Effects of Smoking on Renal Hemodynamics in Healthy Volunteers and in Patients with Glomerular Disease

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Abstract. Patients with renal disease who smoke have a poor renal functional prognosis, but the mechanisms involved have not been explored. In this controlled study, the effects of smoking and sham smoking were compared in 15 healthy normotensive volunteers. All were occasional smokers and abstained from smoking for 48 h as documented by urinary cotinine measurements. These data were compared with those of seven patients with biopsy-confirmed IgA glomerulonephritis, also occasional smokers. Renal clearance examinations were obtained after hydration in the supine position before and while smoking two cigarettes or sham cigarettes in random order on 2 consecutive days. GFR and effective renal plasma flow were determined using In111-diethylenetriamine pentaacetic acid and 131I-hippurate with a dual tracer infusion clearance technique. In an ancillary study with six volunteers, the effect of smoking was compared with the effect of nicotine-containing chewing gum. In healthy volunteers, sham smoking caused a minor but significant increase of mean arterial pressure (MAP) and OFR with no significant change of effective renal plasma flow, filtration fraction (FF), or renovascular resistance. Smoking caused a significant and more marked increase of MAP (from baseline 92.8 ± 8.98 to 105 ± 7.78 mmHg) and heart rate (from 61.7 ± 7.52 to 86.4 ± 9.87 min⁻¹), accompanied by a significant increase in arginine vasopressin (from 1.27 ± 0.72 to 19.9 ± 27.2 pg/ml) and epinephrine (from 37 ± 13 to 140 ± 129 pg/ml). During smoking, GFR decreased in all but one volunteer (from 120 ± 17.7 to 102 ± 19.3 ml/min per 1.73 m²), and this was accompanied by a significant decrease of FF (from 21.3 ± 4.24 to 17.4 ± 3.41%) and an increase in renovascular resistance (from 97.6 ± 27.2 to 108 ± 30.4 mmHg · min/ml per 1.73 m²). These findings were reproduced with nicotine-containing chewing gum. In contrast, when patients with IgA glomerulonephritis smoked, a similar increment in MAP was noted, the changes of FF were not uniform, and a small but consistent increase of urinary albumin/creatinine ratio was observed. An additional 20 volunteers were subjected to the smoking arm of the study for statistical evaluation of the GFR change in patients. The difference between the change of GFR between all volunteers (n = 35) and patients (n = 7) was significant (P < 0.005). It is concluded that the known effects of smoking and nicotine on the sympathetic nervous system and on systemic hemodynamics are accompanied by significant acute changes in renal hemodynamics and albuminuria. These findings are of interest because of the known effects of smoking on progression of renal disease.

Smoking is a significant health hazard (1–3). It is amazing that, in contrast to the well known cardiovascular and oncogenic side effects, the adverse influence of smoking on the kidney has not attracted more interest (4,5). In subjects with primary hypertension, urinary albumin excretion, as an index of renal damage, is highly correlated with smoking (6,7). In patients with type I diabetes mellitus, the key observation of Christiansen of an increased renal risk of albuminuria in smokers (8) was confirmed by numerous subsequent investigators (9–11). The same holds true for patients with type II diabetes (12–15). In established diabetic nephropathy, the rate of progression to renal failure in smokers is higher by a factor of 2, and this is true for both type I and type II diabetes (16). Some information is also available in nondiabetic renal disease. In autosomal dominant polycystic kidney disease, Chapman et al. (17) found that patients with established proteinuria had a greater pack-year smoking history than their nonproteinuric counterparts. A retrospective cohort study of lupus nephritis patients documented that smoking at the time of onset of nephritis was an independent risk factor for accelerated progression to end-stage renal failure (18), and this effect was not explained by differences in hypertension or in immunosuppressive treatment. Finally, preliminary data from the MRFIT (multiple risk factor intervention trial) study indicated that the relative risk of end-stage renal failure was increased by a factor of 1.7 in subjects smoking 20 to 40 cigarettes per day (5).

The potential mechanisms underlying the deleterious effect of smoking on progression of renal disease have not been explored. To address this issue, we compared the acute effects of smoking versus sham smoking in healthy volunteers and in patients with IgA glomerulonephritis. All subjects were occasional smokers, i.e., less than five cigarettes per day, and had...
abstained for 48 h, as documented by cotinine measurements. Systemic hemodynamics (mean arterial pressure [MAP], heart rate) and renal hemodynamics (GFR, effective renal plasma flow [ERPF], filtration fraction [FF], renovascular resistance [RVR]), as well as albuminuria, were assessed in the two groups to identify the changes that occur during smoking.

Materials and Methods

Volunteers

Thirty-five healthy normotensive volunteers with a history of regular but limited cigarette consumption (<10/d) were recruited. There were 25 male and 10 female volunteers, ranging in age from 19 to 46 yr, none of whom used medication. Renal disease was excluded based on the history, physical examination, serum creatinine determination, urine analysis, and renal ultrasonography. Furthermore, seven patients with biopsy-confirmed IgA glomerulonephritis (4 men, three women, age 21 to 45 yr, serum creatinine 0.79 to 1.68 mg/dl, urinary protein 0.04 to 2.5 g/24 h) were examined. There was no evidence of acute exacerbation of glomerulonephritis. Two of these seven patients were hypertensive, but they were off medication 1 d before the study. Medication had included bisoprolol, hydrochlorothiazide, and felodipine. All patients were instructed to adhere to a dietary protein intake of approximately 0.8 g/kg per d.

Protocol

The protocol was approved by the local ethics committee. All subjects gave informed written consent. Both the consecutive 15 volunteers and all patients were exposed in random order on subsequent days to either sham smoking, i.e., sucking a dummy cigarette, or active smoking (Marlboro 100s filter cigarettes containing 1 mg of nicotine per cigarette). All individuals were instructed to stop smoking for 2 d before the study, and this was verified by measuring urinary cotinine concentrations (below 250 ng/ml in all). They were advised to drink approximately 700 ml of liquids before and 400 ml during the study. At 8 a.m., the subjects emptied their bladders and then rested in a supine position in a quiet room for 40 min. Subsequently, they smoked a first cigarette (or sham cigarette) for 10 min. After an interval of 6 min, they smoked a second cigarette (or sham cigarette) for 10 min. (The purpose of the second cigarette was to verify that changes with respect to baseline were consistent and reproducible. This was the case in all volunteers. All calculations were based on the results of the first cigarette. Patients smoked one cigarette only.) After the first 15 volunteers had been examined, 20 additional individuals completed the smoking arm of the study only.

For hormonal measurements, blood was taken at the beginning of the baseline and at the end of the second smoking period from indwelling catheters. Urine was collected at the beginning of the baseline period and at the end of the smoking period.

Ancillary Studies

To determine whether possible effects of cigarette smoking are provoked by nicotine, the effects of smoking and chewing a nicotine-containing chewing gum (Nicorette®, Pharmacia Co., Erlangen, Germany; 6 mg of nicotine) for 16 min were compared in six of the 15 healthy volunteers. This is known to cause a plasma nicotine level of approximately 15 ng/ml (information provided by the manufacturer). Hemodynamic measurements were made during steady-state conditions, which were reached 16 min after the volunteers had begun to chew the gum.

Measurements of Renal Hemodynamics

Using a single compartment dual-tracer infusion clearance and the tracers $^{131}$I-hippurate and $^{111}$In-diethylenetriamine penta-acetic acid (DTPA), we measured both GFR and ERPF in the supine position using the method of Pedersen et al. (19). The clearance examination of subjects began 40 min after simultaneous intravenous injection of 120 μCi $^{131}$I-hippurate and 120 μCi $^{111}$In-DTPA.

A superficial vein of the right arm was used for a continuous infusion clearance. Both tracers were monitored by two scintillation probes placed over the right and left shoulder of each individual. This site is selected because of the large vessels in the probe's field of view. Each detector monitored one of the two radioisotopes by means of energy discrimination. The signals monitored by the probes activated an infusion pump system via feedback control. Two pumps were used, one of which contained $^{131}$I-hippurate, the other $^{111}$In-DTPA. A separate step motor drove the pumps, whereby steady-state conditions were reached. The data from the first 10 min of the clearance examination were discarded, because this time was required to equilibrate the feedback control system. At the end of the baseline clearance period, 10 ml of blood were drawn from the cubital vein of the contralateral arm to obtain a plasma sample. A probe from the infused saline containing each isotope served as standard. A microcomputer registered the motor step rates, documented the serum activity level of each isotope in the probe’s field of view, and carried out the clearance calculations after the activity of the standard and the serum sample had been registered. By using these data, the clearance was calculated using the equation:

$$CI = \frac{I \times A_m}{A_{pl}}$$

where $CI$ is the clearance (ml/min), $I$ is the number of motor steps per time (min$^{-1}$), $A_m$ is activity pumped per motor step (μCi), and $A_{pl}$ is specific activity of plasma (μCi/ml).

The clearance was calculated for 10-min (or for pauses 6-min) time intervals. These separate GFR and ERPF values were then used to compute a mean clearance for any appropriate time interval studied, such as resting and smoking or sham smoking.

Single compartment infusion clearance measurements are highly reproducible. Phantom studies showed that clearance values varied less than 5% in consecutive measurements. Head-on comparison between classical clearance based on urine collection and infusion clearance in the same individual had shown that the measured clearance values differ on average by 8.4% and no more than 11% in individuals with a GFR >50 ml/min (20). This was now reconfirmed. Clearance values (GFR) based on urine collection (without catheterization relying on spontaneous voiding) and single compartment infusion clearance were compared in five individuals studied for 75 min. Clearance based on urine collection was 105 ± 6.51 ml/min and infusion clearance 96.2 ± 10.2 ml/min, the former being slightly, but consistently, higher by an average of 10% (2 to 20%).

Ancillary Measurements

BP and pulse were monitored using Dinamap (R. Criticon, Inc., Tampa, FL). Other measurements included: urinary sodium and creatinine, by Autoanalyzer; cotinine in urine according to the method of Langone et al. (21); active renin by immunoradiometric assay using Renin III generation assay of Diagnostics Pasteur (Paris, France) (22); epinephrine according to a two-step extraction and separation with a cation-exchange HPLC system (Nucleosil 10 SA, Latek Co., Heidelberg, Germany), and subsequent determination as performed by Smedes et al. (23) using electrochemical detection for quantification.
(detection limit 0.1 nmol/L); arginine vasopressin (AVP) with RIA using $^{125}$I-Arg$^8$-vasopressin (New England Nuclear, Dupont Co., Dreieich, Germany), according to Rascher et al. (24); and urinary albumin by laser nephelometry (13).

**Statistical Analyses**

Data are given as mean ± SD. To avoid the problem of multiple testing (Bonferroni), only a few parameters were defined as primary end points for statistical analysis (GFR, ERPF, and FF). In each individual, the mean value for each phase of the examination in the smoking and sham smoking arms was compared using the paired $t$ test. Relative changes (in percentages) between two subsequent periods were also compared, using the paired $t$ test. Comparisons between patients and volunteers were made for the respective periods of the examination using the unpaired $t$ test. For the beta-error analysis to assess the power of the study to detect differences between all volunteers ($n = 35$) and patients ($n = 7$), normality of values was assessed and confirmed in both groups by normal probability plot. For comparison of the change in GFR, it was established that variances in the two groups were approximately equal ($F$ test). One-sided unpaired $t$ test was used.

**Results**

**Effects of Sham Smoking and Smoking in Healthy Volunteers**

Sham smoking caused a minor but significant increase in MAP, but no significant change in heart rate (Table 1), norepinephrine, epinephrine, AVP, or plasma renin activity (PRA) (Table 2). In contrast, smoking caused a major increase of systolic BP and MAP (Table 1), which was accompanied by a significant increase in heart rate, epinephrine, and AVP concentrations, a tendency for an increase in norepinephrine concentrations, and a decrease in PRA (Table 2). Marked interindividual differences in the epinephrine response to smoking were noted: Some individuals exhibited a pronounced increase, whereas many remained below the detection limit.

During sham smoking, in parallel with higher BP, GFR increased slightly with no significant change in ERPF and FF (Table 3). In contrast, smoking caused a highly significant decrease in GFR. The average reduction during the 10-min smoking period was $-15\%$. These changes were consistently noted during the second smoking period as well. The decrease in GFR was accompanied by a decrease in the FF and by an increase in RVR. Urine albumin excretion was below the detection threshold in these hydrated individuals, both before and after smoking.

To obtain more statistical power for comparison between volunteers and patients, an additional 20 volunteers were studied in the smoking arm of the protocol only. The results in the first 15 volunteers were perfectly reproducible, e.g., in the overall cohort of 35 volunteers (baseline versus smoking), MAP increased from $93.5 \pm 8.4$ to $103 \pm 8.3$ mmHg; GFR decreased from $115 \pm 15.2$ to $97.3 \pm 16.9$ ml/min per 1.73 m$^2$; and FF decreased from $21.4 \pm 4.21$ to $17.3 \pm 33\%$. The power analysis is given below.

**The Effect of Chewing a Nicotine-Containing Gum on Renal Hemodynamics in Healthy Volunteers**

To examine whether the changes induced by smoking can be reproduced solely by nicotine, six of the 15 volunteers had a third study period during which they chewed nicotine gum. In principle, all findings seen with cigarette smoking were reproduced by the nicotine-containing gum (Table 4).

**The Effects of Sham Smoking and Smoking on Systemic and Renal Hemodynamics in Patients with IgA Glomerulonephritis**

Sham smoking caused no significant changes in renal or systemic hemodynamics. The effects of smoking on MAP and heart rate were comparable in patients with IgA glomerulonephritis and control subjects (Table 5). In contrast, the direction of change of GFR, ERPF, and FF varied considerably between individuals. As a result, the mean values were not significantly different between the baseline and the smoking periods. Although FF decreased rather consistently in healthy volunteers, i.e., the changes within individuals, the direction of change of FF was inconsistent in subjects with IgA glomerulonephritis.

In contrast to the healthy volunteers, smoking failed to cause a decrease of GFR in the seven patients with IgA glomerulonephritis. Beta-error analysis comparing the GFR change in the smoking arm of the study between all 35 volunteers and seven patients showed that the study had 95% power to detect a 25% difference in the change of GFR between the groups at a significance level of $P < 0.005$. In the patients there was a

| Table 1. Effects of sham smoking and smoking on systemic circulation in 15 healthy volunteers$^a$ |
|---|---|---|---|
| Period | Min | Sham Smoking | Smoking |
| | | MAP (mmHg) | HR (min$^{-1}$) | MAP (mmHg) | HR (min$^{-1}$) |
| Basal | 30 | 93.2 ± 10.9 | 64.2 ± 8.56 | 92.8 ± 8.98 | 61.7 ± 7.52 |
| Cigarette | 10 | 95.6 ± 10.6$^b$ | 64.6 ± 6.94 | 105 ± 7.78$^c$ | 86.4 ± 9.87$^d$ |
| Pause | 6 | 94.9 ± 12.9 | 64.6 ± 6.97 | 102 ± 7.18 | 82.0 ± 9.05 |
| Cigarette | 10 | 95.1 ± 10.7 | 64.5 ± 8.92 | 104 ± 7.55 | 82.5 ± 8.49 |

$^a$ Min, minutes; MAP, mean arterial pressure; HR, heart rate.

$^b$ $P < 0.05$, intraindividual differences basal versus sham smoking by paired $t$ test.

$^c$ $P < 0.0001$, intraindividual differences basal versus smoking by paired $t$ test.

$^d$ $P < 0.001$, intraindividual differences basal versus smoking by paired $t$ test.
Table 2. Hormonal changes during smoking in healthy volunteers

<table>
<thead>
<tr>
<th>Period</th>
<th>Norepinephrine (pg/ml)</th>
<th>Epinephrine (pg/ml)</th>
<th>AVP (pg/ml)</th>
<th>Active Renin (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham Smoking</td>
<td>Smoking</td>
<td>Sham Smoking</td>
<td>Smoking</td>
</tr>
<tr>
<td>Basal</td>
<td>325 ± 129</td>
<td>293 ± 124</td>
<td>29.0 ± 10.0</td>
<td>37.0 ± 13.0</td>
</tr>
<tr>
<td>Cigarette</td>
<td>332 ± 127</td>
<td>348 ± 128</td>
<td>27.0 ± 11.0</td>
<td>140 ± 129b</td>
</tr>
</tbody>
</table>

a AVP, arginine vasopressin.
b P < 0.01, intraindividual differences basal versus smoking by paired t test.
c P < 0.001 by Wilcoxon test for paired differences.
d Median, 4.00 pg/ml; range, 0.90 to 83.9 pg/ml.

Table 3. Renal hemodynamics during sham smoking and smoking in 15 healthy volunteers

<table>
<thead>
<tr>
<th>Period</th>
<th>Min</th>
<th>GFR (ml/min per 1.73m²)</th>
<th>ERPF (ml/min per 1.73m²)</th>
<th>FF (%)</th>
<th>RVR (mmHg · min/ ml · 1.73m²)</th>
<th>GFR (ml/min per 1.73m²)</th>
<th>ERPF (ml/min per 1.73m²)</th>
<th>FF (%)</th>
<th>RVR (mmHg · min/ ml · 1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sham Smoking</td>
<td>Smoking</td>
<td></td>
<td></td>
<td>Sham Smoking</td>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>30</td>
<td>116 ± 14.9</td>
<td>603 ± 114</td>
<td>20.0 ± 2.94</td>
<td>100 ± 39.1</td>
<td>120 ± 17.7</td>
<td>587 ± 91.7</td>
<td>21.3 ± 4.24</td>
<td>97.6 ± 27.2</td>
</tr>
<tr>
<td>Cigarette</td>
<td>10</td>
<td>130 ± 21.8b</td>
<td>627 ± 105</td>
<td>22.3 ± 6.40</td>
<td>84.8 ± 25.0</td>
<td>102 ± 19.3c</td>
<td>603 ± 84.9</td>
<td>17.4 ± 3.41c</td>
<td>108 ± 30.4d</td>
</tr>
<tr>
<td>Pause</td>
<td>6</td>
<td>109 ± 34.3</td>
<td>604 ± 135</td>
<td>18.7 ± 5.46</td>
<td>95.2 ± 40.3</td>
<td>111 ± 23.7</td>
<td>587 ± 103</td>
<td>19.2 ± 2.81</td>
<td>101 ± 25.8</td>
</tr>
<tr>
<td>Cigarette</td>
<td>10</td>
<td>111 ± 18.3</td>
<td>618 ± 113</td>
<td>19.1 ± 4.01</td>
<td>95.4 ± 34.8</td>
<td>100 ± 20.0</td>
<td>577 ± 98.0</td>
<td>17.8 ± 2.49</td>
<td>111 ± 44.3</td>
</tr>
</tbody>
</table>

a ERPF, effective renal plasma flow; FF, filtration fraction; RVR, renovascular resistance.
b P < 0.007, intraindividual differences basal versus sham smoking by paired t test.
c P < 0.001, intraindividual differences basal versus smoking by paired t test.
d P < 0.006, intraindividual differences basal versus smoking by paired t test.

Discussion

In view of the known increase of renal risk conferred by smoking (4,5,8–17), it is of interest to analyze the mechanisms by which smoking affects the kidney. Smoking is known to activate the sympathetic nervous system (25) and to induce secretion of AVP (26). Although the ensuing antidiuresis is well known (27) and has been investigated in detail (28), potential renal hemodynamic effects of smoking in humans have remained largely unexplored.

The main result of the present study is the observation that in healthy individuals, smoking causes an acute decrease in GFR and FF in parallel with an increase in BP and heart rate associated with sympathetic activation. The effect appears to be mediated by nicotine per se, because it could be reproduced by chewing a nicotine-containing gum. This observation excludes a number of other mechanisms that have been discussed to explain effects of smoking, e.g., damage to endothelial cells or microcirculatory disturbances (29–33). We acknowledge, however, that in the genesis of chronic renal effects of smoking, such additional pathomechanisms may definitely play a role.

Smoking accelerates progression of renal disease, as documented by several clinical observations (4,5,8–17). Consequently, it seemed of interest to investigate whether in patients with primary glomerular disease the renal hemodynamic changes induced by smoking were similar compared with volunteers. To address this issue, we studied seven patients with IgA glomerulonephritis, occasional smokers with normal or slightly reduced renal function who had no acute glomerulonephritic episodes at the time of the study. In contrast to the volunteers, no consistent reduction of GFR and FF was seen despite a similar significant increase in systemic BP. We acknowledge that the group sizes were unbalanced, but beta-error analysis showed that the design had sufficient power to detect meaningful differences. It is obvious, then, that the renal hemodynamic effect of smoking is different in healthy individuals and in renal patients, but the precise hemodynamic details will have to be worked out in animal studies. One finding that would be in line with an injurious effect of smoking on glomerular microcirculation and permselectivity is the significant increase in norepinephrine concentration (from 276 ± 184 to 392 ± 215 pg/ml; P < 0.05) and a tendency for an increase in epinephrine (from 20.9 ± 26.8 to 34.0 ± 42.9 pg/ml).

Smoking was accompanied by a minor, but consistent and significant (P < 0.05) increase in urinary albumin/creatinine ratio in all six patients investigated (one female patient refused), i.e., from a median of 55.5 (range, 2.7 to 547) to 74.3 (range, 2.8 to 570) [albumin (mg/L):creatinine (mg/L) × 100]. The finding was replicated and confirmed in the individual patients on two separate occasions.

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Table 4. Comparison of renal hemodynamics between smoking and chewing a nicotine-containing gum in six healthy volunteersa

<table>
<thead>
<tr>
<th>Period</th>
<th>Min</th>
<th>GFR (ml/min per 1.73 m²)</th>
<th>FF (%)</th>
<th>MAP (mmHg)</th>
<th>HR (min⁻¹)</th>
<th>GFR (ml/min per 1.73 m²)</th>
<th>FF (%)</th>
<th>MAP (mmHg)</th>
<th>HR (min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>30</td>
<td>125 ± 19.2</td>
<td>19.6 ± 4.09</td>
<td>87.4 ± 4.20</td>
<td>61.4 ± 7.44</td>
<td>126 ± 18.3</td>
<td>22.0 ± 1.54</td>
<td>91.8 ± 6.20</td>
<td>63.0 ± 6.75</td>
</tr>
<tr>
<td>Cigarette</td>
<td>10</td>
<td>107 ± 14.9b</td>
<td>16.1 ± 3.15b</td>
<td>99.7 ± 6.26c</td>
<td>81.8 ± 11.0c</td>
<td>110 ± 13.6b</td>
<td>19.6 ± 1.55b</td>
<td>99.6 ± 4.22c</td>
<td>77.2 ± 10.9c</td>
</tr>
</tbody>
</table>

a Abbreviations as in Tables 1 and 3.
b P < 0.05, intraindividual differences basal versus smoking by paired t test.
c P < 0.01, intraindividual differences basal versus chewing by paired t test.

Table 5. Renal and systemic hemodynamics during sham smoking and smoking in seven patients with IgA glomerulonephritisa

<table>
<thead>
<tr>
<th>Period</th>
<th>Min</th>
<th>GFR (ml/min per 1.73 m²)</th>
<th>ERPF (ml/min per 1.73 m²)</th>
<th>FF (%)</th>
<th>RVR (mmHg·min/ ml·1.73 m²)</th>
<th>MAP (mmHg)</th>
<th>HR (min⁻¹)</th>
<th>GFR (ml/min per 1.73 m²)</th>
<th>ERPF (ml/min per 1.73 m²)</th>
<th>FF (%)</th>
<th>RVR (mmHg·min/ ml·1.73 m²)</th>
<th>MAP (mmHg)</th>
<th>HR (min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>30</td>
<td>101 ± 16.7</td>
<td>575 ± 53.5</td>
<td>19.6 ± 2.7</td>
<td>100 ± 7.06</td>
<td>92.6 ± 11.0</td>
<td>58.6 ± 8.23</td>
<td>109 ± 18.3</td>
<td>584 ± 88.3</td>
<td>19.8 ± 4.14</td>
<td>97.9 ± 17.6</td>
<td>92.3 ± 12.1</td>
<td>57.9 ± 7.53</td>
</tr>
<tr>
<td>Cigarette</td>
<td>10</td>
<td>104 ± 41.1</td>
<td>570 ± 141</td>
<td>19.2 ± 4.07</td>
<td>97.3 ± 22.4</td>
<td>93.0 ± 11.4</td>
<td>59.4 ± 10.5</td>
<td>111 ± 34.0</td>
<td>600 ± 125</td>
<td>18.9 ± 6.32</td>
<td>116 ± 38.6</td>
<td>105 ± 13.0b</td>
<td>74.3 ± 6.08c</td>
</tr>
</tbody>
</table>

a Abbreviations as in Tables 1 and 3.
b P < 0.005, intraindividual differences basal versus smoking by paired t test.
c P < 0.001, intraindividual differences basal versus smoking by paired t test.
consistent and reproducible, although modest, increase of the urinary albumin/creatinine ratio in patients with glomerular disease.

As for the exact intrarenal hemodynamic changes taking place, we wish to refrain from speculation. It is of interest, however, that in agreement with previous observations we noted an acute increase in BP (34,35) and of sympathetic tone (25). (The increase in BP and in catecholamine levels was similar in patients with glomerulonephritis.) We ascribe the decrease in PRA to the increase in BP. More detailed measurements of systemic hemodynamics have previously shown that cigarette smoking causes a dose-dependent concomitant increase of cardiac output and of peripheral resistance (36–38). The increase in cardiac output is mainly due to tachycardia with only modest changes in stroke volume (38). Whether the increase in vascular resistance is of similar magnitude in all vascular beds, or whether the renal circulation is particularly sensitive to the effects of smoking, remains to be established.

We considered a number of potential artefacts when designing the present study. We were afraid that smoking would induce a number of untoward autonomic responses in nonsmokers, which could confound the results. On the other hand, it appeared difficult to draw adequate conclusions from studies of heavy smokers in whom persistent effects of preceding smoking might not have been adequately washed out. For this report, we decided to study casual smokers with limited cigarette consumption (<10/d) who had abstained from smoking for at least 48 h. The latter was documented by urinary cotinine measurements.

We also considered that conditioned responses might be involved during smoking. To exclude such nonpharmacologic effects of smoking, we included a sham smoking arm in the study. This cautionary measure was well justified: The observation of minor, but consistent, changes in BP and GFR show that sham smoking is not neutral with respect to hemodynamic responses.

Only a few animal experiments on the renal effects of smoking are available (4). In the study of Pawlick et al. (39), anesthetized dogs were examined under three sets of conditions. Nicotine was infused into the renal artery of untreated animals, of animals after pretreatment with propranolol, and of animals subjected to bilateral adrenalectomy. Nicotine increased urine flow rate, electrolyte excretion (Na, Cl), and GFR of control dogs, whereas it decreased urine flow rate, electrolyte excretion, and GFR in dogs pretreated with propranolol or having undergone adrenalectomy. The authors concluded that nicotine was saluretic and diuretic by releasing catecholamines acting on the kidney via beta-adrenergic receptors. Additional studies using adrenoreceptor blockers in humans will be necessary to prove or refute this hypothesis.

We conclude that in healthy individuals, smoking exerts potent and consistent effects on glomerular function, as reflected by a decrease of GFR and FF. The renal hemodynamic response in subjects with glomerular disease is more variable and is accompanied by an increase in albuminuria. In both groups, smoking increased systemic BP (34,35,40), a known promoter of renal injury.

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