fibromuscular dysplasia (FMD) is an uncommon nonatherosclerotic disease of medium-sized arteries. The disease was first described in 1938 by Leadbetter and Burkland and later classified histologically by Harrison and McCormick in the early 1970s.\(^1,2\) Until recently, little progress had been made to elucidate the epidemiology, pathophysiology, and natural history of FMD. The establishment of the United States (US) Registry for FMD has helped make appreciable progress toward understanding this disease.

In January 2009, the US Registry for FMD began enrolling patients at seven centers across the United States. Seven additional centers were added since that time (see the Currently Enrolling Centers in the US Registry for FMD sidebar). The registry is sponsored by the FMD Society of America (www.fmdsa.org) and is coordinated by the University of Michigan Cardiovascular Outcomes Research and Reporting Program (www.mcorrp.org). The registry protocol is approved by the institutional review board of each clinical center. A standardized data collection form is completed at the time of initial enrollment for each participant, which includes demographics, presenting symptoms/signs, comorbidities, family history, medications, physical examination, imaging studies, vascular procedures, renal function, lipid profile, and history of vascular and clinical outcome events.

At each follow-up visit, interval vascular and clinical outcome events are recorded, as well as vascular imaging studies, FMD-related vascular procedures, current medications, select laboratory parameters, and blood pressure measurement. Each center follows a standardized definition document for completing data collection forms. Since the first patients were enrolled in January 2009, enrollment has continued to climb (Figure 1). As of January 9, 2014, there was a total of 951 patients enrolled in the registry.

A wealth of information has come from the registry. Initial data from the first 447 registrants were published in 2012 in *Circulation*, and an additional article highlighting differences between the sexes was published in 2013.\(^3,4\) To date, 10 abstracts have been presented at national scientific meetings. Insights gained from the registry have led to significant changes in our understanding of FMD and our approach to clinical management of this disease. In this article, we summarize some of the key concepts learned from the registry, and highlight changes we have made to clinical practice based on registry data.

### CURRENTLY ENROLLING CENTERS IN THE US REGISTRY FOR FMD AS OF JANUARY 2014\(^a\)

- Cleveland Clinic, Cleveland, OH
- Mount Sinai, New York, NY
- Greenville Health System, Greenville, SC
- University of Michigan, Ann Arbor, MI
- North Central Heart, Sioux Falls, SD
- Mayo Clinic, Rochester, MN
- Ochsner Health Center, Metairie, LA
- University of Virginia Health System, Charlottesville, VA
- Massachusetts General Hospital, Boston, MA
- University of California Davis, Sacramento, CA
- Miami Baptist Cardiac/Vascular Institute, Miami, FL
- University of Kansas, Kansas City, KS
- Vanderbilt Heart, Nashville, TN
- Children’s Hospital of Philadelphia, Philadelphia, PA (pediatric only center)

\(^a\)For a complete list of registry center contact information and local principal investigators visit www.fmdsa.org
LESSON #1: (RE)DEFINING THE COMMON CLINICAL PRESENTATION OF FMD

Although the association between renal FMD and hypertension is very well described, the common clinical manifestations of FMD are actually more diverse (see Figures 2 and 3 for case examples). Among the first 447 patients enrolled in the registry, hypertension was the most common presenting manifestation, affecting 63.8% of patients; however, there was a number of other common signs and symptoms of FMD, including headache (52.4%), pulsatile tinnitus or “swooshing” noise in the ears (27.5%), dizziness (26%), cervical bruit (22.2%), and neck pain (22.2%). Most FMD patients (80%) presented with multiple symptoms/clinical signs at the time of diagnosis. Symptoms are determined largely by the vascular beds involved, and many patients have FMD in multiple arteries. Interestingly, in the era of advanced imaging, a number of patients were identified when imaged for other indications. Incidental FMD was diagnosed in 5.6% of registrants who were asymptomatic at the time of diagnosis. Symptoms are determined largely by the vascular beds involved, and many patients have FMD in multiple arteries. Interestingly, in the era of advanced imaging, a number of patients were identified when imaged for other indications. Incidental FMD was diagnosed in 5.6% of registrants who were asymptomatic at the time of diagnosis. Because presenting symptoms extend beyond hypertension, FMD should be included in the differential diagnosis for patients with other nonspecific complaints, especially headaches, pulsatile tinnitus, neck pain, and/or for patients with cervical bruit.

LESSON #2: FMD INVOLVES MORE THAN THE RENAL ARTERIES

Renal artery FMD is the most common site of disease among patients in the registry (79.7% of patients). However, cerebrovascular (extracranial carotid and vertebral) FMD is nearly as common, with 74.3% of registrants presenting with carotid and 36.6% with vertebral involvement. Nearly two-thirds of patients with renal artery FMD have cerebrovascular FMD and vice versa if assessed with imaging examination. Other commonly affected vascular beds include the celiac/mesenteric arteries (26.3%), intracranial vessel (17%, primarily manifesting as aneurysms), and lower (generally external iliac artery) and upper (generally brachial artery) extremities. Because FMD presents so commonly in multiple vascular beds, particularly the cerebrovascular and renal arteries, it is important to image these territories at least once to identify asymptomatic FMD and associated vascular manifestations (eg, aneurysms and dissections). On the basis of these data, our current clinical approach to patients with FMD is a one-time brain-to-pelvis imaging study with subsequent follow-up studies targeted to areas that are found to have evidence of disease.

Unfortunately, despite the frequent finding of FMD in multiple beds, imaging multiple vascular beds is not a standard practice among all physicians. As of 2011, only 74.5% of registrants with renal artery FMD had ever undergone carotid/vertebral imaging, and only 63.7% of registrants with carotid FMD had undergone intracranial imaging.

LESSON #3: MEN AND WOMEN WITH FMD PRESENT DIFFERENTLY

Although FMD is primarily a disease found in women, outnumbering men 9:1 in the registry, the course of the disease in men seems to be somewhat different. Table 1 demonstrates the difference in arterial involvement by sex. Women with FMD were more likely to present with classic signs and symptoms of carotid FMD, including pulsatile tinnitus, neck pain, and cervical bruit (all P < .05). Headache was also more common in women than in men (57.8% vs 46.8%; P = .17). In contrast, men with FMD were more likely to present with signs and symptoms of visceral involve-
ment: flank/abdominal pain, renal insufficiency, and renal infarction (43.8% vs 14.3%, 9.1% vs 2.2%, and 42.9% vs 4.3%, respectively; all P < .05). Renal artery dissection with infarction represents a “classic” presentation for FMD in a male patient. In addition, male FMD patients had a twofold increase in prevalence of arterial aneurysm (40.8% vs 20.4%; P = .002) and dissection (39.6% vs 20%; P = .0031) compared to female patients. Based upon these data, it seems that FMD in men may have a more complicated vascular course.

LESSON #4: DIAGNOSIS OF FMD REQUIRES LISTENING, BUT MORE IMPORTANTLY, LOOKING

Baseline physical examinations were recorded for patients who were prospectively enrolled in the registry. As of 2012, some physical examination data were available for 92% of patients. Many patients presented with an audible bruit over the affected vascular bed. Carotid bruits were auscultated in 30.5% of patients (bilateral in 18.1%); other bruits included epigastric/abdominal (17.5% of patients) and flank (6.1%).

Despite the frequency of bruits, auscultation is not an adequately sensitive tool for FMD diagnosis in a given vascular bed. Cervical bruit for carotid or vertebral FMD diagnosis was 45.4% sensitive, but abdominal bruit for the diagnosis of renal or mesenteric FMD was only 24% sensitive. However, auscultation was highly specific for FMD involvement in a particular area (cervical bruit was 93.7% specific for extracranial FMD with positive predictive value 95.4%; abdominal bruit 93.3% specific for renal/mesenteric FMD with positive predictive value 92.6%). Therefore, auscultation of a bruit in an FMD patient indicates that there is likely FMD in the associated vascular bed, but lack of bruit does not rule out FMD. Physical examination is an insensitive tool, and imaging is required.

LESSON #5: BEYOND THE STRING OF BEADS: FMD IS A SERIOUS VASCULAR CONDITION

FMD (in its multifocal variant) commonly presents with multiple areas of stenosis and dilatation (string of beads) with related symptoms, but it also may present with morbid vascular events. Arterial dissections and aneurysms were a common finding among patients in the registry. Nearly one in five FMD patients has at least one arterial dissection, and of those, 20% had more than one dissection. The extracranial carotid arteries, followed by the renal arteries, were the most common sites of dissection. Aneurysms were also frequent, with 22.2% of registrants having at least one aortic or arterial aneurysm. Among those, more than one-third had more than one aneurysm. The renal and extracranial carotid arteries were the most common sites for aneurysm. Other common sites for dissections and aneurysms are listed in Table 2.

We do not yet understand why some FMD patients develop dissections or aneurysms and others do not,
nor do we have reliable methods for identifying those FMD patients who are at the greatest risk. As mentioned, our standard clinical practice of brain-to-pelvis cross-sectional imaging (CT angiography or magnetic resonance angiography) at least once for all FMD patients, regardless of the initial site of disease diagnosis, will identify occult aneurysms in these patients.

**LESSON #6: POTENTIAL GENETIC MECHANISMS OF FMD REMAIN UNKNOWN**

FMD is thought to have a genetic component. Early reports suggested an autosomal dominant disease with variable penetrance. Yet, few FMD patients (7.3%) in the registry report a first- or second-degree relative with a diagnosis of FMD. This is lower than previously published rates for familial FMD of approximately 10%. In contrast to low reported rates of familial FMD in the registry, nearly one-quarter of patients report a first- or second-degree relative with aortic or arterial aneurysm, and more than half report a family history of stroke. These data (and others) suggest that the arterial manifestations of FMD may represent a broader inherited arteriopathy (or multiple genetic arteriopathies) with a variable clinical vascular phenotype (eg, presenting as string-of-beads lesions in some patients, aneurysms in others). Investigations related to the genetics of FMD are underway at a number of academic medical centers in the United States and Europe.

**LESSON #7: HALF OF FMD PATIENTS HAVE UNDERGONE A VASCULAR PROCEDURE, THE MAJORITY OF WHICH ARE ENDOVASCULAR**

Half of all patients in the registry have undergone at least one therapeutic vascular procedure for FMD. Among those having undergone at least one procedure, the average number of procedures per patient is 1.9 ± 1.6, with a range of one to 12 procedures. The most common clinical indications for intervention include hypertension (64.6%), dissection (8.2%), aneurysm (7.3%), and headache (6.1%). Endovascular procedures (mainly percutaneous transluminal angioplasty) on the renal arteries predominate. Although most patients had favorable outcomes, procedural complications occurred in 9.8% of patients who underwent a vascular procedure. Arterial dissection was the most commonly reported complication. Technical failures occurred in 6.4% of procedures.

On the basis of these data and our clinical experience, it is clear that many FMD patients benefit from therapeutic vascular intervention, but like all revascularization procedures, patient selection is critical. Operator training and experience in the care of FMD patients is also important, as there are many procedural factors that differ in the treatment of FMD compared to atherosclerosis. For example, for symptomatic renal artery FMD, balloon angioplasty without stenting is the endovascular strategy of choice. Further, the measurement of translesional pressure gradients before and during procedures is critical for understanding the potential for aneurysmal rupture and for determining whether balloon angioplasty alone is sufficient, or stenting is required. In addition, a comprehensive revascularization strategy may include intravascular ultrasound (IVUS) to assess the neointimal layer and evaluate the possibility of mechanical intervention to keep the lumen open. Intravascular brachytherapy may also be considered to reduce the risk of restenosis.

### TABLE 2. PREVALENCE AND VASCULAR DISTRIBUTION OF ARTERIAL DISSECTIONS AND ANEURYSMS IN FIBROMUSCULAR DYSPLASIA (N = 447)\(^{a,b}\)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissection</td>
<td>88 (19.7)</td>
</tr>
<tr>
<td>Carotid artery</td>
<td>68/88 (75)</td>
</tr>
<tr>
<td>Renal artery</td>
<td>19/88 (21.6)</td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>15/88 (17)</td>
</tr>
<tr>
<td>Mesenteric artery</td>
<td>4/88 (4.5)</td>
</tr>
<tr>
<td>Coronary artery</td>
<td>3/88 (3.4)</td>
</tr>
<tr>
<td>Celiac artery</td>
<td>2/88 (2.3)</td>
</tr>
<tr>
<td>Iliac artery</td>
<td>2/88 (2.3)</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>76 (17)</td>
</tr>
<tr>
<td>Renal artery</td>
<td>25/76 (32.9)</td>
</tr>
<tr>
<td>Carotid artery(^c)</td>
<td>16/76 (21.1)</td>
</tr>
<tr>
<td>Aorta</td>
<td>15/76 (19.7)</td>
</tr>
<tr>
<td>Celiac artery</td>
<td>12/76 (15.8)</td>
</tr>
<tr>
<td>Cerebral arteries(^d)</td>
<td>9/76 (11.8)</td>
</tr>
<tr>
<td>Mesenteric</td>
<td>5/76 (6.6)</td>
</tr>
<tr>
<td>Basilar</td>
<td>5/76 (6.6)</td>
</tr>
<tr>
<td>Vertebral</td>
<td>2/76 (2.6)</td>
</tr>
<tr>
<td>Subclavian</td>
<td>2/76 (2.6)</td>
</tr>
<tr>
<td>Popliteal</td>
<td>2/76 (2.6)</td>
</tr>
</tbody>
</table>

\(^{a}\)All vascular beds were not imaged in every patient.\(^{b}\)Reproduced with permission from Olin JW et al. Circulation. 2012;125:3182–3190.\(^{c}\)Carotid artery aneurysm includes extra- and intracranial internal carotid artery and ophthalmic artery.\(^{d}\)Cerebral arteries include anterior, middle, and posterior cerebral arteries.
after renal angioplasty to ensure hemodynamic (as well as angiographic) technical success of the procedure has become standard at many experienced and high-volume FMD clinical centers.

**LESSON #8: THE MEDICAL COMMUNITY RARELY RECOGNIZES SYMPTOMS OF FMD, AND DIAGNOSIS IS OFTEN DELAYED**

There is a significant delay in diagnosis from the time of symptom onset for patients with FMD. In the registry, the mean length of time from first reported FMD symptom (by patient recall) to confirmed diagnosis was 3.6 ± 7.4 years.3,12 In the series from Paris, there was a 9-year delay from the onset of hypertension to the diagnosis of FMD in patients with multifocal FMD.13 In the registry, factors associated with longer time to diagnosis were younger age and hypertension as the presenting symptom.12 Patients with stroke or arterial dissection had a shorter time to diagnosis, reflecting the earlier triage to imaging studies.12 The delay in diagnosis may be due to a number of factors. First, the signs and symptoms of FMD are nonspecific, for example, headache, tinnitus, hypertension, and dizziness. Second, among patients with hypertension, the mean age of onset, 43.1 years, overlaps with the onset of essential hypertension. This makes it difficult to distinguish essential hypertension from FMD-related hypertension based on age alone.

We need to continue to educate the medical community to consider FMD in the differential diagnosis, to ask for other symptoms of this disease in at-risk patients, and to incorporate a thorough vascular examination into the office visit. In a middle-aged woman with hypertension, it is important to include FMD in the differential diagnosis and identify any other symptoms suggestive of FMD, which include abdominal, flank, or neck bruits, headaches (especially migraine type), pulsatile tinnitus, and resistant hypertension. The patient with pulsatile tinnitus and severe migraine headaches, especially if a bruit is present, warrants an investigation to rule out cerebrovascular FMD.

Although we have much to learn about FMD, recognizing the signs and symptoms of this disease and referring patients to qualified health care providers is a vital first step. ■

**For those clinicians and investigators interested in learning more about FMD, the International FMD Research Network Symposium will be held in Cleveland, Ohio, on May 15th and 16th, 2014. The US FMD Registry, as well as other related international vascular registries, will be discussed in detail. A state-of-the-art update on FMD management is included in the program. Please see www.clevelandclinic.org/fmdsymposium for additional details.**

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