Cigarette Smoking Is Associated With Dose-Related and Potentially Reversible Impairment of Endothelium-Dependent Dilation in Healthy Young Adults

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Background. Cigarette smoking is the most important modifiable risk factor for atherosclerosis. Endothelial dysfunction is an early event in atherogenesis, and we hypothesized that smoking might be associated with endothelial damage in the systemic arteries of otherwise healthy young adults.

Methods and Results. We studied noninvasively the brachial arteries of 200 subjects aged 15 to 57 years, all normotensive, nondiabetic with cholesterol level ≤240 mg/dL and no family history of premature vascular disease: 80 control subjects aged 16 to 56 years (mean, 35), 80 current smokers aged 15 to 55 years (mean, 33), and 40 former smokers aged 25 to 57 years (mean, 38). Total lifetime amount smoked varied from 1 to 75 pack years in the smokers. Using high-resolution ultrasound, vessel diameter was measured at rest, during reactive hyperemia (with flow increase causing endothelium-dependent dilation), and after sublingual glyceryl trinitrate (GTN, an endothelium-independent vasodilator). Flow-mediated dilation (FMD) was observed in all the control subjects (10±3.3%; range, 4% to 22%) but was impaired or absent in the smokers (4±3.9%; range, 0% to 17%; P<.0001). FMD in the smokers was inversely related to lifetime dose smoked (6.6±4.0% in very light smokers, 4.0±3.1% in light smokers, 3.2±3.2% in moderate smokers, and 2.6±1.2% in heavy smokers; P<.01). FMD for the former smokers was 5.1±4.1% (range, 0% to 15%). In a multivariate model adjusting for age, sex, cholesterol, smoking history, and vessel size, former smoking was associated with a higher FMD than current smoking (P=.07); when only male former and current smokers were considered, the higher FMD was significant (P=.001) but not for female smokers (P=.24). GTN caused dilation in all subjects (control subjects, 20±5.2%; smokers, 17±5.8%; former smokers, 17.4±5.4%). Vessel diameter, baseline flow, and degree of reactive hyperemia (Doppler estimated) were similar in all groups.

Conclusions. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent arterial dilation in asymptomatic young adults, consistent with endothelial dysfunction. (Circulation. 1993;88[part 1]:2149-2155.)

Key Words • cigarette smoking • atherosclerosis

Cigarette smoking is a major risk factor for atherosclerosis and is strongly associated with coronary, cerebral, and peripheral vascular disease.1-3 The exact components of cigarette smoke responsible for vasculopathy are not known, although nicotine and carbon monoxide have been implicated,4 nor is the mechanism of smoking-related arterial damage. Experimental evidence has suggested that smoking-induced endothelial damage may mediate increased cardiovascular morbidity,5 although Vita et al6 failed to find an association between smoking and coronary endothelial dysfunction in a study of 12 adult smokers undergoing angiography.7 Because endothelial dysfunction is an early event in atherogenesis,8,9 we hypothesized that endothelial dysfunction might be present in the systemic arteries of young adult smokers and that this might be a dose-dependent phenomenon. Furthermore, because recent studies have indicated that cardiovascular risk is lower in smokers who give up cigarettes after a first myocardial infarction,10,11 we investigated former smokers to compare their arterial physiology with that of the subjects who continued to smoke.

Methods

Subjects

Two hundred subjects aged 15 to 57 years were studied; all were normotensive, nondiabetic, had no family history of premature vascular disease, and had plasma total cholesterol ≤240 mg/dL (range, 110 to 240 mg/dL). All were clinically well and on no regular cardiovascular medications. Subjects were recruited from among hospital...
staff, families, friends, and other volunteers over a 1-year period. There were 80 lifelong nonsmokers aged 16 to 56 years (mean, 35 years) (control subjects), 80 current smokers aged 15 to 55 years (mean, 33 years), with 42 men and 38 women in each of these groups, and 40 former smokers (25 to 57; mean, 38 years; 23 men and 17 women). Current smokers were defined as any who had smoked at least 20 cigarettes per day for 1 year (1 pack year) or the equivalent and former smokers as any reformed regular smoker (at least 1 pack year) who had not smoked a cigarette for ≥3 months. All the current smokers had had at least one cigarette in the 12 hours before being studied. Smokers were classified into four groups: very light (16 subjects, 0 to 4 pack years), light (17 subjects, 5 to 9 pack years), moderate (22 subjects, 10 to 19 pack years), or heavy (25 subjects, ≥20 pack years). All subjects gave informed consent, and the study protocol was approved by the local committee on ethical practice.

Study Design

This method has been described elsewhere. The diameter of the target artery was measured from B-mode ultrasound images, using a 7.0-MHz linear array transducer and a standard Acuson 128XP/10 system (Acuson, Mountain View, Calif). In all studies, scans were taken at rest, during reactive hyperemia, again at rest, and after sublingual glyceryl trinitrate (GTN). The subject lay quietly for ≥10 minutes before the first scan. The brachial artery was scanned in longitudinal section 2 to 15 cm above the elbow, wherever the clearest ultrasound image was obtained. The center of the artery was identified when the clearest picture of the anterior and posterior intimal layers was obtained. The transmit (focus) zone was set to the depth of the near wall, in view of the greater difficulty of evaluating the near compared with the far wall “m” line (the interface between media and adventitia). Depth and gain settings were set to optimize images of the lumen/arterial wall interface, images were magnified using a resolution box function (leading to a video line width of approximately 0.065 mm), and machine operating parameters were not changed during any study.

When a satisfactory transducer position was found, the skin was marked, and the arm remained in the same position throughout the study. A resting scan was recorded, and arterial flow velocity was measured using a pulsed Doppler signal at a 70° angle to the vessel, with the range gate (1.5 mm) in the center of the artery. Increased flow was then induced by inflation of a pneumatic tourniquet placed around the forearm to a pressure of 300 mm Hg for 4.5 minutes followed by release. A second scan was taken continuously for 30 seconds before and 90 seconds after cuff deflation, including a repeat flow velocity recording for the first 15 seconds after the cuff was released. Thereafter, 10 to 15 minutes was allowed for vessel recovery, after which a further resting scan was taken. Sublingual GTN spray (400 μg) was then administered, and 3 to 4 minutes later, the last scan was performed.

Data Analysis

Vessel diameter was measured by two observers who were unaware of the smoking status of the subject and the stage of the experiment. The between-observer coefficient of variation for measurement of percent flow-mediated dilation (FMD) was 1.3%. The arterial diameter was measured at a fixed distance from an anatomic marker (such as a fascial plane or a vein seen in cross section) using ultrasonic calipers. Measurements were taken from the anterior to the posterior “m” line at end diastole, incident with the R wave on a continuously recorded ECG. For the reactive hyperemia scan, diameter measurements were taken 45 to 60 seconds after cuff deflation. Four cardiac cycles were analyzed for each scan, and the measurements were averaged. The vessel diameter in scans after reactive hyperemia, 15 minutes’ rest, and GTN was expressed as the percentage relative to the first control scan (100%). Volume flow was calculated by multiplying the velocity-time integral of the Doppler flow signal (corrected for angle) by the heart rate and the vessel cross-sectional area (πr²). The flow velocity used in our calculation was taken from the center of the artery; absolute flow may therefore be overestimated, but relative flow values before and after cuff inflation are accurate. Reactive hyperemia was calculated as the maximum flow recorded in the first 15 seconds after cuff deflation divided by the flow during the resting (baseline) scan.

To assess the accuracy of detecting small changes in vessel diameter, a phantom was constructed that contained 10 “arteries” located 10 mm below the phantom surface. These arteries were measured (in millimeters) 2.8, 3.0, 3.2, 3.4, 3.6, 4.0, 4.1, 4.2, 4.3, and 4.4, mimicking the range of diameters of normal male and female brachial arteries, and were arranged in random order. Two operators scanned each artery three times, with the same instrument settings used during the clinical studies, with images recorded on super-VHS videotape for later off-line analysis. Four independent observers, who were unaware of the characteristics of the phantom, then analyzed each scan on three occasions, in random order. The three measurements made for each scan by each observer were averaged and rounded to the nearest 0.1 mm. The phantom therefore offers four pairs of arteries whose diameters differ by 0.1 mm and seven pairs of arteries whose diameters differ by 0.2 mm. Across 96 observations, a diameter difference of 0.1 mm was estimated accurately (as 0.1 mm) on 52% of occasions; it was underestimated by 0.1 mm on 21% and overestimated by 0.1 mm on 27% of occasions. Across 168 observations, a diameter difference of 0.2 mm was estimated accurately on 67% of occasions; it was underestimated by 0.1 mm on 17% and overestimated by 0.1 mm on 16% of occasions. The mean error for all measurements was <0.05 mm, and no estimate of diameter difference was >0.1 mm in error.

Salivary Cotinine Estimations

Salivary cotinine levels were measured in all the current smokers by a rapid gas–liquid chromatographic method, using a Hewlett-Packard model HP5990A gas chromatograph equipped with a nitrogen detector, as described elsewhere.

Statistics

Descriptive statistics are expressed as mean±SD. The control and smoking groups were compared using two-sample t tests. In the group of current smokers, the relation between pack years smoked and FMD was assessed by one-way ANOVA for the subgroups of very
light, light, moderate, and heavy smokers. The relation between flow-mediated or GTN-induced dilation and other variables was assessed by univariate and multivariate linear regression analysis, with pack years smoked treated as a continuous variable, first for the 80 current smokers only and then for all 200 subjects. The current and former smokers were compared using two-sample t tests. In addition, for the comparison of current and former smokers, multivariate analysis of predictors of FMD included age, sex, cholesterol, and vessel size as well as group (current or former smokers). Statistical significance was inferred at $P \leq .05$.

**Results**

**Control Subjects**

In 80 control subjects, baseline flow was 114±50 mL/min (range, 32 to 248 mL/min), and reactive hyperemia was 484±172% (range, 260% to 900%). The arteries dilated 10±3.3% (range, 4% to 22%) in response to this increase in flow. On multivariate analysis, FMD was correlated inversely with resting vessel diameter ($P=.015$) but not with subject age or cholesterol level. Four control subjects declined sublingual GTN; in the remaining 76, vessel dilation to GTN was 20.1±5.2% (range, 11% to 34%). GTN-induced dilation was also inversely correlated with vessel diameter ($P=.02$), with similar findings to those for FMD on multivariate analysis. The ratio of FMD to GTN-induced dilation was 0.52±0.20 (Table 1).

**Current Smokers**

Age, resting vessel size, cholesterol level, baseline flow, and degree of reactive hyperemia were similar in the smokers and the control subjects (Table 1). FMD was reduced or absent in most of the smokers (4.0±3.9%; range, 0% to 17%; $P<.0001$ compared with control subjects) (Fig 1). FMD was 3.0±2.8% in the male smokers and 5.3±5.9% in the female smokers. Dilation to GTN was also lower in the smoking group (17.0±5.8%; range, 7% to 34%; $P=.002$ compared with control subjects). The ratio of FMD to GTN-induced dilation was 0.24±0.19 ($P<.0001$ compared with control subjects). No subject had ultrasound evidence of narrowing or plaque in the vessel studied.

Subjects with a wide range of cigarette consumption were studied, with (a self-reported) pack year history of 1 to 75 pack years (mean, 19±12.0 for men and 13±8.8 for women; $P=.10$). Salivary cotinine levels measured on the day of study were 5 to 700 ng/mL. FMD was 6.6±4.0% (range, 1% to 17%) in very light smokers, 4.0±3.1% (range, 0% to 16%) in light smokers, 3.2±3.2% (range, 0% to 16%) in moderate smokers, and 2.6±1.2% in heavy smokers (range, 0% to 8%) ($P<.01$ compared with control subjects for all groups) (Fig 2). One-way ANOVA showed that FMD was significantly lower in heavier smokers ($P=.006$). Similar results were obtained when the male and female smokers were analyzed separately. On multivariate analysis of age, sex, vessel size, cholesterol, salivary cotinine, and

**Table 1. Vascular Study Results in 80 Adult Control Subjects, 80 Current Smokers, and 40 Former Smokers**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Subjects</th>
<th>Current Smokers</th>
<th>$P_1$</th>
<th>Former Smokers</th>
<th>$P_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>35.4±9.0</td>
<td>33.6±9.0</td>
<td>.23</td>
<td>38.1±8.4</td>
<td>.11</td>
</tr>
<tr>
<td></td>
<td>(34.28-42)</td>
<td>(30.27-42)</td>
<td></td>
<td>(37.31-45)</td>
<td></td>
</tr>
<tr>
<td><strong>Men: Women</strong></td>
<td>42:38</td>
<td>42:38</td>
<td></td>
<td>23:17</td>
<td>.77</td>
</tr>
<tr>
<td><strong>Cholesterol, mg/dL</strong></td>
<td>178±24</td>
<td>183±34</td>
<td>.32</td>
<td>190±14</td>
<td>.28</td>
</tr>
<tr>
<td></td>
<td>(181,164-205)</td>
<td>(185,158-218)</td>
<td></td>
<td>(192,169-212)</td>
<td></td>
</tr>
<tr>
<td><strong>Pack years</strong></td>
<td>0</td>
<td>16±15</td>
<td>&lt;.0001</td>
<td>13±13</td>
<td>.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(10,6-20)</td>
<td></td>
<td>(11,5-16)</td>
<td></td>
</tr>
<tr>
<td><strong>Salivary cotinine, ng/mL</strong></td>
<td>Not measured</td>
<td>273±190</td>
<td></td>
<td>Not measured</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(34,28-42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vessel size, mm</strong></td>
<td>3.55±0.6</td>
<td>3.70±0.7</td>
<td>.12</td>
<td>3.80±0.6</td>
<td>.51</td>
</tr>
<tr>
<td></td>
<td>(3.53,3.1-3.98)</td>
<td>(3.68,3.1-4.16)</td>
<td></td>
<td>(3.73,3.28-4.2)</td>
<td></td>
</tr>
<tr>
<td><strong>FMD, %</strong></td>
<td>10.0±3.3</td>
<td>4.0±3.9</td>
<td>&lt;.0001</td>
<td>5.1±3.8</td>
<td>.07</td>
</tr>
<tr>
<td></td>
<td>(9.5,7.8-11.4)</td>
<td>(3.4,1.0-5.8)</td>
<td></td>
<td>(4.9,1.2-8.5)</td>
<td></td>
</tr>
<tr>
<td><strong>GTN, %</strong></td>
<td>20.1±5.2</td>
<td>17.0±5.8</td>
<td>.002</td>
<td>17.4±5.8</td>
<td>.88</td>
</tr>
<tr>
<td></td>
<td>(20.2,14.9-23.8)</td>
<td>(17.0,11.9-20.7)</td>
<td></td>
<td>(17.2,12.6-21.6)</td>
<td></td>
</tr>
<tr>
<td><strong>FMD/GTN ratio</strong></td>
<td>0.52±0.20</td>
<td>0.24±0.19</td>
<td>&lt;.0001</td>
<td>0.30±0.20</td>
<td>.12</td>
</tr>
<tr>
<td></td>
<td>(0.52,0.31-0.73)</td>
<td>(0.22,0.02-0.42)</td>
<td></td>
<td>(0.30,0.11-0.54)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline flow, mL/min</strong></td>
<td>114±50</td>
<td>131±74</td>
<td>.10</td>
<td>123±88</td>
<td>.73</td>
</tr>
<tr>
<td></td>
<td>(109,75-151)</td>
<td>(116,75-184)</td>
<td></td>
<td>(121,64-182)</td>
<td></td>
</tr>
<tr>
<td><strong>Hyperemia, %</strong></td>
<td>484±172</td>
<td>471±181</td>
<td>.65</td>
<td>457±195</td>
<td>.61</td>
</tr>
<tr>
<td></td>
<td>(460,340-605)</td>
<td>(445,325-610)</td>
<td></td>
<td>(471,325-575)</td>
<td></td>
</tr>
</tbody>
</table>

Results are expressed as mean±SD (median, interquartile range). FMD indicates flow-mediated dilation; GTN, glyceryl trinitrate–induced dilation; $P_1$, comparison between control subjects and current smokers; and $P_2$, comparison between current and former smokers.

*As measured during the first (resting) scan.*
number of pack years smoked, only vessel size ($P = .01$) and total dose smoked (pack years) ($P = .05$) were related to impairment of FMD (Table 2).

GTN-induced dilation was $18.4 \pm 6.4\%$ (range, 7% to 28%) in very light smokers, $17.5 \pm 2.2\%$ (range, 9% to 29%) in light smokers, $17.8 \pm 5.7\%$ (range, 7% to 34%) in moderate smokers, and $15.5 \pm 5.6\%$ (range, 7% to 29%) in heavy smokers; ANOVA showed no significant association between GTN-induced dilation and total smoking dose as measured in pack years. On multivariate analysis of age, sex, vessel size, cholesterol, cotinine level, and total smoking dose, there was no significant association between GTN-induced dilation and either smoking dose or cotinine level.

**Former Smokers**

Average time since cessation of smoking was $6 \pm 3.8$ years (range, 3 months to 14 years) and was similar for men and women. Cigarette consumption had ranged from 1 to 75 pack years (mean, $15 \pm 14.1$ for men and $9 \pm 7.6$ for women; $P = .15$). Compared with the group of current smokers, the former smokers had similar age, sex distribution, cholesterol levels, number of pack years smoked, vessel sizes, baseline flows, and hyperemia values (Table 1). FMD for the overall group of former smokers was $5.1 \pm 4.0\%$ $(5.2 \pm 2.8\%$ for men and $5.1 \pm 5.2\%$ for women) and was not correlated with time since smoking cessation. GTN-induced dilation was $17.4 \pm 5.5\%$.

In a multivariate analysis comparing the 40 former and the 80 current smokers after adjustment for other variables, former smokers had higher FMD values ($P = .07$). When this analysis was performed for male subjects only, FMD was significantly higher in the former smokers ($P = .001$) (Fig 3); for female subjects, FMD was similar in both groups ($P = .24$).

**TABLE 2. Multivariate Regression Analysis for Determinants of Flow-Mediated Dilation in 80 Current Smokers**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Partial Regression Coefficient</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.11</td>
<td>.46</td>
</tr>
<tr>
<td>Sex</td>
<td>.05</td>
<td>.74</td>
</tr>
<tr>
<td>Vessel size</td>
<td>$-.36$</td>
<td>01</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>$-.04$</td>
<td>.75</td>
</tr>
<tr>
<td>Cotinine</td>
<td>$-.02$</td>
<td>.94</td>
</tr>
<tr>
<td>Pack years</td>
<td>$-.33$</td>
<td>.05</td>
</tr>
</tbody>
</table>

Intercept term, 11.3; F ratio, 4.3; probability level, .001.
analysis for GTN-induced dilation showed no significant difference by group (\(P=.73\)).

A multivariate analysis was also performed for determinants of FMD in all 200 subjects, excluding salivary cotinine as a variable, as it was only measured in the 80 current smokers. This analysis also showed a significant inverse correlation between pack years smoked and FMD (Table 3).

**Discussion**

Endothelium-dependent vasodilation is impaired in apparently healthy young adult smokers. Our data suggest that endothelial dysfunction may occur in the systemic arteries of even very light smokers from adolescence onward, although the likelihood of vascular physiological abnormalities increases with increasing total amount smoked.

In arteries lined by healthy endothelium, increased flow causes dilation of the vessel; this mechanism fails with endothelial dysfunction.\(^{18,19}\) In this study, endothelium-dependent (flow-mediated) dilation was significantly impaired in the group of smokers as a whole compared with control subjects, as was the ratio of flow-mediated to GTN-induced dilation. These data are consistent with an association between smoking and endothelial dysfunction. Other studies have demonstrated a direct toxic effect of tobacco smoke on human endothelium. Smoking two tobacco cigarettes approximately doubles the number of nuclear-damaged endothelial cells in circulating blood;\(^{5,20}\) whereas nontobacco cigarettes have little effect. In addition, pronounced degenerative changes of umbilical artery endothelium have been found at delivery in smoking but not non-smoking mothers.\(^{21}\) The mechanism of smoking-associated endothelial damage is not established but may be related to the effect of smoking on increasing platelet/vessel wall interactions\(^{22,23}\) and/or the inverse relation between cigarette consumption and plasma levels of high-density lipoprotein cholesterol.\(^{24-25}\)

Endothelium-independent vasodilation to GTN was also mildly impaired in smoking adults, suggesting that either less GTN is being delivered to the smooth muscle or that GTN is causing a decreased vasorelaxant effect; therefore, there may be a functional or structural abnormality in the arterial smooth muscle and/or the adventitia in these subjects. This is supported by previous studies showing that GTN-induced dilation is less in atherosclerotic arteries compared with control arteries\(^{26-28}\) and is even impaired in hypercholesterolemic patients with angiographically smooth arteries compared with arteries of control subjects.\(^{26}\) GTN-induced dilation is inversely related to vessel size,\(^{12,29}\) and so the impaired response to GTN in the smokers in our study may be partially due to the slightly larger arterial diameter observed in the group. It should be noted, however, that smooth muscle relaxation to GTN in all groups was sufficiently great to allow endothelium-dependent dilation to take place in response to increased flow.

The dose-dependence of smoking-related endothelial dysfunction supports a causative role for smoking in atherogenesis. We found a stronger association between impaired FMD and pack years smoked (reflecting chronic exposure) than an association with cotinine levels (reflecting acute exposure); therefore, it is unlikely that the effect of smoking on endothelial function

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**TABLE 3. Multivariate Regression Analysis for Determinants of Flow-Mediated Dilation In All 200 Subjects: 80 Control Subjects, 80 Current Smokers, and 40 Former Smokers**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Partial Regression Coefficient</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.10</td>
<td>.08</td>
</tr>
<tr>
<td>Sex</td>
<td>-.10</td>
<td>.20</td>
</tr>
<tr>
<td>Vessel size</td>
<td>-.39</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>.04</td>
<td>.59</td>
</tr>
<tr>
<td>Pack years</td>
<td>-.46</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Intercept term, 15.9; F ratio, 19.2; probability level, <.0001.
is an acute phenomenon. We have observed a threshold for smoking dose and endothelial dysfunction in that all subjects smoking $\geq 20$ pack years had reduced or absent FMD. In a pathological study of 390 young men (15 to 34 years of age), the prevalence of aortic atherosclerosis was strongly related to serum thiocyanate concentration, a marker of recent smoking.\textsuperscript{30} Besides endothelial damage, other mechanisms have been suggested as explanations for the association of smoking and vascular disease, including increased platelet adherence\textsuperscript{12} and aggregation,\textsuperscript{5} increased fibrinogen levels\textsuperscript{31} and decreased plasminogen levels,\textsuperscript{32} arterial spasm,\textsuperscript{33} and reduced capacity of the blood to deliver oxygen.\textsuperscript{34} These studies and our own observations confirm that smoking is an important causative agent for vascular disease and that the earliest structural and functional changes of atherosclerosis may be demonstrated in adolescent and young adult smokers. Although the overall number of smokers in society is decreasing, the high prevalence of regular smoking in young adults shows no sign of significant decline in the last decade.\textsuperscript{35} Our findings suggest that even light smoking at an early age may damage vascular endothelium.

Follow-up for many years would be required to show that young adult smokers with impairment of endothelium-dependent dilation will indeed go on to develop atherosclerosis. However, endothelial dysfunction is an early event leading to atherosclerosis, preceding occlusive vascular disease in both the experimental primate model\textsuperscript{36} and in human heart transplant recipients.\textsuperscript{37} Impaired endothelial function in early life results in abnormal reactions between the vessel wall and platelets and leukocytes, thereby promoting the atherogenic process.\textsuperscript{9}

We have previously described this noninvasive method for assessment of endothelial function in systemic arteries,\textsuperscript{12} based on high-resolution ultrasound and precise measurement of arterial diameter. The theoretical limit of resolution of 7.0 MHz ultrasound in the near field is approximately 0.1 to 0.2 mm (depending on the number of cycles in each ultrasound pulse),\textsuperscript{38} and the ultrasonic calipers are accurate to 0.1 mm. Our phantom experiments have demonstrated that changes in axial distance from the transducer of $\pm 0.1$ mm can be measured accurately. Furthermore, using a 7.0-MHz linear array transducer, we\textsuperscript{12} and others\textsuperscript{39,40} have reported a low coefficient of variation for measurements of arterial diameter (1% to 3% variation between observers) and a high correlation between consecutive control measurements made within a study. Therefore, the measured error (approximately 2%) is significantly less than the difference between smoking and control adults found in this study (approximately 6%).

We have found that endothelium-dependent dilation tended to be better in former than in current smokers, although FMD was not normal in either group. Similarly, a study of coronary arterial pathology demonstrated more severe atherosclerosis in current than nonsmokers, with former smokers having intermediate levels.\textsuperscript{41} These data are consistent with other studies suggesting that the effects of cigarette smoking on vascular physiology may be reversible.\textsuperscript{10,11} Epidemiological studies investigating patients with established atherosclerosis have indicated that the risk of subsequent cardiovascular events is lower in smokers who give up cigarettes\textsuperscript{10,11}; this may be mediated by a reversible effect of smoking on thrombogenesis and/or atherogenesis.\textsuperscript{11} The maximal potential for reversibility would be expected, however, with risk factor modification at a much earlier stage of the disease process, before plaques are established.\textsuperscript{42}

FMD was significantly higher in male former smokers compared with current smokers but not female smokers. Given that the male current smokers had lower FMD than female smokers (accounted for on multivariate analysis by higher pack year consumption and larger vessel size rather than by a sex difference), one may need a larger sample size of female former smokers to demonstrate a significant improvement toward normal. Nevertheless, the data on this small sample of former smokers suggests but does not show conclusively that endothelial function may improve with smoking cessation. The availability of a noninvasive method to perform serial studies of endothelial and smooth muscle function in asymptomatic young adults will allow prospective investigation of the reversibility of abnormal vascular physiology with smoking cessation, and such studies are being undertaken.

Acknowledgments

Dr Celermajer is supported by the British Heart Foundation, Dr Sorensen by the Danish Heart Foundation, and Dr Georgakopoulous by the European Society of Cardiology. This project was funded in part by a grant from Corda. The authors would like to thank Dr C. Feyerabend for performing salivary cotinine estimations and Miss Mary Jane Potter for assistance in preparation of the manuscript.

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Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults.

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Circulation. 1993;88:2149-2155
doi: 10.1161/01.CIR.88.5.2149

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