

## Fibromuscular Dysplasia: State of the Science and Critical Unanswered Questions

### A Scientific Statement From the American Heart Association

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Fibromuscular dysplasia (FMD) is nonatherosclerotic, noninflammatory vascular disease that may result in arterial stenosis, occlusion, aneurysm, or dissection.<sup>1-3</sup> The cause of FMD and its prevalence in the general population are not known.<sup>4</sup> FMD has been reported in virtually every arterial bed but most commonly affects the renal and extracranial carotid and vertebral arteries (in ≈65% of cases).<sup>5</sup> The clinical manifestations of FMD are determined primarily by the vessels that are involved. When the renal artery is involved, the most frequent finding is hypertension, whereas carotid or vertebral artery FMD may lead to dizziness, pulsatile tinnitus, transient ischemic attack (TIA), or stroke. There is an average delay from the time of the first symptom or sign to diagnosis of FMD of 4 to 9 years.<sup>5,6</sup> This is likely because of a multitude of factors: the perception that this is a rare disease and thus FMD is not considered in the differential diagnosis, the reality that FMD is poorly understood by many healthcare providers, and the fact that many of the signs and symptoms of FMD are non-specific, thus leading the clinician down the wrong diagnostic

pathway. A delay in diagnosis can lead to impaired quality of life and poor outcomes such as poorly controlled hypertension and its sequelae, TIA, stroke, dissection, or aneurysm rupture. It should also be noted that FMD may be discovered incidentally while imaging is performed for other reasons or when a bruit is heard in the neck or abdomen in an asymptomatic patient without the classic risk factors for atherosclerosis.

#### Historical Perspective

The first description of FMD is attributed to Leadbetter and Burkland<sup>7</sup> in a 5½-year-old boy with severe hypertension and a renal artery partially occluded by an intra-arterial mass of smooth muscle. He underwent a unilateral nephrectomy of an ectopic pelvic kidney, and his hypertension was cured. The authors stated, "It seems quite obvious that by chance we have stumbled on a peculiar anomaly of development affecting a renal artery."<sup>7</sup> The term fibromuscular hyperplasia was introduced in 1958 by McCormack and associates<sup>8</sup> after their observation of 3 patients with arterial hypertension and renal artery

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stenosis. However, it was not until Palubinskas and Wylie,<sup>9</sup> Hunt,<sup>10</sup> and Kincaid and Davis<sup>11</sup> described in 1961 the arteriographic and clinical manifestations of what was then called fibromuscular hyperplasia that this systemic arteriopathy of obscure origin became widely recognized. McCormack and associates<sup>12</sup> published a detailed pathological-arteriographic correlation of the different types of FMD and how they compared with atherosclerosis, a more common cause of renal artery stenosis. In 1971, Harrison and McCormack<sup>13</sup> proposed a detailed pathological classification (with angiographic correlates) of FMD of the renal artery into 3 distinct types based on the arterial layer most affected: medial, intimal, and adventitial/periarterial.

Extracranial cerebrovascular FMD was first identified angiographically by Palubinskas and Ripley<sup>14</sup> in 1964 as a nonatherosclerotic cause of internal carotid artery stenosis. One year later, Connett and Lansche<sup>15</sup> published the first histologically proven case of FMD of the internal carotid arteries in a 34-year-old woman that resulted in cerebral thrombosis causing right hemiparesis and aphasia. Several years later, a woman with bilateral FMD of the cervical internal carotid arteries was treated with resection of the artery with relief of transient ischemic symptoms.<sup>16</sup> Cerebrovascular FMD has been noted not only in the internal carotid arteries but also in the vertebral arteries and less commonly in the middle cerebral arteries and external carotid arteries and its branches.<sup>17</sup>

In 1974 and 1975, Stanley and colleagues<sup>18–20</sup> published 3 landmark articles on extracranial internal carotid and vertebral artery FMD and the cause, classification, and surgical treatment of patients with renal artery FMD.

In 2011, an expert French/Belgian consensus panel was convened to review the topic of FMD and to make recommendations on diagnosis and management.<sup>2</sup> Data from the first 447 patients enrolled in the United States Registry for Fibromuscular Dysplasia (US Registry) were reported several months after the European Consensus document.<sup>5</sup> These recent publications have added new information about FMD and dispelled some of the myths about this disease that continue to be taught in medical schools and during postgraduate education.

## Epidemiology

The prevalence of FMD in the general population is not known. In one of the largest series of >1000 patients with FMD, 58% of cases involved the renal artery, 32% involved the carotid/vertebral artery, and 10% involved other arteries such as the iliac artery or intracranial vessels.<sup>3,21</sup> Others have suggested that the proportion of renal artery involvement in FMD is as high as 75% of all cases.<sup>22</sup> The prevalence of renal artery FMD has been estimated to be as high as 4 per 100 adults.<sup>22–24</sup> One source of the prevalence data is the renal angiograms of potential renal donors. In a series of 716 potential renal donors for whom 80% of the angiograms were available for retrospective review, 6.6% had FMD.<sup>25</sup> In another series of 1862 patients, 3.8% had angiographic evidence of FMD.<sup>22</sup> A smaller but more recent study confirmed these results.<sup>24</sup> Plouin and associates<sup>3</sup> summarized the results of 4 separate angiographic studies involving 3181 asymptomatic potential kidney donors and found that 139 subjects (4.4%) had angiographic evidence of FMD. Over the course of 2.5 to 7.5

years of follow-up, 26% to 29% of nondonating individuals developed hypertension.<sup>3,22,26</sup> The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial was a randomized trial of maximal medical therapy alone versus maximal medical therapy and renal artery stenting for patients with atherosclerotic renal artery stenosis and hypertension. Data from the angiographic core laboratory showed that among 1014 patients, 58 patients (5.7%; mean age, 71.8 years) were incidentally found to have FMD, again illustrating that FMD is more common than previously suggested.<sup>27</sup> One large autopsy study by Heffelfinger and colleagues<sup>28</sup> with 819 consecutive autopsies found that only 1% of the cases had FMD. Of note, this study was published only in abstract form, and complete details of this report cannot be ascertained. In addition, it is not known whether the angiogram is a more sensitive way of detecting renal FMD than autopsy, nor is it known how carefully the renal arteries were examined. As a result, the prevalence of renal artery FMD in the general population is not known, nor is it known whether it varies by ethnic or racial groups. It is clear that FMD is more common in women than in men by a ratio of 9:1.<sup>5</sup> If FMD is as common as suggested by the studies of potential kidney donors, as many as 5 million Americans may have FMD, most undetected. However, it is important to recognize that this estimate is derived from a population of potential kidney donors, most of whom have a family member affected by chronic kidney disease, and may not be reflective of the general population.

There is limited information on the prevalence of carotid, vertebral, and intracranial FMD. This may be because of the misconception that carotid or vertebral artery FMD is not as common as renal artery FMD, the nonspecific nature of symptoms of cerebrovascular FMD (ie, headache, dizziness), or the potential for asymptomatic presentation.<sup>1,5,29</sup> FMD affects the middle and distal portion of the internal carotid and vertebral arteries and less commonly the intracranial arteries.<sup>5,29</sup> The prevalence of carotid and vertebral artery FMD, as assessed from studies that examined consecutive angiograms, ranges from 0.3% to 3.2%.<sup>29</sup> Because angiograms were likely performed for specific clinical indications, these percentages may be higher than would occur in the general population. The prevalence of cerebrovascular FMD from autopsy data is far lower than that obtained from series in which angiograms were analyzed. Among 20244 consecutive autopsy cases, only 4 had cervical (vertebral) or intracranial FMD.<sup>30</sup> Spontaneous cervical artery dissections are a common cause of stroke in young adults and are associated with FMD of the cervical artery in ≈15% to 20% of cases.<sup>31,32</sup>

The cause of FMD is unknown. Hormonal factors such as estrogen have been proposed, but there is little supporting epidemiological evidence for the role of female hormones beyond the sex and age distribution of FMD. In the US Registry, 91% of registrants were female.<sup>5</sup> FMD has not been associated with the number of pregnancies or the use of oral contraceptives or other hormones.<sup>33</sup> Sang and colleagues<sup>33</sup> reported a case-control study of 33 FMD patients with renal FMD and 61 control subjects and noted a dose-dependent relationship between cigarette smoking and risk of FMD, although this has not been verified by larger or more recent studies.<sup>5,29,33</sup> In the US Registry, only 37% of patients had a history of ever smoking

tobacco.<sup>5</sup> However, Savard and colleagues<sup>33a</sup> reported that the proportion of current smokers was higher among patients with FMD compared with a control group matched for age, sex, systolic blood pressure, number of antihypertensive, and year of visit (30% versus 18%;  $P < 0.001$ ; odds ratio [OR], 2.5; 95% confidence interval [CI], 1.6–3.9).

### Genetic Considerations

Genetic and genomic studies have the potential to advance our understanding of FMD. Identification of genes associated with FMD may elucidate disease mechanisms and facilitate detection, prevention, and therapeutic strategies.<sup>34</sup> To date, both family-based and association methods have been used in small samples of FMD patients. However, no etiologic genes for FMD have been identified. Studies using contemporary genetic approaches with detailed patient phenotyping in larger cohorts are necessary to discover genes linked to FMD.

Several lines of evidence indicate that inherited factors contribute to FMD. A number of individual case reports describe the occurrence of FMD in first-degree relatives of affected individuals.<sup>35–37</sup> In a study of 20 families, Rushton<sup>38</sup> and Gladstien and colleagues<sup>39</sup> classified 60% of cases as familial and found the inheritance pattern to be autosomal dominant with variable penetrance. However, affected family members were identified on the basis of a clinical history of cardiovascular disease or hypertension at an early age without confirmation of FMD diagnosis. Recent studies using renal angiographic definitions estimate familial cases to represent 7% to 11% of all FMD patients.<sup>23,40,41</sup> Of 447 patients entered in the US Registry, only 7.3% of patients reported a confirmed diagnosis of FMD among a family member.<sup>5</sup> In the US Registry, a family history of aneurysm was reported in 23.5% of patients.<sup>5</sup> The phenotypic expression of FMD varies across family members, suggesting a common vascular wall abnormality with variable penetrance in specific vascular beds.<sup>42</sup> Distinct disease patterns have been observed in familial cases, including higher rates of bilateral and multivessel involvement, suggesting that inherited disease may have a more severe phenotype.<sup>40</sup> Larger family studies are ongoing that will provide more precise heritability estimates for FMD.

In general, gene polymorphism associations have not been robust or replicated for FMD. A genetic variant in the angiotensin-converting enzyme (ACE) was associated with FMD in a small case-control study of 43 renal FMD patients and 89 normotensive control subjects but has not been replicated.<sup>43</sup> Case reports described individuals with  $\alpha$ -1 antitrypsin deficiency and FMD, but a large case-control study reported no such association.<sup>44–47</sup> Additional studies have evaluated common variants in *ACTA2*, the gene for smooth muscle cell  $\alpha$ -actin, and elastin genes and found no relation with FMD.<sup>41,48</sup> Blood samples have been collected and stored in a biorepository from among a group of FMD patients enrolled at participating US referral centers. When funding becomes available, genetic analyses will be performed.

Poloskey and colleagues<sup>49</sup> demonstrated that the prevalence of genetic mutations associated with connective tissue disorders, including the *COL31A* gene, transforming growth factor (*TGF*)- $\beta$ 1 and  $\beta$ 2 genes, and the *ACTA2* gene, was negligible in an FMD cohort. In their case series, however, they report

2 patients with distinct novel point mutations in the *TGF*- $\beta$  receptor type 1 gene, mutations of which have been associated with inherited aneurysmal disease.<sup>49,50</sup> Both patients with these *TGF*- $\beta$  receptor type 1 mutations had multifocal disease (medial fibroplasia), had suffered carotid or vertebral artery dissection, had ascending aortic dilatation, and had a family history of sudden death.<sup>49</sup>

In summary, evidence supports a genetic basis for susceptibility to FMD. Multiple barriers have impeded the identification and characterization of genes that may contribute to FMD. Disease rarity hinders the establishment of large cohorts required for robust genetic studies. The disease phenotype in FMD is variable, and it remains possible that genetic abnormalities are confined to specific subsets of FMD patients. Gene-environment interactions may influence the predisposition for FMD and are difficult to detect in small study samples. We anticipate that the application of molecular genetics in future studies will yield novel information on the pathogenesis of FMD. Ideally, complementary genetic approaches, including family-based studies, candidate gene evaluation, and genome-wide association studies, would be pursued to identify potential causative pathways for this disease.

### Histopathological Classification Systems for FMD

In 1971, Harrison and McCormack<sup>13</sup> codified the histological classification system for FMD from a consensus conference between investigators from the Cleveland Clinic and the Mayo Clinic.<sup>12,51</sup> This effort provided a framework for a more organized and reproducible classification of FMD that heretofore had been plagued by erratic and inconsistent description and terminology. This classification system categorized FMD according to the arterial layer involved, namely intimal, medial, and adventitial disease (Table 1). Angiographic correlations have been derived largely from the work of Kincaid and colleagues (Figures 1–3).<sup>53</sup>

Intimal disease is notable for the nonatherosclerotic, noninflammatory accumulation of fibrous tissue in the intima with a moderately cellular component. The internal elastic membrane is preserved and often reduplicated, and intimal disease was believed to account for 1% to 2% of FMD in the early reports. Today, it is likely the second most commonly encountered type of FMD as represented by focal angiographic stenoses (Figure 2).<sup>5</sup>

Medial FMD, the most common histological variant, was originally subdivided into a complex system of 4 subcategories. Medial fibroplasia, characterized by deposition in the media of loose collagen in zones of degenerating elastic fibrils, accounted for 60% to 70% of FMD in initial reports and >90% today.<sup>5</sup> It generates fibromuscular ridges, with resultant arterial stenoses alternating with areas of smooth muscle loss with consequent arterial dilatation. The alternating stenoses and dilatation produce the classic “string of beads” appearance on angiography, typically within the distal two thirds of the main renal artery and its branches and in the mid and distal cervical portions of the internal carotid and vertebral arteries (Figure 1). The internal elastic lamina is deficient in the dilated segments.

Perimedial fibroplasia, previously thought to account for 15% to 25%, now represents approximately <1% of FMD in

**Table 1. Classification of Fibromuscular Dysplasia**

Histological	Angiographic	
Harrison and McCormack (1971) <sup>13</sup>	French/Belgian Consensus (2012) <sup>2</sup>	American Heart Association (2014)
Medial Medial fibroplasia (60%–70%) Perimedial fibroplasia (15%–25%) Medial hyperplasia (5%–15%)	Multifocal	Multifocal
Intimal fibroplasia (1%–2%)	Unifocal (<1 cm) Tubular (≥1 cm)	Focal*
Adventitial (<1%)		

\*There may be multiple areas of focal disease (eg, renal artery and carotid artery in the same patient). Focal and multifocal disease can occur in the same patient.

adults.<sup>5</sup> Perimedial fibroplasia appears to be predominantly a disease of female children. Marked fibroplasia in the outer half of the media results in irregular luminal narrowing. The “beads” (dilated segments) are smaller and less numerous than those seen in medial fibroplasia (Figure 3). The external elastic lamina is generally obliterated by the fibroplasia.

Medial hyperplasia is the least common variant of medial FMD (<1% today) and is notable for medial smooth muscle hyperplasia without significant collagen deposition. The arterial walls are otherwise well preserved, including the elastic laminae.

The third major histological subtype, adventitial or periarterial disease, accounted for <1% of lesions. This is notable for collagen deposition surrounding the adventitia and extending

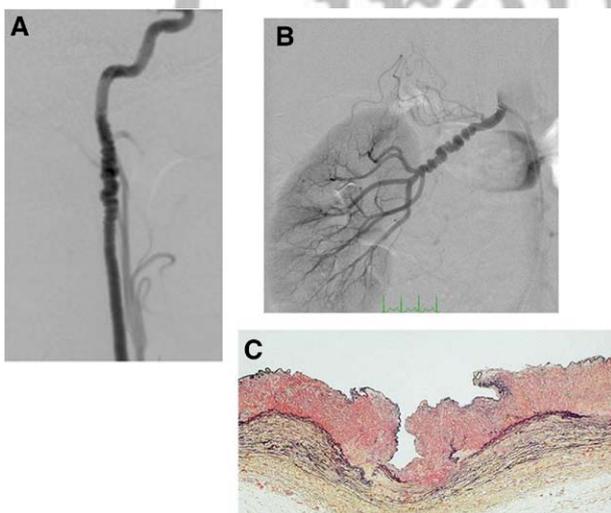
into the periarterial tissue, with focal infiltration of lymphocytes being common.

A host of other classifications of FMD have been proposed, but none have been uniformly accepted because of obtuse terminology and uncertainty of the relationship of the histological variants, given that the pathogenesis is fundamentally unknown.<sup>19,20,54–57</sup>

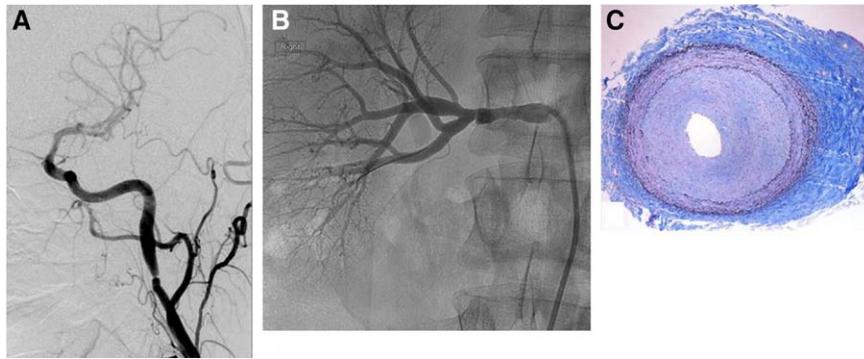
Further limiting the utility of all histopathological classifications is the realization that FMD today is a disease almost exclusively diagnosed radiographically. With the introduction of percutaneous revascularization, the use of surgical bypass and the obtaining of histological specimens have become quite rare. Indeed, in the US Registry, histopathological confirmation of FMD was available for only 14 of 447 patients enrolled (3.3%).<sup>5</sup> The most common arteriographic findings are multiple areas of stenosis and dilatation (string of beads) and tubular and focal stenoses.<sup>53</sup> Medial fibroplasia most commonly presents with a string of beads appearance. Although tubular and focal stenoses are common in intimal fibroplasia, these radiographic appearances have been described with all histological subtypes and are rather nonspecific. Adventitial disease often produces tubular stenoses, but the number of reported adventitial cases has been small.<sup>4,5,12,13</sup> Intraluminal fibrous webs have also been documented histologically, but they may not be visible angiographically. Intravascular ultrasound (IVUS) may reveal their presence, and their subtlety contributes to the difficulty in diagnosing the presence and hemodynamic significance of FMD lesions.<sup>58</sup>

The 2012 French and Belgian consensus statement supported shifting from histological classification to simple radiographic classification, with multifocal, unifocal (<1 cm stenosis), and tubular (≥1 cm) classifications (Table 1).<sup>2</sup> It was further proposed that the latter 2 be combined into 1 definition of unifocal.<sup>2</sup> Unifocal implies a solitary lesion and may not accurately describe patients with multiple focal lesions.

Savard and colleagues<sup>6</sup> have demonstrated that by using a binary angiographic classification, they could discriminate between 2 distinct clinical phenotypes. Of the 337 patients with established renal artery FMD, 276 (82%) were classified as multifocal (ie, string of beads appearance; Figure 1). They demonstrated that patients with unifocal FMD (Figure 2) were younger at diagnosis (30 versus 49 years of age), had onset of hypertension at a younger age (26 versus 40 years of age), were more likely to be male (female-to-male ratio, 2:1



**Figure 1.** Typical arteriographic findings of multifocal fibromuscular dysplasia in the carotid (A) and renal (B) arteries according to the American Heart Association classification system. This angiographic pattern is indicative of medial fibroplasia. There are multiple areas of alternating stenosis and dilatation (string of beads). Note that the disease is located in the mid to distal portion of the internal carotid and renal arteries. C, In medial fibroplasia, there are alternating areas of thinned media and thickened fibromuscular ridges in which the arterial muscle is replaced by fibroplasia with loose collagen. Shown here is a high-magnification photomicrograph demonstrating a gap in the arterial media. Reprinted from Virmani et al<sup>52</sup> with permission from Elsevier. Copyright © 2013, Elsevier, Inc. Photomicrograph courtesy of Renu Virmani, MD, CV Path Institute, Gaithersburg, MD.



**Figure 2.** Arteriographic findings of focal fibromuscular dysplasia in the renal and internal carotid arteries according to the American Heart Association classification system. This angiographic pattern is most consistent with intimal fibroplasia. This can present with a concentric band (focal constriction) as shown in the right internal carotid artery (A) or the right renal artery (B). C, Histopathological findings. There is concentric thickening of the intima. The media and adventitia are relatively normal. Panel C reprinted from Virmani et al<sup>52</sup> with permission from Elsevier. Copyright © 2013, Elsevier, Inc. Photomicrograph courtesy of Renu Virmani, MD, CV Path Institute, Gaithersburg, MD.

versus 5:1), were more likely to undergo revascularization (90% versus 35%), and had a higher rate of cure of hypertension among those revascularized (54% versus 26%).<sup>6</sup> Because all patients in this series presented with hypertension and renal artery FMD, it is not clear whether this phenotypic difference will also be present in those with FMD in other arterial locations.<sup>59</sup>

Acknowledging the practicality and appropriateness of an angiographic classification, we propose an American Heart Association classification that is a minor modification in the classification proposed by the European Consensus (Tables 1 and 2).<sup>2</sup> Multifocal disease is the classic string of beads appearance represented by medial fibroplasia in virtually all adults. Focal disease is without regard to lesion length, is usually caused by intimal fibroplasia, but may also be caused by medial hyperplasia or adventitial FMD. Patients may have simultaneous multifocal and focal disease in different vascular territories. Aneurysms and dissections of medium-sized arteries may occur in patients with imaging features of FMD but are not angiographic subtypes of disease. Arterial tortuosity with coils, kinks, loops, and bends is another angiographic finding in FMD that is common but not specific to the disease. Convincing data

on the association of radiographic appearance with outcome do not exist. The intent of this updated classification system is to allow further standardization of clinical classification of patients with FMD and to optimize future efforts to study clinical outcomes according to disease category. Multifocal and focal FMD may in fact not be the same disease.<sup>59</sup>

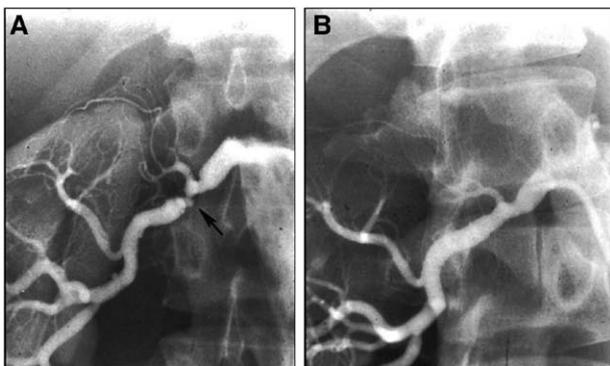
### Clinical Manifestations

The clinical manifestations of FMD are variable and depend on a number of factors; most important among them are the distribution of vascular bed involvement and the type and severity of the vascular lesions (ie, stenoses of various degrees, arterial dissection, arterial aneurysm). In the US Registry, the majority of patients presented with at least 1 clinical symptom or sign, and only 5.6% of patients were truly asymptomatic, although this high prevalence of symptoms reflects the referral nature of the registry cohort.<sup>5</sup> The frequency of initial presenting signs and symptoms of FMD among patients in the US Registry is shown in Table 3.

### Renal Artery FMD

The most common manifestation of renal artery FMD is hypertension, the severity and onset of which are variable. Although FMD should be suspected as a potential diagnosis in the patient with early-onset hypertension (eg, before 35 years of age) or drug-resistant hypertension, it should be noted that the average age of onset of hypertension among patients in the US Registry was 43.1 years, resulting in significant overlap with the population of patients with essential hypertension.<sup>5</sup>

In addition to hypertension, an epigastric or flank bruit on physical examination is a potential manifestation of renal artery FMD. Flank pain may be a manifestation of renal artery dissection or aneurysm but may also occur in patients with renal artery FMD without either of these complications. In the US Registry, abdominal bruit was a presenting sign of disease in 9.4% of patients, whereas on physical examination, bruits were present over the epigastrium or flanks in 17.5% and 6.1% of FMD patients, respectively.<sup>5</sup> Renal insufficiency is an uncommon manifestation of FMD in adults.<sup>5</sup> Renal artery dissection and renal infarction may lead to chronic kidney disease, but progression to end-stage renal disease from FMD



**Figure 3.** Perimedial fibroplasia of the renal artery. The beads (arrow) are smaller and less numerous than in medial fibroplasia (A). Note the nearly normal appearance of the renal artery after percutaneous balloon angioplasty (B). Reprinted from Slovut and Olin.<sup>4</sup> Copyright © 2004, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Images courtesy of Anthony W. Stanson, MD, Mayo Clinic, Rochester, MN.

**Table 2. 2014 American Heart Association Classification of Fibromuscular Dysplasia**

	Multifocal	Focal
Angiographic appearance	Alternating dilatation and constriction of the vessel (string of beads) Areas of dilatation are larger than the normal caliber of the artery Occurs in the mid and distal portion of the renal, internal carotid, and vertebral arteries May occur in any other artery in the body†	Focal concentric or tubular stenosis*
Typical histology	Medial fibroplasia (most common) Perimedial fibroplasia (rare)‡	Intimal fibroplasia (most common) Adventitial (periarterial) fibroplasia (rare) Medial hyperplasia (rare)
Associated features	Aneurysm, dissection, and vessel tortuosity of medium-sized arteries may be present; multifocal and focal lesions may coexist in the same patient	

\*Lesions are not necessarily confined to the mid or distal portion of the artery (ie, can occur in any arterial segment).

†There are no cases of aortic fibromuscular dysplasia that are well documented pathologically.

‡This rare form of fibromuscular dysplasia typically occurs in young girls (eg, those 5 to 15 years of age). Although there is a beaded appearance to the renal arteries, the beads are smaller than the normal renal artery and less numerous. There is often collateralization around the area of stenosis (Figure 3).

alone is quite rare. Interestingly, even among patients with isolated renal artery FMD and well-controlled hypertension, headaches are quite common.<sup>5,60</sup>

**Table 3. Presenting Signs and Symptoms Among Patients in the United States Registry for Fibromuscular Dysplasia<sup>5</sup>**

Symptoms/Signs	n (%) Divided by 447
Hypertension	285 (63.8)
Headache	234 (52.4)
Current headache	135 (30.2)
History of headache	173 (38.7)
Pulsatile tinnitus	123 (27.5)
Dizziness	116 (26)
Cervical bruit	99 (22.2)
Neck pain	99 (22.2)
Tinnitus	84 (18.8)
Chest pain or shortness of breath	72 (16.1)
Flank/abdominal pain	70 (15.7)
Aneurysm	63 (14.1)
Cervical dissection	54 (12.1)
Epigastric bruit	42 (9.4)
Hemispheric transient ischemic attack	39 (8.7)
Postprandial abdominal pain	35 (7.8)
Stroke	31 (6.9)
Claudication	23 (5.2)
Amaurosis fugax	23 (5.2)
Weight loss	23 (5.2)
Horner syndrome	21 (4.7)
Renal artery dissection	14 (3.1)
Azotemia	9 (2)
Myocardial infarction	8 (1.8)
Mesenteric ischemia	6 (1.3)
No symptoms/signs	25 (5.6)

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### Cerebrovascular FMD (Carotid and Vertebral Arteries)

The clinical manifestations of cerebrovascular FMD are highly variable and at times nonspecific. An isolated cervical bruit may be the sole manifestation of carotid or vertebral artery involvement. In the US Registry, cervical bruit was an initial presenting sign of disease in 22.2% of patients.<sup>5</sup> The most common symptom of cerebrovascular FMD is headache, which is often but not always of the migraine type.<sup>5,21,29,61</sup> In the US Registry, 60% of FMD patients experienced significant headaches, approximately one half of which were migraine type in nature, whereas 12.5% of patients reported suffering from daily headaches and an equal percentage required suppressive medication for headache.<sup>5</sup> Pulsatile tinnitus, described by patients as a “swishing,” “swooshing,” or “whooshing” sound in the ears, is a very common symptom of FMD and was a presenting manifestation for more than one quarter (27.5%) of patients enrolled in the US Registry, consistent with other series.<sup>5,61</sup> Neck pain, nonpulsatile tinnitus, and dizziness may occur in 20% to 26% of patients.<sup>5,29,61</sup> The dizziness is usually not true vertigo but a feeling of lightheadedness or wooziness often accompanied by fullness in the head or ears. True syncope episodes are uncommon.<sup>5,29,61</sup>

The most feared and serious sequelae of cerebrovascular FMD include TIA, stroke, subarachnoid hemorrhage, and cervical artery dissection. The frequency of neurological events up to and including the time of enrollment in the US Registry was significant: 13.4% of patient had suffered a hemispheric TIA, 5.2% had experienced amaurosis fugax, 12.1% had experienced cervical artery dissection, and 9.8% had suffered stroke.<sup>5</sup> Focal neurological events may be related to 1 or more of the following mechanisms: severe stenosis producing cerebral hypoperfusion, embolization, thrombosis, dissection, and aneurysm rupture.

The association of FMD with cerebral aneurysms is discussed in detail below. The frequency of subarachnoid hemorrhage among 447 FMD patients in the US Registry was 1.1%, and the combined frequency of carotid, vertebral, cerebral, and basilar artery aneurysms was ≈7% (Table 4).<sup>5</sup>

The association between FMD and cervical (carotid and vertebral) artery dissection has long been recognized.<sup>31,32,62-64</sup> FMD is present in  $\approx 15\%$  to  $20\%$  of patients with a spontaneous dissection of the carotid or vertebral arteries.<sup>31,64-67</sup> In the US Registry, cervical artery dissection was an initial clinical manifestation in  $12.1\%$  of FMD patients, and 88 patients ( $19.7\%$ ) experienced a dissection of at least 1 vessel at some point before or at the time of enrollment in the registry.<sup>5</sup> Common manifestations of cervical artery dissection are severe headache and neck pain. Cranial nerve abnormalities may occur, producing Horner syndrome (ie, unilateral ptosis and miosis). If there is embolization or occlusion of the artery, a TIA or stroke may occur. Multiple cervical dissections may occur simultaneously or within a short period of time.<sup>67-71</sup> Persistent headache severe enough to interfere with the quality of life may occur in up to  $17\%$  of patients after a cervical artery dissection.<sup>72,73</sup> In a study of 200 patients who developed a spontaneous cervical artery dissection, recurrent dissection occurred in 8 patients ( $2\%$ ) within a month after the first dissection and between 1.4 and 8.6 years later in 12 patients ( $1\%/y$ ).<sup>67</sup> If the patients who had a recurrent dissection within the first month are excluded from analysis, the cumulative rate of recurrent dissection was  $3.7\%$ ,  $5.0\%$ , and  $11.9\%$  at 2, 5, and 10 years, respectively.<sup>67</sup> It is not known whether patients with FMD who experience a cervical artery dissection have a similar rate of recurrence.

**Table 4. Prevalence and Vascular Distribution of Arterial Aneurysm and Dissection in the United States Registry for Fibromuscular Dysplasia<sup>5</sup>**

	n (%)
Aneurysm	76/447* (17)
Renal	25/76 (32.9)
Carotid	16/76 (21.1)
Aorta	15/76 (19.7)
Ascending	6/76 (7.9)
Descending	4/76 (5.3)
Abdominal	5/76 (6.6)
Celiac	12/76 (15.8)
Cerebral	9/76 (11.8)
Mesenteric	5/76 (6.6)
Basilar	5/76 (6.6)
Vertebral	2/76 (2.6)
Subclavian	2/76 (2.6)
Popliteal	2/76 (2.6)
Dissection	88/447* (19.7)
Carotid	68 (75)
Renal	19 (22)
Vertebral	15 (17)
Mesenteric	4 (4.5)
Coronary	3(3.4)
Celiac	2 (2.3)
Iliac	2 (2.3)

\*All vascular beds were not imaged for aneurysm or dissection in every patient.

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### Mesenteric FMD

FMD involving the celiac and mesenteric arteries has been reported and may present as an incidental imaging finding, visceral artery aneurysm or dissection, or mesenteric ischemia. In the US Registry, mesenteric ischemia was an uncommon manifestation of FMD, reported in only  $1.8\%$  of patients.<sup>5</sup> Mesenteric FMD presenting as either acute or chronic mesenteric ischemia has most commonly been reported in the pediatric population and has been associated with intimal (ie, focal) disease.<sup>74-76</sup> Among patients in the US Registry, the celiac and mesenteric arteries accounted for  $6.8\%$  of all arterial dissections and  $22.3\%$  of all arterial aneurysms reported (Table 4).<sup>5</sup>

### FMD of the Extremities

FMD involving the extremities most commonly involves the external iliac arteries, although internal and common iliac artery involvement has been reported.<sup>77,78</sup> Lesions below the inguinal ligament are uncommon. Patients with external iliac artery FMD are often asymptomatic, but they may experience claudication or rarely acute limb ischemia. Acute limb ischemia resulting from iliac FMD generally occurs in the setting of arterial dissection.<sup>77,79</sup> A bruit caused by iliac FMD may be heard in the lower abdomen from the umbilicus to the inguinal region. In the US Registry, among patients who were referred for an imaging study for suspected lower-extremity FMD (eg, for symptoms or femoral or abdominal bruit),  $60\%$  were found to have lesions involving the iliac vessels.<sup>5</sup>

FMD involving the upper extremities most commonly involves the brachial arteries, although it has been reported in other vessels. Subclavian involvement has been reported, and when it occurs, it is generally related to intimal (focal) disease. The most common presentation of brachial artery FMD is an asymptomatic imaging finding.<sup>80</sup> In some cases, there may be discrepant blood pressures in the arms. Arm claudication or a bruit heard over the antecubital fossa is uncommon but may occur. Acute upper-extremity or digital ischemia resulting from brachial FMD has been reported, most commonly as a result of a thromboembolic event.<sup>81-83</sup> There are case reports in the literature of FMD-related brachial artery aneurysm.<sup>84</sup>

### FMD of the Coronary Arteries

The coronary manifestations of FMD are an emerging area of clinical research. Coronary artery FMD may present as an acute coronary syndrome typically among patients with FMD in other vascular beds.<sup>85,86</sup> The mechanism of myocardial infarction in some patients has recently been determined to be coronary artery dissection, with arterial lesions most commonly involving the mid to distal left anterior descending artery.<sup>85-87</sup> Lesions in the other coronary vessels have also been reported.<sup>85,86</sup> Fortunately, acute coronary syndrome seems to be an uncommon clinical event among FMD patients. In the US Registry, any coronary artery disease (including atherosclerotic disease) was reported by  $6.5\%$  of patients, with  $3.1\%$  of patients reporting a myocardial infarction and  $1.3\%$  a coronary revascularization procedure.<sup>5</sup> It is not clear how many of these patients actually had FMD of the coronary arteries as opposed to atherosclerotic coronary artery disease.

The diagnosis of coronary FMD may be overlooked because the string of beads appearance occurs infrequently in coronary FMD.<sup>88</sup> It is more common to have distal tapering of the coronary artery with an abrupt transition from the normal coronary artery to the abnormal area, focal stenosis unrelated to atherosclerosis, dissection, or extreme arterial tortuosity.<sup>85,89</sup>

In the forensic pathology literature, there are reported cases of histopathological findings consistent with FMD identified on postmortem examination among individuals with sudden cardiac death.<sup>90-93</sup> In these cases, the sinoatrial and atrioventricular nodal arteries were most commonly involved. Similarly, there are case reports of histopathological findings consistent with FMD of the coronary arteries among victims of sudden infant death syndrome.<sup>94-96</sup> It should be noted that in the large majority of cases of sudden death, there was no antecedent clinical diagnosis of FMD. Thus, it is likely that sinoatrial and atrioventricular nodal artery FMD represents a rare subset of patients who are distinct from the clinical entity described in this article. In data reported by the US Registry, there were no deaths reported during the initial 24 months of follow-up.<sup>97</sup> It is interesting to note that sudden death among first- and second-degree relatives was reported among 19.8% of FMD patients in the registry.<sup>5</sup>

### FMD in the Pediatric Population

A comprehensive discussion of FMD in the pediatric population is beyond the scope of this document. FMD in children is more likely to present as intimal fibroplasia or perimedial fibroplasia than in the adult population.<sup>54,98</sup> Although the presenting symptoms of FMD in children may overlap those of adults (eg, renovascular hypertension, stroke, arterial dissection, aneurysm), intimal fibroplasia can also mimic a systemic necrotizing vasculitis. A rapidly progressing systemic illness may occur with the development of aneurysms and severe arterial occlusive disease, particularly involving the renal and mesenteric arteries, with resultant bowel and kidney infarction. Intracranial stenoses are extremely rare among adults with medial fibroplasia, but Moyamoya-like findings have been described among children with presumed FMD.<sup>99-104</sup> Stenotic lesions in the aorta (presenting as atypical aortic coarctation or middle aortic syndrome) have frequently been reported in the pediatric population, whereas stenotic lesions of the aorta are not encountered in FMD in the adult population.<sup>54,105,106</sup> The differential diagnosis of FMD in the pediatric population includes inflammatory vasculitides such as Takayasu arteritis and systemic noninflammatory arteriopathies such as neurofibromatosis, Grange syndrome, Williams syndrome, and Alagille syndrome.<sup>107-109</sup> It is likely that pediatric FMD represents a separate clinical entity with unique pathogenic factors that have yet to be determined.

### Arterial Aneurysm and Dissection

FMD is associated with the development of arterial aneurysm and dissection. The association of FMD with arterial aneurysms has long been recognized in published case series, with carotid and intracerebral aneurysms and renal aneurysms most commonly reported. The reported prevalence of intracerebral aneurysm among patients with FMD is highly variable, with rates as high as 50% in reported cases series.<sup>21,29,110</sup> Higher estimates of intracranial aneurysm prevalence were reported

among cohorts of patients presenting with subarachnoid hemorrhage. Recent analyses of historical case series have suggested that the prevalence of asymptomatic brain aneurysms among FMD patients averages 7.3%.<sup>110</sup> Renal artery aneurysms have also been reported in multiple case reports and case series of FMD, although the prevalence is not known.<sup>53</sup>

In the US Registry, arterial aneurysm at any location was reported among 17.0% of patients (Table 4).<sup>5</sup> The most common sites of aneurysm were the renal arteries, carotid arteries (including intracranial internal carotid arteries), celiac artery, and cerebral arteries. Interestingly, 15 of 447 patients (3.4%) in the cohort had an aortic aneurysm, a frequency that is higher than would be expected in a cohort of predominantly female patients with median age of 55.7 years. This finding merits further exploration. As previously noted, a family history of aneurysm in a first- or second-degree relative was present in 23.5% of patients in the registry.

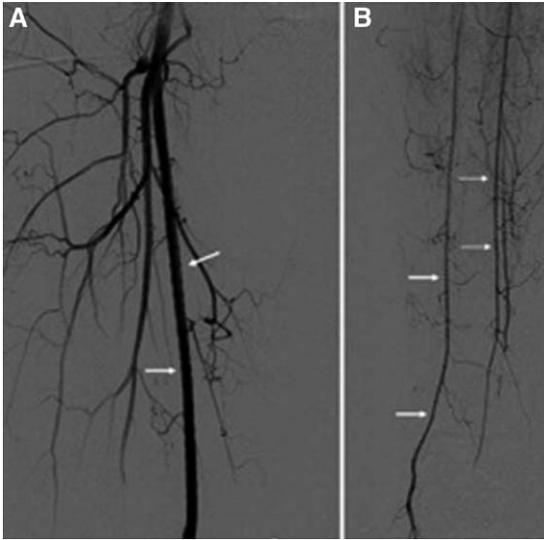
In addition to aneurysm development, arterial dissection as a complication of FMD has long been recognized. It has been estimated that  $\approx$ 15% to 20% of cervical artery dissections are FMD related.<sup>31,32</sup> Renal artery dissection among patients with FMD has long been recognized.<sup>1-4,111-114</sup> These patients often present with flank pain and have evidence of renal infarction on imaging studies. Edwards and colleagues<sup>111</sup> reported a case series of renal artery dissection in 35 patients (24 diagnosed angiographically, 11 diagnosed during autopsy findings). FMD was identified on angiography in 22 of 24 cases (91.7%).<sup>111</sup> Interestingly, among the 35 patients with renal artery dissection described, 32 of 35 (91.4%) were male.

In the US Registry, arterial dissection at any location was reported among 19.7% of patients (Table 4).<sup>5</sup> Among patients who suffered an arterial dissection, 20% had multiple arterial dissections.<sup>5</sup> The most common sites of dissection were the carotid, renal, and vertebral arteries. Visceral (celiac/mesenteric) and iliac artery dissections occurred less commonly. Coronary artery dissection was reported in 3 of 447 patients (<1%) enrolled in the registry (see FMD of the Coronary Arteries above). Importantly, there were no cases of aortic dissection reported among 447 patients. Cervical artery dissection was the presenting manifestation of FMD in 12.1% of patients and renal artery dissection was the presenting manifestation of FMD in 3.1% of patients.<sup>5</sup> Confirming the findings of the case series of renal dissection reported by Edwards and colleagues,<sup>111</sup> in the US Registry, male sex was associated with a higher prevalence of arterial dissection.<sup>115</sup>

## Differential Diagnosis

### Standing Waves or Stationary Waves

Standing waves are undulations associated with a catheter- or contrast-induced spasm of the artery (Figure 4). There are times when this is mistaken for multifocal FMD (medial fibroplasia).<sup>116</sup> However, in standing waves, the undulations are in a regular pattern, without significant stenosis, and this rapidly reverses with infusion of a vasodilator or withdrawal of the catheter.<sup>117</sup> On the other hand, medial fibroplasia produces irregular areas of stenosis and dilatation. It is important to recognize standing waves as an FMD mimic so that a patient is not incorrectly labeled with disease.<sup>116</sup>



**Figure 4.** Standing waves. Note the regular oscillations in the superficial femoral artery (**arrows, A**) and tibial arteries (**arrows, B**). This is often mistaken for fibromuscular dysplasia. Reproduced with permission from Sharma et al.<sup>116</sup> Copyright © 2012, American Heart Association, Inc.

### Atherosclerosis

In the past, patients with FMD were younger and lacked the usual cardiovascular risk factors as compared to patients with atherosclerosis. However, FMD is now being recognized in all age groups, and patients may have both FMD and atherosclerosis.<sup>5,118</sup> Perhaps the factor that distinguishes atherosclerosis from FMD most is that atherosclerosis occurs at the ostium or proximal portion of arteries whereas FMD occurs in the mid to distal portion of these vessels.

### Vasculitis

FMD is a noninflammatory process, whereas vasculitis is defined by marked inflammation of the blood vessels. In large-artery vasculitides such as Takayasu arteritis and giant-cell arteritis, abnormalities of the blood vessel wall (thickening and wall edema) are evident on cross-sectional imaging studies. Arterial stenoses are commonly present in Takayasu arteritis, giant-cell arteritis, and middle aortic syndrome, although these are inflammatory lesions that identify an origin distinct from FMD.<sup>119–122</sup> Aneurysms may be present in these diseases, and the stenoses are commonly tubular or focal in nature. The arteriographic appearance of arterial segments demonstrating long areas of smooth narrowing is classic for vasculitis but not pathognomonic. Acute-phase reactants (erythrocyte sedimentation rate, C-reactive protein) are usually normal in FMD unless there is infarction of the kidney or bowel. Because FMD may occur in multiple vascular territories and cause accelerated hypertension, kidney impairment, TIA, stroke, and abnormalities such as stenosis, aneurysm, or dissection, it may be confused with a vasculitis.

### Segmental Arterial Mediolytic

Segmental arterial mediolysis is a poorly understood condition characterized by spontaneous dissection(s), occlusion, or aneurysm formation, which may be difficult to differentiate from FMD.<sup>123–129</sup>

Similar to FMD, segmental arterial mediolysis is a noninflammatory, nonatherosclerotic arterial disease. Although visceral abdominal arteries are most commonly affected, similar histopathology has been documented in intracranial arteries, iliac arteries, and neonatal coronary arteries.<sup>130–133</sup> Although the histology is clearly distinct from FMD, the radiographic presentation may be indistinguishable. Unfortunately, multiple reports and case series show imaging findings (dissections, stenoses, aneurysms) among patients labeled with segmental arterial mediolysis in the absence of pathological specimens. A definitive diagnosis of segmental arterial mediolysis requires tissue examination.<sup>134,135</sup>

This lesion of segmental arterial mediolysis is characterized by the vacuolar degeneration of smooth muscle cells in the outer media that may extend to the inner aspect with increased deposition of ground substance. Smooth muscle cells are progressively lost with the development of arterial gaps, intramural hemorrhage, and fibrin deposition along the media-adventitia interface.<sup>135,136</sup> These vascular malformations can lead to saccular and fusiform aneurysm formation, dissection, and thrombosis. Histological similarities to cystic medial necrosis exist, and the relationship between these 2 disorders remains to be clarified.<sup>131–133,136</sup>

### Other Associated Diseases

Additionally, lesions similar to those of FMD have been observed angiographically in other diseases. Most notably, FMD-type changes have been described in the vascular variant of the Ehlers-Danlos syndrome, neurofibromatosis type 1, Williams syndrome, reversible cerebral vasoconstriction syndrome, and median arcuate ligament syndrome.<sup>137–140</sup>

### Diagnostic Strategies for Renal FMD

Imaging has become the primary method for diagnosing FMD. Noninvasive imaging studies include duplex ultrasonography, computed tomographic angiography (CTA), and magnetic resonance angiography (MRA), but the gold standard remains catheter-based angiography. In addition to providing a definitive diagnosis in equivocal cases, IVUS and simultaneous pressure measurements can help to assess the hemodynamic significance of a stenosis and the anatomic success after percutaneous intervention.

Studies comparing the diagnostic accuracy of noninvasive imaging have involved primarily patients with atherosclerotic renal artery disease. There is little information specifically addressing the accuracy of noninvasive imaging for renal artery FMD.<sup>141–143</sup>

### Duplex Ultrasound

The examination of the renal arteries by duplex ultrasound requires a high level of skill by the ultrasound technologist and careful oversight by the interpreting physician.<sup>141,143</sup> Duplex ultrasound of the renal arteries typically reveals evidence of arterial stenosis in the affected renal artery, including a step-up in peak systolic velocity in the mid to distal portion of the main renal artery or a delayed systolic upstroke (tardus et parvus waveform) in arterial branches distal to the stenosis. It is important to image the renal artery in its entirety

from the origin to the kidney parenchyma. Suboptimal studies may occur in patients with obesity, in those with excessive bowel gas, and in patients who move or are unable to hold their breath. The renal artery should be imaged from the anterior approach and from an oblique approach (from the kidney to the aorta). Features suggesting FMD include elevated velocities (ie, an abrupt step-up in velocity or velocity shift), turbulence of color or spectral Doppler flow, and tortuosity in the mid and distal segment of the renal artery and its branches. Beading may be visualized on color or power Doppler, but it is not common. It is important to recognize that the Doppler criteria used for atherosclerotic renal artery stenosis cannot be directly extrapolated to determine the severity of renal FMD.<sup>143</sup> It is not possible to give an accurate percentage stenosis in multifocal FMD. Therefore, a more appropriate interpretation would be elevated velocities, tortuosity, and turbulence in the mid and distal renal artery consistent with FMD.

A high-quality duplex ultrasound examination in an experienced center is highly accurate for the diagnosis of renal artery FMD in the main renal artery. Ultrasound loses sensitivity when surveying the branch renal arteries or when trying to identify the presence of aneurysms in the renal parenchyma. In addition to identifying FMD in the renal arteries, duplex ultrasound is an excellent technique to follow patients for restenosis after angioplasty or stent implantation.

### Computed Tomographic Angiography

CTA is a commonly used imaging modality in the diagnosis of renal artery FMD because of its ready availability, excellent spatial resolution (0.5 mm), and ability to generate 3-dimensional multiplanar and volume-rendered images. High spatial resolution and short acquisition time are the major advantages of the current 256-row detector CTA studies. This technology allows visualization of a greater volume per unit time, resulting in reduced pulsation and stair-step artifacts. Assessment of the renal arteries should be performed using vascular windows on a dedicated 3-dimensional workstation. It is imperative to review the data sets using multiple reconstruction formats, including multiplanar reformatted images, shaded surface display, and maximum-intensity projections. The use of all these reformats in addition to the axial “raw data” has been shown to improve the sensitivity and specificity of this imaging modality.<sup>144</sup> Findings on CTA include the classic string of beads of the renal artery in patients with medial fibroplasia (multifocal FMD) and a focal concentric stenosis or tubular stenosis in those with intimal or other nonmedial disease (focal FMD). Wedge-shaped renal infarcts can be visualized in patients with FMD complicated by dissection. Renal artery aneurysms are readily visible. The 3-dimensional nature of the CTA data set can be helpful for treatment planning for renal artery aneurysms in the setting of FMD. Sabharwal and associates<sup>144</sup> retrospectively reviewed 21 hypertensive patients with catheter-based angiography–proven FMD. CTA identified all 42 main renal arteries and all 10 accessory renal arteries. In addition, CTA detected all 40 lesions (100%) that were detected by catheter-based angiography.<sup>144</sup> However, subtle, mild FMD lesions may not be visualized on CTA. In addition, sensitivity is lower for detecting branch vessel involvement. The diagnostic accuracy is limited by the presence of adjacent or overlapping

structures such as the renal veins. Catheter-based angiography is currently the only reliable technology to identify branch disease accurately.<sup>145</sup>

### Magnetic Resonance Angiography

Contrast-enhanced MRA is also a good modality to establish the diagnosis of renal artery FMD, particularly in patients who cannot receive intravenous contrast for CTA.<sup>146</sup> A recent study by Willoteaux and colleagues<sup>147</sup> comparing contrast-enhanced MRA with conventional angiography showed a sensitivity of 97% and specificity of 93% for diagnosing FMD. MRA was more sensitive at detecting a string of beads appearance (97%) than detecting a >50% stenosis (68%). Particular technologies that have been shown to improve the diagnostic accuracy of MRA include real-time contrast bolus monitoring, elliptical centric view ordering, and parallel imaging. Of all technologies, these optimize the delivery of the contrast bolus and decrease the time of data acquisition to reduce motion artifact. Drawbacks to MRA include lower spatial resolution (1–2 mm) than CTA and the inability to use gadolinium-based contrast agents in patients with an estimated glomerular filtration rate <30 mL/min/1.73 m<sup>2</sup> because of concerns about nephrogenic systemic fibrosis. MRA features of FMD are similar to those seen on CTA.

There are times when MRA may show “beading” when in reality none exists secondary to motion artifact. This can be related to respiratory motion artifacts of the abdominal organs caused by the long data acquisition times during contrast-enhanced MRA compared with CTA (15–20 seconds for MRA compared with 1–2 seconds for CTA).

### Catheter-Based Angiography

Catheter-based angiography remains the gold standard imaging modality for renovascular FMD because of its unsurpassed spatial resolution (<0.1 mm). The latest high-resolution monitors that offer digital magnification capabilities further enhance the ability to detect disease in the smaller branch vessels. Catheter-based angiography is the only way to reliably detect branch vessel involvement. Catheter-based renal angiography is a minimally invasive procedure that can be performed on an outpatient basis. The normal renal artery is smooth in contour and gently tapers from its origin as it courses to the renal hilum. In the setting of medial fibroplasia (multifocal FMD), the renal artery is irregular in contour and typically displays the classic string of beads appearance, with multifocal stenoses accompanied by small foci of poststenotic dilatation accounting for the beads (Figure 1). Alternatively, a focal stenosis or long tubular stenosis (Figure 2) can be seen in the less common nonmedial forms of the disease (focal FMD). Atrophy of the kidney may occur with severe stenosis over a long period of time. This is most common with intimal fibroplasia (focal FMD) and perimedial fibroplasia.<sup>4</sup> Renal atrophy is distinctly uncommon in medial fibroplasia.

Traditional angiographic techniques involve a flush aortogram in the visceral aorta through a multi-side-hole catheter to localize the main renal arteries and to confirm the presence or absence of accessory renal arteries. This is typically followed by a selective catheterization of both renal arteries with an appropriate catheter. The presence of a side hole in

the catheter tip will reduce catheter movement during contrast injection. Selective angiography is important because it is the only way to achieve optimal visualization of the main renal artery, renal artery branches, and parenchyma, thus accurately identifying FMD, dissection, or aneurysm. In addition, pressure gradients should be measured to gauge the severity of stenoses (a systolic gradient of  $<10$  mm Hg is considered normal) because accurate visual assessment of the degree of stenosis is not possible with multifocal lesions. Reporting a specific percent stenosis is strongly discouraged, particularly with multifocal FMD, because the severity may appear very mild but still manifest a significant pressure gradient.<sup>58,148</sup> Conversely, the presence of significant beading may not be associated with a hemodynamically significant gradient.

Catheter-based angiography offers the additional advantage of lesion treatment at the same time of diagnosis in symptomatic patients. In addition to measurement of the pressure gradient across the lesion(s), IVUS may be used to further characterize the renal artery and to guide the success of endovascular therapy. Some authors suggest that IVUS may improve the diagnostic accuracy of conventional angiography.<sup>58,148</sup> To date, no study has defined the exact role or utility of IVUS in the diagnosis and treatment of renal FMD.

At present, numerous technologies exist for the diagnosis of renal artery FMD, but catheter-based angiography remains the gold standard. Technological advancements will likely improve the diagnostic accuracy of noninvasive techniques. In routine clinical practice, if there is a high clinical suspicion of renal artery FMD despite inconclusive noninvasive testing, the patient should proceed directly to catheter-based angiography for definitive diagnosis and possible therapeutic intervention if a hemodynamically significant lesion is identified.

### Diagnostic Strategies for Cerebrovascular FMD

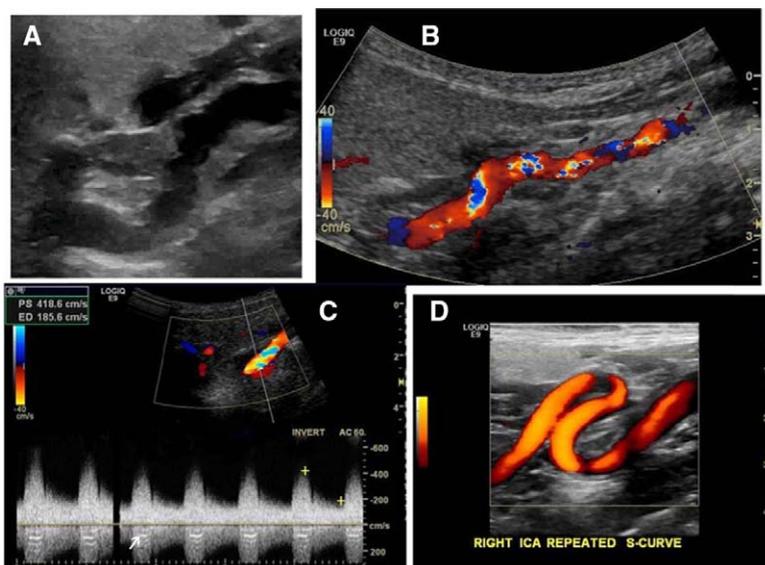
It has recently been recognized that the extracranial internal carotid and vertebral arteries are affected by FMD as commonly as the renal arteries.<sup>5</sup> This finding represents a divergence from the classic FMD paradigm of the renal arteries being the most commonly affected vascular bed.<sup>4,29</sup> Although

there are multiple potential explanations for the increased recognition of cerebrovascular involvement, it is likely that increased physician awareness leading to additional imaging beyond the symptomatic vascular bed (eg, carotid imaging for the patient with hypertension caused by renal FMD) and the availability of high-quality noninvasive imaging modalities for diagnosing FMD have contributed to this trend. As is the case for imaging of the renal artery, catheter-based angiography remains the diagnostic gold standard. There is sparse clinical evidence as to the optimal noninvasive modality for imaging of cerebrovascular FMD, with very few studies having compared modalities directly with catheter-based angiography.

### Duplex Ultrasound

Duplex ultrasonography is a noninvasive, widely available tool for diagnosing carotid artery disorders. Duplex ultrasonography allows visualization of the blood vessel wall and lumen with B-mode or gray-scale imaging while using Doppler (color and spectral Doppler) to assess the characteristics of arterial flow. Doppler interrogation of the carotid arteries allows the detection of velocity shifts indicative of arterial stenosis and allows the assessment of other flow abnormalities such as turbulence. Although most commonly used to diagnose and follow up atherosclerotic disease of the internal carotid arteries, duplex ultrasound also can be used for the diagnosis of nonatherosclerotic disorders of the carotid arteries, including vasculitis, dissection, and FMD.

Duplex ultrasound findings consistent with carotid FMD include the identification of velocity shifts in the mid to distal cervical internal carotid artery and the vertebral arteries with associated turbulence of color flow or the spectral Doppler signal (Figure 5A–5D). These findings are in contrast to atherosclerotic disease, in which significant plaque is generally visualized at or just beyond the carotid bifurcation associated with velocity shift and turbulent flow in the origin or proximal segment of the internal carotid artery at or immediately beyond the plaque. Because of the more distal location of FMD findings on the duplex ultrasound examination, interrogation of the entire internal carotid artery, not just



**Figure 5.** Typical duplex ultrasound findings of carotid fibromuscular dysplasia. **A**, B-mode imaging showing the beading and tortuosity of the mid and distal internal carotid artery. **B**, Color Doppler of the distal internal carotid artery exhibiting the typical pattern of tortuosity and marked turbulence. **C**, Color Doppler showing turbulence and spectral analysis demonstrating high peak systolic (419 cm/s) and end-diastolic velocities (186 cm/s). The “seagull” sign (arrow) indicates that the stenosis is quite severe. **D**, Color power angiography demonstrating severe tortuosity and redundancy (S-curve) of the internal carotid artery.

the segments at or immediately distal to the carotid bulb, is essential. It should be noted that some patients, particularly elderly patients, may present with findings of both atherosclerosis and FMD on carotid duplex ultrasound. In addition to velocity shifts and turbulent flow, beading of the vessel (string of beads) in the mid or distal cervical may be identified, although this is a less common finding (Figure 5A).

There is an interesting finding of severe tortuosity in the distal internal carotid and vertebral arteries in patients with documented FMD (Figures 5D and 6). The cause of tortuosity is not known. Although elongation and redundancy are not specific for FMD, they occur with increased frequency in patients with FMD and may represent another clinical manifestation of FMD. Sethi and colleagues<sup>149</sup> showed that severe tortuosity (S curve) of the internal carotid artery occurred in 37 of 108 patients (34%) with FMD (carotid, vertebral, or renal artery) compared with 2 of 74 age- and sex-matched control patients (2.7%) without FMD (OR, 18.76; 95% CI, 4.36–80.79;  $P < 0.001$ ) and 12 of 74 sex-matched patients (16.2%)  $>70$  years of age without FMD (OR, 2.69; 95% CI, 1.29–5.61;  $P < 0.001$ ). Although the S curve may not be specific to FMD, its presence on a carotid duplex ultrasound in an individual  $<70$  years of age should alert the clinician to the possibility that FMD is present.

To date, no published studies have validated the use of duplex ultrasound for the diagnosis of FMD compared with angiography or other noninvasive imaging modalities.

### Surveillance of Carotid FMD With Duplex Ultrasound

Because of the low-risk (ie, no iodinated contrast and no radiation) and low-cost nature of duplex ultrasound, it is an excellent modality for surveillance of carotid artery FMD. Although there are no evidence-based algorithms for surveillance of carotid artery involvement, a program of duplex ultrasound surveillance every 6 of 12 months initially and then annually is reasonable. A similar noninvasive imaging program (annual imaging with less frequent testing once stability has been established) for carotid FMD was given a *Class IIa* recommendation in the 2011 multisocietal extracranial carotid and vertebral artery disease guidelines.<sup>150</sup> Follow-up studies should optimally be performed in the same accredited vascular laboratory. In most cases, medial fibroplasia of the carotid arteries is not a progressive disease.

### Limitations of Duplex Ultrasound

Although specific velocity-based diagnostic criteria for internal carotid artery stenosis have been developed and validated for atherosclerotic lesions, it is important to recognize that there are no duplex ultrasound criteria for severity of stenosis in FMD that have been angiographically validated. Because of the nature of FMD, specifically of medial fibroplasia (multifocal FMD), which manifests with areas of narrowing and dilatation in tandem (string of beads), standard criteria for stenosis resulting from atherosclerosis at the vessel origin do not apply. In less experienced vascular laboratories, the finding of FMD may be misinterpreted as representing an atherosclerotic lesion and a percentage stenosis erroneously ascribed. Therefore, the following



**Figure 6.** Arterial tortuosity is frequently encountered in patients with fibromuscular dysplasia. Shown is a carotid angiogram demonstrating severe tortuosity caused by elongation of the internal carotid artery (S curve).<sup>149</sup> Also note the mild irregularity immediately before the dilatation of the internal carotid artery.

statement appears to be a more accurate way of interpreting a carotid ultrasound in patients with FMD: There is an increase in velocity (peak systolic velocity 250 cm/sec, EDV 100 cm/sec), turbulence and tortuosity in the mid to distal internal carotid artery consistent with the presence of fibromuscular dysplasia.

Unlike the cervical internal carotid artery, which is well imaged and evaluated with duplex ultrasound, diagnosis of vertebral FMD using duplex ultrasound is challenging because of acoustic shadowing from the vertebral bodies and the limited nature of the vertebral artery assessment performed in most vascular laboratories. Nonetheless, ultrasound findings are similar to those for carotid FMD described above.

Although duplex ultrasound is a readily available tool that may be helpful in the diagnosis of suspected cervical artery dissection, it is inadequate to evaluate internal carotid artery lesions at or above the skull base or dissections involving the distal vertebral arteries.<sup>151–153</sup> For complete evaluation for carotid or vertebral artery dissection, CTA and MRA are the preferred modalities.

Applications of duplex ultrasonography for the diagnosis of intracranial involvement in FMD are very limited. Transcranial Doppler may be used for the diagnosis of intracranial stenosis and for the assessment of collateralization pathways in the brain, but it is generally inadequate to characterize lesions as resulting from FMD versus an alternative pathological process (eg, atherosclerosis). Transcranial Doppler is also inadequate for the assessment for intracranial aneurysm.<sup>29</sup>

### Computed Tomographic Angiography

CTA allows detailed anatomic imaging of the extracranial carotid and vertebral and intracranial vessels. Given that

the pathology of FMD involves the distal cervical segment of the extracranial internal carotid and vertebral arteries, carotid ultrasonography may provide suboptimal views and potentially may not be able to visualize the areas of involvement. Multirow detector CTA allows a detailed evaluation of the extracranial and intracranial cerebrovasculature with the ability to identify FMD, dissections, cerebral aneurysms, and atherosclerosis (Figure 7). Moreover, the images can be reconstructed in the maximal intensity and 3-dimensional projections, allowing detailed anatomic visualization. Unfortunately, there are limited data on the sensitivity of CTA in detecting FMD compared with other imaging modalities in the extracranial and intracranial circulation, but inferences can be made on the basis of comparisons with digital subtraction angiography for carotid disease caused by atherosclerosis and the detection of cerebral aneurysms. Imaging of cerebral aneurysms in the intracranial circulation can be challenging because of bony structures such as the clivus and cavernous wall that may hinder the ability of CTA to detect small cerebral aneurysms. Recent comparisons of digital subtraction angiography and multirow detector CTA showed that CTA had a high sensitivity and specificity in detecting cerebral aneurysms but was less efficient in smaller aneurysms, particularly those <3 mm in size.<sup>154,155</sup> Thus, CTA is a reasonable screening tool for nonruptured aneurysms because endovascular or surgical treatment is not generally performed unless the aneurysm is >5 mm, but it is inadequate in assessing for aneurysms in patients with subarachnoid hemorrhage because aneurysms <3 mm may be missed by CTA.

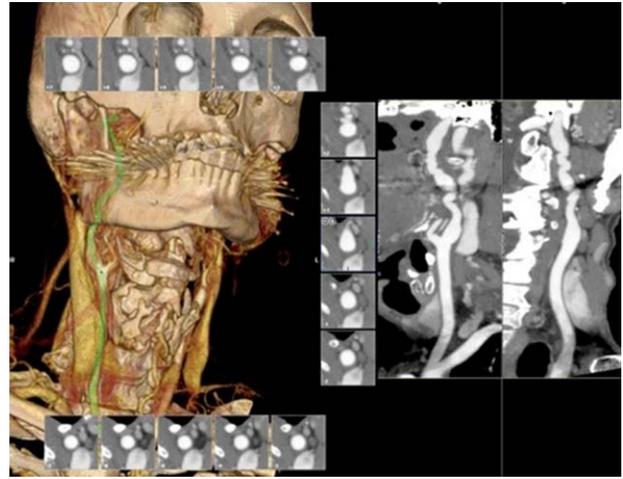
Imaging of the extracranial segment of the internal carotid artery is more reliable with CTA because of less bony obscuration. Comparison of CTA and catheter-based angiography for atherosclerotic carotid stenosis has shown that the diagnostic accuracy is highly correlative, with an accuracy exceeding 97%.<sup>156</sup> CTA has thus been shown to be correlative to catheter-based angiography in other cerebrovascular disorders, but no published correlation studies have rigorously evaluated the diagnostic accuracy of CTA in FMD. Analogous to renal artery imaging, although CTA allows the identification of lesions consistent with FMD in the carotid and vertebral arteries, the assessment of severity of stenosis associated with identified lesions is a challenge.

### Magnetic Resonance Angiography

Similar to CTA, no clinical studies have validated the use of MRA compared with catheter-based angiography for the diagnosis of cerebrovascular FMD. MRA may have the benefit of detecting FMD-associated dissections when T1 fat-saturation images are acquired simultaneously with time-of-flight or gadolinium-enhanced images.<sup>157</sup> Advantages of MR-based technology are the lack of radiation and the lack of iodinated contrast agents, which may make it a reasonable screening tool in younger patients.<sup>157,158</sup> Unfortunately, the specificity and sensitivity of MRA in the diagnosis of FMD are not known.

### Catheter-Based Angiography

Detection of FMD in extracranial vessels with catheter-based angiography was described in small case series >40 years ago.<sup>159,160</sup> Catheter-based angiography remains the gold standard



**Figure 7.** Computed tomographic angiogram showing multifocal fibromuscular dysplasia (FMD) of the right internal carotid artery. The patient also had multifocal FMD and an ophthalmic artery aneurysm on the left side (not shown).

for the diagnosis of FMD, yet it is rarely required for diagnostic purposes in the era of high-quality noninvasive imaging techniques. Osborn and Anderson<sup>161</sup> described the angiographic findings in 25 patients imaged with digital subtraction angiography. Multivessel involvement was present in 6 of 25 subjects (24%). Three angiographic patterns of extracranial FMD were noted by Osborn and Anderson<sup>161</sup> and subsequently confirmed by Mettinger and Ericson.<sup>61</sup> The first is the string of beads pattern, which is the most common manifestation and consistent with multifocal FMD in the American Heart Association classification system (Figure 1A). The second manifestation is the smooth tubular or focal lesion consistent with focal FMD in the American Heart Association classification system. The last described variant is a smooth lesion with associated out-pouching that may appear aneurysmal in nature (described as a diverticulum). This variant may reflect prior arterial dissection with arterial pseudoaneurysm formation.<sup>61,162</sup>

Catheter-based angiography for cerebrovascular FMD is generally reserved for symptomatic patients in whom intervention is contemplated or for cases in which there is uncertainty about the patient's diagnosis or severity of disease. Angiography may also be required for the evaluation of intracranial aneurysms when aneurysm size or exact anatomical location cannot be determined accurately by noninvasive imaging.

### Treatment of FMD

Advances in imaging, medical, and endovascular therapies have made the treatment for patients with FMD less invasive, safer, and more effective. Treatment for patients with FMD may include medical therapy and surveillance; endovascular therapy for stenosis (angioplasty with or without stenting), dissection (stents), or aneurysms (coils, stents); or surgery. Therapeutic decisions depend on the nature and location of vascular lesions (stenosis versus dissection versus aneurysm), the presence and severity of symptoms, prior vascular events related to FMD, the presence and size of aneurysms, and comorbid conditions. Most treatment decisions in patients with FMD are based on data derived from single case reports or small retrospective case series.

### Medical Therapy for the FMD Patient

The efficacy of medical therapies for patients with FMD is hindered by the limited knowledge of the natural history of this disorder and the lack of randomized, clinical trials in this patient population.

#### Antiplatelet and Antithrombotic Agents

In patients who have had an ischemic event, antiplatelet therapy is generally used, although its efficacy has never been demonstrated specifically for symptomatic patients with FMD. Antiplatelet therapy is an integral component of effective secondary prevention after noncardioembolic ischemic stroke. Antiplatelet drugs are risk-reducing agents, not cures.

Although there is convincing evidence that antiplatelet therapy is highly effective in reducing cardiovascular events (myocardial infarction, stroke, and vascular death) in patients with atherosclerotic disease, there is no such evidence in patients with FMD because of a lack of randomized, prospective trials.

Most experts recommend aspirin 75 to 325 mg daily for all patients (symptomatic and asymptomatic) with cerebrovascular FMD as long as there is no contraindication to its use.<sup>1,2,5,29</sup> This makes physiological sense, especially in the setting of multifocal FMD, because there are multiple fibrous webs along with areas of arterial dilatation that could serve as a nidus for platelet deposition. In the 2011 multisocietal extracranial carotid and vertebral artery disease guidelines, the administration of antiplatelet therapy to patients with FMD of the carotid arteries (regardless of symptoms) was given a *Class IIa* indication, although no specific agent or dosing regimen was recommended.<sup>150</sup> There are no data on the use of aspirin in renal, mesenteric, coronary, or peripheral artery FMD, but it is reasonable to use 75 to 325 mg aspirin to reduce the likelihood of platelet adherence to intravascular webs. Patients who are treated with balloon angioplasty alone or angioplasty with stenting are treated in the same way as patients with atherosclerotic disease who have undergone intervention.

Most patients who have experienced a dissection of an extracranial artery (other than aortic dissection) are treated with either heparin (or low-molecular-weight heparin) and warfarin for 3 to 6 months or antiplatelet therapy (aspirin with or without clopidogrel) for the same time period, but neither therapy is evidence based.<sup>32,163,164</sup> In the 2011 carotid and vertebral artery disease guidelines, the management of cervical artery dissection with heparin or low-molecular-weight heparin followed by oral anticoagulation with warfarin for 3 to 6 months and ultimately antiplatelet therapy is given a *Class IIa* recommendation.<sup>150</sup> The Cervical Artery Dissection in Stroke Study (CADISS) is an ongoing clinical trial comparing antiplatelet therapy with anticoagulation in the acute treatment (stroke or TIA within 7 days of the index event) of patients with extracranial cervical artery dissection.<sup>165</sup> Kennedy and associates<sup>166</sup> recently published data from the nonrandomized arm of the CADISS trial and performed a meta-analysis of the optimal medical therapy for patients with carotid or vertebral artery dissection (antiplatelet versus anticoagulant therapy), including 40 nonrandomized trials involving 1636 patients. There was no difference in the rate of recurrent stroke in the 2 groups (2.6% antiplatelet versus 1.8% anticoagulant therapy).

However, the stroke rate was lower than reported in previous studies.<sup>166</sup> No information is available on the use of the newer oral direct thrombin inhibitors or factor Xa inhibitors in the management of cervical artery dissection.

Formal guidelines for the medical management of renal, mesenteric, or peripheral arterial dissection associated with FMD do not exist. As is the case for extracranial cerebrovascular dissection, antiplatelet therapy or anticoagulant therapy has been used in the management of patients with FMD and of patients with non-FMD-associated renal artery dissection, but the practice has not been systematically evaluated.<sup>167,168</sup> In the presence of renal artery thrombus, the use of systemic anticoagulation is appropriate. In dissection without thrombosis, treatment with aspirin alone, aspirin and clopidogrel, or anticoagulant therapy with heparin followed by warfarin is appropriate. As is the case in cerebrovascular dissection, the usual course of oral anticoagulant therapy is 3 to 6 months, generally followed by antiplatelet therapy.

#### Antihypertensive Therapy

Hypertension attributable to FMD is mediated in large part by the renin-angiotensin-aldosterone system in response to renal ischemia. Before the advent of ACE inhibitors, renovascular hypertension was particularly difficult to control.<sup>169–171</sup> Mixed cohorts consisting of patients with both atherosclerotic and fibromuscular renal artery disease demonstrated effective blood pressure control with the use of ACE inhibitors.<sup>170–173</sup> In a cohort of patients with FMD, renal artery angioplasty acutely lowered renin and aldosterone secretion.<sup>174</sup> Angioplasty also reduced measures of oxidative stress in a small cohort of patients with renovascular hypertension, including FMD, further supporting a role for the renin-angiotensin-aldosterone system in the pathogenesis of FMD-induced hypertension.<sup>175</sup>

Considerable accumulated clinical experience has demonstrated ACE inhibitors and angiotensin receptor blockers (ARBs) to be effective antihypertensive agents in patients with FMD. Aside from 2 case reports suggesting regression of stenoses after ARB therapy, there are no convincing data on the impact of these agents on the progression of renal artery lesions.<sup>176,177</sup>

Recent work in the Marfan and Loeys-Dietz syndromes implicates abnormalities in TGF- $\beta$  signaling in the pathogenesis of aortic aneurysms, and losartan therapy may prevent the development of aneurysms or decrease the rate of aneurysm expansion.<sup>178–180</sup> Brooke and colleagues<sup>179</sup> demonstrated in pediatric patients with Marfan syndrome that treatment with losartan (17 patients) and irbesartan (1 patient) significantly decreased the rate of change in aortic root diameter from  $3.54 \pm 2.87$  mm/y during previous medical therapy to  $0.46 \pm 0.62$  mm/y during ARB therapy.

The presence of TGF- $\beta$  receptor-1 variants in 2 patients with cerebrovascular FMD and aortic dilatation has been reported, although a causal association could not be ascertained.<sup>49</sup> Because TGF- $\beta$  signaling is important in vascular wall remodeling and aneurysm formation, the use of ARBs as first-line therapy in the management of FMD is reasonable until the relationship between TGF- $\beta$  and FMD is clarified.

Although acute kidney failure after the administration of renin-angiotensin-aldosterone system-modulating agents is

uncommon, it is more likely to occur in the setting of hemodynamically significant bilateral renal artery stenosis and often when the patient is in a sodium-depleted state (eg, concomitant diuretic therapy). Therefore, kidney function should be monitored closely after the initiation of an ACE inhibitor or ARB in patients with renal FMD. If a second medication is required, the addition of a thiazide diuretic a reasonable choice.<sup>181</sup> It should be noted that hypertension after renal artery dissection may be more difficult to manage, particularly in the initial period after the dissection event when intravenous agents may be required.<sup>168</sup>

Because the ideal blood pressure target in patients with FMD is unknown, it is reasonable to follow the recommendations of the Seventh Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.<sup>181</sup> There are no studies on the use of ACE inhibitors or ARBs to prevent the progression of renovascular lesions in normotensive patients with FMD.

### Cardiovascular Risk Factors and Lifestyle Modification

Given the unknown pathogenesis of FMD, at the present time, there are no proven therapies to prevent or slow the progression of FMD. A better understanding of the pathogenesis of FMD is needed to facilitate development of new therapeutic options for patients with this disease. Despite this, general principles of cardiovascular health should be used in the care of the patient with FMD for general wellness and to prevent the development of additional vascular disease, particularly atherosclerosis. From a lifestyle perspective, the major modifiable risk factor for FMD is smoking. Although the impact of smoking cessation on FMD progression has not been studied, it is a sensible intervention to prevent atherosclerotic events such as myocardial infarction, stroke, and peripheral artery disease.<sup>33,182,183</sup> In a study of 337 patients with renal artery FMD, Savard and colleagues<sup>184</sup> have shown that 30% of FMD patients were current smokers compared with 18% in a group of age- and sex-matched control patients with essential hypertension ( $P < 0.001$ ). They also have suggested that FMD patients who currently smoke may have a more aggressive course with earlier-onset hypertension and subsequent increased and earlier diagnosis of FMD.<sup>33a</sup>

Because FMD is a noninflammatory, nonatherosclerotic disease, the role of statins is uncertain. The ability of statins to reduce intimal hyperplasia in atherosclerotic disease is controversial, and their utility in FMD has not been studied.<sup>185</sup> One retrospective study demonstrated no impact of statins on restenosis rates in FMD.<sup>186</sup> At this time, there are insufficient data to make specific recommendations on the use of statins in patients with FMD, and there is no evidence that supports the routine use of statins for the purpose of slowing disease progression among FMD patients. Therefore, patients should be treated according to published consensus guidelines.<sup>187-189</sup>

Finally, given the more frequent occurrence of FMD in women than in men, concern has been raised about the possible effect of oral contraceptive use on the development and progression of FMD. As previously discussed, existing data suggest that there is no strong association, but adequately powered studies have not definitively addressed

this question.<sup>19,33</sup> Although discontinuation of oral contraceptives should be considered in any woman with hypertension, there is no evidence that ongoing use will contribute to the progression of FMD. Likewise, although there may be similar theoretical concerns about the use of systemic hormone replacement therapy in postmenopausal women with FMD, there are inadequate data at this time for specific treatment recommendations. In general, if hormone replacement therapy is required, it is recommended that it be prescribed at the lowest effective dose and for the shortest duration necessary. In general, hormone replacement therapy should not be prescribed for FMD patients who have previously suffered an ischemic stroke or TIA.

## Revascularization for Renal Artery FMD

### Indications for Renal Artery Revascularization

Revascularization by percutaneous transluminal angioplasty (PTA) or surgery should be considered in patients with renal artery FMD and the appropriate clinical presentation. Indications for renal artery revascularization are as follows:

1. Resistant hypertension (failure to reach goal blood pressures in patients on an appropriate 3-drug regimen including a diuretic).<sup>181</sup>
2. Hypertension of short duration with the goal of a cure of hypertension.
3. Renal artery dissection; rarely is intervention needed, but if so, stenting is generally the procedure of choice.
4. Renal artery aneurysm(s); surgical resection, endovascular coiling, or placement of a covered stent is usually used.
5. Branch renal artery disease and hypertension; some lesions can be treated with PTA, but if this is not possible, surgical revascularization may be required, often with bench repair.
6. Preservation of renal function in the patient with severe stenosis, especially in the pediatric population with perimedial fibroplasia or intimal fibroplasia.<sup>190-193</sup>

Randomized, controlled trials of revascularization versus medical therapy in patients with renal artery FMD have not been performed. The negative trials on stent implantation for atherosclerotic renal artery disease do not apply to patients with FMD given the differing pathophysiology and natural history of these 2 vascular disorders. The natural history of medial fibroplasia is generally benign. Several older studies suggested that medial fibroplasia in the majority of patients progressed with time.<sup>190,191</sup> However, these reports had significant methodological flaws, and convincing evidence of the risk of new lesions developing or prevalent lesions worsening in these patients is lacking. It is the consensus of this American Heart Association writing committee that progression in medial fibroplasia is an uncommon occurrence. It can be challenging to accurately determine progressive stenosis over time because visual estimation of luminal stenosis in renal artery FMD is not feasible. Progressive deterioration in renal function or a decline in renal size should prompt consideration of revascularization, although this is quite uncommon in the adult population with FMD.<sup>5</sup> Although stabilization or improvement in kidney function has been reported in a small

number of patients, long-term outcome data on the preservation of renal function after revascularization are lacking.<sup>194,195</sup> Revascularization of medial fibroplasia in the absence of hypertension or renal impairment is not indicated.

Given the prevalence of FMD in otherwise healthy individuals, it is likely that some individuals with FMD develop essential hypertension not mediated by hemodynamically significant renovascular disease. In the US Registry, the mean age at the time of diagnosis of FMD was 52 years, and the mean age at the onset of high blood pressure was 43 years.<sup>5</sup> Distinguishing primary (essential) from renovascular hypertension among patients with renal artery FMD can often be difficult, and the decision to pursue revascularization is predicated on clinical indicators beyond the simple presence of FMD.

### Endovascular Revascularization

Trinquart and colleagues have demonstrated that the younger the patient, and the shorter the duration of hypertension, the greater the likelihood of cure with angioplasty or surgical bypass in patients with renal FMD.<sup>196</sup> Therefore, in younger patients with recent onset of hypertension, percutaneous angioplasty may be considered first-line therapy with the goal of cure of hypertension. In patients with long-standing hypertension, adherence to the usual indications for revascularization (ie, resistant hypertension, noncompliance with antihypertensive medications, intolerable side effects, or loss of renal mass or progressive renal insufficiency) is prudent.<sup>197</sup> PTA offers many advantages over traditional surgical repair. It is less invasive and less expensive, has a lower morbidity, can be performed on an outpatient basis in many cases, and has a markedly reduced recovery time. Consequently, PTA of the renal artery is the procedure of choice for patients with renal artery FMD and hypertension in the appropriate clinical setting.

### Technique of Renal PTA

The common femoral artery has traditionally been used as the access site for diagnostic angiography of the renal arteries. Recently, enthusiasm has increased for radial artery access. The preference and experience of the operator should determine the best approach. Imaging should include a full evaluation of the ostia, main renal artery, renal artery branches, and parenchyma of each kidney. The arteriogram can be unreliable in assessing the degree of stenosis, mandating the use of pressure gradient evaluation. Through the diagnostic catheter, a 0.014-in pressure wire can be passed through the renal artery lumen to assess the translesional pressure gradient, quantifying the hemodynamic significance of the arteriographic findings.<sup>148</sup> There is growing interest, although few published data, on the use of IVUS in the evaluation of renal artery FMD. Small series have demonstrated abnormalities consistent with FMD in areas with borderline or otherwise normal angiographic appearance.<sup>58,198</sup> Given the difficulty in ascertaining hemodynamic significance of minor angiographic irregularities or in localizing a culprit lesion within long stretches of stenotic vessel, IVUS may permit more thorough and targeted intervention without repeated exposure to radiation and contrast.<sup>148,199</sup>

The ability to detect intraluminal webs missed by angiography may permit PTA of an otherwise normal-appearing vessel. A potential exists for better outcomes with IVUS-directed PTA,

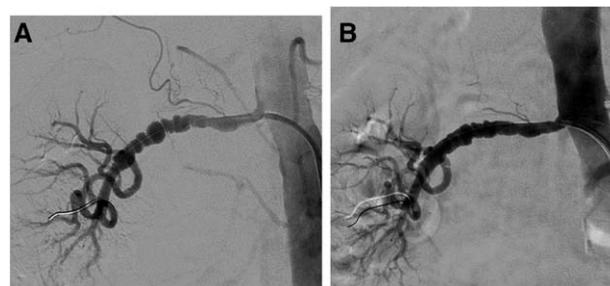
and further research is required to determine the utility of this technique in FMD.

Intervention is usually performed through a guide or sheath placed at the ostium of the renal artery. Wire of any size (0.014–0.035 in) can be used to support balloon delivery and lesion traversal. In general, smaller wires provide less support but enable very-low-profile balloons to be used. Care should be taken not to use 0.014-in wires that are designed to cross occlusions because distal advancement into the renal parenchyma can cause perforation.

In general, balloons should be sized to the diameter of the normal vessel. As mentioned, IVUS can assist in this decision, or a conservative balloon size can be tried initially and gradually increased (0.5–1.0 mm) to the size of the normal artery until resolution of the translesional gradient. The patient's symptoms should be assessed during each balloon inflation. Severe pain during balloon inflation suggests an oversized balloon and should result in immediate balloon deflation and repeat angiography to assess for vessel injury such as dissection or rupture. Traditional semicompliant balloons are recommended rather than cutting, scoring, or thermal balloons. For lesions resistant to traditional balloon angioplasty, cutting or scoring balloons have been used, but they potentially carry a higher risk for arterial rupture and are not recommended by this writing committee.<sup>200–202</sup>

The post-PTA arteriographic appearance of the renal artery may be suboptimal, or the artery may look normal when it is not. Thus, it is important to be certain that the pressure gradient is obliterated to confirm success of the intervention<sup>1</sup> (Figure 8).

In contrast to atherosclerotic disease, primary stenting of the renal artery is not recommended for any FMD subtype, although nonmedial FMD (ie, intimal) may have a higher rate of restenosis with PTA compared with medial fibroplasia.<sup>201</sup> The pathology of FMD can be responsive to PTA with minimal arterial recoil. Stenting should be reserved for lesions that fail balloon angioplasty or develop a flow-limiting dissection.<sup>186,203,204</sup> Recurrence rates are high for lesions that require stenting, and these patients should be considered for surgical treatment before recalcitrant lesions are reflexively stented. This is particularly important in the distal renal artery and smaller renal arteries that have a higher propensity for in-stent restenosis. Stent fracture requiring surgical bypass has recently been reported in 2 patients with renal FMD.<sup>205</sup>



**Figure 8.** Multifocal fibromuscular dysplasia of the right renal artery. **A**, Before angioplasty. Note the multiple constrictions and poststenotic dilations (string of beads) in the mid and distal renal artery. The pressure gradient was 35 mmHg. **B**, After angioplasty. Although the artery does not look normal, there is improvement in the angiographic appearance, and the postangioplasty pressure gradient was now zero.

Endovascular stent graft placement can be considered for main renal artery aneurysms.<sup>206–208</sup> Open surgical repair of severe branch vessel disease with or without aneurysms is preferred. Coil embolization has been used for branch artery aneurysms, but no data exist on the long-term efficacy of this technique.

Intraprocedural anticoagulation (generally with heparin) is recommended to minimize potential thromboembolic complications during balloon angioplasty. An activated clotting time >200 seconds is routinely used as a measure of therapeutic anticoagulation during the procedure. Arterial spasm can be encountered during the angioplasty procedure, especially in cases involving treatment of branch vessel disease. This can easily be managed with the administration of intra-arterial vasodilators such as papaverine (30–60 mg) or nitroglycerin (100–200 µg). After PTA, antiplatelet therapy with aspirin (75–325 mg) is recommended.

### Outcomes of Renal Artery PTA

Hypertension attributed to renal artery FMD has traditionally been considered quite amenable to revascularization, although reported cure rates vary widely across multiple series (Table 5). Davies and colleagues<sup>186</sup> determined that clinical improvement after PTA is less likely among patients >50 years of age, those with a hypertension duration >8 years, those with dyslipidemia, and patients with a fasting blood glucose >110 mg/dL. Most series are retrospective and are hampered by short follow-up, variable definition of cure, incomplete end-point assessment, and limited description of patient characteristics. Combined analysis of multiple studies suggests a less robust impact on hypertension.

A nonsystematic review of 10 published case series reported a 50% cure rate after PTA over a poorly defined period of follow-up.<sup>220</sup> A review of 26 series reported a cure rate of 42%.<sup>221</sup> Smit and colleagues<sup>222</sup> reported 51 patients in whom FMD was diagnosed during renal angiography and compared them with a matched group of 51 patients who had hypertension and normal renal arteries on renal angiography. The groups were similar in baseline characteristics. The patients with FMD had better blood pressure control after PTA with a decrease in the number of antihypertensive medications compared with the control group under intensified medical treatment involving an increased number medications. Trinquart and colleagues<sup>196</sup> performed the only systematic review of 47 published series with reasonable reporting of outcome assessment. In this review, 45.7% (95% CI, 39.8–51.7) of patients undergoing PTA had blood pressure cure as defined by the individual studies. When the analysis was restricted to studies defining cure as blood pressure <140/90 mm Hg without antihypertensive therapy, the cure rate fell to 35.8% (95% CI, 25.5–46.8). With further restriction of this analysis to series reporting at least 20 patients, the cure rate was only 26.7% (95% CI, 17.0–37.7). The combined rate of cure or blood pressure improvement was 86.4% (95% CI, 83.2–89.3) across all studies. Older patients (OR, 0.48 [95% CI, 0.39–0.59] for each 10-year increase in age) and patients with a longer duration of hypertension (OR, 0.39 [95% CI, 0.23–0.67] for each 5-year increase in duration) were less likely to be cured. Repeat PTA was performed in 18.2% (95% CI, 11.0–26.8) of patients from 10 series, and in those studies that evaluated renal function at follow-up, no statistically significant change in creatinine was found. On the basis of an analysis of 2 studies, medial (string

**Table 5. Results of Percutaneous Transluminal Angioplasty in Patients With Renal Artery Fibromuscular Dysplasia and Hypertension**

Study	Year	Patients, n	Technical Success Rate, %	Effect on Blood Pressure, %			Follow-up, Mean (Range), mo	Complication Rate, %
				Cured	Improved	Unimproved		
Sos et al <sup>209</sup>	1983	31	87	59	34	7	16 (4–40)	6
Baert et al <sup>210</sup>	1990	22	83	58	21	21	26 (6–72)	NR
Tegtmeyer et al <sup>211</sup>	1991	66	100	39	59	2	39 (1–121)	13
Bonelli et al <sup>212</sup>	1995	105	89	22	63	15	43 (0–168)	11 (major)
Jensen et al <sup>213</sup>	1995	30	97	39	47	14	12 (NR)	3 (major)
Davidson et al <sup>214</sup>	1996	23	100	52	22	26	NR	12 (minor)
Klow et al <sup>215</sup>	1998	49	98	26	44	30	9 (1–96)	0
Birrer et al <sup>194</sup>	2002	27	100	74*		26	10 (NR)	7.4
Surowiec et al <sup>216</sup>	2003	14	95	79*		21	NR	28.5
de Fraissinette et al <sup>217</sup>	2003	70	94	14	74	12	39 (1–204)	11
Kim et al <sup>200</sup>	2008	16	79	13	80	7	24 (1–60)	16
Davies et al <sup>186</sup>	2008	29	100	72*		18	24†	8 (minor)
Mousa et al <sup>218</sup>	2012	35	100	6	63	31‡	58	NR

NR indicates not reported.

\*The percentage shown is the total for cured and improved.

†Median value.

‡Estimated.

Modified and updated from Slovut and Olin.<sup>4</sup> Copyright © 2004, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Modified from Olin and Sealove<sup>1</sup> with permission from Elsevier. Copyright © 2011, Society for Vascular Surgery.

of beads or multifocal) disease was less likely to be cured than nonmedial (unifocal) disease. This should be compared with a more recent retrospective series of 30 patients in whom angioplasty of nonmedial disease was technically successful in only 65% of lesions compared with 88.2% across all studies in the systematic review.<sup>201</sup> Lower technical success rates for PTA of nonmedial disease have been demonstrated in other series.<sup>212,223,224</sup> Although this 65% success rate is lower than traditionally observed with medial disease (multifocal FMD), improvement in or cure of hypertension was reported in 70% of patients. Despite a potentially lower technical success rate in focal disease, the blood pressure response does not necessarily appear to be worse than that achieved in multifocal FMD. Although the systematic review of Trinquart and colleagues<sup>196</sup> is the most comprehensive analysis of the impact of revascularization to date, it is inherently limited by the heterogeneity of its underlying case series. No randomized, controlled trial of intervention has been performed in renal artery FMD.

Complication rates after renal PTA are usually minor, with hematoma being the most common.<sup>225</sup> Major complications, including hemorrhage, dissection, stent migration, vessel thrombosis, and emboli, are seen in up to 6.3% (95% CI, 4.1–9.0) of patients with a mortality rate 0.9% (95% CI, 0.3–1.7).<sup>196</sup>

A study on the long-term outcomes of FMD patients undergoing PTA of the renal artery was recently reported.<sup>218</sup> Forty-three procedures were performed in 35 patients (91% women; mean age, 61.9 years). The technical success rate was 100%. Hypertension cure occurred in 6% and improvement in 63% of patients. Freedom from worsening hypertension was 93%, 75%, and 41% at 1, 5, and 8 years, respectively. Primary patency was 95%, 71%, and 50% and primary assisted patency was 100%, 100%, and 100% at 1, 5, and 9 years, respectively.

### Surgical Revascularization for Renal Artery FMD

The typical FMD patient with multifocal disease of the main renal artery is first offered PTA because of the previously discussed advantages and established efficacy. There are patients, however, in whom the expected outcome from surgery may be better than that expected with PTA. Examples include patients with small renal arteries (<4 mm), branch disease, especially when associated with aneurysms, or extensive intimal or perimedial fibroplasia. Secondary surgical repair after failed PTA should be considered early in the decision process before chronic ischemia leads to loss of cortical thickness. Although no large, randomized, clinical trials in adults exist to define the most appropriate initial revascularization approach, a systematic review reported hypertension cure rates of 36% and 54% and major complication rates of 6% and 15% in the PTA and open surgical groups, respectively.<sup>196</sup> This report also confirmed that salutary blood pressure responses were more likely among younger patients.

### Surgical Techniques for Renal FMD

The use of open arterial reconstructive surgery of properly selected FMD patients with renovascular hypertension is relatively well defined.<sup>19,20,226–239</sup> It is important that the primary revascularization procedure be successful because nephrectomy is common with reoperation.

Aortorenal bypass in adults is most often performed in situ with autologous reversed saphenous vein.<sup>240</sup> Dacron or expanded polytetrafluoroethylene conduits may also be used in reconstructing these vessels. Because vein grafts in children may become aneurysmal, autologous hypogastric artery grafts and direct aortic reimplantations of the renal artery are favored in the pediatric population.<sup>54,240–243</sup> Ex vivo renal revascularizations are usually reserved for complex occlusive or aneurysmal disease affecting branch vessels.<sup>244,245</sup>

Nonanatomic bypass procedures are an important therapeutic option in treating select patients with renovascular hypertension.<sup>246–249</sup> The hepatic artery or iliac arteries may be used as sites of origin for bypass grafts to the renal artery, especially when originating a graft from the aorta would entail unacceptable risk. Use of the splenic artery in situ for a left-sided splenorenal bypass is appropriate in adults, but only after ascertaining that this vessel and the celiac trunk are free of stenotic disease. Splenorenal bypasses are not recommended in children because of the potential existence of a celiac artery growth arrest that may not be evident at the time of reconstruction but may evolve later.

### Outcomes of Surgical Revascularization

Surgical revascularization has historically been documented to have excellent outcomes, with hypertension cure rates ranging from 33% to 72% in adult case series (Table 6) and 36%–70% in children (Table 7). Salutary blood pressure responses were more likely among younger patients. More recent surgical series have shown somewhat lower surgical hypertension cure rates, and this has been attributed to the use of PTA as initial therapy for most cases, leaving the most complex disease for open surgery. In particular, 2 contemporary reports on the effect on hypertension noted cure, improved, and failure rates after PTA of 27%, 60%, 13% and after surgery of 36%, 31%, and 33% (with a 2% mortality), respectively.<sup>258,260</sup> Both studies represent poorer outcomes than either group had expected on the basis of earlier experience. It is important to note, however, that combined rates of cure or improvement with surgery do not appear to be worse than with PTA. Operative mortality in this group of patients should be exceedingly rare. In a recent review 105 operative procedures for the treatment of FMD, there were no operative deaths.<sup>271</sup>

Similar to PTA, differences among series with regard to reported clinical outcome after surgical revascularization reflect variation in patient population. For instance, older patients may have essential hypertension and FMD. Revascularization in these patients would be less likely to cure their hypertension, whereas younger hypertensive patients (particularly those <30 years of age) are more likely to have renovascular hypertension that resolves with surgical revascularization.<sup>196,228,266,269</sup>

### Surveillance After Renal Artery Revascularization

The optimal postrevascularization monitoring protocol has not been established. Oertle and colleagues<sup>272</sup> reported a series of 12 patients with FMD treated by PTA who subsequently underwent repeat angiography; 9 had recurrent hypertension and 3 did not. Of the patients with recurrent hypertension, 4 (44.4%) had restenosis and 3 (33%) had a de novo stenosis. None of the patients without recurrent hypertension

**Table 6. Results of Surgical Treatment of Renal Fibromuscular Dysplasia in Adults**

Institution	Year	Patients, n	Follow-up, mo	Results, %		
				Cure	Improvement	Failure
Buda et al <sup>250</sup>	1976	42	72	76	14	10
Stoney et al <sup>251</sup>	1978	24	36	38	52	10
Bergentz et al <sup>231</sup>	1979	40	36	66	24	10
Lawrie et al <sup>232</sup>	1980	113	49	43	24	33
Jakubowski et al <sup>252</sup>	1981	75	36	50	22	3
Stoney et al <sup>237</sup>	1981	78	67	66	32	1
Stanley et al <sup>239</sup>	1982	144	60	55	39	6
Novick et al <sup>253</sup>	1987	120	36	63	30	7
van Bockel et al <sup>230</sup>	1987	53	77	53	34	13
Hagg et al <sup>254</sup>	1987	22	36	55	36	9
Hansen et al <sup>255</sup>	1992	43	24	43	49	8
Murray et al <sup>256</sup>	1994	68	90	74	23	2
Andersen et al <sup>226</sup>	1995	40	40	33	57	10
Wong et al <sup>257</sup>	1999	19	56	31	58	11
Reiher et al <sup>258</sup>	2000	101	66	36	31	33
Chiche et al <sup>244</sup>	2003	30	62	96	0	4
Marekovic et al <sup>259</sup>	2004	72	132	80	10	10
Carmo et al <sup>260</sup>	2005	26	29	27	60	13
Lacombe and Ricco <sup>261</sup>	2006	25	69	84	12	4
Crutchley et al <sup>245</sup>	2007	37	34	15	65	20
Total		1172				

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had evidence of restenosis. Edwards and colleagues<sup>273</sup> demonstrated that a reduction in the ratio of renal artery to aorta peak systolic velocity to <3.5 on duplex ultrasonography after PTA or surgery correlates with clinical improvement in blood pressure. In a series of 13 patients with FMD in 15 arteries imaged by duplex ultrasonography 1 day and 3, 6, and 12 months after PTA, 4 arteries (26.7%) developed restenosis.<sup>195</sup> These lesions were confirmed by repeat angiography. Similar restenosis rates of 23% to 28% have been documented by

duplex ultrasonography at 12 and 60 months.<sup>186,194</sup> Monitoring by CTA is less studied, with 1 series describing restenosis in 4 of 18 segments (22%) from 12 patients over a mean of 18.3 months.<sup>200</sup> Therefore, restenosis occurs in ≈25% of patients within 1 year after PTA. In a review of published case series of PTA for FMD with reported rates of imaging findings of restenosis, it is unclear whether these findings in fact truly represent restenosis or patients who were suboptimally treated initially. In other words, if the interventionalist determined

**Table 7. Results of Surgical Treatment of Renal Fibromuscular Dysplasia in Children**

Institution	Year	Patients, n	Follow-up, mo	Sex, n		Results, %		
				Male	Female	Cure	Improvement	Failure
Stoney et al <sup>263</sup>	1975	14*	120	8	6	86	7	7
Lawson et al <sup>264</sup>	1977	25	48	12	13	68	24	8
Novick et al <sup>265</sup>	1978	27	120	13	14	60	19	19
Martinez et al <sup>228</sup>	1990	56	91	33	23	66	23	11
O'Neill et al <sup>266</sup>	1998	50	96	24	26	70	26	4
Lacombe et al <sup>267</sup>	2003	83	112	49	34	87	5	8
Chalmers et al <sup>268</sup>	2000	10	24	5	5	70	20	10
Piercy et al <sup>269</sup>	2005	25	46	12	13	36	56	8
Stanley et al <sup>243</sup>	2006	97	50	39	58	70	27	3
Huang et al <sup>270</sup>	2008	17	68	(9)†	(8)†	57	39	4
Total		404		204	200			

\*Pediatric patients with renovascular hypertension, including fibromuscular dysplasia.

†Estimated.

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anatomic success by only visually inspecting the renal artery (as opposed to normalizing the pressure gradient and using IVUS), he or she may be under the false assumption that the lesion had been completely treated initially when in fact it was not (Table 8). The presence of restenosis generally correlates with recurrent hypertension, although accurate data on the proportion of patients with recurrent hypertension in the absence of restenosis by duplex ultrasonography are lacking.

It is reasonable to obtain duplex ultrasonography at the first office visit after PTA to establish a baseline after the procedure. Serial imaging every 6 months for the first 24 months and then yearly is recommended. The development of

restenosis or worsening hypertension should lead to consideration of angiography and repeat PTA. After surgical revascularization, a similar imaging strategy may be justified. There is no role for CTA or MRA after revascularization for routine surveillance in the absence of aneurysmal disease.

### Revascularization for Carotid or Vertebral FMD

Unlike atherosclerotic vascular disease, for which surgery or stenting may be performed to reduce the risk of a hemispheric ischemic event, in patients with cerebrovascular FMD, revascularization is reserved only for symptomatic

**Table 8. Common Misconceptions Regarding Fibromuscular Dysplasia**

Misconception	Fact
All coronary, carotid, and renal artery disease is caused by atherosclerosis.	FMD can cause renal, visceral, cerebrovascular, extremity, and coronary disease. In the US Registry, the mean age at diagnosis of FMD was 51.9±13.4 y (range, 5–83 y). Many patients have few or no atherosclerotic risk factors. Whereas atherosclerosis occurs at the origin or proximal portion of the vessel, FMD occurs in the mid and distal part of the artery.
The severity of multifocal FMD (medial fibroplasia) can be accurately ascertained by visual inspection of the angiogram.	There is no accurate way to determine the degree of stenosis by visual inspection of an arteriogram or other imaging studies. IVUS or measurement of pressure gradient should be obtained in the renal arteries before and after angioplasty in patients with FMD. As many as one third of patients have no demonstrated angiographic stenosis after angioplasty yet have residual stenosis by pressure gradient or IVUS imaging.
Duplex ultrasound velocities predict degree of carotid or renal FMD severity or both.	The degree of “stenosis” cannot be determined by Doppler velocity shift. Contrary to the Doppler assessment in atherosclerotic carotid or renal artery disease, no diagnostic velocity criteria exist for cerebrovascular or renal FMD. Rather than 1 area of stenosis in atherosclerosis, there are multiple areas of stenosis and dilatation in multifocal FMD, making the flow characteristics completely different from patients with atherosclerosis. On ultrasound reports, we recommend a statement such as, “There is an increased velocity (PSV, 450 cm/s), turbulence and tortuosity in the mid and distal renal (or carotid) artery consistent with FMD.” * which is a much more accurate statement than assigning a degree of stenosis (eg, 50%–70%) to an artery.
Patients with renal or carotid artery FMD undergoing intervention should receive a stent.	There is no indication for stent placement in FMD under most circumstances. Angioplasty alone is all that is needed to resolve the pressure gradient and to normalize the appearance on IVUS. FMD occurs in the mid to distal portion of the blood vessel; therefore, a stent in the renal artery in which restenosis occurs will make surgical repair more complex. The only indications for stent implantation are failure to achieve a desirable result with PTA alone (rare) and dissection during the procedure.
The most common presentation for carotid FMD is TIA or stroke.	Although TIA, stroke, and cervical dissection can occur with carotid FMD, the most common presentations are with nonspecific symptoms. Nonspecific symptoms for carotid FMD include headaches, dizziness, light-headedness, and pulsatile tinnitus (audible swishing or whooshing sound in the ear). Carotid FMD can also be asymptomatic and detected incidentally via imaging for another reason or when a cervical bruit is appreciated.

FMD indicates fibromuscular dysplasia; IVUS, intravascular ultrasound; PSV, peak systolic velocity; PTA, percutaneous transluminal angioplasty; TIA, transient ischemic attack; and US Registry, United States Registry for Fibromuscular Dysplasia.

\*If the presence of beading is demonstrated on ultrasound imaging (ie, with B mode, color Doppler, or color power angiography), it should be noted in the written report.

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patients (with the management of extracranial and intracranial aneurysms an exception to this principle). As previously discussed, medical therapy, particularly antiplatelet therapy, is the mainstay of management of the patient with carotid and vertebral artery FMD.

The multisocietal guideline on the management of patients with extracranial carotid and vertebral artery disease stated that revascularization is not recommended for asymptomatic patients with carotid artery FMD (*Class III*), regardless of the severity of stenosis.<sup>150</sup> In this document, revascularization for carotid FMD (angioplasty with or without stenting) is given a *Class IIIa* recommendation for patients with retinal or hemispheric cerebral ischemic symptoms related to FMD of the ipsilateral carotid artery. For retinal ischemia, it seems reasonable to try antiplatelet therapy before endovascular therapy. Although many operators recommend PTA for a hemispheric event, others believe a trial of antiplatelet therapy should be instituted before proceeding with PTA.

The indications for intervening in carotid artery FMD are for the infrequent patient with recurrent cerebral ischemic events despite optimal medical therapy, often in the setting of dissection, or for those in whom antiplatelet/anticoagulant therapy is contraindicated.<sup>150</sup> Generally, PTA alone is performed with the use of a stent reserved for recalcitrant lesions or postangioplasty flow-limiting dissection. As with renal intervention, assessment of luminal improvement during carotid intervention for FMD not involving dissection can be difficult with angiography alone, and IVUS can be a useful adjunct. Because of the typical involvement of carotid FMD in or extending to the distal internal carotid artery, the use of distal embolic protection filters can be difficult and often impossible, given the lack of an adequate landing zone for the device (which typically requires at least 2 cm), and they are not easily or safely advanced into the petrous portion of

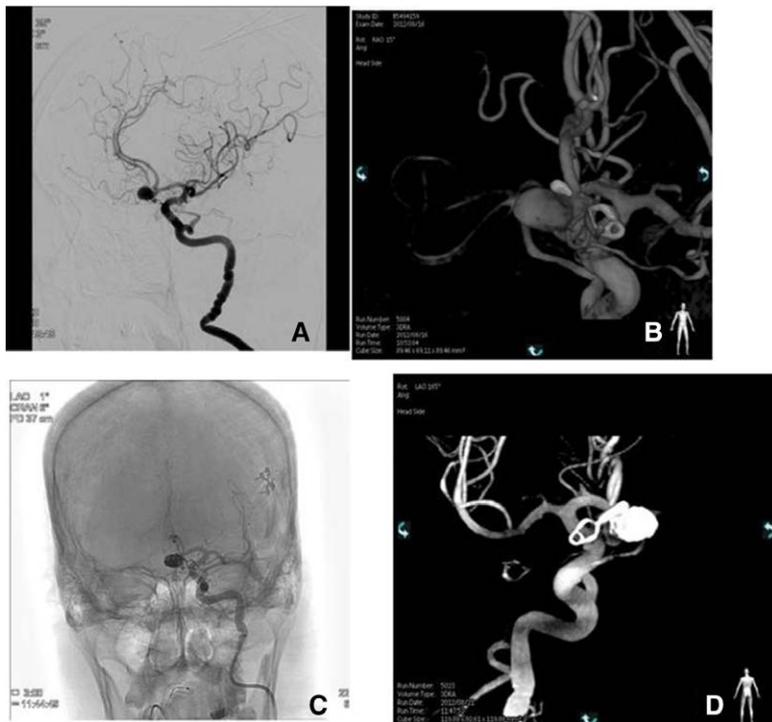
the internal carotid artery. Although proximal flow occlusion (with flow arrest or reversal) would be a technically acceptable alternative form of embolic protection, it is not clear that protection of any variety would significantly add to the safety of the procedure.

The other indication for endovascular intervention in the patient with carotid or vertebral artery FMD is pseudoaneurysm formation, usually the result of a prior dissection. Typically, therapy is offered when the pseudoaneurysm is symptomatic (eg, pulsatile tinnitus, severe headache, neck pain) or shown to be expanding on serial evaluations. Various approaches have been described to manage pseudoaneurysm, including self-expanding bare metal stents (with or without additional coil embolization of the pseudoaneurysm behind the stent) and covered stents (either self-expanding or balloon-expandable stents). Low rates of complication and high rates of success have been noted with most of these approaches.<sup>274</sup> With advances in catheter and balloon technology and operator expertise, there is little role for surgery in the modern treatment of extracranial carotid or vertebral artery FMD.<sup>56,275–280</sup> However, surgical treatment may be indicated for intracranial or extracranial aneurysms or pseudoaneurysms.

The medical therapy of carotid and vertebral artery dissections is discussed above. If the patient has continued neurological ischemia or a new neurological event while on anticoagulation or antiplatelet therapy, the artery should be stented if feasible from an anatomic standpoint.<sup>150</sup>

### Cerebral Aneurysm in Patients With FMD

Touze and colleagues<sup>29</sup> summarized data from 6 studies of patients with FMD and noted that the prevalence of cerebral aneurysm or subarachnoid hemorrhage varied between 3% and 49%. It is estimated that roughly 2% to 5% of the US



**Figure 9.** Carotid artery fibromuscular dysplasia (FMD) with intracranial aneurysm. **A**, Catheter-based angiogram (oblique projection) of the left internal carotid artery showing multifocal FMD of the prepetrous segment and an anterior communicating artery aneurysm that had previously been treated with microsurgical clipping. **B**, A 3-dimensional rotational angiogram showing the clip and aneurysm recurrence. **C**, Angiogram showing treatment of the aneurysm with electrolytically detachable coils from an endovascular approach with overlay of the prior clip. **D**, A 3-dimensional rotational angiogram showing the relationship of the clip and coil mass in successful retreatment of the aneurysm.

population harbors a cerebral aneurysm.<sup>281</sup> The majority of cerebral aneurysms are acquired sporadically and are associated with FMD, as well as connective tissue disorders and polycystic kidney disease.<sup>282</sup> The prevalence of brain aneurysm may be higher among FMD patients with carotid artery involvement than among patients with renal FMD, but studies considering this association are small and may overestimate the true association.<sup>19</sup> Several reports show a high prevalence of cerebral aneurysms in patients with carotid or vertebral FMD, with estimates as high as 50%.<sup>18,61</sup> These reports overestimate the true prevalence because cerebral angiography was performed on patients with cerebral aneurysms resulting from a subarachnoid hemorrhage or other symptoms such as headaches. Thus, there may be an overestimate of patients with this condition as a result of the exclusion of asymptomatic patients. Cloft and colleagues<sup>110</sup> tried to adjust for this bias in a meta-analysis to estimate the association of carotid or vertebral FMD and cerebral aneurysms. They found that 7.3% of patients with carotid or vertebral artery FMD harbored a nonruptured incidental cerebral aneurysm. This may be in the upper range of the CI of the general population, but the association likely exists. This writing committee recommends that all patients with FMD in any location be screened for intracranial aneurysms by CTA or MRA.

The treatment options for patients who present with cerebral aneurysms associated with FMD are no different from the general population. Patients who present with subarachnoid hemorrhage caused by a rupture of the aneurysm require early intervention to prevent rebleeding because the risk of a rebleed is 4% within the first 24 hours and 2%/d thereafter.<sup>284</sup> Thus, the American Heart Association guidelines recommend early treatment to secure the aneurysm with either endovascular coil embolization or microsurgical clipping with a craniotomy.<sup>285</sup> A single randomized, controlled trial in 2143 patients comparing coiling of a ruptured aneurysm with clipping showed a 7.4% absolute reduction in morbidity and mortality favoring coiling.<sup>286</sup> Certain aneurysms may not be amenable to coil embolization because of a wide neck or unfavorable geometric features; thus, microsurgical clipping is often thought to be safer in those cases (Figure 9).

Patients with nonruptured cerebral aneurysms present a more challenging clinical dilemma because the natural history of these aneurysms is not as well defined. The International Subarachnoid Aneurysm Trial (ISAT) longitudinally followed up patients with nonruptured aneurysms and found an association with size and location to be predictive of subsequent rupture.<sup>281</sup>

Recently, the UCAS (Unruptured Cerebral Aneurysm Study) Japan Investigators published data on patients enrolled from 2001 to 2004 with newly identified unruptured cerebral aneurysms.<sup>287</sup> Their cohort included 5720 patients with a saccular aneurysm of  $\geq 3$  mm with mean age 62.5 years, 68% of whom were women. The overwhelming majority of aneurysms (91%) were incidentally identified. Rupture developed in 111 patients during 11 660 aneurysm-years of follow-up. The investigators determined that rupture risk increased with increasing aneurysm size (compared with 3- to 4-mm reference); the hazard ratio for 5- to 6-mm aneurysms was 1.13 (95% CI, 0.58–2.22), for 7- to 9-mm aneurysms was 3.35

**Table 9. Top Research Priorities in FMD**

Determination of the prevalence of FMD in the general population of women 18–65 y of age.
Understanding of unique biological and genetic determinants of FMD, including identification of determinants of arterial bed involvement and the development of arterial narrowing versus aneurysm vs dissection
Understanding the role of sex hormones in the pathogenesis of FMD, including the female preponderance of the disease and the potential contribution of exogenous hormones (oral contraceptives and systemic hormone replacement) to its pathogenesis
Creation of a rational and cost-effective approach to vascular screening for patients with FMD identified in 1 vascular bed (ie, what additional imaging should be obtained for a patient with isolated renal FMD)
Development and validation of Doppler criteria for diagnosis of carotid and renal medial fibroplasia using duplex ultrasound
Characterization of the natural history of FMD in the symptomatic and asymptomatic patient population, including disease progression and interval development of major vascular events (eg, stroke, arterial dissection, mortality); development of tools for risk stratification of FMD patients and prognosis based on these data
Determination of the prevalence of cerebral aneurysms in FMD patients and if FMD patients with cerebral aneurysms are at higher risk of subsequent rupture
Characterization of the risk of pregnancy associated with FMD (eg, risk of uncontrolled hypertension, arterial dissection)
Characterization and understanding of the mechanisms of headache among FMD patients and development of effective treatment algorithms for symptom prevention and treatment
Determination of the feasibility of a randomized, clinical trial of optimal therapy for primary/secondary prevention of stroke/TIA among patients with cerebrovascular FMD
Determination of the feasibility of a randomized, clinical trial of medical therapy vs endovascular therapy for treatment of hypertension among patients with renal FMD

FMD indicates fibromuscular dysplasia; and TIA, transient ischemic attack.

(95% CI, 1.87–6.00), for 10- to 24-mm aneurysms was 9.09 (95% CI, 5.25–15.74), and for  $\geq 25$ -mm aneurysms was 76.26 (95% CI, 32.76–177.54).<sup>287</sup>

In determining which patients with asymptomatic cerebral aneurysm should be offered treatment, it is reasonable to consider a number of factors in addition to aneurysm size, including the patient's age, extent of comorbidities, current smoking history, multiplicity of aneurysms, and family history of a previously ruptured aneurysm. Data from the UCAS Japan cohort also determined that aneurysm location may be an important consideration in clinical decision making because aneurysms in the posterior and anterior communicating arteries had a nearly 2-fold increased likelihood of rupture (hazard ratio, 1.90 and 2.02, respectively) compared with aneurysms in the middle cerebral artery.<sup>287</sup> Similarly, aneurysms at the basilar tip have been shown to be associated with increased rupture risk.<sup>288</sup> The American Association of Neurosurgery guidelines suggest that it is reasonable to offer treatment to asymptomatic patients <60 years of age with an aneurysm >5 mm and for all healthy patients <70 years of age with aneurysms >10 mm.<sup>289</sup> For older patients, decision making is more complex, with comorbidities and aneurysm location playing an important role.

### **Common Misconceptions in FMD**

A number of commonly held misconceptions concerning FMD are continually repeated in the literature. A summary of these misconceptions and their clarification was recently published by Olin and Sealove<sup>1</sup> and is presented in Table 8.

### **Critical Unanswered Questions and Areas for Future Research**

There is a great need for additional research into the pathogenesis, diagnostic approach, and natural history and outcomes of FMD. To date, there have been no randomized, controlled trials of medical therapies or endovascular treatment (versus

medical therapies) for FMD. The writing committee has identified 11 research priorities in the field of FMD (Table 9) and hopes that this document will serve as an impetus for additional research in this field. Given the uncommon nature of FMD, funding for research is challenging. Significant advances in our understanding of FMD will undoubtedly require collaboration across a large network of research and clinical centers in the United States and abroad.

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\*Modest.

†Significant.

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\*Modest.

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# Circulation

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**Fibromuscular Dysplasia: State of the Science and Critical Unanswered Questions: A Scientific Statement From the American Heart Association**

Jeffrey W. Olin, Heather L. Gornik, J. Michael Bacharach, Jose Biller, Lawrence J. Fine, Bruce H. Gray, William A. Gray, Rishi Gupta, Naomi M. Hamburg, Barry T. Katzen, Robert A. Lookstein, Alan B. Lumsden, Jane W. Newburger, Tatjana Rundek, C. John Sperati and James C. Stanley

on behalf of the American Heart Association Council on Peripheral Vascular Disease, Council on Clinical Cardiology, Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Radiology and Intervention, Council on Epidemiology and Prevention, Council on Functional Genomics and Translational Biology, Council for High Blood Pressure Research, Council on the Kidney in Cardiovascular Disease, and Stroke Council

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