

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Coronary Artery Manifestations of Fibromuscular Dysplasia



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ABSTRACT

Fibromuscular dysplasia (FMD) involving the coronary arteries is an uncommon but important condition that can present as acute coronary syndrome, left ventricular dysfunction, or potentially sudden cardiac death. Although the classic angiographic "string of beads" that may be observed in renal artery FMD does not occur in coronary arteries, potential manifestations include spontaneous coronary artery dissection, distal tapering or long, smooth narrowing that may represent dissection, intramural hematoma, spasm, or tortuosity. Importantly, FMD must be identified in at least one other noncoronary arterial territory to attribute any coronary findings to FMD. Although there is limited evidence to guide treatment, many lesions heal spontaneously; thus, a conservative approach is generally preferred. The etiology is poorly understood, but there are ongoing efforts to better characterize FMD and define its genetic and molecular basis. This report reviews the clinical course of FMD involving the coronary arteries and provides guidance for diagnosis and treatment strategies. (J Am Coll Cardiol 2014;64:1033-46) © 2014 by the American College of Cardiology Foundation.

Fibromuscular dysplasia (FMD) is an arteriopathy distinct from atherosclerosis or vasculitis that may result in stenosis, aneurysm, dissection, or occlusion. It predominantly affects middle-aged women but may occur at any age in both sexes (1,2). The renal, carotid, and vertebral arteries are most frequently involved, but FMD has been reported in virtually every artery in the body (1,3,4). Although clinically manifest FMD with involvement of the coronary arteries arises less frequently, it is important to recognize and treat appropriately. Coronary involvement with FMD may result in significant morbidity and mortality from coronary artery dissection, leading to acute coronary syndrome with myocardial infarction and left ventricular dysfunction. There has been recent interest in spontaneous coronary artery dissection (SCAD) and its frequent association with FMD

(5-8), but there is no comprehensive published review of coronary artery manifestations of FMD to guide physicians in the diagnosis and management of this important and underrecognized condition.

EPIDEMIOLOGY AND DEMOGRAPHICS

In 1965, Hill and Antonius (9) first reported the pathology and clinical histories of 2 patients with FMD and coronary artery involvement. However, in the 5 decades since this initial report, many descriptions of FMD involving the coronary arteries have been small autopsy series or case reports (10). Clinically manifest FMD with coronary artery involvement is believed to be rare, but its true prevalence is unknown. This is partly due to a lack of specific coronary findings or symptoms before an acute event. Importantly, while

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Manuscript received June 16, 2014; revised manuscript received July 10, 2014, accepted July 11, 2014.

ABBREVIATIONS AND ACRONYMS

FMD = fibromuscular dysplasia

IVUS = intravascular
ultrasound

LAD = left anterior descending

OCT = optical coherence
tomography

SCAD = spontaneous coronary
artery dissection

a “string of beads” appearance can be diagnostic of FMD in the renal, carotid, and other arterial beds, this appearance rarely, if ever, occurs in the coronary arteries. Rather, as discussed later, most patients with coronary artery manifestations of FMD present with SCAD or smooth narrowing and are subsequently found to have typical FMD findings in the noncoronary arteries.

The demographics of patients with coronary artery manifestations of FMD are similar to those of patients with FMD in other locations. The mean age at diagnosis of the first 447 patients enrolled in the U.S. Registry for FMD was 51.9 ± 13.1 years (range of 5 to 86 years), and 91% were female (2). Hypertension was the most common cardiovascular risk factor (71%) due to renal artery FMD, but other cardiovascular risk factors were infrequent (37.2% were current or past smokers, and 42% were being treated with a statin). In comparison, in a series of 7 patients diagnosed antemortem with coronary artery manifestations of FMD, all were women between 42 and 56 years of age (11). Similarly, in a series of 50 patients with SCAD in which 86% had confirmed FMD, the mean age was 51 ± 9.6 years (range 31 to 84 years), and the cardiovascular risk profile was similar to that reported in the U.S. Registry for FMD (5).

ETIOLOGY

Although various hypotheses have been proposed to explain the etiology of FMD in general and its coronary artery manifestations, the cause remains unknown. Many of the reports speculating about the biological etiology were published decades ago, with few subsequently published reports. It is most likely that subjects with FMD carry a genetic predisposition, because 7% to 11% of first-degree relatives have FMD (2,12,13). Further evidence that this is a genetically mediated disease was derived from the U.S. Registry for FMD, in which 53.5% of first- or second-degree relatives had a stroke (many before 60 years of age), 23.5% had an aneurysm, and 19.8% died suddenly (2). On the basis of pedigree studies, some have suggested that FMD may be due to an autosomal dominant trait with variable penetrance (14,15). However, the genetics underlying FMD remain poorly understood. One group of investigators used scanning electron microscopy to perform ultrastructural analyses of surgical specimens from 20 renal arteries with FMD (16). They hypothesized that encasement of the vasa vasorum by connective tissue leads to worsening medial ischemia, subsequent transformation of smooth muscle cells to myofibroblasts, and progression of disease.

Finally, because more than 90% of patients with FMD are women, including those with SCAD (5,17), estrogen is an attractive culprit in the development of FMD. However, there is no concrete evidence that estrogen or other hormones play a role in the development of FMD or its coronary manifestations.

On the basis of the available evidence at present, the generally accepted consensus is that FMD is likely a multifactorial disease with varying contributions from genetic, gender/hormonal, and environmental influences (18).

PATHOLOGY AND CLASSIFICATION

The histological appearance of renal artery FMD has been well characterized. In 1938, Leadbetter and Burkland (19) first described FMD in a 5½-year-old African-American boy with severe hypertension. The renal artery was occluded by an “intra-arterial mass of smooth muscle.” The patient subsequently underwent unilateral nephrectomy of an ectopic pelvic kidney, and his hypertension was cured. In an angiographic-pathological correlation study, Harrison and McCormack (20) separated renal artery FMD into 3 groups on the basis of whether the intima, media, or adventitia of the renal arterial wall was involved (Table 1). In this early report, the media was affected in 80% to 90% of cases, and medial fibroplasia was the most common medial subtype. Because of collagen deposition that is seen histologically in medial fibroplasia, areas of arterial stenosis and post-stenotic dilation develop. This corresponds to the “string of beads” appearance on angiography that is classically associated with renal artery FMD (21). Unlike the situation for renal artery FMD, reliable reports of the histological characteristics of FMD affecting the coronary arteries are essentially nonexistent and no histological classification system has been proposed.

Histopathologic classification played an early (and now somewhat historical) role in managing patients with FMD during the era pre-dating catheter-based endovascular interventions, when clinically significant lesions were managed surgically. In the contemporary era, most patients with FMD who undergo revascularization of the coronary artery (or any other affected arteries) do so via an endovascular approach. Therefore, pathological specimens of vessels from patients with FMD are now rarely available (18). This has led to the evolution of a newer FMD classification system on the basis of angiography (Table 1, Figure 1) (18,20,22). Prior angiographic-pathological correlative studies showed that multifocal FMD (“string of beads”) is associated with medial fibroplasia, whereas

focal FMD is typically associated with intimal fibroplasia, medial hyperplasia, or adventitial fibroplasia (20,21,23-25). Thus, the new angiographic FMD classification is conveniently translatable back to the original histopathologic designations. Nevertheless, while this new classification on the basis of angiographic appearance of a peripheral artery is straightforward, it has limited utility for classifying coronary artery involvement associated with FMD due to the unique manifestations of this disease in the coronary arterial bed.

PRESENTATION

The majority of patients with coronary artery manifestations of FMD present with dissection of an epicardial artery (left anterior descending [LAD], circumflex, or right coronary artery) or a major branch, which clinically leads to unstable angina, myocardial infarction, left ventricular dysfunction, or potentially sudden cardiac death (11,26-28). There are autopsy reports of sudden cardiac death purported to be secondary to FMD of “small coronary arteries,” with obliteration of the sinoatrial or atrioventricular nodal arteries, resulting in fatal arrhythmias (29-33). However, in these reports, FMD was not sought or confirmed in any other blood vessel; thus, “small coronary artery” FMD likely represents a separate disease process (18). Among 488 patients in the U.S. Registry for FMD who were enrolled for ≥1 year and with ≥1 follow-up visit, there were only 4 deaths (0.8%) during a median follow-up period of 23.9 months (34). Notably, none were due to coronary manifestations of FMD; 3 of these deaths were due to malignancy, and 1 patient who died was lost to follow-up (34).

In patients presenting acutely due to coronary artery manifestations of FMD, electrocardiographic findings may be suggestive of acute ischemia with or without ST-segment elevation, and there are often elevated cardiac biomarkers (creatinase-myocardial band or troponin) (11). According to the 2012 3rd Universal Definition (35), SCAD presenting as myocardial infarction is classified as a type 2 infarction, which is considered to be primarily due to a condition other than atherosclerotic coronary artery disease and includes other disorders (e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachyarrhythmias/bradyarrhythmias, anemia, respiratory failure, and hypotension). Recent data indicate that in the mostly female population presenting with SCAD and type 2 myocardial infarction, FMD may be identified in other vascular territories in the majority of cases (5-7).

TABLE 1 Classification of FMD

Classification of FMD		
Histological: 1971 (20)	Angiographic: French/Belgian Consensus 2012 (22)	Angiographic: American Heart Association 2014
Medial fibroplasia	Multifocal	Multifocal
Perimedial fibroplasia		
Medial hyperplasia		
Intimal fibroplasia	Unifocal (<1 cm)	Focal
Adventitial fibroplasia	Tubular (≥1 cm)	

Modified from Olin et al. (18).
 FMD = fibromuscular dysplasia.

DIAGNOSIS

FMD with coronary artery involvement should be considered in any patient without cardiac risk factors presenting with acute coronary syndrome or new left ventricular dysfunction, and especially in middle-aged women who are found to have isolated involvement of a mid-distal coronary artery with normal coronary arteries elsewhere.

When considering FMD, numerous features in the patient’s history and physical examination may suggest this diagnosis (Table 2). The manifestations of noncoronary FMD depend on the arterial bed affected, most often hypertension with renal artery FMD and headache or pulsatile tinnitus with cervical vessel involvement.

At the present time, catheter-based angiography is the only validated and accurate method of diagnosing coronary artery involvement and there are no studies documenting the utility of other noninvasive imaging modalities for diagnosing coronary artery manifestations of FMD. A number of distinct angiographic

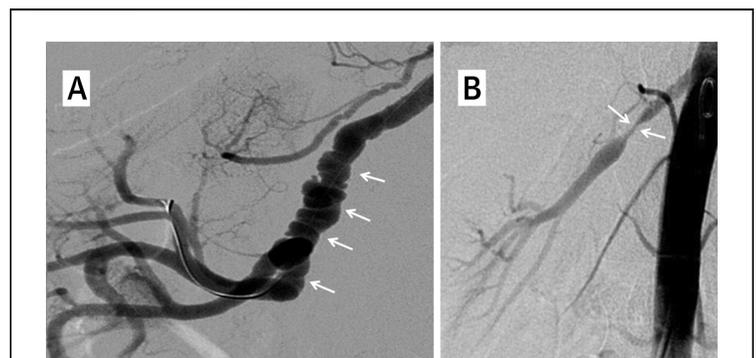


FIGURE 1 Angiographic Classification of Noncoronary FMD: Multifocal Versus Focal

(A) Multifocal renal artery FMD with alternating stenosis and dilation, creating the classic “string of beads” appearance on angiography (arrows). (B) Angiography showing focal renal artery FMD (arrows). FMD = fibromuscular dysplasia.

TABLE 2 Common Presenting Clinical Features of FMD

History (listed in order of decreasing frequency):

Hypertension
Headache
Pulsatile tinnitus
Dizziness
Neck pain
Nonpulsatile tinnitus

Physical examination

Bruit: cervical, epigastric, or flank
Cranial nerve abnormalities
Other focal neurological deficits
Horner syndrome

Other

Aneurysm
Dissection (renal, carotid, vertebral, coronary)

Adapted with permission from Olin et al. (2).
Abbreviation as in Table 1.

findings are supportive of this diagnosis (Table 3, Central Illustration) and include angiographically obvious SCAD (Figures 2 to 4), smooth narrowing or distal tapering typically with intramural hematoma (Figure 5), spasm, and tortuosity. These features often overlap, and more than one may be appreciated in the same patient or even in the same coronary artery. SCAD is the most common presentation of FMD involving the coronary arteries (Figures 2 to 4). There are isolated case reports of FMD manifesting with a “string of beads” appearance of the coronary arteries; however, in the few articles describing this, the “beading” does not have the characteristic appearance of that seen in noncoronary FMD and probably represents another angiographic appearance of dissection (27,28). The appearance of distal tapering or long, smooth narrowing in the middle of the artery may also represent dissection or intramural hematoma (Figure 5) (11,26,36). Lesions are usually well

demarcated on angiography, with a discrete transition from normal to diseased coronary artery (Figure 5) (3,11). Often, there is involvement of a single epicardial vessel with otherwise normal appearing coronary arteries (11). It is important to administer intra-arterial vasodilators to be certain that spasm is not accounting for these angiographic findings. Arterial tortuosity is an additional aspect of FMD involving the coronary arteries (and other vascular territories) (37), although this alone would seem unlikely to cause symptoms and is not specific for FMD.

Intravascular ultrasound (IVUS) is an excellent adjunctive imaging modality for use in the coronary or other vascular beds. In combination with angiography, IVUS provides enhanced information about all layers of the arterial wall to help distinguish coronary artery manifestations of FMD from other forms of coronary disease (Figure 4) (38). Generally, fibrous tissue and collagen correlate with echogenic signals on IVUS, whereas smooth muscle hyperplasia corresponds to echolucency.

Optical coherence tomography (OCT) is yet another intracoronary imaging modality that may be a useful adjunct in the diagnosis of coronary artery involvement with FMD (Figure 2) (39). OCT generates 3-dimensional images from optical scattering within tissue. With OCT, the fibrous and collagen deposition in coronary arteries with FMD involvement appears bright (high reflectivity) and smooth muscle hyperplasia looks dark (low reflectivity) (39). A potential concern when performing OCT with current systems is the need to evacuate blood from the vessel lumen by high-flow intracoronary contrast injection. Overly aggressive contrast injection may theoretically be associated with propagation of a coronary dissection.

There are several potential pitfalls in diagnosing coronary artery manifestations of FMD. For example, changes secondary to FMD may be confused for atherosclerosis. When doubt arises, IVUS or OCT may be particularly helpful for further lesion evaluation, with attention paid to differentiating the typical appearance of coronary artery manifestations of FMD from that of atherosclerotic disease (presence of lipid, plaque, and calcification) (40). An additional discriminatory factor is the location of the disease, because FMD tends to affect the mid or distal segments of the artery whereas atherosclerosis often involves the proximal portion of an artery (Figures 2 to 5) (11,26). In 2 case series with a total of 10 patients with FMD and involvement of the LAD artery, 90% had involvement of the mid and/or distal segment (11,26).

Although difficult to quantify, these angiographic features also have clinical prognostic significance. The

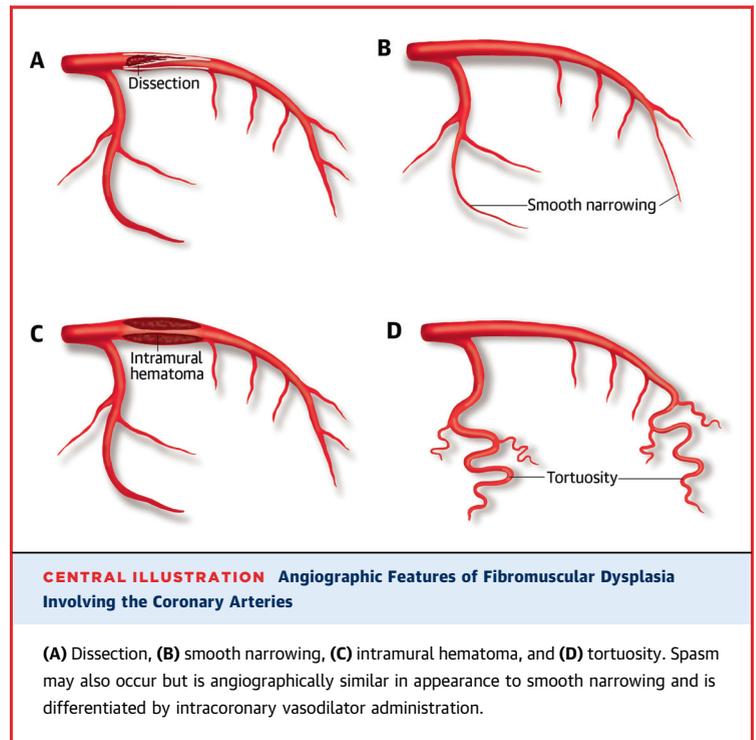
TABLE 3 Angiographic Features of FMD Involving the Coronary Arteries

Feature	Comments
SCAD	Dissection with obvious radiolucent area, flap, extraluminal cap, or contrast staining
Smooth narrowing or distal tapering	Increasingly recognized as coronary dissection with intramural hematoma visualized by IVUS or OCT
Intramural hematoma	May arise de novo and be appreciated by IVUS or OCT or after stent implantation with a new stenotic lesion appearing a few millimeters from the proximal or distal stent edge (Figure 4)
Spasm	A component of coronary spasm may occur; intra-arterial nitroglycerin usually relieves
Tortuosity	Coronary artery tortuosity may be present. Tortuosity is a frequent finding in other vascular beds (carotid, vertebral, renal) in patients with FMD

IVUS = intravascular ultrasound; OCT = optical coherence tomography; SCAD = spontaneous coronary artery dissection; other abbreviations as in Table 1.

clinical course of smooth narrowing or distal tapering is usually favorable, with healing typically noted on repeat angiography at 4 to 6 weeks (Figure 5) (40). However, angiographically visible SCAD is likely to be associated with acute coronary syndrome and may even be fatal in rare cases (5,8).

To classify a patient as having FMD affecting the coronary arteries, visualization of FMD in other vascular territories is mandatory. There are 2 good reasons to perform cross-sectional imaging from the head to the pelvis in every patient who presents with SCAD or the other coronary artery findings discussed in the preceding text: to determine if FMD is present in any other vascular bed and to determine if there is evidence of aneurysm(s) or dissection(s) in any other blood vessel. Although magnetic resonance angiography can accurately identify aneurysms and dissections, the resolution is often not sufficient to identify FMD in the distal renal or carotid arteries (18). The resolution of computed tomographic angiography is superior to that of magnetic resonance angiography and is the recommended cross-sectional imaging modality in these circumstances (18). If catheter-based angiography is required to confirm the diagnosis of FMD or evaluate lesion severity, a potential pitfall to avoid is classifying the patient as having FMD when in fact stationary or standing waves are present (Figure 6) (41,42). There are 2 distinguishing features: in multifocal FMD, the beading is larger than the normal caliber of the artery and occurs in an irregular pattern, whereas standing waves are regular oscillations of the artery and administration of



nitroglycerin abolishes the spasm and returns the artery to normal.

DIFFERENTIAL DIAGNOSIS

The diagnosis of coronary artery manifestations of FMD is challenging, and several conditions need to be

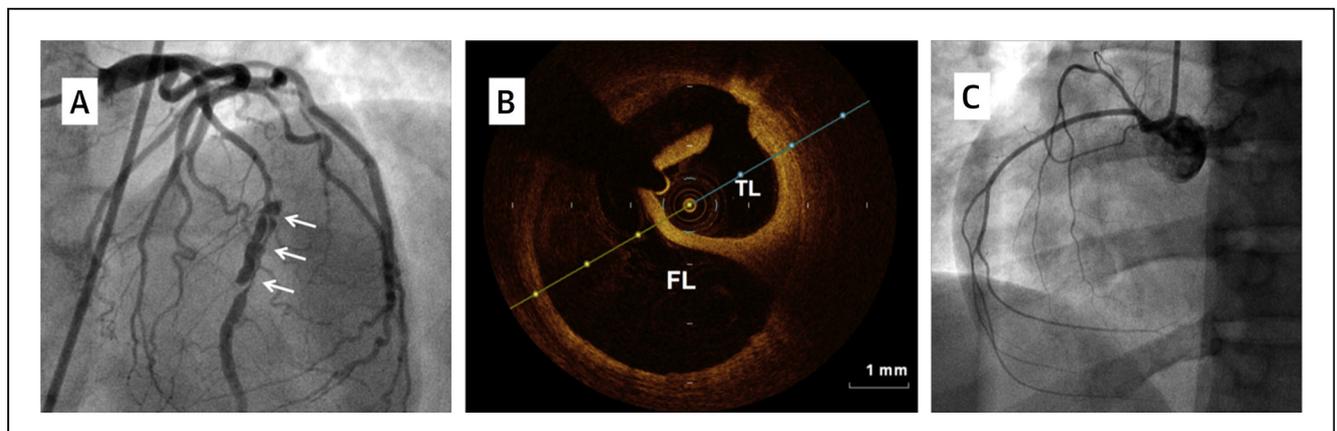


FIGURE 2 SCAD of the LAD Artery

A 34-year-old female patient presented with ST-segment elevation myocardial infarction 7 days after cesarean delivery of a healthy newborn. The pregnancy was complicated by hypertension. (A) Coronary angiography showing the left coronary system in a cranial projection, revealing extensive dissection of the mid-LAD coronary artery (arrows). (B) Optical coherence tomography of the dissected LAD artery, showing the true lumen (TL) and false lumen (FL). (C) Angiographically normal right coronary artery of the same patient. Original images are presented here, but this case was previously reported (124). LAD = left anterior descending; SCAD = spontaneous coronary artery dissection.

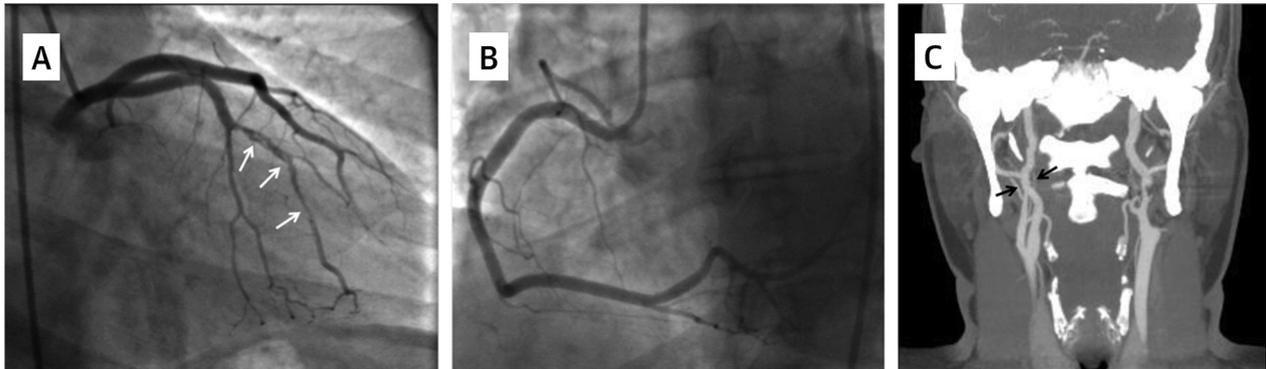


FIGURE 3 SCAD of the Left Circumflex Artery

A 37-year-old female patient presented with a troponin-positive non-ST-segment myocardial infarction. The patient had a pre-existing diagnosis of FMD with renal and carotid artery involvement. **(A)** Coronary angiography showing the left coronary system in a right anterior oblique-caudal projection. **Arrows** indicate dissection involving the obtuse marginal branch of the left circumflex with mottled appearance, narrowing, and filling defect. Note the normal, smooth appearance of the other vessels and segments. **(B)** Angiographically normal right coronary artery of the same patient. **(C)** Computed tomographic angiography of the carotid and vertebral arteries. Note the tortuosity and beading in the mid and distal portion of the right internal carotid artery (**arrows**), typical of multifocal FMD. The carotid bifurcation (the site where atherosclerosis occurs) is normal. Abbreviations as in [Figures 1 and 2](#).

carefully considered in the differential diagnosis ([Table 4](#)). Obtaining a detailed history is a fundamental part of the evaluation. For most patients, catheter-based angiography will be necessary to evaluate and treat cardiac ischemia; treatment and prognosis may vary on the basis of the predominant coronary manifestation (e.g., SCAD vs. smooth narrowing).

Excluding Ehlers-Danlos syndrome type IV, the vascular subtype, is important because this may also manifest as coronary artery dissection ([43,44](#)). Patients with Ehlers-Danlos syndrome type IV often have a small body habitus with characteristic facial appearance (large eyes, small chin, thin nose and lips, lobeless ears), pale translucent skin, easy bruising, and hypermobile joints ([45](#)). This disease often has a more fulminant course than FMD involving the coronary arteries, with 25% of patients presenting by 20 years of age and more than 80% experiencing life-threatening complications by 40 years of age ([46](#)). Identifying a mutation in the gene for type III procollagen (*COL3A1*) confirms the diagnosis ([46](#)).

Takayasu arteritis and giant cell arteritis are large vessel vasculitides that predominantly affect the aorta and its branches but can involve the coronary arteries in up to 30% of cases ([47,48](#)). Like those with FMD, patients with Takayasu arteritis affecting the coronary arteries are typically young women presenting with angina and, less commonly, myocardial infarction ([49](#)). On physical examination, they may have a discrepancy in arm blood pressures; absent or

decreased radial, brachial, and/or carotid pulses; supraclavicular and cervical bruits; or the murmur of aortic regurgitation ([50,51](#)). Laboratory testing is notable for elevated erythrocyte sedimentation rate and C-reactive protein level ([49,52](#)). Cross-sectional imaging with computed tomographic angiography or magnetic resonance angiographic is useful in evaluating the aortic wall thickness, the size of the ascending aorta, and the presence of aortic valve thickening ([51](#)). Catheter-based angiography is the gold standard for diagnosis of coronary artery involvement. Severe, focal stenosis of the left main trunk is common ([51](#)). There may also be focal or tubular stenosis of the proximal or mid coronary artery (usually the LAD) ([49,50](#)).

Cocaine use should also be considered in the differential diagnosis. In contrast to the typical patient with FMD, patients who use cocaine and have cardiac symptoms are most frequently male and smoke cigarettes ([53-55](#)). Urine toxicology screening may be diagnostic for cocaine ingestion ([56](#)). If symptoms are suggestive of ischemia and warrant angiography, stenotic lesions in one or more coronary arteries are most commonly seen ([57,58](#)). This reflects that vasoconstriction from cocaine use increases narrowing at regions of underlying atherosclerotic coronary disease and that cocaine use accelerates atherosclerotic plaque formation ([59,60](#)). Patients who use cocaine may also develop cardiac hypertrophy, myocardial infarction, dilated cardiomyopathy, obstructive small vessel disease, and myocarditis ([61,62](#)).

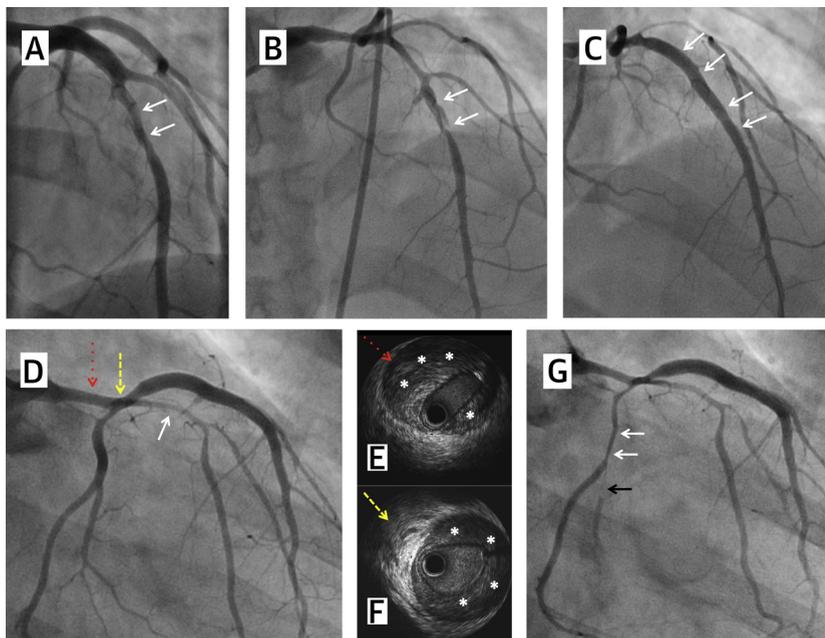


FIGURE 4 SCAD of the LAD Artery With Intramural Hematoma

A 40-year-old woman presented 10 days after a third-trimester miscarriage with troponin-positive non-ST-segment elevation myocardial infarction. **(A)** Coronary angiography revealed SCAD of the mid-LAD artery (**white arrows**). No stent was placed, and she was managed medically with a heparin drip and tight blood pressure control for 48 h. She was then discharged from the hospital on aspirin, clopidogrel, a beta-blocker, and a statin. She returned 5 days post-discharge with recurrent non-ST-segment elevation myocardial infarction and underwent **(B)** repeat coronary angiography that showed worsening dissection of the LAD artery (**white arrows**). Due to ongoing cardiac ischemia and worsening dissection, the proximal and mid-LAD arteries were then stented (**white arrows**) **(C)**. **(D)** Caudal coronary angiographic view after stenting, with re-expansion of the LAD artery but smooth narrowing of the mid-distal left main artery (**red arrow**), ostial LAD (**yellow arrow**), and ramus intermedius (**white arrow**). **(E and F)** Intravascular ultrasound performed immediately after percutaneous intervention revealed a large intramural hematoma (**asterisks**) in the mid-distal left main artery (**red arrow**), which extended into the LAD artery (**yellow arrow**). Over the next 2 days, she continued to have intermittent chest pain and rising troponin levels; she therefore underwent a third cardiac catheterization and was found to have **(G)** new severe proximal narrowing of the left circumflex artery (**white arrows**) and an occluded first obtuse marginal artery (**black arrow**), with patent intervention sites. No further intervention was performed, and the patient improved with medical therapy over the following days. Transthoracic echocardiography revealed a mild-moderately decreased ejection fraction (46%), and she was ultimately discharged home on aspirin, clopidogrel, a beta-blocker, and an angiotensin-converting enzyme inhibitor. She has remained well for 1 month post-discharge and awaits formal evaluation for FMD. Abbreviations as in [Figures 1 and 2](#).

Coronary artery spasm or Prinzmetal angina (63), which causes angina at rest, may present in a similar fashion to FMD with coronary artery involvement. Smoking is a major risk factor for coronary artery spasm (64). On angiography, coronary artery spasm typically occurs at a localized segment of an epicardial coronary artery but can affect multiple segments of the same or different arteries (65). Diffuse coronary spasm has also been described (66). ST-segment elevation on an electrocardiogram that coincides with rest angina supports the diagnosis (66). If necessary, coronary spasm can be induced by provocative testing using intravenous or intracoronary ergonovine or acetylcholine (65). Resolution of the stenosis with intravenous vasodilator administration can distinguish this entity from FMD (66).

Myocardial bridging, which occurs when part of an epicardial coronary artery is embedded in the myocardium, can present like FMD involving the coronary arteries with angina, myocardial infarction, or, rarely, sudden cardiac death due to arterial compression during systole (67-73). This phenomenon mostly affects the mid-LAD artery and creates what is known as a tunneled artery (Figure 7) (74,75). Although this is a congenital abnormality, most patients present after 30 years of age (74). Angiography is the gold standard for diagnosis and shows systolic narrowing of the affected coronary artery that disappears during diastole (“the milking effect”) (76). Intracoronary injection of nitroglycerin may cause the relative degree of stenosis to increase because the intramyocardial segment of the vessel is constrained

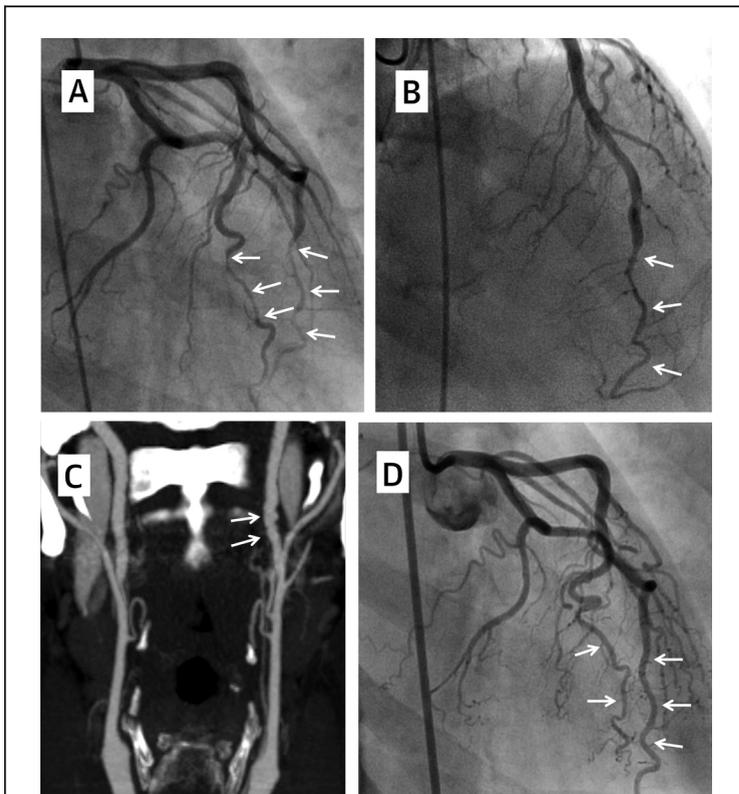


FIGURE 5 Smooth Coronary Artery Narrowing in a Patient With FMD

A 52-year-old woman with a history of migraine presented with non-ST-segment elevation myocardial infarction and was found to have smooth narrowing and distal tapering involving the LAD and left circumflex arteries. **(A)** Coronary angiography with caudal view showing distal smooth tapering of the LAD and left circumflex arteries (**arrows**). **(B)** Cranial view showing distal smooth tapering of the LAD artery (**arrows**). Several aliquots of both intracoronary nitroglycerin and intracoronary verapamil were administered over a 15-min period without any effect. **(C)** In the same patient, computed tomographic angiography of the carotid arteries is notable for a beaded appearance of the mid and distal portions of the cervical left internal carotid artery (**arrows**), consistent with FMD. The patient was managed conservatively with aspirin and clopidogrel. **(D)** Repeat coronary angiography 1 month after initial cardiac catheterization was angiographically normal, likely representing healed dissection of the LAD and left circumflex arteries (**arrows**). Abbreviations as in **Figures 1 and 2**.

and unable to respond, while the other coronary segments dilate in response to nitroglycerin (77,78).

Finally, acute coronary syndrome secondary to atherosclerotic plaque rupture or erosion must always be included in the differential diagnosis. Like FMD, atherosclerosis can manifest as stenotic lesions in one or more epicardial coronary arteries. In uncertain cases, either IVUS and/or OCT can be used to visualize plaque morphology (79-81). Additionally, atherosclerotic plaque is most common in older patients with risk factors including diabetes, hypertension, cigarette smoking, and hyperlipidemia (82-93).

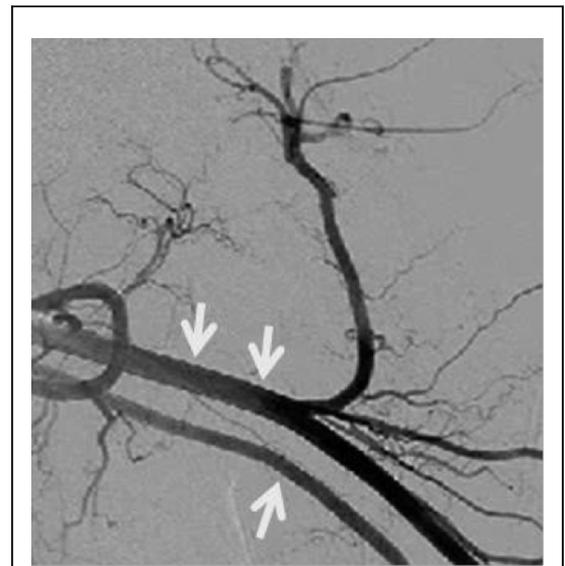


FIGURE 6 Standing Waves

Arteriography of the axillary artery showing standing waves (**arrows**). Standing waves are due to catheter-induced spasm, and typically the administration of nitroglycerin will result in a normal-appearing artery. Note the regular oscillations that occur with standing waves, in contrast to the appearance of the “string of beads” (**Figure 1**), where the “beads” are larger than the normal caliber of the artery.

SCAD

SCAD occurs when an expanding hematoma leads to separation of the layers of the coronary arterial wall (**Figures 2 to 4**) (5,94). Of importance, recent studies have suggested that FMD may be present in a majority of patients with SCAD (5,95), but SCAD may also arise in the absence of FMD. In a study of 50 patients with nonatherosclerotic SCAD, 86% of all patients had imaging consistent with FMD of at least one non-coronary artery (5). Importantly, 6% of patients were not screened for FMD, indicating that the total proportion may be higher. Other studies have corroborated these findings (95). It should be noted that the high prevalence of FMD in patients with SCAD is on the basis of very few studies and this association has only recently been recognized. In studies published before 2005, imaging of peripheral vessels (renal, carotid, vertebral, mesenteric arteries) was not performed; therefore, the association of SCAD and FMD was not recognized (96,97). Additionally, in a recent analysis of 738 patients enrolled in the U.S. Registry for FMD, 165 (22.4%) had a dissection of an artery other than the aorta (98). Of those 165 patients, the carotid arteries were involved in 73%, vertebral arteries in 19%, renal arteries in 16%, and coronary

TABLE 4 Differential Diagnosis of FMD Involving the Coronary Arteries

	Patient Demographics and Any Pertinent Examination Findings	Risk Factors	Appearance on Angiography	Arterial Region Affected	Adjunctive Testing
FMD	Female, mean age at diagnosis of 52 yrs, hypertension, cervical or abdominal bruit	Hypertension, strenuous activity, absence of typical risk factors of atherosclerosis	One or more features: SCAD, smooth narrowing or distal tapering, intramural hematoma, spasm, tortuosity	Mid-distal epicardial coronary arteries (most commonly LAD) but any coronary artery can be involved	OCT and IVUS; acute phase reactants, autoimmune markers, and complete blood cell count should be normal
Ehlers-Danlos syndrome type IV	Younger than 40 yrs of age, small body habitus, characteristic facial appearance, translucent skin, easy bruising, hypermobile joints	Family history	Dissection and/or aneurysm of any artery	Epicardial coronary arteries and any other artery in the body	Mutation in the COL3A1 gene
Takayasu arteritis	Female, younger than 40 yrs of age, hypertension, absent or decreased pulses, bruits, murmur of aortic regurgitation	None known	Focal stenosis in the left main trunk, focal stenosis in proximal or mid-coronary artery (usually LAD), aneurysm of ascending aorta, aortic regurgitation, thickening of the aortic wall and aortic valve; also affects other major branches of the aorta such as subclavian, axillary, and renal arteries; although less common, may affect the lower extremity arteries		Elevated erythrocyte sedimentation rate and C-reactive protein level; exclude infection such as tuberculosis
Cocaine vasculitis	Men with fewer cardiovascular risk factors, ECG may show ST-segment elevations, hole in nasal septum	Smoking; acute hypertension may be associated with cocaine ingestion	Stenosis, spasm, aneurysm	Epicardial coronary arteries	Urine toxicology
Coronary vasospasm	Middle-aged men and women, ST-segment elevations on ECG that correlate with anginal symptoms	Smoking	Localized occlusion at one or more segments or diffuse occlusion	Epicardial coronary arteries	Provocative testing with ergonovine or acetylcholine
Myocardial bridging	Older than 30 yrs of age	Hypertrophic cardiomyopathy	Narrowing during systole that disappears during diastole ("milking effect")	Middle segment of the LAD artery; also rarely arises in other coronary vessels/segments	Intracoronary administration of nitroglycerin
Atherosclerotic plaque	Generally older than 60 yrs of age	Diabetes, hypertension, smoking, hyperlipidemia, family history of coronary artery disease	Stenosis	Epicardial coronary arteries	OCT and IVUS

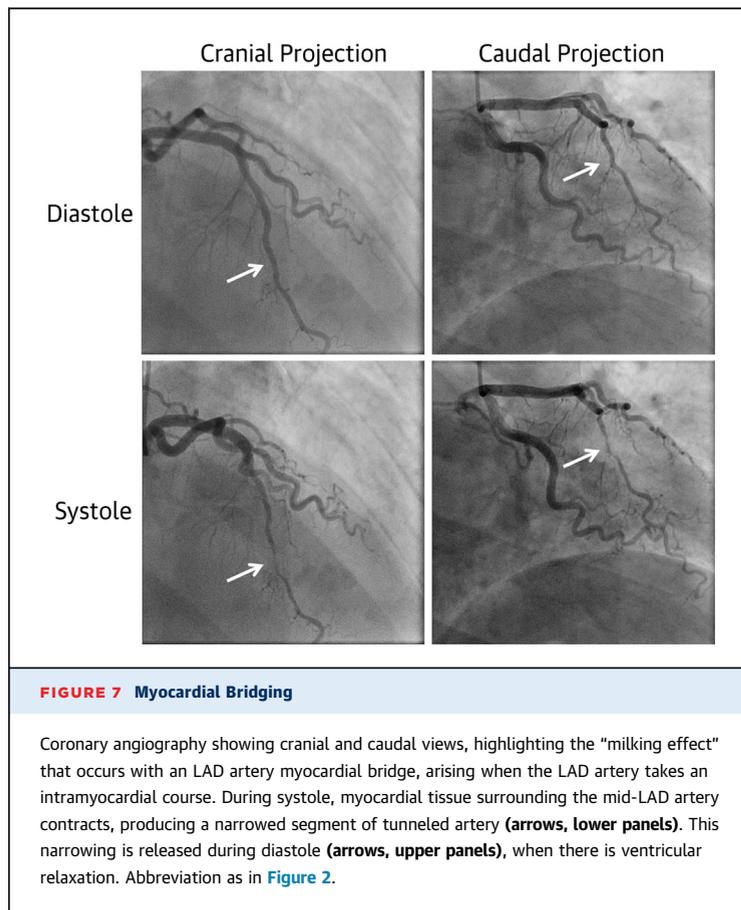
ECG = electrocardiography; LAD = left anterior descending; other abbreviations as in Tables 1 and 3.

arteries in 4.8%. Again, this probably represents an underestimation because FMD was not often considered or looked for as the underlying disorder in patients presenting with SCAD before the publication of recent studies (5,7,8,99).

Published accounts of SCAD mirror those of FMD involving the coronary arteries, confirming that these are likely a similar disease in many patients. Patients with SCAD are predominantly female, with a mean age of approximately 50 years at diagnosis, and often have no cardiovascular risk factors other than hypertension (5,100-102). Estrogen may be implicated in SCAD, because a significant number of cases of SCAD occur in the post-partum period (8). According to an analysis of more than 50 cases of post-partum SCAD, the majority of dissections occurred within 2 weeks of delivery (103). The hormonal and hemodynamic changes in the peripartum, delivery, and post-partum period may account for the association between SCAD and post-partum status. Hormonal

changes during pregnancy have been shown to have effects on the arterial wall, possibly predisposing to dissection in the coronary vasculature, in conjunction with the increased cardiac output that occurs throughout pregnancy and especially during delivery (104-106).

Angiography in a patient with SCAD may reveal multiple lumens, luminal narrowing, intimal flap, slow clearing of contrast, contrast staining, intra-arterial thrombus (arising due to the exposure of subintimal tissues to blood), and sparing of the proximal region of the coronary artery (Figures 2 to 4) (5). IVUS and OCT are useful adjuncts in visualizing the dissection and extent of intramural hematoma (Figures 2 and 4) (94,100,107-109). A classification system for SCAD was recently proposed: type 1, angiographically evident arterial wall contrast agent staining; type 2, diffuse stenosis of varying severity; and type 3, SCAD with appearance similar to an atherosclerotic lesion (40).



On the basis of retrospective studies, the estimated incidence of SCAD detected on all coronary angiograms ranges from 0.07% to 1.1% (102,110-112). Tweet et al. (8) retrospectively reviewed data on 87 patients with angiographically proven SCAD and found multivessel SCAD in 23% of patients. Conservative management in 31 patients and coronary artery bypass in 7 patients resulted in an uncomplicated hospital course. However, percutaneous intervention resulted in technical failure in 15 patients (35%) and 1 death. During a median follow-up of 47 months, 15 patients (17%) had recurrent SCAD, often in a previously unaffected coronary artery. Mortality was 1.1% at 1 year and 7.7% at 10 years. FMD was present in 8 of 16 (50%) femoral angiograms taken from the femoral artery access sheath before closure device placement. However, FMD was not routinely considered in these patients. In other series, the prognosis of patients who presented with SCAD was good, especially if they survived their initial event, with up to 95% 2-year survival (113,114). Importantly, the dissection tends to heal spontaneously and uncomplicated cases have good outcomes without intervention (5,99,115).

THERAPY

Caring for a patient with FMD and coronary artery involvement can be challenging, because there is limited objective evidence to guide therapy and no scientifically based recommendations due to the absence of prospective trials or even large observational case series. Therefore, therapy is on the basis of case reports and limited case series with extrapolation of therapies from nonrandomized publications.

In stable patients without active myocardial ischemia, a conservative approach avoiding percutaneous or surgical intervention is generally preferred for managing coronary artery manifestations of FMD. This is because SCAD (whether there is obvious dissection or long smooth narrowing) will typically heal spontaneously (Figure 5) (5,8,99,113). If stenting is performed, the dissection flap has a propensity to propagate proximally or distally beyond the stented segment, or intramural hematoma may arise (Figure 4). Therefore, avoidance of percutaneous coronary intervention or coronary artery bypass graft surgery is recommended unless the patient has refractory ischemia despite an optimal medical regimen.

A reasonable approach to the medical management of a patient with FMD and clinically manifest coronary artery involvement is dual antiplatelet therapy with clopidogrel 75 mg daily and aspirin 75 to 81 mg daily for up to 1 year if tolerated and without bleeding complications (99,116). Thereafter, aspirin alone should be continued indefinitely. The role of antithrombotic therapy in coronary dissection is not known. A beta-blocker may also be considered, with the rationale being that by reducing blood pressure and heart rate, beta-blocker therapy reduces coronary shear forces that may help to reduce the risk of further coronary dissection (99). Concomitant hypertension, whether or not attributed to renal artery FMD, should be treated to goal (18).

In unstable patients or those with active myocardial ischemia, an interventional approach may be required. Although angioplasty alone is preferred for renal artery FMD, intracoronary stent implantation is usually required in patients with SCAD. Care must be taken to avoid stent or vessel overdilation, because this may lead to propagation of coronary dissection at the stent edges. Therefore, avoiding high balloon inflation pressures and using smaller-sized stents may be advisable (38). The use of adjunctive intracoronary imaging with IVUS or OCT during percutaneous coronary intervention can help to avoid balloon or stent oversizing, optimize stent placement, and minimize complications (38). Coronary artery bypass graft surgery should be reserved for patients

with multivessel involvement who have good distal target vessels. Although not commonly performed for this indication, coronary bypass surgery can be life-saving when used in the appropriate setting (8).

There is no evidence that statin therapy is beneficial in patients with FMD and/or dissection, and published guidelines do not address this question (117). Therefore, statin therapy should be initiated with the objective of correcting dyslipidemia, as per guideline criteria (18). Due to their pleiotropic effects, some physicians recommend statins for patients with acute coronary syndrome, regardless of its etiology (atherosclerotic or otherwise) or the patients' lipid status. It should be noted that there is no clinical evidence for this approach in patients with type 2 (nonatherosclerotic) myocardial infarction.

There are no data to support or refute the use of oral contraceptives or other hormonal replacement therapy in FMD with coronary artery involvement. The available data regarding hormonal therapy are specific for atherosclerotic coronary artery disease (117,118). We allow use of oral contraceptives for prevention of pregnancy or other hormonal therapy for debilitating post-menopausal symptoms. However, in the absence of a compelling reason to use hormonal therapy, we advise against their use until more data become available.

Cardiac rehabilitation is advisable for all patients with coronary artery manifestations of FMD. This may be especially helpful in overcoming a young patient's anxiety related to experiencing an unprovoked and unanticipated coronary event. However, due to the rare association of SCAD with extreme physical activity (116,119,120), we advise against strenuous sports or lifting of heavy weights.

ONGOING RESEARCH

Without question, further research into coronary artery manifestations of FMD is required. Indeed, more must be learned about all aspects of this disease, including its epidemiology, etiology, pathology, diagnosis, and optimal treatment. Efforts to screen and identify more patients with coronary artery

involvement are already under way at several institutions as part of the U.S. Registry for FMD, the Canadian Registry, and the Mayo Clinic SCAD Registry (2,6-8,99). The U.S. Registry for FMD currently has more than 1,000 participants, and as it continues to grow, more precise information will be learned about the prevalence of coronary artery involvement and the subsequent outcomes of these patients. Detailed study of the cellular, molecular, and genetic etiology of FMD involving the coronary arteries and other vascular territories will potentially open the door for targeted therapies in the future. Our own laboratory is presently engaged in research to better understand these aspects of FMD (121,122).

CONCLUSIONS

Since its relatively recent initial description, a great deal has been learned about coronary artery involvement with FMD. However, it is important to recognize that the association of SCAD and FMD is on the basis of very few studies with small numbers of patients. To determine the true prevalence of FMD in patients with SCAD, cross-sectional imaging (computed tomographic angiography or magnetic resonance angiography) from the head to the pelvis should be obtained in all patients with SCAD. Coordinated, large-scale projects such as the U.S. Registry for FMD and the French Registry for FMD have provided much needed clinical information (2,22,123). Nevertheless, FMD remains a medical enigma at the genetic and molecular levels. It is hoped that the intense research efforts currently under way will eliminate much of the mystery surrounding FMD and its coronary manifestations, enabling clinicians to provide patients with a clear diagnosis and, in the future, effective and evidence-based treatment.

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KEY WORDS acute coronary syndrome, coronary vessel anomalies, fibromuscular dysplasia, left ventricular dysfunction, myocardial infarction