

Original Paper

# Associations of Smoking with Alterations in Renal Hemodynamics May Depend on Sex – Investigations in Potential Kidney Donors

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## Key Words

Smoking • Renal hemodynamics • Effective renal plasma flow • Glomerular hydrostatic pressure

## Abstract

**Background/Aims:** Cigarette smoking is a risk factor for renal damage, but little is known about subclinical effects of smoking on renal hemodynamics and parameters of renal function in humans. We examined the associations of smoking with systemic and renal hemodynamics and renal function parameters in healthy individuals. **Methods:** Data from 196 potential living kidney donors were analysed retrospectively. Mean arterial blood pressure (MAP), effective renal plasma flow (ERPF) and creatinine clearance had been measured. We additionally calculated parameters of renal hemodynamics. Data were analyzed for the effects of smoking and sex dependent on age and MAP. **Results:** Systemic and renal hemodynamic parameters did not differ between smokers and non-smokers. In non-smokers of both sexes MAP was negatively correlated with ERPF, and higher MAP was associated with increased renal vascular resistance and with afferent arteriolar resistance, with glomerular pressure ( $P_G$ ) remaining constant. However, in male, but not in female smokers, ERPF and  $P_G$  increased with MAP. A correlation of age with a steeper decline in ERPF in male smokers was lost in multiple regression analysis. **Conclusions:** As compared to women, smoking men may exhibit an increased glomerular hydrostatic pressure, which is a known promoter of kidney damage.

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## Introduction

Cigarette smoking is one of the major self-inflicted cardiovascular risk factors increasing the risk of premature morbidity and mortality [1-3]. Previous studies have demonstrated that adverse cardiovascular effects of smoking go hand in hand with renal function impairment, independent of underlying renal disease [4-6], and accelerate deterioration of renal function to end-stage renal failure [7, 8]. Mechanisms underlying smoking-induced renal impairment are not completely understood. However, endothelial injury promoted by smoking as well as atherosclerotic changes, have been recognized as two major factors [9, 10]. Increased microalbuminuria- and proteinuria-rates representing significant and early indicators of renal damage have repeatedly been related to chronic cigarette smoking [11-13]. It has also been shown that cigarette smoking has acute as well as chronic effects on systemic and renal hemodynamics. Long-term smoking has been associated with elevated blood pressure and reduced renal plasma flow [14-18]. Acute nicotine application induces an increase in arterial blood pressure as well as an alteration in renal function and hemodynamics [19, 20]. These findings indicate alterations of renovascular responses to increases in blood pressure in chronic smokers. There is little data regarding the effects of chronic cigarette smoking on renal hemodynamics and function in otherwise healthy individuals, but the existing evidence supports the concept of a detrimental influence of cigarette smoking on kidney function [21]. Advancing age and sex are well known factors in renal function decline and progression of renal disease, which need to be considered when effects of smoking are investigated [22, 23].

Therefore, to clarify the role of chronic smoking on renal function in a healthy, normotensive population and to determine its effects on renal hemodynamic parameters, we assessed the interaction between systemic blood pressure and renal hemodynamics as well as functional parameters in smokers and non-smokers dependent on age and sex.

## Materials and Methods

### *Study population*

Medical records of 196 individuals (n = 124 women, 72 men) aged 27 to 70 years (mean age  $\pm$ SD 46.7  $\pm$ 10.9 years) included in the living kidney donor program at Essen University Hospital, Germany, between 1998 and 2010, were reviewed retrospectively. Prior to kidney donation all potential donors underwent extensive diagnostic procedures to exclude relevant renal and extra-renal diseases. Individuals with renal insufficiency or a history of hypertension, cardiovascular disease, diabetes mellitus, metabolic syndrome or malignancies were excluded from the living kidney donor program [24]. Smoking status and habits were quantified based on self-report. Of the 196 individuals 37 % (n = 43 women, 29 men) were chronic smokers, which is in agreement with the smoking prevalence seen in Western Europe [25]. For the purpose of this study chronic smoking was defined as a habit of long term regular smoking of at least one cigarette on a daily basis [26]. Demographic characteristics as well as clinical and laboratory data of the selected subjects are shown in table 1. If multiple test results were present, those closest to kidney donation were analysed.

### *Blood pressure and laboratory measurements*

Ambulatory 24-hour blood pressure (BP) registrations were performed with an oscillometric device (Mobil-O-Graph® Holter-RR 24 h ABP-Monitor, I.E.M. GmbH, Stolberg Germany). Venous blood samples were collected for analysis of routine blood parameters.

### *Renal hemodynamic parameters and renal function*

Effective renal plasma flow (ERPF) was assessed via  $^{99m}\text{Tc}$ -mercaptoacetyltriglycine- ( $^{99m}\text{Tc}$ -MAG<sub>3</sub>) and  $^{131}\text{I}$ -hippuran- ( $^{131}\text{I}$ -OIH) clearance-measurements.  $^{99m}\text{Tc}$ -MAG<sub>3</sub>- and  $^{131}\text{I}$ -OIH clearance values are known to show a highly significant correlation (in our case R = 0.98, P < 0.001), with a  $^{99m}\text{Tc}$ -MAG<sub>3</sub>/ $^{131}\text{I}$ -OIH clearance ratio of approximately 0.60 [27]. We observed similar results when correlating ERPF estimated from  $^{99m}\text{Tc}$ -MAG<sub>3</sub>- and by  $^{131}\text{I}$ -OIH-clearance, respectively, and therefore decided only to present correlation analyses with ERPF estimated by  $^{99m}\text{Tc}$ -MAG<sub>3</sub>-clearance.

**Table 1.** Clinical characteristics and surrogate parameters for cardiovascular risk (group mean averages ± SD) in total and separately for men and women. Abbr.: BMI = Body Mass Index, MAP = Mean Arterial Pressure, BP = Blood Pressure, HDL = High Density Lipoprotein

Parameter	Total	Women	Men	t-Test
	n= 196	n= 124 (63%)	n=72 (37%)	P
Age (years)	46 ± 10	47 ± 10	42 ± 10	0.001
BMI (kg/m <sup>2</sup> )	25.5 ± 4	25.3 ± 5	25.9 ± 3	ns
MAP (mmHg)	85 ± 6	84 ± 6	87 ± 5	0.007
Systolic BP (mmHg)	115 ± 8	114 ± 8	117 ± 7	0.03
Diastolic BP (mmHg)	71 ± 6	70 ± 6	72 ± 6	0.03
Heart rate (bpm)	74 ± 11	73 ± 10	74 ± 13	ns
Plasma total cholesterol (mg/dL)	217 ± 40	217 ± 39	218 ± 41	ns
Plasma HDL cholesterol (mg/dL)	59 ± 8	63 ± 16	50 ± 14	<0.001
Fasting glucose (mg/dL)	90 ± 8	89 ± 7	90 ± 9	ns

Glomerular filtration rate (GFR) was calculated using the endogenous creatinine-clearance. This was determined from the 2x2-hour urinary creatinine excretion rate divided by plasma creatinine concentration. Both GFR and ERPF values were corrected for standard body surface area (1.73 m<sup>2</sup>). The filtration fraction (FF) was calculated as the ratio of GFR and ERPF and is expressed in percent [28]. Renal vascular resistance (RVR) was calculated as the ratio of mean arterial blood pressure (MAP) to ERPF [29]. Intrarenal hemodynamics, such as glomerular hydrostatic pressure (P<sub>G</sub>), afferent (R<sub>A</sub>) and efferent (R<sub>E</sub>) arteriolar resistance, cannot be measured directly in humans. They were therefore calculated according to the formulae established by Gomez et al. [30, 31], (Abbreviations see page 619):

$$P_G = \frac{GFR}{K_{FG}} + H_T + 5 \times \left( \frac{TP}{FF} \times \log e \frac{1}{1-FF} - 2 \right)$$

$$R_A = \frac{MAP - P_G}{ERBF} \times 1328 \quad (1328 = \text{conversion factor})$$

$$R_E = \frac{GFR}{K_{FG} \times (ERBF - GFR)} \times 1328$$

#### Statistical analysis

Analyses were performed using SPSS Software (release 17.0; SPSS Inc., Chicago, IL, USA). Quantitative data are expressed as mean ± standard deviation and as n (%) for categorical variables. Data were analysed for the influence of chronic smoking habits in the total study population as well as in men and women, respectively. T-tests were used to compare the differences of variables between population groups. In smokers and non-smokers overall and subdivided according to sex, linear univariate regression analyses were performed to test correlations between renal function and renal hemodynamic parameters with age and MAP. A multiple linear regression test was then used to evaluate the relationship between ERPF and MAP, after adjusting for age and sex in non-smokers and smokers. P-values of ≤0.05 were considered statistically significant.

## Results

### Patients' cohorts

Screening data from 196 potential living kidney donors (total cohort n = 196, mean age 46 ± 10 years; women n = 124, 47 ± 10 years; men n = 72, 42 ± 10 years) were included in the analyses.

### Demographic characteristics of the total cohort and according to sex

Demographic data as well as surrogate parameters for cardiovascular risk of the total cohort and separately for men and women are summarized in table 1: Men were significantly younger than women and had higher blood pressure and lower HDL cholesterol. There was no significant difference in body mass index, heart rate, total cholesterol and fasting glucose between the sexes. Smoking prevalence and number of pack years were similar in men and women. 72 of 196 individuals were chronic smokers (37% of the total cohort; 35% of men, and 38% of women).

**Table 2.** Summary of clinical characteristics (group mean averages  $\pm$ SD) for non-smokers and smokers, with subgroups for men and women. Abbr.: \* = percent of total population, § = percent of smokers, nSm = Non Smoker, Sm = Smoker, BMI = Body Mass Index, MAP = Mean Arterial Pressure, BP = Blood Pressure, HDL = High Density Lipoprotein

Parameter	Non Smoker (nSm)			Smoker (Sm)			t-Test				
	All n=124 (65%)	Women (a) n=81 (65%)	Men (b) n=43 (35%)	All n=72 (37%*)	Women (c) n=43 (60%§/ 38%*)	Men (d) n=29 (40%§/ 35%*)	P nSm vs. Sm	P (a) vs. (b)	P (a) vs. (c)	P (c) vs. (d)	P (b) vs. (d)
Age (years)	46 $\pm$ 10	48 $\pm$ 10	42 $\pm$ 10	45 $\pm$ 10	46 $\pm$ 10	42 $\pm$ 10	ns	0.002	0.03	ns	ns
BMI (kg/m <sup>2</sup> )	26.2 $\pm$ 4	26.1 $\pm$ 4	26 $\pm$ 3	24.8 $\pm$ 3	24.8 $\pm$ 4	25.0 $\pm$ 3	ns	ns	ns	0.04	ns
Pack years				18 $\pm$ 9	17 $\pm$ 9	21 $\pm$ 10			ns		
MAP (mmHg)	85 $\pm$ 6	84 $\pm$ 6	88 $\pm$ 5	85 $\pm$ 6	85 $\pm$ 7	85 $\pm$ 5	ns	0.001	ns	ns	0.005
Systolic BP (mmHg)	115 $\pm$ 8	114 $\pm$ 8	120 $\pm$ 6	115 $\pm$ 8	115 $\pm$ 9	114 $\pm$ 7	ns	0.001	ns	ns	0.008
Diastolic BP (mmHg)	71 $\pm$ 6	70 $\pm$ 10	74 $\pm$ 5	70 $\pm$ 6	70 $\pm$ 6	70 $\pm$ 5	ns	0.002	ns	ns	0.009
Heart rate (bpm)	74 $\pm$ 11	75 $\pm$ 9	74 $\pm$ 13	73 $\pm$ 11	71 $\pm$ 9	74 $\pm$ 13	ns	ns	ns	ns	ns
Plasma total cholesterol (mg/dL)	221 $\pm$ 38	220 $\pm$ 40	222 $\pm$ 35	213 $\pm$ 41	211 $\pm$ 38	215 $\pm$ 50	ns	ns	ns	ns	ns
Plasma HDL cholesterol (mg/dL)	59 $\pm$ 15	63 $\pm$ 15	51 $\pm$ 12	58 $\pm$ 18	64 $\pm$ 18	48 $\pm$ 15	ns	<0.001	<0.001	ns	ns
Fasting glucose (mg/dL)	90 $\pm$ 8	90 $\pm$ 7	91 $\pm$ 8	89 $\pm$ 8	89 $\pm$ 2	90 $\pm$ 9	ns	ns	ns	ns	ns

*Demographic characteristics according to smoking status and sex*

Table 2 shows cardiovascular and metabolic variables for the subgroups of non-smokers and smokers in total and separately for men and women. Taken as a whole, smokers did not differ from non-smokers with regard to age, body mass index, systemic hemodynamics, lipid status and fasting glucose levels. Both non-smoking and smoking men were younger than women in the respective subgroups. In non-smokers blood pressure was higher in men. There was no sex-dependent difference in blood pressure values in smokers.

*Renal hemodynamics of the total cohort and according to sex*

Table 3 presents renal hemodynamics and renal function parameters for the total cohort and separately for men and women. Men had higher values for plasma creatinine, creatinine clearance, filtration fraction, <sup>99m</sup>Tc-MAG<sub>3</sub>- and <sup>131</sup>I-OIH- clearance.

*Renal hemodynamics according to smoking status and sex*

Table 4 summarizes renal hemodynamics and renal function parameters for non-smokers and smokers in total and separately for men and women. Overall, renal hemodynamics and parameters of kidney function were similar in smokers and non-smokers. Irrespective of smoking status, plasma creatinine, creatinine clearance and filtration fraction were higher in men. <sup>99m</sup>Tc-MAG<sub>3</sub>- and <sup>131</sup>I-OIH- clearances were similar in non-smokers of both sexes but were higher in smoking men.

*Correlation analyses*

*Correlations of ERPF and GFR with age.*

In the total cohort (n =196), GFR and ERPF significantly decreased with age, with no significant difference between the sexes (GFR: R =-0.32, P <0.001, ERPF: R =-0.37, P <0.001). Overall smoking status did not influence the negative correlation of GFR and ERPF with age.

The age-related decline in ERPF was steeper in male smokers than in non-smokers but did not differ in non-smoking and in smoking women (non-smoking men R =-0.35, P <0.01; smoking men R =-0.53,

**Table 3.** Renal function parameters in total and separately for men and women. Abbr.: MAG3 = Mercaptoacetyl triglycine, I-OIH = I-Hippuran, RVR = Renovascular Resistance

Parameter	Total	Women	Men	t-Test
	n= 196	n= 124 (63%)	n=72 (37%)	P
Creatinine clearance (ml/min/1.73 m <sup>2</sup> )	97 ± 17	92 ± 16	104 ± 17	<0.001
MAG3 Clearance (ml/min/1.73m <sup>2</sup> )	257 ± 33	254 ± 32	262 ± 34	ns
I-OIH Clearance (ml/min/1.73m <sup>2</sup> )	431 ± 54	426 ± 55	439 ± 52	ns
Filtration fraction (%)	23 ± 4	22 ± 4	24 ± 4	0.02
RVR (mmHg*min/L)	0.2 ± 0.03	0.19 ± 0.03	0.2 ± 0.03	ns
Plasma creatinine (mmol/L)	0.94 ± 0.2	0.88 ± 0.1	1.1 ± 0.1	0.001

**Table 4.** Renal function parameters for non-smokers and smokers, with subgroups for men and women. Abbr.: \* = percent of total population, § = percent of smokers, nSm = Non Smoker, Sm = Smoker, MAG3 = Mercaptoacetyl triglycine, I-OIH = I-Hippuran, RVR = Renovascular Resistance

Parameter	Non Smoker (nSm)			Smoker (Sm)			t-Test		
	All n=124	Women (a) n= 81 (65%)	Men (b) n= 43 (35%)	All n= 72 (37%*)	Women (c) n= 43 (60%§/ 38%*)	Men (d) n= 29 (40%§/ 35%*)	(a) vs. (b)	(c) vs. (d)	P
Creatinine clearance (ml/min/1.73 m <sup>2</sup> )	96 ± 17	92 ± 17	104 ± 17	97 ± 17	91 ± 14	106 ± 17	ns	0.001	ns
MAG3 Clearance (ml/min/1.73 m <sup>2</sup> )	254 ± 34	254 ± 34	255 ± 33	262 ± 32	255 ± 29	274 ± 33	ns	0.02	0.04
I-OIH Clearance (ml/min/1.73 m <sup>2</sup> )	426 ± 54	426 ± 58	426 ± 48	440 ± 51	427 ± 48	459 ± 51	ns	0.01	0.01
Filtration fraction (%)	23 ± 4	22 ± 4	24 ± 4	22 ± 4	22 ± 4	23 ± 4	ns	ns	ns
RVR (mmHg*min/L)	0.2 ± 0.03	0.2 ± 0.03	0.2 ± 0.03	0.2 ± 0.02	0.19 ± 0.03	0.18 ± 0.02	ns	ns	0.03
Plasma creatinine (mmol/L)	0.9 ± 0.2	0.9 ± 0.1	1.0 ± 0.1	0.9 ± 0.2	0.9 ± 0.1	1 ± 0.2	ns	<0.001	<0.001

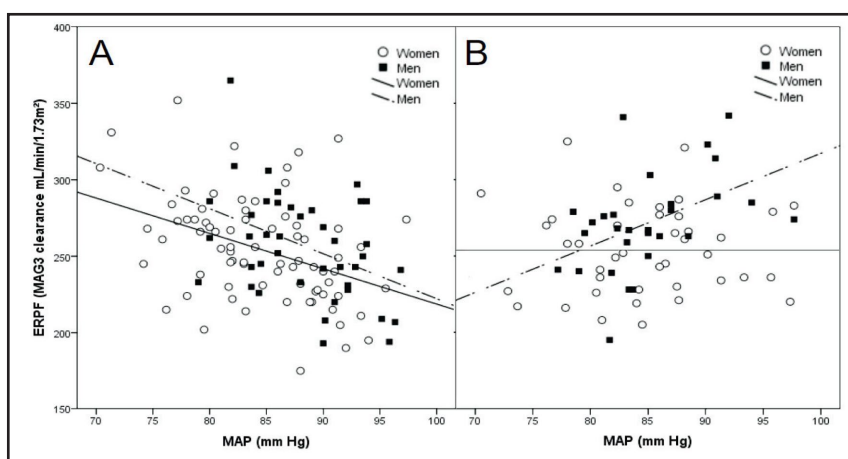
P <0.001; non-smoking men vs. smoking men P =0.05; non-smoking women R =-0.28, P <0.01, smoking women R =-0.34, P <0.05). However, this correlation was lost in multiple regression analysis (see below).

**Correlations of ERPF and GFR with MAP** Figure 1 shows the relationship between ERPF and MAP for non-smokers (figure 1A) and smokers (figure 1B) along with the corresponding subgroups (women and men). In non-smokers there was a significant negative correlation between ERPF and MAP (R= -0.34, P< 0.001) in women as well as in men (R= -0.304, P< 0.01; R= -0.379, P< 0.05, respectively), which remained significant after adjusting for age and sex (R= -0.38; P< 0.001). Smokers overall showed no significant association between MAP and ERPF (R= 0.17; P= ns).

However, in smokers sex-dependent differences emerged: In men but not in women, ERPF increased in parallel with MAP (male smokers: R= 0.44; P< 0.05, female smokers: R= 0.05; P= ns). In a multiple regression analysis ERPF remained significantly associated with sex, smoking status and MAP (R =0.868; P =0.01; sex P =0.015; smoking P =0.006; MAP P =0.001) but not with age. On correlating GFR and MAP, GFR remained constant independent of MAP in the overall population, and there were no significant differences between the subgroups of chronic smokers and non-smokers or between sexes (data not shown).

**Influence of MAP on intrarenal hemodynamics.** The relationship between intrarenal hemodynamics and MAP is shown in figure 2. In non-smokers, lower values for ERPF in the presence of higher MAP were associated with increased RVR (R=

**Fig. 1.** Variations of effective renal plasma flow (ERPF) with mean systemic arterial pressure (MAP) for non-smokers (A) and chronic smokers (B) and within these groups for women (○) and men (■).



0.69;  $P < 0.001$ ; figure 2A). The increase in RVR did not differ between non-smoking men and women (women  $R = 0.70$ ;  $P < 0.001$ , men  $R = 0.68$ ;  $P < 0.001$ ). In smokers, higher MAP was associated with higher RVR in women but not in men (women  $R = 0.56$ ;  $P < 0.001$ , men  $R = 0.20$ ;  $P = \text{ns}$ , figure 2B).

As illustrated in figure 2, in non-smokers  $R_A$  was significantly and positively correlated with MAP with no difference between the sexes (men  $R = 0.75$ ;  $P < 0.001$ , women  $R = 0.78$ ;  $P < 0.001$ ).  $R_E$  showed a tendency to be elevated with higher MAP, but this was not statistically significant (men  $R = 0.18$ ;  $P = \text{ns}$ , women  $R = 0.12$ ;  $P = \text{ns}$ ; figure 2G). Glomerular pressure  $P_G$  remained constant in non-smokers and there was no significant correlation with MAP (non-smoking men and women  $R = 0.14$ ,  $P = \text{ns}$ ; figure 2E).

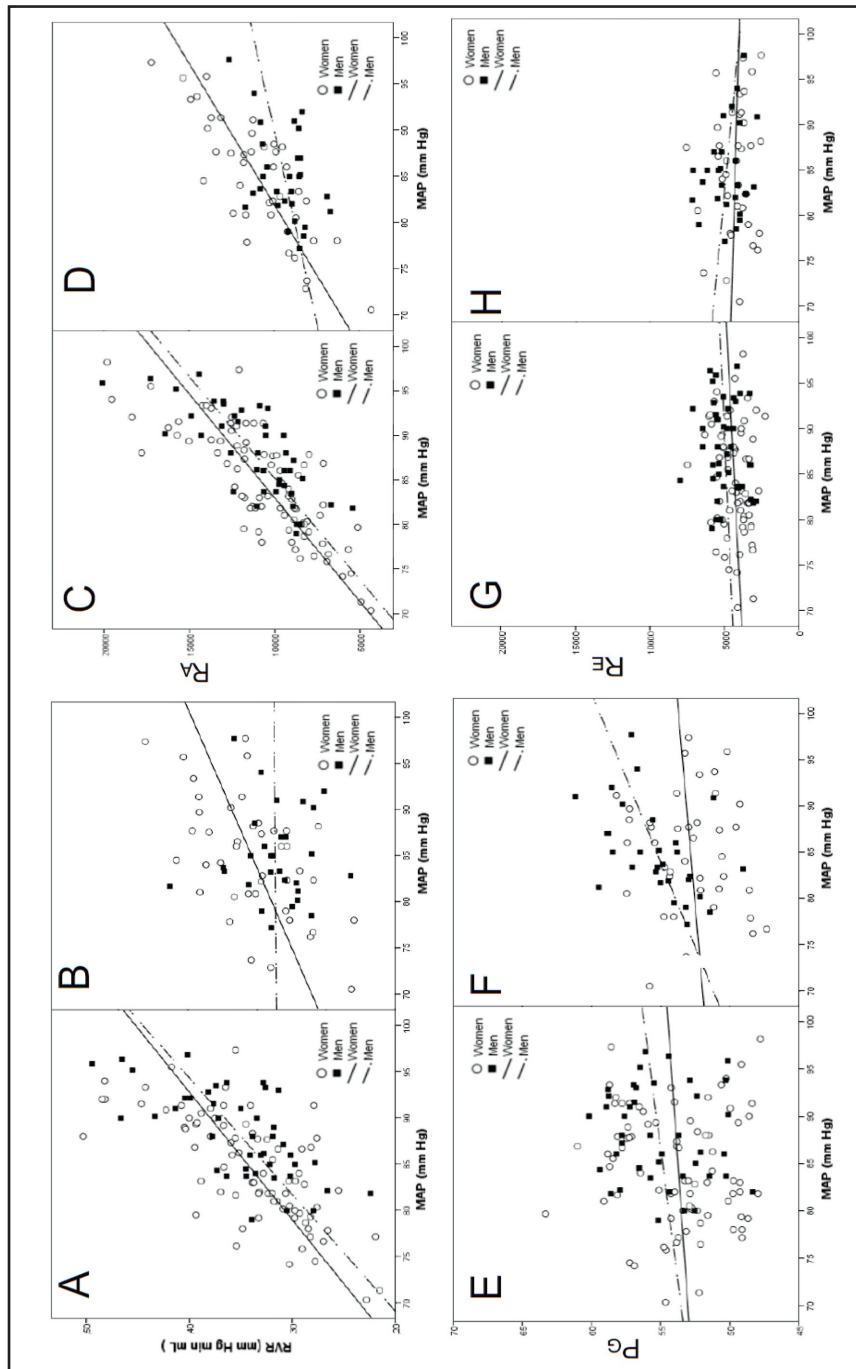
Again within the subgroup of chronic smokers differences between the sexes were revealed: In smoking women results for intrarenal hemodynamics resembled those of non-smoking individuals ( $R_A$   $R = 0.81$ ,  $P < 0.001$ ;  $R_E$   $R = 0.10$ ,  $P = \text{ns}$ ;  $P_G$   $R = 0.14$ ,  $P = \text{ns}$ ;  $P = \text{ns}$  vs. non-smoking women; figure 2 D/F/H). However, in male smokers,  $R_A$  increased less with higher MAP than in non-smokers (male smokers:  $R = 0.42$ ;  $P < 0.05$ ;  $P < 0.05$  for the correlation and vs. male non-smokers); in smoking men  $R_A$  also increased less with higher MAP than in female smokers ( $P < 0.05$ ). In male smokers, glomerular pressure  $P_G$  was significantly positively correlated with MAP ( $R = 0.48$ ;  $P < 0.01$ ; figure 2F), while there was no significant association between MAP and  $R_E$  in smoking men ( $R = 0.2$ ;  $P = \text{ns}$ ; figure 2H).

*Correlations of FF with age or MAP.* No correlation was found for FF with age or MAP, either in the whole population or in any subgroup (data not shown).

## Discussion

Our study is the first to show in humans in vivo that renal autoregulation in smokers may vary dependent on sex. Significant sex-specific differences between smokers and non-smokers emerged, when renal hemodynamics and functional parameters were related to mean arterial pressure. Our data suggest that men may be more susceptible than women to smoking-induced alterations of intrarenal hemodynamics. Analyses were performed in healthy individuals from a living kidney donor program. As far as our cohort in total is concerned, subject characteristics reflect those from other studies and epidemiological data with regard to several core parameters: More women than men were evaluated as living kidney donors [32]. Blood pressure was higher in men, as were creatinine values, GFR and filtration fraction [33-35].

When relating ERPF to mean arterial pressure we found an increasing influence of blood pressure in smoking men but not in smoking women: In female chronic smokers ERPF remained constant independent of systemic blood pressure. At the same time afferent and efferent arteriolar resistance responses in smoking women were similar to those of non-



**Fig. 2.** Variations of renovascular resistance (RVR; panels A/B), afferent arteriolar resistance (RA; panels C/D), efferent arteriolar resistance (RE; panels G/H) and glomerular pressure (Pg; panels E/F) with mean systemic arterial pressure (MAP) for non-smokers (panels A/C/E/G) and chronic smokers (panels B/D/H/F) and within these groups for women (○) and men (■).

smokers, and glomerular hydrostatic pressure remained unaffected by blood pressure changes. However, in male chronic smokers ERPF increased in parallel with blood pressure. This can likely be attributed to a lesser MAP-associated increase in afferent arteriolar resistance in this group.

Earlier studies in healthy humans have shown that a rise in blood pressure (even within the normal range) causes vasoconstriction of renal afferent arterioles and thereby reduces renal plasma flow, thus protecting the glomerulus against hyperfiltration [16-18, 36].

In contrast our results indicate that in men chronic cigarette smoking may increase glomerular hydrostatic pressure via vasodilatory mechanisms in the afferent arteriole. This is in line with results of Halmai et al., who showed in healthy male chronic smokers as well as

in animal studies that cigarette smoking affects renal autoregulation by inducing relaxation and in parallel a decrease in the resistance index of the renal arteries [37]. This seems counterintuitive since a wealth of data has shown that chronic cigarette smoking changes and ultimately damages endothelial function [38-40]. A comprehensive review of endothelial dysfunction associated with smoking and nicotine in various regional vascular beds has recently been published by Toda & Toda [40]. Nicotine but also other toxic substances found in cigarette smoke promote oxidative stress, impaired nitric oxide bioavailability, increased endothelin production and vascular inflammation, which lead to endothelial and vascular smooth muscle dysfunction and ultimately to hypertension [40, 41]. The biochemical mechanisms of smoking-induced cellular damage are based on the over-production of vasoconstrictor and nitric-oxide-scavenging reactive oxygen species through decreased tetrahydrobiopterin (BH<sub>4</sub>)-concentrations and NADPH diaphorase activity [40]. These, in turn, can contribute to mitochondrial ATP-depletion and cellular damage [42].

Our data, however, suggest an exaggerated effect of endogenous vasodilators in the renal vasculature of male chronic smokers. The underlying mechanisms in this setting remain to be defined. While persistent oxidative stress is one of the leading perpetrators of endothelial dysfunction, not all oxidative stress results in vasoconstriction. Free oxygen radicals and related reactants can evoke vasoconstriction as well as vasodilation [43]: e.g. both hydrogen peroxide and hydroxyl radical, stemming from superoxide anion reactions, act as direct vasodilators of vascular smooth muscle and as stimulants of nitric oxide generation from the endothelium. From our results we would have to speculate that in otherwise healthy men the balance of vasoconstrictor and vasodilator substances generated in response to chronic smoking may be tipped towards vasodilation at least in some vascular beds, e.g. in preglomerular arterioles. A resultant lag in preglomerular vasoconstriction in the presence of increasing blood pressure values may characterize an early defect in renal hemodynamic autoregulation in male chronic smokers that has not been described previously. The phenomenon of an increased endothelium-dependent vasodilation in the kidney in the presence of reduced endothelial function in the systemic circulation has recently been described by Cherney et al. in patients with uncomplicated type 1 diabetes mellitus [44].

In our study changes in renal hemodynamics in smoking men did not translate into changes in GFR. This may be due to the small sample size. It would seem feasible that an increased ERPF with higher blood pressure values precedes an increase in GFR. In the long term smoking-induced alterations in renal hemodynamics combined with rising blood pressure could thus result in hyperfiltration and promote loss of renal function. This is where the proposed mechanisms for renal damage associated with chronic smoking meet those of early diabetic nephropathy. In line with this, a number of large cross sectional studies have described an association of chronic smoking with glomerular hyperfiltration [10-13, 45]. Brenner's hyperfiltration theory suggests that elevated glomerular pressure, i.e. glomerular hypertension, induces and maintains nephropathy by adding a hemodynamic burden [46, 47]. As a consequence a vicious circle is established, with an accelerated progression of renal impairment and overt nephropathy [48, 49].

Men have consistently been pointed out to be at greater risk of smoking-associated renal function impairment. Findings in women are contradictory [8, 26, 50]. In a population-based cross-sectional study Briganti et al. showed that smoking increased the risk of renal impairment in men but not in women with an odds ratio of 3.6 [13].

Sex based differences in the incidence and severity of vascular disease are well documented [51]. Emerging evidence suggests that sex-hormone-dependent differences in handling of vascular oxidative stress may play an important role for this phenomenon. Effects of oestrogens and androgens on endothelial function in healthy individuals likely contribute to the development of glomerular sclerosis [52-55]. Oestrogens are supposed to protect the vasculature from oxidant injuries, e.g. induced by smoking, in women [56, 57]. In general, oestrogens are thought to be responsible for the fact that premenopausal women suffer less from arterial hypertension and cardiovascular disease than men or postmenopausal women [57, 58]. From this it might be expected that menopause would affect associations of smoking



with altered renal hemodynamics. This was not the case in our cohort, possibly due to the small number of menopausal smoking women.

Interpretation of our findings is limited by several factors: The screening measures for individuals prior to kidney donation were not primarily designed for scientific observation, otherwise a different method for establishing GFR might have been chosen. The retrospective study design, the cross-sectional nature of the data and the relatively small number of subjects additionally demand that any conclusions should be taken with caution.

### Conclusion

Nevertheless, in summary our data suggest that female sex may protect against detrimental effects of smoking on renal autoregulation. The sex-dependent differences were unmasked only when blood pressure levels were taken into account, indicating a putative additive effect of smoking and blood pressure. Of note, in our study this was true even for blood pressure values in the normal range. An increased glomerular hydrostatic pressure as calculated for male smokers may be an important factor promoting a loss of renal function.

### Conflict of Interests

The authors of this manuscript state that they have nothing to disclose.

### Abbreviations

$P_G$  = Glomerular hydrostatic pressure (mmHg);  $K_{FG}$  = Filtration coefficient of glomerular capillaries (is known to be  $0.154 \pm 0.018$  (mL/sec/mmHg); GFR = Glomerular filtration rate (mL/min);  $H_T$  = Hydrostatic pressure in the Bowman's space (assumed to be 10 mmHg); TP = Plasma total protein concentration (g/dL); FF = Filtration fraction (GFR/ERPF);  $R_A$  = Afferent arteriolar resistance;  $R_E$  = Efferent arteriolar resistance; ERBF = Renal blood flow rate (ERPF x  $1/1 - \text{Hematocrit}$ ) (mL/min).

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