm 28 days after femoropopliteal bypass).

Patient characteristics are displayed in Table 1. As shown, patients with a postoperative cardiovascular event were older and were more likely to be female and have diabetes, hypertension, chronic renal insufficiency, and known coronary artery disease. Total, LDL, and HDL cholesterol were lower and creatinine was higher in the patients with an event. Carotid endarterectomy was less common in patients with an event than in those without an event. Unexpectedly, patients with an event were more likely to be taking an ACE inhibitor and β-blockers and less likely to have a history of smoking, possibly related to the greater preponderance of patients with coronary disease and hypertension in this group, which may have resulted in altered medical management and behavior.

Brachial Artery Ultrasound Results

Average flow-mediated dilation was 6.7±4.7% (n=187), and average nitroglycerin-mediated dilation was 10.6±6.3% (n=64). Brachial artery parameters for patients with and without a cardiovascular disease event are displayed in Table 2. As shown, patients with an event had significantly lower flow-mediated dilation and larger baseline brachial artery diameter. Extent of reactive hyperemia and responses to nitroglycerin did not predict events. Clinical characteristics categorized by tertile of flow-mediated dilation are displayed in Table 3. Patients with diabetes were more likely to have lower flow-mediated dilation, and there was a trend for an
Endothelial Dysfunction and Cardiac Events

Gokce et al

TABLE 1. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>No Event (n=142)</th>
<th>Event (n=45)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63±11</td>
<td>71±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>17</td>
<td>36</td>
<td>0.008</td>
</tr>
<tr>
<td>Race, % black</td>
<td>16</td>
<td>24</td>
<td>0.26</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>39</td>
<td>62</td>
<td>0.007</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>65</td>
<td>80</td>
<td>0.06</td>
</tr>
<tr>
<td>Chronic renal insufficiency, %</td>
<td>18</td>
<td>44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Known coronary disease, %</td>
<td>32</td>
<td>51</td>
<td>0.02</td>
</tr>
<tr>
<td>History of heart failure, %</td>
<td>4</td>
<td>16</td>
<td>0.004</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>44</td>
<td>28</td>
<td>0.03</td>
</tr>
<tr>
<td>Known hypercholesterolemia, %</td>
<td>55</td>
<td>51</td>
<td>0.65</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>184±46</td>
<td>159±50</td>
<td>0.01</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>107±36</td>
<td>88±41</td>
<td>0.02</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>42±13</td>
<td>37±11</td>
<td>0.05</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>181±160</td>
<td>151±85</td>
<td>0.34</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.0±0.7</td>
<td>1.8±2.4</td>
<td>0.001</td>
</tr>
<tr>
<td>White blood cell count, 1000/μL</td>
<td>8.3±3.0</td>
<td>9.0±2.8</td>
<td>0.20</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>37.1±6.8</td>
<td>36.8±4.9</td>
<td>0.32</td>
</tr>
<tr>
<td>Carotid surgery, %</td>
<td>30</td>
<td>11</td>
<td>0.01</td>
</tr>
<tr>
<td>ACE-inhibitor therapy, %</td>
<td>35</td>
<td>56</td>
<td>0.01</td>
</tr>
<tr>
<td>β-Blocker therapy, %</td>
<td>42</td>
<td>40</td>
<td>0.79</td>
</tr>
</tbody>
</table>

TABLE 2. Brachial Artery Parameters

<table>
<thead>
<tr>
<th></th>
<th>No Event</th>
<th>Event</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline brachial diameter, mm</td>
<td>3.8±0.7</td>
<td>4.0±0.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Reactive hyperemia, % increase</td>
<td>400±320</td>
<td>500±370</td>
<td>0.89</td>
</tr>
<tr>
<td>Flow-mediated increase in diameter, mm</td>
<td>0.27±0.18</td>
<td>0.19±0.11</td>
<td>0.001</td>
</tr>
<tr>
<td>Flow-mediated dilation, %</td>
<td>7.3±5.0</td>
<td>4.9±3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nitroglycerin-mediated dilation, %</td>
<td>10.7±6.2</td>
<td>10.3±7.2</td>
<td>0.84</td>
</tr>
</tbody>
</table>

inverse relation between white blood cell count and endothelial function.

Predictive Value of Endothelial Function

As shown in the Figure, event-free survival differed according to tertile of flow-mediated dilation by log-rank test. Notably, the survival curves overlapped for patients in the lower 2 tertiles. Table 4 displays the number of cardiovascular disease events when patients were categorized as having low flow-mediated dilation (lower 2 tertiles, ≤8.1%) or high flow-mediated dilation (upper tertile, >8.1%). As shown, patients with high flow-mediated dilation had significantly fewer events than patients with low flow-mediated dilation. The presence of low brachial artery flow-mediated dilation had a sensitivity of 89%, a specificity of 40%, a positive predictive value of 32%, and a negative predictive value of 92% for cardiovascular disease events.

The variables that met the entry criterion (univariate P<0.10) and were included in the Cox proportional-hazards model were age, chronic renal insufficiency, carotid surgery, flow-mediated dilation, sex, diabetes mellitus, hypertension, history of coronary disease, history of congestive heart failure, history of smoking, and baseline brachial diameter. The independent predictors of cardiovascular disease events were older age, chronic renal insufficiency, noncardiot surgery, and lower brachial artery flow-mediated dilation (Table 5).

Troponin I is a well-recognized marker of myocardial necrosis and adverse outcome and has been suggested to be a better indicator of perioperative infarction than creatine kinase-MB fraction.2 However, it is not uniformly recognized as an end point in studies of surgical risk. We therefore repeated the analysis after exclusion of troponin I elevation as an event. As shown in the Figure, brachial artery flow-mediated dilation remained a significant predictor of outcome by log-rank test. With this definition of an event, low brachial artery flow-mediated dilation had a sensitivity of 95%, a specificity of 37%, a positive predictive value of 15%, and a negative predictive value of 98% for cardiovascular disease events. In the Cox proportional-hazards model, the independent predictors of events were decade of age (OR 2.0, 95% CI 1.2 to 3.3; P=0.006) and low brachial artery flow-mediated dilation (OR 9.0, 95% CI 1.2 to 68; P=0.03).

Discussion

This prospective study demonstrated that impaired flow-mediated dilation of the brachial artery independently predicts short-term cardiovascular events in patients undergoing vascular surgery. No relation was observed between nitroglycerin-mediated dilation and events or extent of reactive hyperemia and events, and the predictive value of flow-mediated dilation was independent of vessel size. These latter observations imply that the results cannot be explained by
altered function of vascular smooth muscle, variation in the stimulus for vasodilation, or the larger vessel size in patients with events, which is known to be associated with decreased flow-mediated dilation. Thus, the study supports a relation between brachial artery endothelial dysfunction and cardiovascular events.

Two previous invasive studies examined the relation between endothelial dysfunction in the coronary circulation and cardiovascular risk. Suwaidi and colleagues tested endothelial function by intracoronary acetylcholine infusion in 157 patients with mild coronary atherosclerosis. During 28-month follow-up, 6 patients had a cardiovascular event, and all 6 had evidence of severe endothelial dysfunction. Schächinger and colleagues assessed coronary endothelial vasomotor function in response to acetylcholine and nitroglycerin infusion, the cold pressor test, and/or increased flow in 147 patients undergoing cardiac catheterization. During 7.7-year follow-up, 16 patients had a cardiovascular event, and both endothelium-dependent vasodilation and endothelium-independent vasodilation were worse in those patients with an event.

Although the total numbers of events were small, those 2 studies suggest a pathogenic link between coronary endothelial dysfunction and cardiovascular disease. It has been increasingly recognized that events such as acute myocardial infarction, unstable angina, and ischemic stroke often result from plaque rupture with subsequent thrombosis formation and vasospasm. An important relation between inflammation and plaque vulnerability has also been recognized. Loss of the vasodilator, antithrombotic, and anti-inflammatory properties of the endothelium likely contributes to these events.

Several prior studies addressed the question of whether study of endothelial function in a peripheral artery also provides prognostic information about cardiac events. Perticone and colleagues examined endothelial function in forearm microvas-

Relation between endothelial function and event-free survival after vascular surgery. Kaplan-Meier curves are shown for each tertile of brachial artery flow-mediated dilation. Left, Analysis included any cardiovascular event (cardiac death, myocardial infarction, unstable angina, ischemic ventricular fibrillation, stroke, or elevated troponin I). By log-rank test, survival curves for low and middle tertiles did not differ (P=0.93), but both differed from upper tertile (P=0.0008 and P=0.001, respectively). Right, Analysis considered the same events except elevated troponin I. By log-rank test, survival curves for low and middle tertiles did not differ (P=0.76), but both differed from upper tertile (P=0.005 and P=0.009, respectively).

TABLE 4. Numbers of Events According to Flow-Mediated Dilation

<table>
<thead>
<tr>
<th>Flow-Mediated Dilation</th>
<th>Low and Middle Tertiles (≤8.1%)</th>
<th>High Tertile (&gt;8.1%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>125</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Cardiac death, n</td>
<td>3</td>
<td>0</td>
<td>0.55</td>
</tr>
<tr>
<td>Myocardial infarction, n</td>
<td>11</td>
<td>1</td>
<td>0.07</td>
</tr>
<tr>
<td>Unstable angina/ischemic ventricular fibrillation, n</td>
<td>2</td>
<td>0</td>
<td>0.55</td>
</tr>
<tr>
<td>Stroke, n</td>
<td>3</td>
<td>0</td>
<td>0.55</td>
</tr>
<tr>
<td>Elevated troponin I, n</td>
<td>21</td>
<td>4</td>
<td>0.05</td>
</tr>
<tr>
<td>Any event (primary end point), n</td>
<td>40</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Events other than elevated troponin I, n</td>
<td>19</td>
<td>1</td>
<td>0.005</td>
</tr>
</tbody>
</table>
sels in response to intra-arterial agonist infusion in 225 patients with newly diagnosed hypertension. Patients with lower vasodilator responses to acetylcholine were more likely to suffer a cardiac or vascular event. In a recent study, Heitzer and coworkers demonstrated that coronary disease patients with impaired forearm microvessel responses to acetylcholine developed more cardiovascular events over a 4.5-year follow-up period. In a retrospective noninvasive study using brachial ultrasound, Neunteufl and colleagues observed an inverse relation between flow-mediated dilation and events in a group of 74 patients undergoing cardiac catheterization. However, the majority of events in that small study were revascularization procedures, and the predictive value of endothelial dysfunction for this outcome was lost after controlling for extent of coronary artery disease. Thus, the present study is the first study to demonstrate that noninvasive assessment of brachial artery endothelial function provides independent prognostic information and is the only prospective study using noninvasive methodology.

One implication of the present study is the possible role of endothelial function in assessment of postoperative risk in patients undergoing vascular surgery. Average flow-mediated and nitroglycerin-mediated dilation were low in this group of patients with peripheral atherosclerosis compared with normal subjects. However, many subjects had relatively preserved endothelial function, and the high negative predictive value of the test suggests that it potentially could be useful for identifying individuals at lower risk for perioperative cardiovascular events. Preoperative risk assessment is an important clinical problem, and the utility of other modalities for assessing preoperative risk has been questioned. One potential approach would be to combine the results of endothelial function testing with other tests or clinical scoring systems of surgical risk.

Given the relatively small number of subjects, it is clear that further studies will be required before this methodology can be considered a clinical tool for preoperative risk assessment. Because we studied only a minority of patients undergoing vascular surgery during the period of recruitment, another limitation is the possibility of enrollment bias. However, this issue seems unlikely to be important, because the patient characteristics in the present study are quite similar to prior studies of this question.

Although the present study suggests that brachial artery endothelial dysfunction predicts short-term risk in a high-risk group of patients, the long-term predictive value in lower-risk populations remains an open question. Endothelial dysfunction is an early occurrence in the atherogenic process and might serve as a surrogate marker of cardiovascular disease with utility for risk assessment and evaluation of new therapies. Other modalities have been proposed for this purpose, including electron-beam CT scanning and assessment of carotid intimal thickness. A potential advantage of testing flow-mediated dilation is the unique information gained about vascular function. In contrast, the other modalities largely provide information about the presence and severity of fixed anatomic disease, which may be less relevant to the pathogenesis of events.

In summary, this prospective study of consecutive patients undergoing nonemergent vascular surgery demonstrates that endothelial dysfunction is an independent predictor of postoperative cardiovascular events. In particular, the patients with relatively preserved endothelial function had a very low risk. These findings add to the growing evidence that endothelial dysfunction contributes to the pathogenesis of cardiovascular disease. In addition, the study demonstrates that noninvasive assessment of endothelial function in a peripheral artery provides prognostic information. Ongoing studies will provide further information about the clinical utility of studying brachial artery endothelial function.

**Acknowledgments**

Dr. Gokce is the recipient of a Mentored Patient-Oriented Research Career Transition Award from the National Institutes of Health (K23 HL04425). Dr. Watkins is supported by NIH grant HL-48152 and a grant from the Research Administration of the Department of Veterans Affairs. Drs. Vita and Keaney are the recipients of Established Investigator Awards from the American Heart Association. The work was supported by a Specialized Center of Research in Ischemic Heart Disease grant from the NIH (HL-55993) and NIH grants HL-60886 and HL-52936. The authors gratefully acknowledge Monika Holbrook, David Kahn, MD, and Maryann Barry for their assistance with data collection for this study.

**References**

Risk Stratification for Postoperative Cardiovascular Events via Noninvasive Assessment of Endothelial Function: A Prospective Study

_Circulation_. 2002;105:1567-1572; originally published online March 11, 2002;
doi: 10.1161/01.CIR.0000012543.55874.47
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/105/13/1567

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/