Association Between 2 Angiographic Subtypes of Renal Artery Fibromuscular Dysplasia and Clinical Characteristics

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Background—Initially based on histology, the diagnosis of renal artery fibromuscular dysplasia (FMD) is now based mostly on angiographic appearance because arterial tissue samples are rarely available. This retrospective cross-sectional study aimed to assess the clinical relevance of a binary angiographic classification of FMD lesions (unifocal or multifocal) based on computed tomography or magnetic resonance angiography.

Methods and Results—Adult patients diagnosed with FMD in a single tertiary care center for hypertension management were identified by screening of electronic files. FMD lesions were reviewed and classified according to computed tomography or magnetic resonance angiography as multifocal if there were at least 2 stenoses in the same arterial segment; otherwise, they were classified as unifocal. Of 337 patients with established renal artery FMD, 276 (82%) were classified as multifocal. Patients with unifocal and multifocal lesions differed significantly in median age at diagnosis of FMD (30 and 49 years) and hypertension (26 and 40 years), sex distribution (female:male ratio, 2:1 and 5:1), initial blood pressure (157/97 and 146/88 mm Hg), current smoking (50% and 26%), prevalence of unilateral renal artery lesions (79% and 38%), presence of kidney asymmetry (33% and 10%), renal revascularization procedures (90% and 35%), and hypertension cure rates in patients who underwent revascularization (54% and 26%).

Conclusions—A binary angiographic classification into unifocal or multifocal renal artery FMD is straightforward and discriminates 2 groups of patients with different clinical phenotypes. (Circulation. 2012;126:3062-3069.)

Key Words: fibromuscular dysplasia • hypertension, renal • renal artery obstruction

Fibromuscular dysplasia (FMD) is a heterogeneous group of idiopathic, nonatherosclerotic, relatively rare vascular diseases leading to the narrowing of medium-sized arteries, mostly the renal and internal carotid arteries.1,2 Renal artery FMD is the second most frequent cause of renovascular hypertension.3 Pathological classifications of FMD were proposed in the 1960s,4–6 and consensus classifications were subsequently proposed by Harrison and McCormack7 and Stanley et al.8 They identified 3 main types of FMD according to the dominant arterial wall layer involved: intimal fibroplasia, present in <10% of cases; medial fibroplasia, the most frequent type of FMD (rarer medial FMD lesions are perimedial fibroplasia and medial hyperplasia); and adventitial or periarterial fibroplasia, which is the rarest FMD subtype.1,7,8

Surgery for renal artery FMD makes pathological specimens available and allows the use of pathological classifications. In recent years, however, most patients with renal artery FMD needing intervention have undergone percutaneous angioplasty rather than surgical reconstruction. A recent meta-analysis of interventions for renal artery FMD after 1995 identified only 1 published surgical series but 24 angioplasty series.9 Consequently, contemporary classification needs to be based on the angiographic appearance of FMD lesions. Pathological-angiographic correlation studies indicate that a string-of-beads appearance is associated with medial fibroplasia,4–6 whereas other angiographic aspects, either focal or tubular, are not associated with any specific type of FMD (Table 1).

In the present study, we investigated whether a binary angiographic classification of FMD into unifocal and multifocal types discriminated between distinct clinical phenotypes.

Methods

Patients

We screened the electronic medical record database at our institution and the computerized collection of minutes of the multidisciplinary surgery for renal artery FMD making pathological specimens available and allows the use of pathological classifications. In recent years, however, most patients with renal artery FMD needing intervention have undergone percutaneous angioplasty rather than surgical reconstruction. A recent meta-analysis of interventions for renal artery FMD after 1995 identified only 1 published surgical series but 24 angioplasty series.9 Consequently, contemporary classification needs to be based on the angiographic appearance of FMD lesions. Pathological-angiographic correlation studies indicate that a string-of-beads appearance is associated with medial fibroplasia,4–6 whereas other angiographic aspects, either focal or tubular, are not associated with any specific type of FMD (Table 1).

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Table 1. Pathological Classifications of Renal Artery FMD and Corresponding Angiographic Appearance

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Classification, n</th>
<th>Frequency, %</th>
<th>Angiographic Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCormack et al, 1966</td>
<td>67</td>
<td>Intimal fibroplasia, 14</td>
<td>21</td>
<td>Focal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medial fibroplasia, 15</td>
<td>22</td>
<td>String of beads</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibromuscular hyperplasia, 7</td>
<td>10</td>
<td>Focal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subadventitial fibroplasia, 31</td>
<td>46</td>
<td>Focal or beaded</td>
</tr>
<tr>
<td>Harrison et al, 1967</td>
<td>60, excluding patients with aneurysms only</td>
<td>Medial thickening, 44</td>
<td>73</td>
<td>Multifocal beaded pattern, 31/44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Periarterial, 16</td>
<td>27</td>
<td>Focal, tubular or multifocal</td>
</tr>
<tr>
<td>Kincaid et al, 1968</td>
<td>60 with pathological examination</td>
<td>Intimal, 5</td>
<td>8</td>
<td>Focal or tubular, 5/5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medial, 53</td>
<td>88</td>
<td>Multifocal, 38/53</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Periarterial, 2</td>
<td>3</td>
<td>Tubular, 2/2</td>
</tr>
<tr>
<td>Harrison and McCormack, 1971</td>
<td>NR (consensus document)</td>
<td>Intimal fibroplasia</td>
<td>1–2</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secondary intimal fibroplasia</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medial fibroplasia with mural aneurysm</td>
<td>60–70</td>
<td>String of beads</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medial hyperplasia</td>
<td>5–15</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perimedial fibroplasia</td>
<td>15–25</td>
<td>May be beaded</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Periareterial fibroplasia</td>
<td>&lt;1</td>
<td>NR</td>
</tr>
<tr>
<td>Stanley et al, 1975</td>
<td>177 (25 children), 86 specimens suitable for classification</td>
<td>Intimal fibroplasia</td>
<td>~5</td>
<td>Focal or tubular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medial hyperplasia</td>
<td>~1</td>
<td>Focal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medial fibroplasia</td>
<td>~85</td>
<td>A continuum of disease angiographically</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perimedial dysplasia</td>
<td>~10</td>
<td>Focal, occasionally multiple constrictions</td>
</tr>
</tbody>
</table>

FMD indicates fibromuscular dysplasia; NR, not reported.

meetings for adult patients for whom the diagnosis of FMD was considered between January 1, 1986, and November 30, 2011. We also cross-checked research databases used in the Hypertension Unit and the Department of Genetics. The weekly meetings are attended by hypertension specialists, vascular radiologists, and vascular surgeons. We accepted cases as FMD without further verification if the diagnosis was confirmed at multidisciplinary meetings and if angiographic reports mentioned a typical string-of-beads appearance. Other records and imaging studies were reviewed by at least 2 authors (S.S., P.-F.P., A.A.) to ascertain FMD diagnosis. Our diagnostic pathway meets the recent recommendations of a European consensus panel.10 Echo Doppler is not specific enough to diagnose renal artery FMD and was used only for screening. Computed tomography angiography (CTA), magnetic resonance angiography (MRA), and catheter-based angiography were used for diagnostic confirmation. CTA and MRA are noninvasive and specific enough to rule in FMD but not sensitive enough to rule it out in case of high clinical suspicion. Catheter-based angiography was performed when revascularization was medically justified and when the diagnosis remained uncertain after CTA or MRA. The procedure for the inclusion of patients was consistent with French institutional guidelines.

Diagnostic Criteria

In accordance with current definitions,1,7,8 we considered the diagnosis of renal artery FMD in patients with nonatherosclerotic stenosing lesions affecting the trunk or branches of the renal arteries in the absence of aortic wall thickening or biochemical evidence of inflammation and in the absence of known syndromic arterial disease such as type I neurofibromatosis, pseudoxanthoma elasticum, vascular Ehlers-Danlos syndrome, Williams syndrome, or Alagille syndrome.10

Angiographic classification was based on imaging studies performed before any renal artery intervention. Cases with confirmatory CTA or MRA performed before 1990 were not retained to ensure the quality and availability of imaging studies.

CTAs of the renal arteries and aorta were performed until 2005 on a 4-row multislice CT scanner (Somatom; Siemens AG, Erlangen, Germany) with a slice thickness of 1 mm and subsequently on a GE LightSpeed VCT 64-slice scanner (GE Medical Systems, Milwaukee, WI) with a slice thickness of 0.625 mm. Nonionic contrast medium (100 mL Xenetix, 350 mg iodine/mL; Guerbet, Roissy, France) was injected with a power injector into a peripheral vein at a rate of 4 to 5 mL/s, followed by a 30-mL saline flush. The helical acquisition was initiated after the bolus reached the abdominal aorta with a triggering system. MRA examinations were performed on a 1.5-T scanner (Excite until 2005, Excite HDx currently; General Electric Medical Systems, Waukesha, WI) with multichannel body array coil. Bolus tracking was used to monitor the arrival of contrast agent at the abdominal aorta. Gadoterate meglumine (Dotarem; Guerbet, Roissy, France) was injected at 1.8 mL/s, followed by a 30-mL saline flush, with an automated power injector (Optistarr, Mallinckrodt). The sequence parameters for the image acquisition varied as follows for the coronal orientation: repetition time/echo time, 3 to 6/1 to 2 milliseconds; flip angle, 25° to 35°; number of signals acquired, 0.5 to 1; section thickness, 1.8 to 2.2 mm; pixel size, 1.2 to 0.8 and 1.5 to 1.1 mm; and overall acquisition time, ≤5 seconds. The vascular field of view was tailored to each patient to include the kidneys, celiac trunk, superior and inferior mesenteric arteries, and common and external iliac arteries. CTA and MRA data were analyzed on a computer workstation (Advantage Workstation, AW4.4, GE Medical Systems).

We limited inclusion to cases with renal artery FMD with or without FMD lesions in other vascular beds. FMD lesions were classified according to their radiological appearance as either unifocal (presence of a single focal or tubular stenosis; Figure 1A and 1B) or multifocal (presence of ≥2 stenoses on a given vessel segment with or without the typical string-of-beads appearance; Figure 1C–1F).3,6,8,11 Patients who had unifocal FMD lesions on a segment of renal arteries but multifocal FMD lesions on another segment or another vascular bed were classified as having multifocal FMD. The presence of renal artery dissections or aneurysms without direct evidence of an FMD stenosing lesion was not considered sufficient to diagnose FMD.12 The extent of renal artery FMD lesions was scored 1 to 4, depending on the presence of unilateral or bilateral
lesions involving renal artery trunk, branches, or both as previously published13:1

/11005 trunk or branch(es), but not both, affected on 1 side; 2
/11005 trunk and branch(es) affected on 1 side; 3
/11005 trunk or branch(es), but not both, affected on both sides; and 4
/11005 trunk and branch(es) affected on both sides. Renal asymmetry was defined as a difference

/11022 mm in the bipolar length between the 2 kidneys on ultrasound.14

Hypertension cure was defined as a blood pressure <140/90 mm Hg in the absence of any antihypertensive drug.

Clinical Data Retrieval
We extracted clinical and biological data collected at the first visit to our unit. For patients referred after FMD had been diagnosed elsewhere, we considered clinical and biochemical data collected at the first visit to our unit if it occurred within 1 year of the diagnosis of FMD and if there had been no renal artery intervention during this period. We estimated creatinine clearance using the Cockcroft-Gault formula15 normalized for body surface area considering intrinsic limits of each equation16 and the fact that most creatinine measurements were not done with current standards.

Statistical Methods
Comparisons were performed between unifocal and multifocal FMD. Quantitative variables are reported as medians and 25th and 75th percentiles and were compared with the Mann-Whitney test. Nominal and ordinal variables are reported as numbers and percentages and were compared with the Fisher exact test and the trend χ² test, respectively. Because of the large difference in the distribution of age and sex between the 2 groups, we tested whether values of P<0.05 for unadjusted comparisons remained <0.05 after adjustment for age and sex. Adjusted comparisons were performed with ANOVA for continuous variables and with the Mantel-Haenszel test for binary variables. Age at evaluation (FMD diagnosis) was dichotomized into ≤40 or >40 years for these adjustments. Reported P values are 2 sided, and because of the exploratory nature of the study, no adjustment was made for multiple comparisons. Stata 9.2 (Stata Corp, College Station, TX) was used for statistical analyses.

Results
Patient Screening and Selection
A query of databases found 700 patient records in which the diagnosis of FMD was mentioned at least once. Among all these potential FMD patients, 363 were excluded for the
most frequent type (82%). Almost all patients were referred with unifocal and multifocal FMD. Multifocal FMD was the cervical arteries were assessed in 24 of 61 patients with neurological symptoms or complications or in those patients referred elsewhere within the year preceding the first visit to our unit and did not undergo any renal artery intervention in the meantime.

**Characteristics of FMD Patients at the First Visit**

There were <20% missing data for all baseline variables except estimated creatinine clearance (21% missing data), renal asymmetry (28% missing data), and other vascular bed imaging. Indeed, since 2009, we have systematically assessed extrarenal arteries in patients with renal artery FMD. Before then, extrarenal vascular beds were assessed mostly in patients with neurological symptoms or complications or in patients with digestive symptoms or intermittent claudication. Cervical arteries were assessed in 24 of 61 patients with unifocal FMD and in 127 of 276 patients with multifocal FMD; digestive arteries, in 16 and 97 patients, respectively; and iliofemoral arteries, in 22 and 123 patients, respectively.

Table 2 reports characteristics at presentation of patients with unifocal and multifocal FMD. Multifocal FMD was the most frequent type (82%). Almost all patients were referred for hypertension, including 22 patients after a recent neurological event (stroke, vertebral or carotid artery dissection, or intracranial aneurysm rupture) related to cervical artery FMD (19 with multifocal FMD, 3 with unifocal FMD). Patients with unifocal FMD were younger (age distribution is shown in Figure 3), were more frequently current smokers, and had higher blood pressure levels at presentation than patients with multifocal FMD. Kidney asymmetry was more frequent in patients with unifocal FMD. FMD more frequently affected the right renal artery in both subtypes. Patients with multifocal FMD more frequently had bilateral lesions and had a higher renal artery score than patients with unifocal FMD.

**Renal Artery Interventions and Characteristics at Follow-Up**

Most (53 of 61, 87%) patients with unifocal FMD but fewer than half (105 of 276, 38%) of those with multifocal FMD...
had undergone a renal artery intervention at any time (nephrectomy, surgical reconstruction, or percutaneous angioplasty; unadjusted and adjusted \( P < 0.001 \)). For those patients who had at least 1 intervention, the median number of interventions was 1 (25th and 75th percentiles, 1 and 2) for both FMD subtypes (\( P = 0.49 \) for the difference).

Among patients who had a clinical follow-up visit at our unit \( > 365 \) days after the diagnosis of FMD, 28 of 31 with unifocal FMD (90%) and 50 of 141 with multifocal FMD (35%) had undergone renal artery intervention (adjusted and unadjusted \( P < 0.001 \); Table 3). The decreases from baseline to follow-up in systolic blood pressure and in the number of antihypertensive agents administered were larger for patients with unifocal FMD than with multifocal FMD. When the comparison was restricted to patients who had undergone renal artery interventions, those with unifocal and multifocal FMD had similar drops in systolic blood pressure (\(-29 \text{ mm Hg} [25\text{th and 75\text{th percentiles, } } -51 \text{ and } -14 \text{ mm Hg}] \text{ and } -29 \text{ mm Hg} [25\text{th and 75\text{th percentiles, } } -48 \text{ and } -19 \text{ mm Hg}; \ P = 0.86] \). However, the proportion of patients cured of hypertension was 54% (15 of 28) for unifocal FMD and 26% (13 of 50) for multifocal FMD (\( P = 0.03 \)). This difference remained significant after adjustment for sex and age (\( P = 0.02 \)).

Table 3. Characteristics at Follow-Up >365 Days for Patients With Unifocal or Multifocal Renal Artery FMD With First Visit Before October 1, 2010

<table>
<thead>
<tr>
<th></th>
<th>Unifocal (n=52)</th>
<th>Multifocal (n=213)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with clinical follow-up &gt;365 d, n (%)</td>
<td>52 31 (60%)</td>
<td>213 141 (66%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Follow-up duration, y</td>
<td>31 4 (2, 8)</td>
<td>141 4 (3, 9)</td>
<td>0.39</td>
</tr>
<tr>
<td>Renal artery intervention during follow-up, n (%)</td>
<td>31 28 (90%)</td>
<td>141 50 (35%)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Current smoker, at last follow-up, n (%)</td>
<td>31 9 (29)</td>
<td>139 24 (17)</td>
<td>0.14</td>
</tr>
<tr>
<td>Body mass index at last follow-up, kg/m²</td>
<td>30 23 (22, 26)</td>
<td>130 25 (22, 28)</td>
<td>0.25</td>
</tr>
<tr>
<td>Systolic blood pressure at last follow-up, mm Hg</td>
<td>31 123 (114, 130)</td>
<td>139 124 (114, 135)</td>
<td>0.54</td>
</tr>
<tr>
<td>Change in systolic blood pressure, mm Hg</td>
<td>31 -30 (−53, −14)</td>
<td>138 -20 (−37, −5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diastolic blood pressure at last follow-up, mm Hg</td>
<td>31 77 (74, 85)</td>
<td>139 74 (67, 82)</td>
<td>0.06</td>
</tr>
<tr>
<td>Change in diastolic blood pressure, mm Hg</td>
<td>31 -19 (−35, −3)</td>
<td>138 -14 (−27, −2)</td>
<td>0.14</td>
</tr>
<tr>
<td>Antihypertensive agents at last follow-up, n</td>
<td>31 0 (0, 1)</td>
<td>140 2 (1, 3)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Change in number of antihypertensive agents, n</td>
<td>31 1 (−1, 0)</td>
<td>139 0 (−1, 1)</td>
<td>0.006</td>
</tr>
<tr>
<td>Estimated creatinine clearance at last follow-up,* mL · min⁻¹ · 1.73 m⁻²</td>
<td>25 130 (109, 153)</td>
<td>106 124 (108, 146)</td>
<td>0.45</td>
</tr>
<tr>
<td>Change in estimated creatinine clearance,* mL · min⁻¹ · 1.73 m⁻²</td>
<td>25 42 (24, 53)</td>
<td>98 41 (27, 56)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

FMD indicates fibromuscular dysplasia. The number of patients available for analysis is shown for each variable. Values are numbers of patients (percentage) for binary variables and median (25th, 75th percentiles) for quantitative variables.

*From the Cockcroft-Gault formula.
Discussion

Since the advent of renal artery percutaneous angioplasty, few patients with FMD have undergone primary surgical revascularization; furthermore, any surgery usually follows 1 or more attempts at percutaneous angioplasty. Consequently, unaltered pathological samples are rarely available, so the diagnosis and classification of FMD has to be based on the angiographic appearance of stenoses and exclusion criteria (The disease affects medium-sized arteries; it is neither atherosclerotic nor inflammatory; and there is no known syndromic vascular disease).

Previous and Current Angiographic Classifications

Several series published in the 1960s and 1970s described comparisons of pathology and catheter-based angiography. These studies led to an angiographic classification in which the beaded aspect was a specific but not sensitive correlate of the medial-type FMD (see Table 1). Several later series used a pathological terminology (eg, intimal, medial, or subadventitial fibroplasia), although pathological specimens were not available. More recent series dichotomized renal artery FMD into 2 subtypes according to various criteria: multifocal or unifocal, medial or nonmedial, or FMD with or without a beaded or string-of-pearls appearance. Other series considered FMD to be present only when angiography showed beads or a string of pearls. Twenty-four of the 47 studies reporting percutaneous angioplasty in patients with FMD did not indicate the criteria used to diagnose FMD. To avoid these confusing considerations, we propose a binary angiographic classification into multifocal or unifocal disease. This classification is possible from CTA or MRA, both of which are minimally invasive imaging tests. In the present angiographic classification, unifocal FMD includes focal or tubular FMD, sometimes called nonmedial FMD. Multifocal FMD is defined by the presence of multiple stenoses on a given vessel segment with or without the string-of-beads appearance. Patients with or without the typical string-of-beads pattern did not differ in clinical presentation, distribution of lesions, or number of interventions; therefore, we considered them together (Table I in the online-only Data Supplement). This finding strengthens the view that patients with multifocal FMD stenoses represent a relatively homogeneous subgroup, whether stenoses alternate with arterial dilatations or not. Our data show that this binary angiographic classification, at least at the renal artery level, distinguishes patients who also differ by several clinical traits, making them 2 distinct entities.

Comparison Between Unifocal and Multifocal FMD

In our series of adult patients with established renal artery FMD, 61 of the 337 patients (18%) showed the unifocal pattern. This proportion is similar to that reported in the angiographic/pathological series by McCormack et al (31%), Kincaid et al (11%), and Stanley et al (16%; see Table 1) and in a recent meta-analysis of angioplasty in FMD (30%). However, nonmedial FMD accounted for only 8.6% of 302 cases in the US registry of FMD. The difference between the proportion of nonmedial FMD in the US registry may have several explanations: The spectrum of patients differs because the US registry dealt with FMD at any vascular bed whereas patients with cervical artery FMD only (without renal artery FMD) were excluded from the present series; angiographic criteria used to define medial-type and nonmedial-type FMD across the 9 participating US centers were not reported; and the type of FMD was not recorded in 145 patients from this registry. Using a similar terminology and similar diagnostic methods should help to compare observations across centers and conclude whether the observed difference in the prevalence of unifocal (or nonmedial) FMD is linked to diagnostic criteria, patient presentation, or the vascular beds involved.

In addition to the angiographic appearance, various clinical characteristics differed between unifocal and multifocal FMD patients. A higher proportion of unifocal than multifocal FMD patients were men, and unifocal FMD was diagnosed almost 20 years earlier than multifocal FMD. Bilateral lesions were less frequent in unifocal than multifocal FMD patients. At referral, blood pressure was higher and renal asymmetry was more frequent for unifocal FMD than multifocal FMD patients. Among patients with a follow-up of >365 days, unifocal FMD patients more frequently underwent renal artery intervention, perhaps because the degree of unifocal stenosis is more easily evaluated by noninvasive angiography and unifocal lesions are more amenable to angioplasty. There was also a larger drop in blood pressure and in the number of antihypertensive agents in patients with unifocal FMD; this was explained by a higher proportion of renal artery interventions because the blood pressure drop was similar in both subgroups if only revascularized patients are considered. The overall cure rate was 36% after angioplasty, entirely consistent with published results. However, our results suggest that hypertension cure rates are higher in patients with unifocal FMD (54%) than in those with multifocal FMD (26%). Patients with unifocal FMD were younger, had a shorter duration of hypertension at diagnosis of FMD, and displayed renal asymmetry more frequently than patients with multifocal FMD. All these findings increase the probability of true renovascular hypertension rather than associated essential hypertension. Moreover quantifying stenosis grade is notoriously difficult in multifocal FMD. Consequently, patients with nonhemodynamically significant multifocal FMD and associated essential hypertension may be advised to undergo angioplasty, resulting in a disappointing blood pressure outcome.

The few previous articles comparing clinical characteristics of FMD subtypes are consistent with our results. McCormack et al reported that 9 of 14 patients with intimal FMD and 3 of 15 patients with medial FMD were male. Stewart et al and Stanley et al stated that intimal fibroplasia (with a nonbeaded aspect) occurs more frequently in children and young adults. Meaney et al and Goncharenko et al reported that patients with nonbeaded renal artery FMD more frequently had progressive stenoses. In a previous study of sporadic and apparently familial FMD, we found the same age and sex differences between unifocal and multifocal FMD as in the present study. These various findings suggest
that unifocal FMD and multifocal FMD are distinct entities. The unifocal FMD type (with no predictable histological substrate) appears to be a precocious, severe, and progressive form of FMD, whereas the multifocal type (mostly reflecting medial fibroplasia) presents as a relatively diffuse but milder arterial disease. Our data concerning extrarenal FMD should be considered with caution, however, because, until recently, we did not systematically investigate cervical arteries in patients with renal artery FMD.

Study Strengths and Weaknesses
Our study is based on a large number of carefully selected and well-characterized patients with FMD. It relies on contemporary, easily available imaging tests, CTA and MRA. We performed multiple comparisons, so some of the values of \( P < 0.05 \) may have been due to chance alone. However, most differences were highly significant (\( P < 0.001 \)) and can therefore be regarded with confidence. Our study is retrospective and exposed to referral biases. The retrospective design has limitations, including missing data, especially for extrarenal vascular imaging. Consequently, robust conclusions cannot be drawn about the prevalence of concomitant FMD lesions on other vascular beds. Recent data show that the prevalence of cervical artery lesions in patients with FMD has been underestimated, and this is probably the case in this series also. Indeed, only hypertensive patients are referred to our center, leaving out those who present with signs or symptoms suggesting cervical artery FMD but do not have high blood pressure. In contrast, the computerized and structured data recording for clinical care resulted in few missing data for other variables. All our patients had renal artery FMD, and most were referred on the basis of resistant hypertension or hypertension diagnosed at a young age. This may explain why the median age at referral for the present series was lower than those for series that included patients with cervical artery FMD. Finally, CTA and MRA allow FMD to be diagnosed reliably but do not quantify stenosis grade. Therefore, we did not attempt to relate blood pressure levels or other variables. All our patients had renal artery FMD, and most were referred on the basis of resistant hypertension or hypertension diagnosed at a young age. This may explain why the median age at referral for the present series was lower than those for series that included patients with cervical artery FMD. Finally, CTA and MRA allow FMD to be diagnosed reliably but do not quantify stenosis grade. Therefore, we did not attempt to relate blood pressure levels or other variables. All our patients had renal artery FMD, and most were referred on the basis of resistant hypertension or hypertension diagnosed at a young age. This may explain why the median age at referral for the present series was lower than those for series that included patients with cervical artery FMD.28

Perspectives
An essential step toward collaborative studies on rare diseases is to establish a consensus for definition and classification. Our results indicate that minimally invasive angiography reliably distinguishes 2 types of FMD. Collecting prospective data from a large number of patients with FMD in international databases should help to elucidate the pathophysiology of FMD and to confirm whether the natural history correlates with the angiographic phenotype.

Conclusions
Our analysis suggests that a binary angiographic classification into unifocal and multifocal types of FMD is clinically relevant. Unifocal and multifocal types of FMD have differing nonangiographic phenotypes. Unlike histological classifications that can be applied only to operated patients, the angiographic classification can be used for all FMD patients. It should facilitate future pathophysiological, epidemiological, clinical, and genetic studies.

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Fibromuscular dysplasia is a heterogeneous group of idiopathic, noninflammatory, and nonatherosclerotic stenosing vascular diseases mostly involving renal and cervical arteries. It is the second most frequent cause of renovascular hypertension. Its historical classification based on histology is no longer relevant now that percutaneous revascularization has replaced surgery in most cases. In this study, we describe an angiographic classification of renal artery fibromuscular dysplasia lesions into a unifocal and a multifocal subtype. Fewer patients have unifocal lesions (18% of all patients with renal artery fibromuscular dysplasia), and their characteristics contrast with those of patients with multifocal lesions: They are younger at diagnosis (30 versus 49 years); the proportion of women is lower (69% versus 83%); they are more often current smokers (50% versus 26%) with higher blood pressure levels (157/97 versus 146/88 mm Hg); the disease is more often unilateral (79% versus 38%); they are more amenable to revascularization (90% versus 35%); and have a higher cure rate when revascularization is performed (54% versus 26%).
Association Between 2 Angiographic Subtypes of Renal Artery Fibromuscular Dysplasia and Clinical Characteristics
Sébastien Savard, Olivier Steichen, Arshid Azarine, Michel Azizi, Xavier Jeunemaitre and Pierre-François Plouin

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**SUPPLEMENTAL MATERIAL**

**Supplemental Table 1. Comparison between cases of multifocal fibromuscular dysplasia with and without the typical string-of-beads appearance**

<table>
<thead>
<tr>
<th></th>
<th>Multifocal FMD with string-of-beads (n = 205)</th>
<th>Multifocal FMD without string-of-beads (n = 71)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>205 30 (15)</td>
<td>71 17 (24)</td>
<td>0.10</td>
</tr>
<tr>
<td>Personal history of hypertension</td>
<td>205 191 (93)</td>
<td>71 67 (94)</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis of hypertension, years</td>
<td>189 40 [32, 48]</td>
<td>67 39 [29, 52]</td>
<td>0.74</td>
</tr>
<tr>
<td>Age at diagnosis of FMD, years</td>
<td>205 49 [43, 57]</td>
<td>71 50 [38, 63]</td>
<td>0.84</td>
</tr>
<tr>
<td>FMD site: right, unilateral</td>
<td>205 64 (31)</td>
<td>71 21 (30)</td>
<td></td>
</tr>
<tr>
<td>left, unilateral</td>
<td>205 13 (6)</td>
<td>71  7 (10)</td>
<td>0.62</td>
</tr>
<tr>
<td>bilateral</td>
<td>205 128 (62)</td>
<td>71  43 (61)</td>
<td></td>
</tr>
<tr>
<td>Median renal artery score</td>
<td>205 3 [1, 3]</td>
<td>71 3 [1, 4]</td>
<td>0.59</td>
</tr>
<tr>
<td>Scoring 1</td>
<td>205 56 (27)</td>
<td>71 20 (28)</td>
<td></td>
</tr>
<tr>
<td>Scoring 2</td>
<td>205 21 (10)</td>
<td>71  8 (11)</td>
<td></td>
</tr>
<tr>
<td>Scoring 3</td>
<td>205 82 (40)</td>
<td>71 21 (30)</td>
<td></td>
</tr>
<tr>
<td>Scoring 4</td>
<td>205 46 (22)</td>
<td>71 22 (31)</td>
<td></td>
</tr>
<tr>
<td>Renal artery interventions at any time</td>
<td>205 77 (38)</td>
<td>71 28 (39)</td>
<td>0.65</td>
</tr>
<tr>
<td>Difference of kidney length &gt;20 mm on initial ultrasound</td>
<td>146 14 (10)</td>
<td>49  5 (10)</td>
<td></td>
</tr>
</tbody>
</table>

The number of patients available for analysis is shown for each variable. Values are numbers of patients (percentage) for binary variables and median [25th centile, 75th centile] for quantitative variables. FMD, fibromuscular dysplasia.