A Positive Family History of Premature Coronary Artery Disease Is Associated With Impaired Endothelium-Dependent Coronary Blood Flow Regulation

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Background—The aim of the study was to determine whether a positive family history of coronary artery disease is related to impaired coronary blood flow regulation.

Methods and Results—In 150 patients with angiographically normal or minimally diseased coronary vessels, risk factors for coronary artery disease, the extent of atherosclerosis and endothelium-dependent vasomotor responses to acetylcholine, and endothelium-independent blood flow regulation by papaverine or adenosine were assessed. Coronary blood flow responses to acetylcholine were reduced in a dose-dependent manner in patients with a positive family history ($P=0.030$). By multivariate analysis, hypercholesterolemia ($P=0.001$), age ($P=0.002$), and a positive family history ($P=0.008$) remained predictors of coronary blood flow increase to acetylcholine. The extent of atherosclerotic coronary artery disease was, by multivariate analysis, an additional independent predictor of acetylcholine-induced blood flow ($P=0.014$), but also of endothelium-independent blood flow regulation ($P=0.001$). A positive family history had additive effects in addition to the other risk factors, such as hypercholesterolemia or increased age. Angiotensin-converting-enzyme genotype polymorphism had no influence either on endothelium-dependent or endothelium-independent coronary blood flow responses. However, in a subset of 28 patients, homocysteine (which is, in part, genetically determined) was inversely related to maximal acetylcholine-induced blood flow regulation ($r=-0.47, P=0.012$).

Conclusions—The results of this study demonstrate, for the first time, that a positive family history of coronary artery disease is an important predictor of impaired endothelium-dependent coronary blood flow regulation in humans. The influence of a positive family history is independent of other well known risk factors but instead aggravates endothelial vasodilator dysfunction associated with hypercholesterolemia and increased age, suggesting important interacting effects between genetic and environmental risk factors. (Circulation. 1999;100:1502-1508.)

Key Words: coronary disease ■ endothelium ■ circulation ■ acetylcholine ■ blood flow

Endothelium plays a crucial role in the control of vascular tone and proliferation processes in the coronary arteries. Modulation of coronary vasomotor tone by endothelial dysfunction might contribute to the manifestation of myocardial ischemia. In coronary vessels with atherosclerotic lesions, paradoxical vasoconstriction in response to sympathetic activation or exercise might contribute to impaired blood flow supply, resulting in myocardial ischemia. However, in the absence of epicardial stenosis, myocardial blood flow is regulated predominantly by the coronary microvasculature in vessels <200 μm in diameter. Therefore, in patients without epicardial atherosclerosis, myocardial ischemia might be related to microvascular dysfunction. Thallium perfusion defects during exercise in selected patients with minimal coronary disease have been shown to be associated with attenuation of endothelium-dependent vasodilation of the coronary microcirculation. Thus far, hypercholesterolemia, increased age, and atherosclerosis have been identified as risk factors for impaired endothelium-dependent vasodilatation of the coronary resistance vessels.

In studies of conduit arteries, such as the brachial artery and the epicardial vessels, a positive family history for coronary artery disease has been shown to predict an impaired endothelium-dependent vasomotor response to acetylcholine. However, the effects of a positive family history of coronary artery disease on coronary endothelial dysfunction in the microcirculation have not been reported so far, probably because the effects of other risk factors might have obscured the influence of a positive family history. A genetically determined impairment of coronary blood flow regu-
lation might contribute to the pathophysiology of myocardial ischemia. More importantly, alterations of coronary blood flow might be of pathophysiological relevance for epicardial atherosclerotic lesion formation, because blood flow determines vessel wall shear stress, which stimulates endothelium-dependent vasodilation and subsequent remodeling. Shear stress is the physiological stimulus for endothelial nitric oxide production, which not only mediates vasodilation but also has antiatherosclerotic properties by its influence on vascular wall proliferation processes,10 most likely favorably affecting compensatory enlargement of atherosclerotic epicardial vessels. Indeed, recent studies have documented a pivotal role of nitric oxide for vascular remodeling in response to increased blood flow.11 Thus, we analyzed whether a positive family history of coronary artery disease is an additional independent risk factor for impaired coronary blood flow regulation.

Methods

Patient Population

In 150 patients undergoing routine diagnostic catheterization for evaluation of chest pain or PTCA of single vessel disease, a vessel without significant obstruction (LAD or LCX) was examined. Patients with unstable angina, vasospastic angina pectoris, recent myocardial infarction, valvular heart disease, clinical evidence of heart failure, or left ventricular hypertrophy were excluded.

Hypertension was defined as a history of hypertension 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 adjusted for age and sex. Smoking status was divided into 3 categories: never smoked; quit smoking: >2 pack-years cigarette smoking but non-smoker for >1 year; still smoking: >2 pack-years smoked and currently a smoker. However, all smokers refrained from smoking at least 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 before 60 years of age, such as a history of myocardial infarction, coronary artery bypass surgery, angina pectoris, or pathological exercise tolerance test diagnostic of ischemia. Extent of disease was defined as normal (smooth vessels in the entire coronary tree), minimal disease (luminal irregularities <30% focal stenosis in any vessel) or coronary artery disease (significant stenosis >50% in another vessel than the vessel under study).

Written informed consent was obtained from all patients before the study. The study protocol had been approved by the ethical committees of the University of Freiburg and the University of Frankfurt. The vasomotor responses of 71 of these patients were already reported previously.5,12

Study Design

Vasoactive therapy, including calcium channel blockers, long-acting nitrates, and β-blockers was discontinued for at least 24 hours and angiotensin-converting enzyme (ACE) inhibitors for at least 3 days before the study. Using a standard percutaneous femoral approach with Judkins technique, a 3F Monorail Doppler catheter (Schneider) with a 20-MHz pulsed Doppler crystal was advanced into the left anterior descending artery or left circumflex artery by a 0.014-inch guidewire; alternatively, a 0.014-inch Doppler wire (Cardiometrics) was used to determine the parameters of coronary blood flow. The study protocol has been previously described:13 in brief, endothelium-mediated dilation was analyzed by infusion of increasing dosages of the endothelium-dependent vasodilator acetylcholine to achieve estimated concentrations of 10^{-6} to 10^{-4} M into the vessel under study. Endothelium-independent blood flow response was assessed in 132 patients using injection of 7 mg papaverine (n = 98) into the midportion of the vessel under study or infusion of 2.4 mg/min adenosine over 2 minutes (n = 34).

Quantitative Coronary Angiography

As previously reported,13 quantitative coronary angiography by automatic contour detection technique14 was performed to determine cross-sectional area of the artery in a 6- to 8-mm long segment immediately distal to the radiopaque tip of the Doppler catheter/wire. This technique was also used to assess maximal epicardial vasomotor response and to exclude limitations of coronary artery flow caused by epicardial coronary artery constriction (>60% cross-sectional area reduction) in response to acetylcholine by measuring the most constricting epicardial artery segment. Coronary flow index was calculated by multiplying the mean Doppler-derived blood flow velocity, obtained immediately before contrast injection, with the computed cross-sectional area of the vessel segment distal to the tip of the Doppler catheter. Coronary blood flow response to the infused substance was defined as infusion-induced percent change of coronary flow index.

Exercise Testing

Standardized exercise stress testing was performed by bicycle ergometry, beginning at a workload of 50 W and increasing in 25-W increments every 3 minutes. Exercise was terminated if the patient was unable to maintain a cycling frequency >50 rpm due to physical exhaustion, angina or dyspnea, or evidence of myocardial ischemia with documented planar or downsloping ST-segment depression ≥1 mm 80 ms after the J point.

ACE Genotype Polymorphism

Total genomic DNA was extracted from whole blood with a DNA purification kit (Qiagen). The insertion/deletion polymorphism in intron 16 of the ACE gene was identified by conventional polymerase chain reaction.15

Homocysteine Measurements

After overnight fasting, samples of venous blood were drawn into tubes containing EDTA. Plasma was separated from blood cells by immediate centrifugation. Protein-bound homocysteine was reduced to free homocysteine and enzymatically converted to Adenosyl-L-homocysteine. Homocysteine was measured by an enzyme immunoassay (Axis, Homocystein EIA, Oslo, Norway) with spectrophotometric detection at 450 nm.

Statistical Analysis

All data are expressed as mean±SD unless otherwise stated. Statistical comparisons were made by t test or 1-way ANOVA. Dose response curves were compared by a general linear model (repeated measurements). Categorical variables were compared by χ2 test. Linear regression analysis was used to compare vasomotor responses with age, serum cholesterol, HDL, LDL, or homocysteine levels. For the maximal acetylcholine-induced vasomotor response, a multivariate analysis using multiple stepwise linear regression techniques was performed. A forward entry stepping algorithm was used with the entry criteria probability of F (0.05). Statistical significance was assumed if the null hypothesis could be rejected at P=0.05. All statistical analysis was performed using SPSS for Windows 8.0 (SPSS Inc).

Results

Patient Characteristics

The characteristics of the 150 patients are summarized in Table 1. There was no significant relation between a positive family history and other risk factors, including ACE genotype polymorphism. Patients with a positive family history were slightly younger but this difference did not reach statistical significance. However, there was a significant relation be-
tween a positive family history and the extent of disease. The mean increase of coronary blood flow index was 19\(\pm\)29% for 10\(^{-8}\) M acetylcholine, 48\(\pm\)54% for 10\(^{-7}\) M acetylcholine, and 118\(\pm\)113% for 10\(^{-6}\) M acetylcholine. Endothelium-independent blood flow increased by 360\(\pm\)157% during stimulation with papaverine or adenosine, as assessed in 132 patients.

Coronary Blood Flow Responses

By univariate analysis, maximal acetylcholine-induced coronary blood flow increase was significantly impaired in patients with a positive family history, angiographic evidence of atherosclerosis, increasing age, and hypercholesterolemia (Table 2). Total serum cholesterol levels and serum LDL cholesterol levels, but not HDL cholesterol, were inversely related with acetylcholine-induced blood flow increase. Hypertension, diabetes mellitus, gender, and smoking status had no significant effect on coronary blood flow responses. Acetylcholine-induced coronary blood flow responses were dose-dependently reduced in patients with a positive family history \((P=0.030)\) (Figure 1). Similarly, extent of disease and hypercholesterolemia were associated with dose-dependently blunted acetylcholine-induced coronary blood flow responses.

Endothelium-independent regulation of the coronary microvasculature was significantly blunted in patients with a positive family history and those with angiographic evidence of atherosclerosis (Table 3). In addition, women had a reduced endothelium-independent vasodilation compared with men. Thirty-eight of the 53 women were postmenopausal without hormone replacement therapy (5 women were premenopausal, 10 postmenopausal women took hormones). No effect on endothelium-independent coronary blood flow regulation was observed for hypertension, hypercholesterolemia, diabetes mellitus, smoking status, and age.

Multivariate Analysis

By multivariate analysis, hypercholesterolemia \((P=0.001)\), age \((P=0.002)\), positive family history \((P=0.008)\), and extent

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**TABLE 1. Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Negative Family History (n=100)</th>
<th>Positive Family History (n=50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54(\pm)9.6</td>
<td>52(\pm)12</td>
<td>0.32</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>34/66</td>
<td>0.63</td>
</tr>
<tr>
<td>Extent of disease</td>
<td></td>
<td></td>
<td>0.036</td>
</tr>
<tr>
<td>Normal</td>
<td>47 (47)</td>
<td>13 (26)</td>
<td></td>
</tr>
<tr>
<td>Minimal disease</td>
<td>29 (29)</td>
<td>23 (46)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>24 (24)</td>
<td>14 (28)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>39 (39)</td>
<td>24 (48)</td>
<td>0.29</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td>38 (38)</td>
<td>0.55</td>
</tr>
<tr>
<td>Still</td>
<td>38 (38)</td>
<td>16 (32)</td>
<td></td>
</tr>
<tr>
<td>Quit</td>
<td>28 (28)</td>
<td>15 (30)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>34 (34)</td>
<td>19 (38)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (9)</td>
<td>8 (16)</td>
<td>0.21</td>
</tr>
<tr>
<td>Lipid status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>57 (57)</td>
<td>24 (48)</td>
<td>0.30</td>
</tr>
<tr>
<td>Serum cholesterol level, mg/dL</td>
<td>234(\pm)44</td>
<td>241(\pm)56</td>
<td>0.46</td>
</tr>
<tr>
<td>Serum LDL level, mg/dL</td>
<td>155(\pm)42</td>
<td>162(\pm)50</td>
<td>0.45</td>
</tr>
<tr>
<td>Serum HDL level, mg/dL</td>
<td>52(\pm)16</td>
<td>50(\pm)13</td>
<td>0.66</td>
</tr>
<tr>
<td>ACE genotype polymorphism</td>
<td></td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>20 (23)</td>
<td>5 (11)</td>
<td></td>
</tr>
<tr>
<td>ID</td>
<td>45 (52)</td>
<td>27 (61)</td>
<td></td>
</tr>
<tr>
<td>DD</td>
<td>22 (25)</td>
<td>12 (27)</td>
<td></td>
</tr>
<tr>
<td>n=87</td>
<td>n=44</td>
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<td></td>
</tr>
</tbody>
</table>

**TABLE 2. Risk Factors for CAD and Maximal Acetylcholine-Induced Blood Flow Increase**

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>129(\pm)110</td>
<td>104(\pm)107</td>
<td>0.16</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>148(\pm)121</td>
<td>94(\pm)91</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>121(\pm)111</td>
<td>108(\pm)92</td>
<td>0.61</td>
</tr>
<tr>
<td>Family history for CAD</td>
<td>132(\pm)115</td>
<td>91(\pm)91</td>
<td>0.025</td>
</tr>
<tr>
<td>Sex</td>
<td>103(\pm)100</td>
<td>128(\pm)114</td>
<td>0.17</td>
</tr>
</tbody>
</table>

**Figure 1.** Acetylcholine-induced coronary blood flow increase for positive and negative family history of coronary artery disease \((P=0.030)\) (from general linear model, repeated measurements). Values are mean\(\pm\)SEM.
Extent of disease $P=0.049)$ remained statistically significant independent predictors. In contrast, the extent of atherosclerosis was not associated with this parameter of endothelium-dependent coronary blood flow response, indicating a general impairment of blood flow regulation in patients with atherosclerosis, not limited to the endothelium.

Epicardial vasomotor responses were correlated with acetylcholine-induced coronary blood flow responses in both patients with a positive family history ($r=0.41; P=0.003$) and those without a family history ($r=0.30; P<0.001$) of coronary artery disease. If epicardial vasomotor response to acetylcholine was included in the multivariate analysis, acetylcholine-induced blood flow response is independently determined by maximal epicardial acetylcholine-induced vasomotor response ($P=0.032$), a positive family history ($P=0.035$), and age ($P=0.040$).

### ACE Genotype Polymorphism

In 131 patients, blood was available for analysis of the ACE genotype polymorphism. ACE genotypes were not associated with maximal acetylcholine-induced blood flow increases ($P=0.53$) or the ratio of acetylcholine-induced to endothelium-independent blood flow increase ($P=0.93$). Dividing patients into those bearing the D allele or the II genotype of the ACE polymorphism did not reveal statistically significant differences in the dose-blood flow response to acetylcholine (Figure 2). In addition, endothelium-independent blood flow increase was not statistically significantly different between patients bearing the II genotype ($367\pm14%)$, ID genotype ($367\pm14%)$, and DD genotype ($367\pm14%$). There was also no significant association between ACE genotype polymorphism and epicardial vasomotor responses to acetylcholine ($P=0.75$).

### Homocysteine Levels

We measured plasma homocysteine concentrations in 28 of our patients at the time of coronary blood flow measurement. There was a significant inverse relation between acetylcholine-induced increases in coronary blood flow and

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**TABLE 3. Risk Factors for CAD and Endothelium-Independent Blood Flow Regulation**

<table>
<thead>
<tr>
<th>t test</th>
<th>Endothelium-Independent Blood Flow Increase, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypertension</td>
<td>367±161</td>
<td>350±152</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>351±148</td>
<td>367±146</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>363±157</td>
<td>334±163</td>
</tr>
<tr>
<td>Family history for coronary artery disease</td>
<td>378±162</td>
<td>323±139</td>
</tr>
<tr>
<td>Sex</td>
<td>297±155</td>
<td>391±149</td>
</tr>
</tbody>
</table>

1-way ANOVA

<table>
<thead>
<tr>
<th>Extent of disease</th>
<th>Normal</th>
<th>Minimal</th>
<th>CAD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>404±151</td>
<td>348±152</td>
<td>312±157</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>350±171</td>
<td>380±136</td>
<td>353±161</td>
<td>0.62</td>
<td></td>
</tr>
</tbody>
</table>

Linear regression analysis

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Hypercholesterolemia</th>
<th>Extent of disease</th>
<th>Diabetes</th>
<th>Smoking status</th>
<th>Family history for CAD</th>
<th>Hypercholesterolemia</th>
<th>Adjusted $R^2$</th>
<th>Significance (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>−0.16</td>
<td>−0.10</td>
<td>0.01</td>
<td>−0.20</td>
<td>0.03</td>
<td>0.02</td>
<td>0.02</td>
<td>−0.26</td>
<td>0.18</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Standardized Coefficient $P$ 0.002 0.22 0.014 0.94 0.22 0.08 0.01 0.001 0.15 0.08

**TABLE 4. Multivariate Analysis**

<table>
<thead>
<tr>
<th>Acetylcholine$_{max}$-Induced Blood Flow Increase</th>
<th>Endothelium-Independent Blood Flow Increase</th>
<th>Ratio Acetylcholine$_{max}$: Endothelium-Independent Blood Flow Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standardized Coefficient</td>
<td>Standardized Coefficient</td>
<td>P</td>
</tr>
<tr>
<td>Age</td>
<td>−0.25</td>
<td>0.002</td>
</tr>
<tr>
<td>Sex</td>
<td>−0.10</td>
<td>0.22</td>
</tr>
<tr>
<td>Extent of disease</td>
<td>−0.20</td>
<td>0.014</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.01</td>
<td>0.94</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.03</td>
<td>0.71</td>
</tr>
<tr>
<td>Smoking status</td>
<td>0.02</td>
<td>0.81</td>
</tr>
<tr>
<td>Family history for CAD</td>
<td>−0.21</td>
<td>0.008</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>−0.26</td>
<td>0.001</td>
</tr>
<tr>
<td>Adjusted $R^2$</td>
<td>0.18</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Significance (ANOVA) $<0.001$ $<0.001$ 0.017
homocysteine plasma levels (Figure 3). In contrast, endothelium-independent coronary blood flow responses were unaffected by homocysteine plasma levels ($r = -0.17, P = 0.39$).

Relation Between Coronary Blood Flow Responses and Exercise Testing
In 107 of our patients, standardized exercise tests by bicycle ergometry were performed. As illustrated in Figure 4A, the coronary blood flow response to acetylcholine was significantly related to the maximal workload achieved during exercise testing. A similar relation was found for the endothelium-independent blood flow responses (Figure 4B). In contrast, neither exercise-induced angina pectoris ($P = 0.80$) nor ST-segment alterations ($P = 0.92$) demonstrated any relation with endothelium-dependent coronary blood flow responses or endothelium-independent responses.

Discussion
The results of this study demonstrate, for the first time, that a positive family history of coronary artery disease is an important predictor of impaired endothelium-dependent coronary blood flow regulation in humans. The influence of a positive family history is independent of other well known risk factors, and it aggravates endothelial vasodilator dysfunction associated with hypercholesterolemia and increased age, suggesting important additive effects of genetic and environmental risk factors.

Limited endothelium-dependent vasodilation of the coronary microcirculation might not only trigger myocardial ischemia in the absence of flow limiting epicardial stenosis$^{4,16,17}$ but may also play a role for progression of epicardial disease. Progression of atherosclerotic lesions is currently believed to be due to proliferative processes within the vascular wall as well as failure of compensatory enlargement of the arteries (remodeling) as plaques grow. Vascular remodeling is strictly endothelium-dependent$^{18}$ and requires the release of nitric oxide by the endothelium. Thus, impaired blood flow regulation associated with a positive family history of coronary artery disease may facilitate progression of atherosclerotic lesion formation.

Importantly, the results of the present study demonstrate that the vasodilator capacity of the coronary microcirculation is related to the maximal workload during exercise stress testing. In a recent, large, population-based cohort study, exercise capacity was the strongest predictor of subsequent cardiac events$^{19}$ Taken together, these data indeed support the conclusion that impaired endothelium-dependent increases in coronary blood flow may play a role for progression of coronary artery disease. In line with results of the present study, Cannon and coworkers have recently shown that impaired coronary endothelial blood flow responses did not account for ischemic-appearing ST-segment depression in patients with normal coronary arteries$^{20}$. However, we have previously shown that in selected patients, exercise-induced myocardial ischemia, as documented by thallium perfusion, is associated with a blunted endothelium-dependent coronary blood flow response.$^4$ Thus, exercise testing might be of limited value to provide objective evidence of myocardial ischemia in patients without flow-limiting coronary stenoses. In addition, whereas exercise-induced ST-segment depression is predictive of subsequent cardiac events in patients with documented coronary artery disease,$^{21,22}$ neither exercise-induced angina nor ST depression predicted subsequent cardiac events in a cohort study.$^{19}$

Determinants of Coronary Blood Flow Regulation
The finding of an impaired endothelium-dependent coronary blood flow regulation in patients with a positive family
history extends reports of impaired conductance vessel vaso-
motor regulation.\textsuperscript{9,23} Importantly, a positive family history of
coronary artery disease further aggravates the impairment of
endothelial coronary blood flow regulation in patients with
established risk factors and evidence of atherosclerosis.

The relation between a positive family history and endo-
thalial dysfunction points toward a genetic determination of
impaired endothelial vasodilator function. The ACE genotype
deletion polymorphism has previously been associated with a
positive family history of coronary artery disease.\textsuperscript{24} Because
increased plasma ACE activity has been found in patients
with the D allele, the ACE polymorphism might indeed
contribute to endothelial vasodilator dysfunction. However,
our results, in line with a previous study on flow-dependent
dilation of the brachial artery,\textsuperscript{25} do not provide evidence for
an association between ACE polymorphism and impaired
endothelium-dependent vasodilation.

Genetic defects in enzymes necessary for homocysteine
metabolism, leading to high plasma concentrations of homo-
cysteine, are associated with the development of severe
atherosclerosis during childhood.\textsuperscript{26} However, plasma concen-
trations of homocysteine are slightly elevated in many pa-
tients who have no enzymatic defect in homocysteine metab-
olism.\textsuperscript{27} Moreover, homocysteine has been shown to decrease
the bioavailability of nitric oxide,\textsuperscript{28} and elevated homocys-
teine levels are associated with a blunted endothelium-
dependent dilation of the brachial artery.\textsuperscript{29,30} Indeed, in
a small subset of patients of the present study, homocysteine
concentrations were inversely related to the endothelium-
dependent coronary vasodilator responses. These data not
only document a role for homocysteine plasma levels to interfere with endothelium-dependent coronary blood flow
regulation in humans but may also provide insights into a
potential link between impaired coronary endothelial vasodi-
lator function and a positive family history for coronary
artery disease.

Limitations
In order to have a large number of patients to assess coronary
blood flow regulation, we decided to pool patients with endo-
thelium-independent vasodilatation induced by 2 different sub-
stances, namely papaverine and adenosine. This might introduce
an error in the study results. However, we believe this is
outweighed by the large sample size. In addition, 6 of the
patients were studied with papaverine as well as adenosine,
demonstrating a close correlation between both tests of endo-
thelium-independent coronary blood flow increases ($r=0.86$).

The extent of atherosclerosis was assessed by angiography,
which underestimates the true amount of atherosclerotic plaque
burden, as can be seen by intravascular ultrasound.\textsuperscript{31} Therefore,
we might have misclassified patients with early disease as
having normal coronary arteries. Thus, the nonquantitative
division into 3 different stages is just a coarse classification of
the extent of coronary atherosclerotic disease.

In summary, coronary blood flow responses to endotheli-
um-dependent stimuli are affected by morphological alter-
ations of the atherosclerotic epicardial arteries and risk
factors acting directly on the endothelium in the coronary
microcirculation and conductance vessels. A positive family
history exerts additive effects to the other risk factors asso-
ciated with impaired blood flow increase to endothelial
stimulation; this might be relevant for development and
progression of coronary artery disease. Homocysteine plasma
levels, which are at least in part genetically determined, might
provide a potential link between a positive family history of
early coronary artery disease and blunted coronary blood flow
regulation. However, further studies should aim to identify
additional genetic determinants of an impaired cor-
oral endothelial vasodilator function, which might allow
researchers to stratify patients with high risk for progression of
coronary artery disease.

Acknowledgments

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(SFB 553). The expert technical assistance of B. Jung for quantita-
tive coronary angiography and S. Ficus for performing the ACE
genotyping is acknowledged.

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