Association of smoking with phenotype at diagnosis and vascular interventions in patients with renal artery fibromuscular dysplasia

Sébastien Savard, Arshid Azarine, Xavier Jeunemaitre, Michel Azizi, Pierre-François Plouin, Olivier Steichen

Title: Association of smoking with phenotype at diagnosis and vascular interventions in patients with renal artery fibromuscular dysplasia

Manuscript number: HYPE201200838R2

Author(s): Olivier Steichen, Hôpital Tenon
Sébastien Savard, Hôpital Européen Georges Pompidou
Arshid Azarine, Hôpital Européen Georges Pompidou
Xavier Jeunemaitre, Université Paris-Descartes
Michel Azizi, Hôpital Européen Georges Pompidou
Pierre-François Plouin, Hôpital Européen Georges Pompidou

Association of smoking with phenotype at diagnosis and vascular interventions in patients with renal artery fibromuscular dysplasia

Sébastien Savard[a], Arshid Azarine[b], Xavier Jeunemaitre[c,d,e], Michel Azizi[a,d], Pierre-François Plouin[a,d], Olivier Steichen[f,g]

[a] Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Hypertension Unit, Paris, F-75015, France;
[b] Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Department of Vascular Radiology, Paris, F-75015, France;
[c] Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Department of Genetics and Reference Centre for Rare Vascular Diseases, Paris, F-75015, France;
[d] Université Paris-Descartes, Faculté de Médecine, Paris, F-75006, France;
[e] INSERM, UMRS 970, Paris Cardiovascular Research Center, Paris, F-75015, France;
[f] Assistance Publique-Hôpitaux de Paris, Hôpital Tenon, Department of Internal Medicine, Paris, F-75020, France;
[g] Université Pierre et Marie Curie Paris 6, Faculté de Médecine, Paris, F-75006, France.

Short title: Smoking and renal artery FMD

Abstract word count: 242
Text word count: 5240

Corresponding author: Olivier Steichen
Service de Médecine Interne, Hôpital Tenon, 4 rue de la Chine, F-75020 Paris, France
Tel: (+33) 1 56 01 78 31; Fax: (+33) 1 56 01 70 82 ; E-mail: olivier.steichen@tnn.aphp.fr

Abstract

The pathogenesis of fibromuscular dysplasia (FMD) remains unclear, but tobacco use is thought to be involved. This retrospective cross-sectional study aimed to evaluate smoking first as a risk factor for renal artery FMD diagnosis and second as a modifier of the clinical and radiological phenotype of this disease. We retrieved 337 adult patients diagnosed with FMD in a referral center for hypertension management, who were first individually matched to controls with essential hypertension for sex, age, systolic blood pressure, number of antihypertensive drugs and year of visit. Smoking status and other relevant data were collected at first visit. The proportion of current smokers was higher for patients with FMD than for the controls (30 and 18%, respectively, $p < 0.001$; odds ratio 2.5 [95% confidence interval: 1.6 to 3.9]). Second, characteristics of FMD were compared between current smokers and other patients. Among patients with multifocal FMD, current smokers experienced an earlier diagnosis of hypertension (36 vs 42 years, respectively, $p<0.001$) and FMD (43 vs 51 years, $p<0.001$) than other patients, and a greater likelihood of renal artery interventions (57% vs 31%, $p<0.001$) and of kidney asymmetry (21% vs 4%, $p=0.001$). In conclusion, current smoking is associated with a higher likelihood of renal artery FMD diagnosis. Rather than a higher incidence of FMD, this may reflect a more aggressive course in smokers, who have earlier hypertension leading to increased and earlier recognition of the disease. Smoking cessation should be strongly encouraged in patients with FMD.

Key words: fibromuscular dysplasia; hypertension, renal; renal artery obstruction; smoking**.**

Introduction

Fibromuscular dysplasia (FMD) is a group of idiopathic, segmental and non-atherosclerotic diseases of the arterial walls leading to the stenosis of medium-sized arteries, including the renal and internal carotid arteries in particular.[1] The pathogenesis of this rare vascular disease is unknown,[2, 3] but it has been suggested that a genetic predisposition[4-7] or environmental factors, such as exposure to estrogens[3, 8] or repeated mechanical trauma, may be involved.[8, 9] Smoking, a recognized potent cause of vascular disease,[10] was also identified as a potential factor contributing to FMD in previous small, observational studies.[9, 11-13]

The aim of this retrospective cross-sectional study was to evaluate smoking as a risk factor for renal artery FMD diagnosis and as a disease modifier. We first compared the prevalence of current smoking between patients with FMD and matched controls with essential hypertension. We then compared the clinical and radiological phenotype between current smokers and other patients with FMD.

Patients and Methods

Patients with FMD

The screening and selection of patients with FMD have been described elsewhere.[14] Briefly, we reviewed the medical charts of all adult patients for whom a diagnosis of FMD was considered between January 1st 1986 and November 30th 2011 at a single institution. In accordance with the current definition of renal artery FMD, we accepted the diagnosis in patients with non-atherosclerotic stenosing lesions affecting the trunk or branches of renal arteries in the absence of aortic wall thickening or biochemical evidence of inflammation and in the absence of known syndromic arterial disease.[15] Isolated renal artery aneurysm or dissection was not considered sufficient to diagnose FMD.[16] The classification of FMD as

unifocal (presence of a single stenosis on a given vessel, regardless of its length) or multifocal (presence of two or more stenoses on a given vessel segment) was based on radiological data.[14]

Controls with essential hypertension

Each case with renal artery FMD was paired with a control patient with essential hypertension (EH) matched for sex, age [± 2 years], systolic blood pressure (BP) [± 10 mmHg], number of antihypertensive drugs used and year of first visit [± 2 years]. Patients with essential hypertension were identified by screening our institution's electronic medical record database. The medical charts of selected controls were reviewed manually to check that these individuals were not pregnant and had not subsequently been diagnosed with secondary hypertension.

Retrieval of clinical data

We extracted clinical and biological data collected from patients during their first visit to our unit. For patients referred after FMD had been diagnosed elsewhere, data was collected only if the first visit to our unit occurred within one year of the diagnosis of FMD and if no renal artery intervention had been performed during this period. For the matching procedure, multivariate imputation was used to attribute initial systolic BP values or numbers of antihypertensive drugs to FMD patients when these data were missing. The imputed values were used for the matching procedure only and are not reported in the descriptive statistics. Patients were asked if they did currently smoke tobacco on a regular basis (the vast majority smoke on a daily basis). Those who answered positively were classified as current smokers. Patients who declared having quitted tobacco smoking were classified as former smokers,

regardless of the time delay since smoking cessation. Ever smokers included current and former smokers. The remaining patients were classified as never smokers.

Creatinine clearance was estimated with the Cockcroft-Gault formula,[17] normalized for body surface area, because most creatinine measurements were not calibrated to isotope dilution mass spectrometry (ruling out the CKD-EPI equation) and because most patients with renal artery FMD have a glomerular filtration rate > 60 ml/min (ruling out the MDRD equation).[18] Renal asymmetry was defined as a difference larger than 20 mm in bipolar length between the two kidneys on ultrasound scans.[11] Procedures followed were in accordance with institutional guidelines.

Statistical methods

The detailed baseline and demographic characteristics of the FMD patients have been reported elsewhere.[14] A case versus control analysis was first performed between patients with FMD and matched controls with essential hypertension; comparisons were performed with conditional logistic regression. An exposed versus not exposed analysis was then performed between current smokers and other patients with FMD. Quantitative variables are reported as medians and quartiles and were compared with the Mann-Whitney test. Nominal and ordinal variables are reported as numbers and percentages and were compared with the Fisher's exact test and Chi² test for trend, respectively. Factors associated with renal asymmetry were studied by binomial logistic regression analysis.

Quantitative variables were not categorized for logistic regression studies. Linearity between the logit and quantitative variables was checked graphically. Interaction tests were carried out to check for heterogeneity in the comparison of subtypes, for patients with FMD and essential hypertension. The Wald test was used to assess statistical significance.

The single pre-established hypothesis was that current smoking is more prevalent among FMD patients than matched controls; a p value < 0.05 considered significant for this comparison. All other comparisons were hypothesis-generating and due to the exploratory nature of the study, no adjustment was made for multiple comparisons: the lesser the p value, the less likely it is to be a chance finding.

Stata 9.2 (Stata-Corp, College Station, Texas, USA) was used for statistical analyses.

Results

Selection and characteristics of the patients

By querying databases, we identified 700 patient records in which FMD diagnosis was mentioned at least once. We ascertained the diagnosis of renal artery FMD in 337 patients (61 patients with unifocal and 276 with multifocal FMD). The other 363 cases were excluded, mostly because initial imaging data were unavailable to ascertain the diagnosis or because current diagnostic criteria were not met (Figure).

Smoking status was available for 326/337 (97%) patients with FMD, including 268 patients with multifocal disease and 58 with unifocal disease. Smoking status was completely available for 324/337 (96%) patients with EH. The remaining 13 patients were not currently smoking at the time of their visit, but we do not know if they were former or never smokers.

Most patients were female (80%) and of the multifocal subtype (82%). Both hypertension and FMD were diagnosed earlier in patients with unifocal FMD (26 and 30 years, respectively) than in patients with multifocal FMD (40 and 49 years, respectively, $p < 0.001$ for both comparisons). A larger proportion of patients with unifocal FMD were current smokers (50% vs 26%, $p < 0.001$), were diagnosed with kidney asymmetry (33 vs 10%, $p < 0.001$) and had undergone a renal artery intervention at some time (87 vs 38%, $p < 0.001$).

Smoking in patients with fibromuscular dysplasia and controls

Table 1 reports the comparisons of cases with renal artery FMD and matched controls with essential hypertension. No significant interaction was found between FMD subtype (unifocal or multifocal) and any of these comparisons. FMD patients were more likely than controls to be current smokers (30% vs 18%, $p < 0.001$; odds ratio 2.5 [95% confidence interval: 1.6 to 3.9]) or to have smoked at some point in their lives (ever smokers, 50% vs 37%, $p = 0.001$; odds ratio 1.8 [95% confidence interval: 1.3 to 2.5]). Patients with essential hypertension had a higher body mass index than FMD patients. Although they had the same age and sex and similar plasma creatinine concentrations than FMD patients, estimated creatinine clearance according to the Cockcroft-Gault formula was higher in patients with essential hypertension due to higher body weights.

Associations with smoking status

Among patients with multifocal FMD, Kruskall-Wallis tests comparing current smokers, former smokers and patients who had never smoked revealed significant differences regarding sex ($p = 0.01$), age at hypertension diagnosis ($p = 0.002$), age at FMD diagnosis ($p < 0.001$), kidney asymmetry ($p = 0.002$), performance and number of renal interventions ($p = 0.001$ and $p = 0.007$). Post hoc comparisons showed that all these differences, with the exception of that for sex, were due to a difference between current smokers and the other two groups, which were therefore combined. For unifocal FMD, there were too few former smokers (n=4) for meaningful comparisons across the three groups. We therefore combined the groups of former smokers and patients who had never smoked, as for patients with multifocal disease.

In patients with multifocal FMD, current smoking was associated with a younger age at diagnosis of hypertension and of FMD and with a higher frequency of renal artery interventions (Table 2). In patients with unifocal FMD, current smoking was associated with higher baseline blood pressure (BP) (Table 3).

Renal ultrasound data were available for 243 patients and renal asymmetry was observed in 35 of them (on the right side in 21 cases). Smoking status was unknown for 3 patients with documented renal asymmetry. Current smoking was associated with a higher frequency of renal asymmetry in both multifocal and unifocal FMD. In univariate analysis, renal asymmetry was associated with current smoking, unifocal FMD and ipsilateral unilateral renal artery stenosis (Table 4). In multivariate analysis, current smoking and unifocal FMD remained independently associated with renal asymmetry, whereas the association with ipsilateral unilateral renal artery stenosis was no longer significant. Only 9 patients had a kidney length < 8 cm, always on one side only; creatinine clearance of these patients ranged from 38 to 118 ml/min/1.73m² (2 patients < 60 ml/min/1.73m²).

Discussion

The first key finding from this study is that the proportions of current smokers and ever smokers were significantly higher in patients with FMD than in matched controls with essential hypertension. A second major finding is the association of current smoking with an earlier hypertension and FMD diagnosis and with a higher frequency of renal asymmetry and a higher prevalence of renal artery interventions, in patients with multifocal disease.

Comparison with previous studies and interpretation of the results

Recently published data from the US FMD Registry, which holds data from 2008 to 2011, revealed that 37.2% of FMD patients were ever smokers (current or former smokers).[19] Previous small studies have compared the prevalence of smoking in FMD patients and matched controls (Table 5).[9, 12, 13, 20] As expected, given recent anti-smoking campaigns, the proportions of smokers among FMD patients and their controls were higher in older series. However, all studies concur in reporting a higher proportion of current or ever smokers in FMD patients than in controls. A single small study in patients with multifocal FMD compared the presentation of subjects with (n=24) and without (n=26) a history of smoking.[11] In this previous study, smoking was associated with a younger age at diagnosis (39 *vs*. 49 years, p<0.01) and a higher prevalence of unilateral renal atrophy (67% *vs*. 27%, p<0.01).

Our study confirms and extends these findings, providing information about the influence of current and past smoking in patients with unifocal or multifocal FMD. The association between smoking and FMD diagnosis is equivocal. As about 50% of our FMD patients have never smoked, cigarette smoking cannot be considered a prerequisite for the development of the disease. Nonetheless, smoking may provoke FMD lesions in susceptible individuals and therefore increase the true incidence of the disease.

On the other side, smoking may only worsen pre-existing arterial lesions and thus increase the likelihood and/or magnitude of clinical consequences of the disease. Smoking has indeed many deleterious effects on vessels, decreasing the production of nitric oxide and prostacyclin, and accelerating the development of both atherosclerosis and thrombosis.[10] Current exposure to cigarette smoke may amplify the endothelial dysfunction underlying renovascular hypertension[21] or favor the development of atherosclerosis or thrombosis. These

mechanisms could explain the worsening of dysplastic stenoses or superimposed atherosclerotic lesions.

In our patients with multifocal FMD, current smoking was strongly associated with a younger age at diagnosis of hypertension and of FMD and with more renal asymmetry. The finding of a more severe disease course in current smokers suggests that the association between smoking and FMD diagnosis reflects a more aggressive course in smokers, with earlier hypertension leading to more frequent and earlier recognition of the disease, rather than a truly higher incidence of FMD in smokers.

In other words, the association between smoking and FMD diagnosis may reflect an ascertainment bias: FMD patients would be more likely to be referred to hypertension units like ours if they are current smokers because of a more severe anatomical or clinical disease. Conversely, FMD patients who do not smoke have a less severe clinical phenotype, closer to essential hypertension, or may even be asymptomatic. In both cases, FMD is much less likely to be diagnosed.

Strengths and weaknesses of the study

This study is based on a large number of well characterized patients with FMD and controls carefully matched on the basis of year of first visit, age, sex, BP and number of types of antihypertensive drug used. Matching for the year of first visit was particularly important, due to secular trends in smoking habits. This study was retrospective, and is therefore subject to several limitations, including missing data. However, computerized and structured data recording during routine clinical care resulted in there being less than 15% missing data for clinical variables. The results previously obtained in retrospective analyses of this clinical

database have consistently been confirmed in prospective studies.[22, 23] Our results are also subject to possible referral bias and caution is therefore required when extrapolating to FMD patients who are not typically referred to a hypertension unit, like those with asymptomatic or predominantly cervical FMD. Ascertainment bias can also not be excluded: smokers could be more actively screened for hypertension than non-smokers, explaining a younger age at hypertension diagnosis, and hence FMD diagnosis. Details about the amount and duration of smoking were not consistently recorded at the first visit and their impact could not be analyzed. The number of patients with unilateral FMD was limited and no firm conclusion can be drawn for this subgroup. Moreover, observed BP difference in this subgroup may be confounded by the difference in number of antihypertensive medication, although it was not statistically significant. The performance of multiple comparisons entails a risk of *p* values < 0.05 being due to chance alone. However, highly significant differences ($p < 0.001$) can be considered reliable.

Perspectives

Research perspectives

This study indicates that current smoking is associated with a higher incidence of FMD or, most likely, with more frequent and earlier diagnosis. Current smoking is also associated with more severe consequences of renal ischemia (kidney asymmetry), leading to a larger number of renal interventions. Further studies are required to assess the impact of the amount and duration of smoking and elucidate the mechanisms by which smoking influences the expression and course of FMD. Endothelial dysfunction may play a role that is currently being evaluated at our center.

Clinical perspectives

The prevalence of current smoking is greater in FMD patients than in matched controls. Current smoking is associated with more severe and/or more rapidly progressing disease in patients with multifocal FMD. This study highlights the critical importance of encouraging FMD patients to quit smoking.

Acknowledgments

The authors would like to thank Dr Michael Frank, Dr Jacques Julien, Dr Antoine Chedid and Dr Béatrice Fiquet for their contribution to FMD patient recruitment and data collection.

Sources of funding

Sébastien Savard received a financial support from *la Société Québécoise d'Hypertension Artérielle*, *la Société Québécoise de Néphrologie*, *La Faculté de Médecine de l'Université Laval* (McLaughlin Scholarship Program), and from *La Fondation du Centre Hospitalier Universitaire de Québec* for his post-doctoral work.

Competing financial interests

None.

References

1. Slovut DP, Olin JW. Fibromuscular dysplasia. *N Engl J Med*. 2004;350:1862-1871.
2. Olin JW, Sealove BA. Diagnosis, management, and future developments of fibromuscular dysplasia. *J Vasc Surg*. 2011;53:826-836 e821.
3. Plouin PF, Perdu J, La Batide-Alanore A, Boutouyrie P, Gimenez-Roqueplo AP, Jeunemaitre X. Fibromuscular dysplasia. *Orphanet J Rare Dis*. 2007;2:28.
4. Mettinger KL, Ericson K. Fibromuscular dysplasia and the brain. I. Observations on angiographic, clinical and genetic characteristics. *Stroke*. 1982;13:46-52.
5. Pannier-Moreau I, Grimbert P, Fiquet-Kempf B, Vuagnat A, Jeunemaitre X, Corvol P, Plouin PF. Possible familial origin of multifocal renal artery fibromuscular dysplasia. *J Hypertens*. 1997;15:1797-1801.
6. Perdu J, Boutouyrie P, Bourgain C, Stern N, Laloux B, Bozec E, Azizi M, Bonaiti-Pellie C, Plouin PF, Laurent S, Gimenez-Roqueplo AP, Jeunemaitre X. Inheritance of arterial lesions in renal fibromuscular dysplasia. *J Hum Hypertens*. 2007;21:393-400.
7. Rushton AR. The genetics of fibromuscular dysplasia. *Arch Intern Med*. 1980;140:233-236.
8. Luscher TF, Keller HM, Imhof HG, Greminger P, Kuhlmann U, Largiader F, Schneider E, Schneider J, Vetter W. Fibromuscular hyperplasia: extension of the disease and therapeutic outcome. Results of the University Hospital Zurich Cooperative Study on Fibromuscular Hyperplasia. *Nephron*. 1986;44 Suppl 1:109-114.
9. Sang CN, Whelton PK, Hamper UM, Connolly M, Kadir S, White RI, Sanders R, Liang KY, Bias W. Etiologic factors in renovascular fibromuscular dysplasia. A case-control study. *Hypertension*. 1989;14:472-479.

10. Powell JT. Vascular damage from smoking: disease mechanisms at the arterial wall. *Vasc Med*. 1998;3:21-28.

11. Bofinger A, Hawley C, Fisher P, Daunt N, Stowasser M, Gordon R. Increased severity of multifocal renal arterial fibromuscular dysplasia in smokers. *J Hum Hypertens*. 1999;13:517-520.

12. Mackay A, Brown JJ, Cumming AM, Isles C, Lever AF, Robertson JI. Smoking and renal artery stenosis. *Br Med J*. 1979;2:770.

13. Nicholson JP, Teichman SL, Alderman MH, Sos TA, Pickering TG, Laragh JH. Cigarette smoking and renovascular hypertension. *Lancet*. 1983;2:765-766.

14. Savard S, Steichen O, Azarine A, Azizi M, Jeunemaitre X, Plouin PF. Association Between Two Angiographic Subtypes of Renal Artery Fibromuscular Dysplasia and Clinical Characteristics. *Circulation*. 2012 ;126:3062-3069.

15. Persu A, Touze E, Mousseaux E, Barral X, Joffre F, Plouin PF. Diagnosis and management of fibromuscular dysplasia: an expert consensus. *Eur J Clin Invest*. 2012;42:338-347.

16. Stanley JC. Renal artery fibrodysplasia. In: Novick AC, Scable J, Hamilton G, eds. *Renal Vascular Disease*. London: WB Saunders; 1996:21-23.

17. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.

18. Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. *Ann Intern Med*. 2012;156:785-795.

19. Olin JW, Froehlich J, Gu X, Bacharach JM, Eagle K, Gray BH, Jaff MR, Kim ES, Mace P, Matsumoto AH, McBane RD, Kline-Rogers E, White CJ, Gornik HL. The

United States Registry for Fibromuscular Dysplasia: Results in the First 447 Patients. *Circulation*. 2012;125:3182-3190.

20. Boutouyrie P, Gimenez-Roqueplo AP, Fine E, Laloux B, Fiquet-Kempf B, Plouin PF, Jeunemaitre X, Laurent S. Evidence for carotid and radial artery wall subclinical lesions in renal fibromuscular dysplasia. *J Hypertens*. 2003;21:2287-2295.

21. Higashi Y, Sasaki S, Nakagawa K, Matsuura H, Oshima T, Chayama K. Endothelial function and oxidative stress in renovascular hypertension. *N Engl J Med*. 2002;346:1954-1962.

22. Jeunemaitre X, Chatellier G, Kreft-Jais C, Charru A, DeVries C, Plouin PF, Corvol P, Menard J. Efficacy and tolerance of spironolactone in essential hypertension. *Am J Cardiol*. 1987;60:820-825.

23. Milliez P, Girerd X, Plouin PF, Blacher J, Safar ME, Mourad JJ. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. *J Am Coll Cardiol*. 2005;45:1243-1248.

Novelty and Significance

1) What Is New

– Current smoking is associated with a higher likelihood of renal artery FMD diagnosis.

– Rather than a higher incidence of FMD, this may reflect a more aggressive course in smokers, who have earlier hypertension possibly leading to increased and earlier recognition of the disease.

2) What Is Relevant?

– Smoking cessation should be strongly encouraged in patients with FMD.

3) Summary

– The proportion of current smokers was higher for patients with FMD than for matched controls with essential hypertension (odds ratio 2.5).

– Among patients with multifocal FMD, current smokers experienced an earlier diagnosis of hypertension and FMD than other patients, and a greater likelihood of renal artery interventions and of kidney asymmetry.

Figure legends

Figure. Flow diagram showing the selection of patients with fibromuscular dysplasia

*Takayasu arteritis, 8; Alagille syndrome, 4; renal artery spasm related to pheochromocytoma, 3; pseudo-xanthoma elasticum, 2; Ehlers-Danlos syndrome, 2; Williams syndrome, 1.

FMD, fibromuscular dysplasia; CTA, computed tomography angiography; MRA, magnetic resonance angiography.

Table 1. History and clinical characteristics of cases with renal FMD and matched controls with essential hypertension (EH) at first visit

Variables	FMD (*n* = 337) No	FMD (*n* = 337) Values	EH (*n* = 337) No	EH (*n* = 337) Values	*p*
Matched variables					
Year of first visit to our unit	337	2004 [1999, 2008]	337	2004 [1999, 2008]	-
Age at first visit, years	337	47 [36, 55]	337	46 [36, 55]	-
Male, *n*	337	66 (20%)	337	66 (20%)	-
Systolic BP, mmHg	289	147 [130, 166]	337	145 [132, 161]	-
Number of antihypertensive drugs, *n*	289	2 [1, 3]	330	2 [1, 2]	-
Non-matched variables					
Age at diagnosis of hypertension, years	316	38 [27, 47]	314	40 [29, 48]	0.40
Family history of hypertension, *n*	266	170 (64%)	283	192 (68%)	0.16
History of diabetes, *n*	328	13 (4%)	331	23 (7%)	0.09
History of hypercholesterolemia, *n*	329	88 (27%)	327	82 (25%)	0.45

Current smokers, *n*	326	98 (30%)	337	59 (18%)	<0.001
Current + former smokers, *n*	326	164 (50%)	324	121 (37%)	0.001
Body mass index, kg/m²	286	23 [20, 26]	331	25 [22, 29]	<0.001
Estimated creatinine clearance,* ml/min/1.73m^2	267	87 [74, 103]	277	93 [76, 113]	0.001

The number of observations available for analysis (No) is shown for each variable. Values are the numbers of patients (percentage) for binary variables and median [quartiles] for quantitative variables. FMD, fibromuscular dysplasia; BP, blood pressure.

*determined with the Cockcroft-Gault formula

Table 2. Comparison of history and characteristics at multifocal FMD diagnosis between between current smokers and the other patients

	Multifocal FMD (n = 268)				
	Not current smokers* (n = 199)		Current smokers (n = 69)		
Variables	No	Values	No	Values	p
Male, n	199	30 (15%)	69	15 (22%)	0.26
Personal history of hypertension, n	199	183 (92%)	69	67 (97%)	0.17
Age at diagnosis of hypertension, years	181	42 [33, 51]	67	36 [26, 43]	< 0.001
Age at diagnosis of FMD, years	199	51 [45, 60]	69	43 [35, 49]	< 0.001
History of diabetes, n	199	8 (4%)	69	4 (6%)	0.51
History of hypercholesterolemia, n	199	62 (31%)	69	16 (23%)	0.22
Systolic BP, mmHg	174	146 [128, 162]	59	148 [130, 167]	0.48
Diastolic BP, mmHg	174	87 [76, 98]	59	91 [77, 104]	0.14
Number of antihypertensive drugs, n	174	2 [1, 3]	59	2 [1, 3]	0.42
Body mass index, kg/m²	173	24 [21, 27]	58	22 [20, 26]	0.03

Serum creatinine concentration, µmol/l	163	72 [64, 82]	55	72 [65, 85]	0.63
Estimated creatinine clearance[†]	162	85 [73, 100]	55	89 [76, 103]	0.18
Renal asymmetry, *n*	139	6 (4%)	53	11 (21%)	0.001
Renal artery intervention, *n*	199	61 (31%)	69	39 (57%)	< 0.001

The number of observations available for analysis (No) is shown for each variable. The values shown are the numbers of patients (percentage) for binary variables and median [quartiles] for quantitative variables. [*]Not current smokers includes patients who had never smoked (n = 137) and former smokers (n = 62); [†]determined with the Cockcroft-Gault formula normalized for body surface area (ml/min/1.73m^2). FMD, fibromuscular dysplasia; BP, blood pressure.

Table 3. Comparison of history and characteristics at unifocal FMD diagnosis between current smokers and the other patients

	Unifocal FMD (n = 58)				
	Not current smokers* (n = 29)		Current smokers (n = 29)		
Variables	No	Values	No	Values	p
Male, n	29	9 (31%)	29	10 (34%)	1
Personal history of hypertension, n	29	28 (97%)	29	29 (100%)	1
Age at diagnosis of hypertension, years	28	26 [20, 35]	29	28 [21, 38]	0.75
Age at diagnosis of FMD, years	29	29 [25, 42]	29	31 [25, 38]	0.72
History of diabetes, n	29	0 (0%)	29	1 (3%)	1
History of hypercholesterolemia, n	29	5 (17%)	29	5 (17%)	1
Systolic BP, mmHg	28	147 [130, 178]	26	164 [154, 172]	0.05
Diastolic BP, mmHg	28	91 [80, 106]	26	103 [96, 118]	0.01
Number of antihypertensive drugs, n	28	2 [1, 3]	26	1 [1, 2]	0.66
Body mass index, kg/m²	28	22 [20, 24]	26	21 [19, 23]	0.36
Serum creatinine, µmol/l	26	80 [67, 95]	23	80 [70, 92]	0.88

Estimated creatinine clearance[†]	26	91 [73, 109]	23	90 [84, 112]	0.73
Renal asymmetry, *n*	22	3 (14%)	24	12 (50%)	0.01
Renal artery intervention, *n*	29	24 (83%)	29	26 (90%)	0.71

The number of observations available for analysis (No) is shown for each variable. The values shown are the numbers of patients (percentage) for binary variables and median [quartiles] for quantitative variables. [*]Not current smokers includes patients who have never smoked ($n = 25$) and former smokers ($n = 4$); [†]determined with the Cockcroft-Gault formula normalized for body surface area (ml/min/1.73m^2). FMD, fibromuscular dysplasia; BP, blood pressure.

Table 4. Unilateral kidney asymmetry in patients with renal artery FMD

	Renal asymmetry		No renal asymmetry		Univariate	Multivariate[¥]
Variables	No	Values	No	Values	OR [95% CI]	OR [95% CI]
Current smoking	32	23 (72%)	206	54 (26%)	7.2 [3.1, 16.5]	6.0 [2.6, 14.0]
Unifocal FMD	35	16 (46%)	208	32 (15%)	4.6 [2.2, 9.9]	3.7 [1.6, 8.6]
Same-side unilateral stenosis	35	18 (51%)	208	53 (26%)	3.1 [1.5, 6.4]	Not included

The number of observations available for analysis (No) is shown for each variable. The values shown are the numbers of patients (percentage) for binary variables and median [quartiles] for quantitative variables. FMD, fibromuscular dysplasia; CI, confidence interval;

Table 5. Prevalence of smoking in patients with fibromuscular dysplasia and controls in published studies

Studies	Number of patients		Definition of smokers	Definition of controls	Smoking prevalence		*p*
	FMD	controls			FMD	Controls	
Mackay *et al.* 1979 [12]	18	18	Current	Age- and sex-matched outpatients with essential hypertension	72%	39%	< 0.05
	18	18	Current	Age- and sex-matched inpatients with essential hypertension	72%	44%	NS
Nicholson *et al.* 1983 [13]	21	158	Current + former	Age-matched patients with essential hypertension	71%	41%	< 0.001
Sang *et al.* 1989 [9]	33	61	Current + former	Renal transplant donors with normal arteries, no matching	79%	53%	0.003
Boutouyrie *et al.* 2003 [20]	70	70	Current	Age-, sex- and SBP-matched patients with essential hypertension referred to a specialist clinic	37%	20%	< 0.05

This study 2012	337	337	Current	Patients with essential hypertension matched for age, sex, SBP, number of drugs and year of visit	30%	18%	< 0.001

FMD, fibromuscular dysplasia; NS, not significant; SBP, systolic blood pressure