Prognostic Impact of Coronary Vasodilator Dysfunction on Adverse Long-Term Outcome of Coronary Heart Disease

Volker Schächinger, MD; Martina B. Britten, MD; Andreas M. Zeiher, MD

Background—Endothelial vasodilator dysfunction is a characteristic feature of patients at risk for coronary atherosclerosis. Therefore, we prospectively investigated whether coronary endothelial dysfunction predicts disease progression and cardiovascular event rates.

Methods and Results—Coronary vasoreactivity was assessed in 147 patients using the endothelium-dependent dilator acetylcholine, sympathetic activation by cold pressor testing, dilator responses to increased blood flow, and dilation in response to nitroglycerin. Cardiovascular events (cardiovascular death, unstable angina, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary bypass grafting, ischemic stroke, or peripheral artery revascularization) served as outcome variables over a median follow-up period of 7.7 years. Patients suffering from cardiovascular events during follow-up (n = 16) had significantly increased vasoconstrictor responses to acetylcholine infusion (P = 0.009) and cold pressor testing (P = 0.002), as well as significantly blunted vasodilator responses to increased blood flow (P < 0.001) and the intracoronary injection of nitroglycerin (P = 0.001). Impaired endothelial and endothelium-independent coronary vasoreactivity were associated with a significantly higher incidence of cardiovascular events by Kaplan-Meier analysis. By multivariate analysis, all tests of coronary vasoreactivity were significant, independent predictors of a poor prognosis, even after adjustment for traditional cardiovascular risk factors or the presence of atherosclerosis itself.

Conclusions—Coronary endothelial vasodilator dysfunction predicts long-term atherothrombotic disease progression and cardiovascular event rates. Thus, the assessment of coronary endothelial vasoreactivity can provide pivotal information as both a diagnostic and prognostic tool in patients at risk for coronary heart disease. (Circulation. 2000;101:1899-1906.)

Key Words: coronary disease ■ endothelium ■ prognosis ■ acetylcholine ■ myocardial infarction

The endothelium is a complex endocrine and paracrine organ that affects vasoregulation, smooth muscle cell proliferation, platelet aggregation, monocyte and leukocyte adhesion, and thrombosis,1 all of which are cardinal features in the pathogenesis and progression of atherosclerosis.2 Indeed, experimental studies have demonstrated that the functional integrity of the endothelium exerts potent antiatherothrombotic effects.3–6 Clinically, endothelial function is most often assessed as a vasodilator response to pharmacological or mechanical stimuli. Numerous studies have shown that the presence of coronary atherosclerotic lesions is associated with impaired endothelium-mediated regulation of vascular tone.7–12 More importantly, endothelial vasodilator dysfunction has been observed in patients with traditional coronary risk factors, even in the absence of evidence for atherosclerotic lesions, which suggests that the endothelium is both a target and a mediator of atherosclerosis.13,14 Thus, the hypothesis has been forwarded that endothelial vasodilator function may serve as an index integrating the overall stress imposed by coronary risk factors.15

If such a concept was correct, then coronary endothelial vasodilator dysfunction would not only predict coronary disease progression and cardiovascular event rates, but the assessment of endothelial vasodilator function would emerge as an important diagnostic and prognostic tool in patients with coronary heart disease. Therefore, we prospectively investigated whether coronary endothelial dysfunction predicts disease progression and cardiovascular event rates.

Methods

Patient Population

The patient population was composed of 147 consecutive patients undergoing an assessment of coronary endothelial vasoreactivity; the minimum duration of follow-up was >12 months. A total of 112 patients were studied at the University of Freiburg, Germany, from 1988 to 1994, and 35 patients were studied at the University of Frankfurt, Germany, from 1995 to 1997. The study protocol was approved by the ethics committees of both universities, and informed
consent was obtained from each patient. Patients undergoing either routine diagnostic catheterization for the evaluation of chest pain or percutaneous transluminal coronary angioplasty (PTCA) for single-vessel disease were studied. In patients undergoing PTCA, another vessel without significant obstruction was examined (either the left anterior descending or left circumflex artery). Patients with unstable angina, vasospastic angina pectoris, recent myocardial infarction, valvular heart disease, clinical evidence of heart failure, or left ventricular hypertrophy were excluded from the study.

The following risk factors for coronary artery disease were assessed at the time of coronary vasoreactivity testing: hypertension, hypercholesterolemia, smoking, family history, and evidence of atherosclerosis.

Hypertension was defined as a history of hypertension (blood pressure $>140/90$ mm Hg) for $>2$ years that required the initiation of antihypertensive therapy by the primary physician. Hypercholesterolemia was defined as fasting total serum cholesterol values exceeding the 75th percentile when adjusted for age and sex. Smoking was defined as a history of smoking for $>2$ pack-years. However, all smokers refrained from smoking $>4$ hours before examination. A positive family history for coronary artery disease was defined as evidence of coronary artery disease in a parent or sibling who was younger than 60 years of age at the time of diagnosis. Angiographic evidence of atherosclerosis was defined as luminal irregularities in any vessel. However, luminal narrowing had to be $<30\%$ stenosis in the tested vessel.

Long-Term Follow-Up
Clinical long-term follow-up was performed using a questionnaire that was sent to patients and primary physicians. All information regarding potential cardiovascular events was validated by source data, including the analysis of repeat coronary angiograms, discharge letters, or charts of hospital stays.

The following events were assessed during long-term follow-up. Death from any cause was documented. Cardiovascular death was defined as death due to a myocardial or cerebral infarction or documented sudden cardiac death. Unstable angina pectoris was defined as hospitalization due to unstable angina pectoris of Braunwald classification IIIB or IIIB. Myocardial infarction was defined as an elevation of creatine kinase levels $>2$ times the upper limit or new ST elevations ($>0.1$ mV) in $>2$ leads. PTCA counted only when performed in a newly developed (de novo) stenosis during follow-up. Coronary artery bypass grafting (CABG) was defined as the necessity of CABG in $>1$ de novo lesion during long-term follow-up. Similarly, peripheral bypass revascularization was defined as the need for the surgical revascularization of a de novo stenosis of the peripheral arteries. Ischemic stroke was defined as clinical evidence of stroke without intracranial hemorrhage on brain imaging studies.

Cardiovascular events included the occurrence of cardiovascular death, unstable angina pectoris, myocardial infarction, PTCA, CABG, ischemic stroke, or revascularization of peripheral arteries during long-term follow-up. Cardiovascular events that could be related to the vessel in which vasoreactivity was initially tested were classified as target vessel-related events.

Because angiotensin-converting enzyme (ACE) inhibitors and statins might influence both endothelial vasodilator function and disease progression, chronic therapy with these drugs during long-term follow-up was documented.

Study Design
Vasoactive therapy, including calcium channel blockers, long-acting nitrates, and $\beta$-blockers, was discontinued $>24$ hours before cardiac catheterization. ACE inhibitors were discontinued $>3$ days before the study. The study protocol has been previously described in detail. In brief, the endothelium-dependent vasodilator acetylcholine ($10^{-8}$ to $10^{-4}$ mol/L) was subselectively infused via an infusion catheter into the vessel under study. Sympathetic activation by cold pressor testing was performed by immersing the patient’s hand in ice water for 90 seconds. Flow-dependent dilation was assessed either 90 seconds after the injection of 7 mg of papaverine or 2 minutes after the infusion of 2.4 mg/min adenosine into the midportion of the vessel under study to maximally increase blood flow. Flow-dependent dilation was assessed in a proximal coronary arterial segment exposed to the increased blood flow but not to the vasodilator agents papaverine or adenosine. Nitroglycerin (0.2 to 0.3 mg) was injected into the ostium of the left main stem to assess maximal endothelium-independent epicardial vasodilator capacity.

Quantitative Coronary Angiography
Videodigitized end-diastolic frames were analyzed by an automatic contour detection technique, as previously described. A 6- to 8-mm proximal coronary artery was measured to obtain a mean diameter after the various tests. Acetylcholine and cold pressor test responses were measured in a predefined segment immediately distal to the tip of the infusion catheter. In the same segment, flow-dependent dilation could be assessed after advancing the infusion catheter further distally in the majority of patients. The accuracy, reproducibility, and inter- and intraobserver variability of these measurements have been published previously.

Statistical Analysis
Data are expressed as mean $\pm$ SD. Statistical comparisons were made by Student’s $t$ test if data were normally distributed; otherwise, they were made by the nonparametric Mann-Whitney $U$ test. Cumulative event rates were estimated by Kaplan Meier survival curves for categorical variables. Probability values were determined by the use of the log-rank statistic. For Kaplan-Meier analyses, vasoconstriction ($<0\%$ luminal area change) to acetylcholine or cold pressor testing was considered abnormal, whereas vasodilation ($>20\%$ luminal area change) was classified as a normal response. In addition, Cox regression analysis was used to examine the potential relationships between continuous variables and events during the follow-up period. Multivariate analysis using Cox regression techniques was performed to examine potential interactions among the entered covariates. The variables included in the models were coronary artery disease progression, chronic therapy with these drugs during long-term follow-up.

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Patient Characteristics</th>
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<tbody>
<tr>
<td>Age, y</td>
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<tr>
<td>Sex, female/male</td>
</tr>
<tr>
<td>Angiographic evidence of atherosclerosis</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Positive family history of coronary artery disease</td>
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<tr>
<td>Lipid status</td>
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<tr>
<td>Serum cholesterol level, mg/dL</td>
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<tr>
<td>Serum LDL level, mg/dL</td>
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<td>Serum HDL level, mg/dL</td>
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Values are mean $\pm$ SD or n (%). LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

<table>
<thead>
<tr>
<th>TABLE 2. Cardiovascular Events During Long-Term Follow-Up</th>
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</thead>
<tbody>
<tr>
<td>Event</td>
</tr>
<tr>
<td>Sudden death</td>
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<tr>
<td>Unstable angina pectoris</td>
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<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>PTCA</td>
</tr>
<tr>
<td>CABG</td>
</tr>
<tr>
<td>Peripheral bypass revascularization</td>
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<tr>
<td>Ischemic stroke</td>
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</table>
Coronary Vasoreactivity and Prognosis

During the initial testing of coronary vasoreactivity, 145 patients received an intracoronary infusion of acetylcholine. Flow-dependent dilation was analyzed in 119 patients, 81 patients underwent cold pressor testing, and 142 patients received an intracoronary injection of nitroglycerin.

Infusion of the maximum dose of acetylcholine elicited vasodilation in 50 patients (34%) and vasoconstriction in 95 patients (66%). The mean epicardial luminal area change was $-9.9 \pm 26\%$. Sympathetic activation by cold pressor testing was associated with epicardial artery vasodilation in 29 patients (36%), whereas vasoconstriction was observed in 52 patients (64%), with a mean change in epicardial luminal area of $-4.2 \pm 18\%$. Increased blood flow resulted in a mean epicardial luminal area change of $15 \pm 11\%$. An injection of nitroglycerin resulted in a mean epicardial luminal area change of $34 \pm 20\%$.

As illustrated in Figure 1, patients experiencing cardiovascular events during follow-up had significantly increased vasoconstrictor responses to acetylcholine infusion and cold pressor testing, as well as significantly blunted vasodilator responses to increased blood flow and an intracoronary injection of nitroglycerin.

Figure 2 shows the cumulative proportion of patients without cardiovascular events according to the presence of a vasodilator or vasoconstrictor response to acetylcholine or cold pressor testing, as well as according to tertiles of flow-dependent or nitroglycerin-induced epicardial artery dilation. The incidence of cardiovascular events was significantly higher in patients exhibiting vasoconstrictor responses to acetylcholine or cold pressor testing. Likewise, the incidence of cardiovascular events increased significantly with decreasing vasodilator responses to increased blood flow or nitroglycerin.

Cox regression analysis using the vasomotor responses as continuous variables also demonstrated a significant association with the combined end point of cardiovascular events, with $P=0.056$ for acetylcholine testing, $P=0.002$ for cold pressor testing, $P=0.0006$ for flow-dependent dilation, and $P=0.004$ for nitroglycerin-induced vasodilator response. In addition, flow-dependent dilation normalized to nitroglycer-
in-mediated vasodilator capacity still remained a significant predictor (P=0.039) for the occurrence of cardiovascular events during follow-up. Thus, impaired coronary endothelial vasodilation is associated with a significantly higher incidence of cardiovascular events during long-term follow-up.

**Multivariate Analysis**

To identify coronary endothelial vasodilator dysfunction as an independent predictor of cardiovascular events during long-term follow-up, multivariate analyses were performed; these included the classic risk factors for coronary artery disease and angiographic evidence of atherosclerosis. As shown in Table 3, the independent predictors of a poor outcome were impaired endothelial vasoreactivity, angiographically visible coronary atherosclerosis, and arterial hypertension. Cholesterol serum levels achieved only borderline significance after controlling for the presence of angiographically visible atherosclerosis. Although the significance levels did vary slightly for the individual tests applied, in part because of the different number of patients studied, all 3 tests assessing the various mechanisms of endothelium-mediated coronary vasoregulation proved to be independent predictors of cardiovascular events during long-term follow-up. However, a blunted vasodilator response to nitroglycerin also remained a significant independent predictor of a poor long-term outcome, suggesting that endothelium-dependent and endothelium-independent vasodilator capacity are important for atherosclerotic disease progression.

**Target Vessel–Related Events**

Finally, because previous studies suggested that coronary endothelial vasoreactivity may be heterogeneous, a reanalysis of the data was performed in which only cardiovascular events related to the coronary artery in which vasoreactivity testing was performed were counted. A total of 10 events restricted to the initially tested target vessel occurred during long-term follow-up (PTCA, 5 patients; CABG, 6 patients; myocardial infarction, 1 patient; 2 patients had both PTCA and subsequent CABG). As for overall cardiovascular events, target vessel–related events during follow-up were associated with a significantly increased vasoconstrictor response to acetylcholine (P=0.02) and cold pressor testing (P=0.01), as well as significantly blunted coronary vasodilator responses to increased blood flow (P=0.001) and nitroglycerin (P=0.009) and reduced flow-dependent dilation normalized for nitroglycerin-induced dilator capacity (P=0.02). Because a different protocol to induce flow-dependent dilation was used in 16 patients (adenosine), the data for the 103 patients receiving papaverine to stimulate increased blood flow were analyzed separately; they gave essentially identical results.

Figure 3 illustrates the coronary angiogram of a patient who developed an acute coronary syndrome 3.7 years after...
the testing of coronary vasoreactivity. This patient’s focal coronary atherosclerotic disease progression during follow-up correlated closely with the profound vasconstrictor response to acetylcholine, indicating endothelial vasodilator dysfunction at the time of the initial study.

**Discussion**

The results of the present study demonstrate that coronary endothelial vasodilator dysfunction is an independent predictor of atherosclerotic disease progression and cardiovascular event rates. The predictive power of coronary endothelial function on the clinical outcome of coronary artery disease strongly supports the concept that endothelial function serves as an integrating index of overall coronary risk factor stress. Thus, the assessment of coronary endothelial vasoreactivity seems to be an important diagnostic and prognostic tool in coronary artery disease. This is the first study to show the long-term prognostic significance of coronary vasoreactivity, thereby extending very recently published observations that endothelium-mediated coronary blood flow regulation might contribute to ischemic manifestations of coronary artery disease.17

Coronary endothelial vasoreactivity was assessed by different stimuli to elicit endothelium-dependent vasodilation. Acetylcholine, the classic stimulus for endothelium-mediated relaxation, acts via muscarinic membrane receptors with signal transduction through G proteins to mediate the release of the predominantly relaxing factor nitric oxide,18 as well as an endothelium-derived hyperpolarizing factor19 that counteracts the direct vasoconstrictor effects of acetylcholine via muscarinic receptors on the smooth muscle layer. A vasodilator response to acetylcholine indicates preserved endothelial vasodilator function.20 Increased blood flow elicits the strictly endothelium-dependent vasodilator response by activating endothelial nitric oxide synthase through phosphatidylinositol-3-OH kinase/Akt-mediated phosphorylation of the enzyme.21 Sympathetic activation by cold pressor testing integrates the effects of adrenergic receptor stimulation in both the endothelium and the smooth muscle cell layer and flow-dependent epicardial vasodilation secondary to increased coronary blood flow due to augmented myocardial demand.8,16,22 Previous studies have demonstrated that coronary vasomotor responses to the sympathetic activation induced by mental stress or cold pressor testing correlate closely with vasomotor responses to acetylcholine,11,23 suggesting that a coronary vasodilator response to sympathetic activation reflects the functional integrity of the endothelium.16

**Endothelial Dysfunction and Prognosis**

In the present study, all 3 tests to assess coronary endothelial vasoreactivity were independent predictors of cardiovascular event rates, indicating that the predictive power of endothelial dysfunction is not limited to a specific mechanism to mediate endothelium-dependent dilation. Importantly, the predictive value of coronary endothelial vasodilator dysfunction was independent of the classic risk factors for coronary artery disease. Indeed, when the vasomotor responses of the different tests to assess coronary endothelial vasoreactivity were entered into the multivariate analyses, the classic risk factors were no longer significant, independent predictors of a worse clinical outcome during follow-up, with the exception of arterial hypertension. Moreover, coronary endothelial vasodilator dysfunction remained an independent predictor of disease progression, even after controlling for angiographic evidence of coronary atherosclerosis, suggesting that even once atherosclerosis is present, coronary endothelial vasodilator dysfunction is important. Thus, the assessment of coronary endothelial vasoreactivity may indeed serve as an integrating index of the overall stress imposed by risk factors on the arterial wall.

Although previous studies showing a close correlation between the presence of well-established risk factors and endothelial dysfunction supported a role for endothelial function to predict an intermediate biological outcome, the results of the present study now firmly establish coronary endothelial vasodilator dysfunction as an independent prognostic parameter for an adverse long-term outcome of coro-

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**TABLE 3. Multivariate Cox Regression Analyses**

<table>
<thead>
<tr>
<th></th>
<th>Acetylcholine-Induced Vasoreactivity (n = 145)</th>
<th>Cold Pressor Test–Induced Vasoreactivity (n = 81)</th>
<th>Flow-Dependent Vasoreactivity (n = 119)</th>
<th>Nitroglycerine-Induced Vasoreactivity (n = 142)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE</td>
<td>P</td>
<td>B</td>
</tr>
<tr>
<td>Vasoreactivity</td>
<td>-0.026</td>
<td>0.014</td>
<td>0.053</td>
<td>-0.042</td>
</tr>
<tr>
<td>Angiographic evidence of atherosclerosis</td>
<td>2.3</td>
<td>1.2</td>
<td>0.047</td>
<td>1.5</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>2.10</td>
<td>0.87</td>
<td>0.016</td>
<td>1.8</td>
</tr>
<tr>
<td>Serum cholesterol level</td>
<td>0.010</td>
<td>0.007</td>
<td>0.13</td>
<td>0.007</td>
</tr>
<tr>
<td>Sex</td>
<td>0.76</td>
<td>0.77</td>
<td>0.33</td>
<td>0.61</td>
</tr>
<tr>
<td>Smoking</td>
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<td>0.86</td>
<td>0.94</td>
<td>0.34</td>
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<tr>
<td>Diabetes</td>
<td>0.34</td>
<td>0.70</td>
<td>0.62</td>
<td>0.69</td>
</tr>
<tr>
<td>Age</td>
<td>-0.035</td>
<td>0.041</td>
<td>0.39</td>
<td>-0.011</td>
</tr>
<tr>
<td>Positive family history of coronary artery disease</td>
<td>-0.32</td>
<td>0.59</td>
<td>0.59</td>
<td>0.47</td>
</tr>
</tbody>
</table>
nary heart disease. These data considerably extend previous findings showing that coronary endothelial vasodilator dysfunction might contribute to the acute ischemic manifestations of coronary artery disease.24–27

Endothelium-Independent Dysfunction and Prognosis

In addition to endothelial vasodilator dysfunction, however, the impaired dilator response to exogenous nitric oxide also seems to be of prognostic significance in patients with coronary artery disease. Indeed, previous studies showed a significant inverse relationship between the arterial dilator response to nitroglycerin and endothelium-dependent dilation.12,28,29 Taken together, these findings suggest that the abnormality in vasodilator function in patients at risk for atherosclerosis is not only confined to endothelium-dependent mechanisms, but may also comprise an impairment in smooth muscle dilator function. One might speculate that the blunted coronary vasodilation in patients with a poor prognosis might simply reflect the presence of atherosclerosis, leading to increased stiffness of the vessel wall. However, these patients exhibited significantly enhanced constrictor responses to acetylcholine and cold pressor testing, indicating the presence of preserved vasoreactivity of the smooth muscle cell layer. Nevertheless, the present study in humans can obviously not define the mechanisms responsible for the association between impaired coronary vasodilator function and the progression of atherosclerosis.

However, it is well documented that atherosclerotic risk factors are associated with the overproduction of oxygen-derived free radicals in the vascular wall.30–32 Reactive oxygen species can directly activate a whole array of genes implicated in the pathogenesis and progression of atherosclerosis via nuclear factor kappa B–mediated transcriptional activation,33 and they also avidly scavenge both endogenous and exogenous nitric oxide, thereby decreasing the bioavailability of nitric oxide to the smooth muscle cell.34 Thus, it is tempting to speculate that a blunted dilator response mirrors the oxidative stress imposed on the vascular wall, which in turn will determine atherosclerotic disease progression. Increased oxidative stress might affect the bioactivity of both endogenous and exogenous nitric oxide. However, the fact

Figure 3. Coronary vasoreactivity and atherosclerotic disease progression. Top left shows baseline coronary angiogram of a patient in whom focal paradoxical vasoconstriction to acetylcholine occurred in the proximal left anterior descending artery (top right) at the time of the initial vasomotor testing (arrow indicates tip of acetylcholine infusion catheter). Injection of nitroglycerin (bottom left) demonstrates only minimal vasodilation and unmask an atherosclerotic plaque at the site of paradoxical vasoconstriction to acetylcholine. During follow-up 3.7 years later, the patient was admitted to the hospital with an acute coronary syndrome. Coronary angiography revealed focal progression of atherosclerotic disease (bottom right) at the site of the initial paradoxical vasoconstriction to acetylcholine.

Baseline  
Acetylcholine  
Nitroglycerin  
Follow up (3.7 years)
that flow-dependent vasodilation is of prognostic importance, even after normalization to endothelium-independent, nitroglycerin-induced vasodilation, clearly underscores the role of endothelial dysfunction.

Somewhat surprisingly, lipid-lowering therapy with statins was not an independent predictor of improved outcome in our patient population. This finding might be explained either by the rather small number of patients to detect any beneficial effects of statin therapy on disease progression or by the still-restricted use of statins in the late 1980s and early 1990s, when most patients were initially studied. Lipid-lowering therapy was initiated only in patients who had considerably elevated total cholesterol levels. Currently ongoing multicenter trials will ultimately determine whether an improvement in coronary endothelial function by statin treatment is directly related to the well-established beneficial effects of statins on prognosis in patients with coronary artery disease.35

Limitations

Although the number of patients and, thus, the number of events seems to be rather small, the present study represents the largest patient cohort studied to date to assess coronary endothelial vasodilator function, and it is also the first to report clinical outcome over a 7.7-year (median) observation period. Nevertheless, larger trials with larger patient populations should be performed to confirm our data and, more importantly, to establish the potential beneficial role of reversing coronary endothelial dysfunction by interventional strategies for long-term atherosclerotic disease progression. Moreover, although all consecutive patients undergoing this highly invasive protocol were included in the long-term follow-up analysis, long-term evaluation was not a prespecified end point at the time of coronary vasoreactivity testing. Finally, enrollment of patients in the study was based on a successfully performed invasive assessment of coronary vasoreactivity with intracoronary instrumentation, which might have introduced a selection bias. However, clinical follow-up was completed for all patients initially studied. Thus, despite the limitations mentioned above, we think that our data demonstrate, for the first time, that endothelial dysfunction of large epicardial arteries is important for coronary atherosclerotic disease progression.

In summary, the results of the present study demonstrate that coronary endothelial vasodilator dysfunction predicts long-term atherosclerotic disease progression and cardiovascular event rates. Thus, the assessment of coronary endothelial vasoreactivity can provide pivotal information, both as a diagnostic and prognostic tool in patients at risk for coronary heart disease. Importantly, establishing coronary endothelial vasodilator dysfunction as a prognostic index that integrates the overall stress imposed by coronary risk factors might provide a tool to predict the impact of an intervention on coronary disease progression and cardiovascular event rates, as previously suggested by the beneficial effects of cholesterol-lowering therapy on coronary endothelial vasodilator function.36,37

Acknowledgments

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References


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