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Spontaneous Coronary Artery Dissection

Prevalence of Predisposing Conditions Including Fibromuscular Dysplasia in a Tertiary Center Cohort

Jacqueline Saw, MD,* Donald Ricci, MD,* Andrew Starovoytov, MD,* Rebecca Fox, MSc,* Christopher E. Buller, MD†

Vancouver, British Columbia, and Toronto, Ontario, Canada

Objectives We sought to evaluate the prevalence of fibromuscular dysplasia (FMD) and other predisposing conditions among spontaneous coronary artery dissection (SCAD) patients.

Background Spontaneous coronary artery dissection is considered rare. However, we observed many young women with SCAD and concomitant FMD.

Methods Spontaneous coronary artery dissection patients were identified prospectively and retrospectively at Vancouver General Hospital over the past 6 years. Coronary angiograms were meticulously reviewed by 2 senior interventional cardiologists. Identified patients were contacted for prospective evaluation at our SCAD clinic, and screening for FMD of renal, iliac, and cerebrovascular arteries was performed with computed tomography angiography or magnetic resonance angiography, if not already screened during the index angiogram. Potential predisposing and precipitating conditions for SCAD were extracted from clinical history.

Results We identified 50 patients with nonatherosclerotic SCAD from April 2006 to March 2012. Average age was 51.0 years, and almost all were women (98.0%). All presented with myocardial infarction (MI), 30.0% had ST-segment elevation, and 70.0% had non–ST-segment elevation MI. Only 1 was postpartum, and 2 were involved in intense isometric exercises. Emotional stress was reported in 26.0% before the MI. Twelve percent had >1 dissected coronary artery. Most SCAD patients had FMD of ≥1 noncoronary territory (86.0%): 25 of 43 (58.1%) renal, 21 of 43 (48.8%) iliac, and 20 of 43 (46.5%) cerebrovascular (6 of 43, 14.0% had intracranial aneurysm). Five had incomplete FMD screening.

Conclusions Nonatherosclerotic SCAD predominantly affects women, and most have concomitant FMD. We suspect these patients have underlying coronary FMD that predisposed them to SCAD, but this requires proof from histology or intracoronary imaging of the affected coronary arteries. (J Am Coll Cardiol Intv 2013;6:44–52) © 2013 by the American College of Cardiology Foundation

From the *University of British Columbia, Vancouver General Hospital, Vancouver, British Columbia, Canada and †St. Michael's Hospital, Toronto, Ontario, Canada. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Spontaneous coronary artery dissection (SCAD) has been reported to be a rare cause of acute coronary syndrome (ACS) and sudden cardiac death (SCD). The first autopsy report involved a 42-year-old woman with SCD in 1931 (1). Subsequently a pooled analysis of Medline published cases from 1931 to 2008 reported 440 cases of SCAD (2). We have previously suggested, however, that SCAD is underdiagnosed and might be more prevalent than previously recognized. Difficulty distinguishing dissection from atherosclerotic obstruction combined with a low clinical index of suspicion might account for under-diagnosis. Our single center retrospective review of young women (age ≤50 years) undergoing coronary angiography after myocardial infarction (MI) revealed that one-quarter had SCAD as the underlying mechanism (3).

Spontaneous coronary artery dissection is defined as a separation of the coronary arterial wall by hemorrhage, with or without an associated intimal tear. There are 2 proposed patterns of SCAD, the first initiated by an intimal tear that leads to propagating medial dissection, and the second by a dissecting medial hematoma, perhaps initiated by rupture of vaso vasorum (4). The former etiology might be visualized as multiple lumens (true and false), intimal flap, or slow clearing of contrast dye on angiograms. The latter might manifest as luminal narrowing or occlusion by intramural hematoma compression, thus mimicking stenosis due to atherosclerosis. Adjunctive intracoronary imaging with intravascular ultrasound or optical coherence tomography might be valuable in these instances to diagnose intramural hematoma.

Spontaneous coronary artery dissection is often classified according to the associated predisposing condition and has been broadly divided into atherosclerotic and nonatherosclerotic. Nonatherosclerotic associations have included peripartum state, connective tissue disorders, systemic inflammatory conditions, and coronary artery spasm. Those without identifiable predisposition have been labeled as idiopathic. Intense exercises with increased cardiocirculatory stresses and shear forces against the coronary arterial wall can precipitate SCAD among patients with or without these predisposing conditions.

Our group was the first to describe an association between fibromuscular dysplasia (FMD) and SCAD in a consecutive case series (5). The prevalence of FMD and other predisposing conditions among patients with SCAD is unknown. Thus, we seek to describe the relative prevalence of predisposing associations with SCAD and to evaluate their in-hospital outcomes.

Methods

We sought to identify all patients seen with SCAD at Vancouver General Hospital from April 1, 2006, to March 1, 2012, with both prospective and retrospective methods. Patients prospectively identified in our cardiac catheterization laboratory or referred to our SCAD outpatient clinic from local British Columbia hospitals constituted the primary source. We also searched for the keywords "coronary dissection," "FMD," and fibromuscular dysplasia in our cardiac catheterization database among coronary angiograms performed during the interval of interest to retrospectively identify additional cases. For the purpose of this report, we excluded patients judged to have atherosclerosis as the underlying condition causing SCAD.

The coronary angiograms were reviewed by 2 senior interventional cardiologists (J.S. and D.R.). In the absence of prior coronary intervention or trauma, SCAD was confirmed to be present when 1 of the following 3 criteria were met: 1) characteristic multiple radiolucent lines separating true and false lumens, often with contrast dye hang-up (or staining) (Fig. 1); 2) as previously described by Pate et al. (6), a long obstructive stenosis typically involving the mid to distal vessel with abrupt demarcation from normal proximal segments that did not respond to intracoronary nitroglycerin or that subsequently normalized on repeat angiograms and without atherosclerotic changes in other vessels (Fig. 2); or 3) adjunctive intracoronary imaging (intravascular ultrasound or optical coherence tomography) showing intramural hematoma (Fig. 3). The coronary segment involved with SCAD was defined as per the Bypass Angioplasty Revascularization Investigation classification (7). The number of coronary arteries dissected and the segments involved were recorded. Results from repeat coronary angiography or intracoronary imaging were recorded.

Abbreviations and Acronyms

ACS = acute coronary syndrome
CTA = computed tomography angiography
FMD = fibromuscular dysplasia
MI = myocardial infarction
MRA = magnetic resonance angiography
RCA = right coronary artery
SCAD = spontaneous coronary artery dissection
SCD = sudden cardiac death

Baseline characteristics of patients with confirmed SCAD were extracted from the cardiac catheterization database and from relevant clinical source documents. Conventional cardiovascular risk factors, medication on presentation, hospital presentation, electrocardiogram changes, in-hospital events, and angiographic and noninvasive imaging characteristics were recorded.

Combining extracted data with focused histories obtained in our SCAD clinic, we sought to identify the presence of conditions with previously recognized association with SCAD, including recent pregnancy, inherited connective tissue disorders, systemic inflammatory conditions predisposing to arteritis, and coronary artery spasm. We screened for noncoronary FMD by performing invasive or noninvasive angiography in up to 3 vascular territories: renal, iliac,

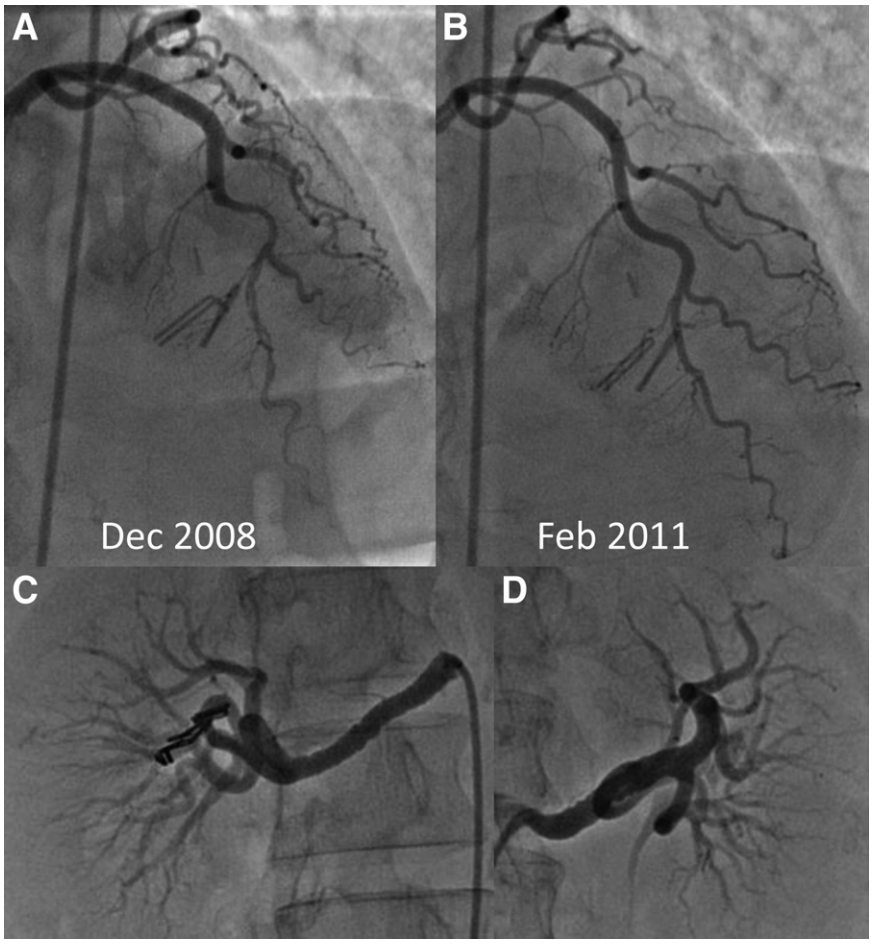

Figure 1. Dissection of LAD and Subsequent Healing in Patient With FMD

(A) Coronary angiogram showing dissected mid to distal left descending artery (LAD) and of second diagonal artery in December 2008, with radiolucent lines separating multiple lumens. **(B)** Repeat angiography in February 2011 showing healed dissections with normal-appearing mid to distal LAD and the second diagonal artery. **(C)** Mild irregularity of the mid right renal artery representing fibromuscular dysplasia (FMD) changes. **(D)** More prominent irregularity of the proximal to mid left renal artery representing FMD changes.

and cerebrovascular. Local patients identified as possible SCAD prospectively tended to have renal angiography coincident with the index coronary angiogram on the basis of our prior experience with this condition (6). In addition, many patients had iliofemoral angiograms performed ipsilateral to their femoral sheath routinely for sheath management. Patients who were not initially screened for renal or iliac involvement angiographically were scheduled to undergo noninvasive computed tomography (CTA) or magnetic resonance angiography (MRA), recognizing the intrinsic limitations of these lower resolution noninvasive techniques for diagnosing minimal or mild FMD. For assessment of cerebrovascular FMD, noninvasive CTA or MRA were performed.

The diagnosis of FMD was made on the basis of angiographic (invasive or noninvasive) imaging, because histopathology was not available and the angiographic appearance depends on the histopathologic subtypes (8). The most common subtype is medial fibroplasia, which appears angiographically as a "string of beads" appearance where the beading represents areas of stenosis alternating with dilation and the beads are larger than the normal caliber of the artery. Other much less common subtypes are intimal fibroplasia (might appear as focal or tubular stenosis angiographically), perimedial fibroplasia (less numerous beading pattern, with smaller beads than normal caliber of artery), adventitial fibroplasia (which might appear similar to intimal fibroplasia), and medial hyperplasia (rare and requires pathological diagnosis) (8,9).

Statistical analysis. Baseline continuous variables were expressed as mean ± SD, and baseline discrete variables were expressed as mean and percentages. Statistical analysis was

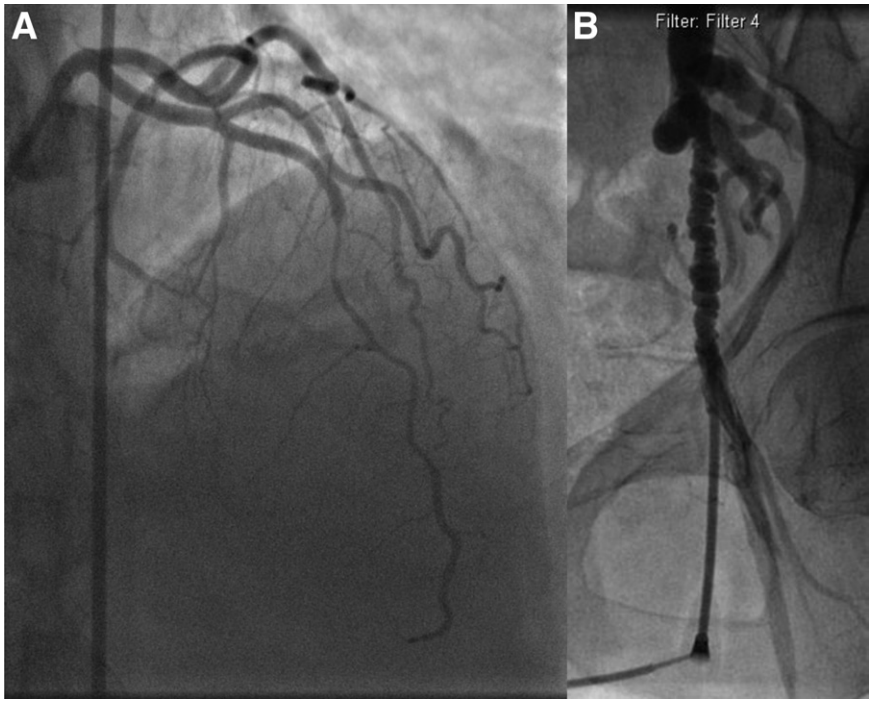

Figure 2. Long Dissection of LAD in Patient With Severe Iliac FMD

(A) Coronary angiogram showing long dissected mid left descending artery (LAD) with abrupt demarcation from normal proximal segment. **(B)** Left femoral angiogram showing severe left external iliac artery fibromuscular dysplasia (FMD) with classic string-of-beads appearance, with distinctive bands alternating with aneurysms.

performed with the SPSS software (IBM SPSS Version 20, Armonk, New York).

Results

We identified 50 patients with nonatherosclerotic SCAD over the past 6 years; 43 were identified at Vancouver General Hospital, and 7 were referred from local British Columbia hospitals. Baseline characteristics of these patients are described in Table 1. The average age was 51.0 ± 9.6 (range 34.1 to 84.4) years, and almost all were women (49 of 50, 98.0%). Patients had low body mass index (23.4 ± 4.6 kg/m^2) and relatively low prevalence of cardiovascular risk factors, except for hypertension affecting 30.0% of patients. Although SCAD was observed in all races, most were Caucasian (82.0%). Significant proportions of these patients were postmenopausal (45.0%) and/or had history of migraines (27.0%) and/or depression (29.0%). One woman had prior cerebral aneurysm surgery.

Hospital presentations of these SCAD patients are described in Table 2. All patients presented with troponin-positive ACS with chest and/or arm pain, with mean peak troponin I of 6.7 ± 8.7 μg/l (range 0.08 to 33.0). Thirty percent of patients presented with ST-segment elevation MI, and 70% had non–ST-segment elevation MI (ST depression or T inversion 26.0%, nonspecific ST-T changes 18.0%, and normal ST-T segments 26.0%). The mean ejection fraction in-hospital was 59.1 ± 8.1%. The mean angiographic stenosis was 73.8 ± 24.2% with Thrombolysis In Myocardial Infarction (TIMI) flow grade of 0 in 14% of patients, TIMI flow grade 1 in 10%, TIMI flow grade 2 in 12%, and TIMI flow grade 3 in 64%. Nine patients underwent revascularization: 7 had coronary stenting, and 2 underwent coronary artery bypass surgery (1 had extensive retrograde dissection from mid left descending artery (LAD) to the left main and circumflex arteries; and 1 underwent bypass because of concomitant severe aortic stenosis requiring valve replacement). All patients survived their hospital admission and were discharged at a mean of 2.7 ± 2.6 days.

The coronary angiographic findings are reported in Table 3. Most (88.0%) patients had 1 isolated coronary artery dissection, 8.0% had 2 separate dissected coronary arteries, and 4.0% had extension of dissection involving >1 coronary artery. Approximately one-third (40.0%) of SCAD affected the LAD or its branches, approximately one-third (34.0%) affected the circumflex artery or its branches, and approximately one-third (32.0%) affected the right coronary artery (RCA) or its branches. The LAD seemed to be the most

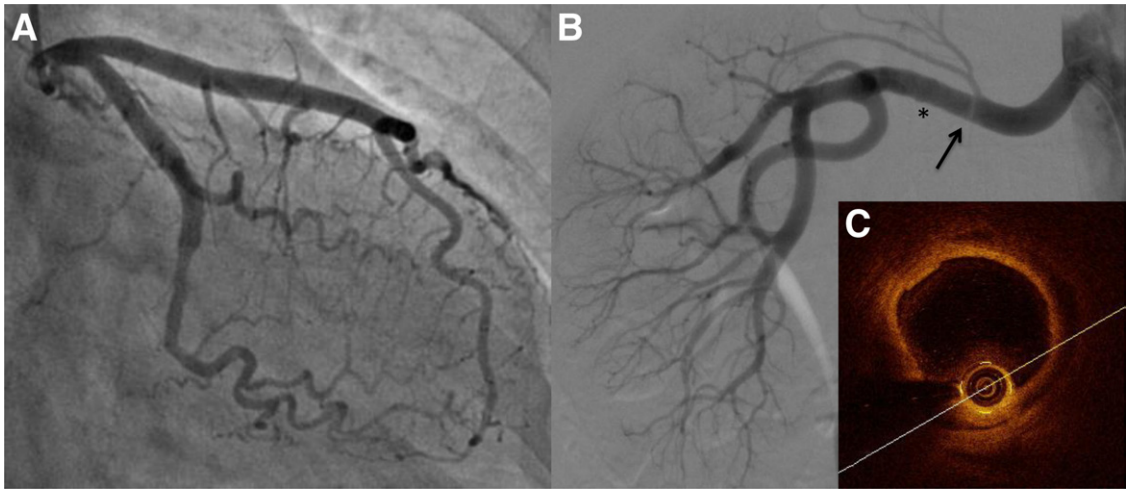

Figure 3. Mild Circumflex Stenosis Due to Intramural Hematoma in Fibromuscular Dysplasia Patient

(A) Diffuse moderate stenosis in the mid circumflex artery representing dissection with intramural hematoma (which could be easily mistaken for atherosclerotic changes). **(B)** Digital subtraction angiography of the right renal artery showing fibromuscular dysplasia (FMD) with a distinct band **(arrow)** immediately just distal to a small superior branch, and minor irregularities just distal to the band **(*)**. These abnormalities are mild and not likely to be visualized with noninvasive imaging, such as computed tomography or magnetic resonance angiography. **(C)** Optical coherence tomography image of mid circumflex artery showing intramural hematoma of the dissected segment.

commonly dissected artery (36.0%), followed by the branches of the circumflex artery (30.0%) (ramus intermedius, obtuse marginal, and left posterolateral), and branches of the RCA (28.0%) (right posterior descending and right posterolateral). The most commonly affected initiating segment was the mid LAD (24.0%). Spontaneous coronary artery dissection typically affected the mid to distal segments of the coronary arteries, with only 1 patient presenting with proximal LAD dissection (she was 9 days postpartum). Ten

Table 1. Baseline Characteristics of Nonatherosclerotic SCAD Patients (N = 50)

Age (yrs)	51.0 ± 9.6
Female	98.0%
Height (cm)	165.6 ± 6.6
Weight (kg)	64.6 ± 15.1
Body mass index (kg/m^2)	23.4 ± 4.6
Race	
Caucasian	82.0%
African-Canadian	2.0%
East Asian	10.0%
South Asian	6.0%
Diabetes mellitus	4.0%
Dyslipidemia	20.0%
Hypertension	30.0%
Current smoker	8.0%
Family history of CAD	28.0%
Previous MI	2.0%
Cerebrovascular disease	2.0%*
Peripheral arterial disease	0%
Migraines	27.0%
Postmenopausal	45.0%
Depression	29.0%

Values are mean ± SD or %. *Prior cerebral aneurysm surgery.
CAD = coronary artery disease; MI = myocardial infarction; SCAD = spontaneous coronary artery dissection.

Table 2. Hospital Presentation of the SCAD Patients (N = 50)

Acute coronary syndrome	100%
Elevated troponin I	100%
Troponin I levels (μg/l)	6.7 ± 8.7
Ejection fraction	59.1% ± 8.1%
Revascularization performed (PCI or CABG)	18.0% (n = 9)
PCI	14.0% (n = 7)
CABG	4.0%* (n = 2)
Precipitating factor for SCAD	
Emotional stress	26.0%
Exercise related	16.0%
Heavy isometric weights	6.0%†
Regular cardio workout	10.0%
Postpartum	2.0%
Electrocardiogram	
ST-segment elevation	30.0%
ST depression or T inversion	26.0%
Nonspecific ST-T changes	18.0%
Normal ST-T segments	26.0%

Values are % or mean ± SD. *One had extensive retrograde dissection to left main requiring emergent coronary artery bypass graft (CABG), and 1 had CABG because of simultaneous severe aortic stenosis. †Two were lifting weights ≥50 lbs. in the gymnasium. One was lifting her 40-pound child into the car.
PCI = percutaneous coronary intervention; SCAD = spontaneous coronary artery dissection.

Table 3. Coronary Artery Angiographic Findings in the SCAD Patients (N = 50)

LAD	36.0%
Proximal LAD	2.0%
Mid (including extension to distal) LAD	24.0%
Distal LAD	10.0%
LAD branches	4.0%
Diagonal arteries	2.0%
Septal perforator	2.0%
Circumflex artery	4.0%
Mid circumflex artery	4.0%
Circumflex artery branches	30.0%
Ramus intermedius	10.0%
Obtuse marginal or left posterolateral	20.0%
RCA	4.0%
Mid to distal RCA	4.0%
RCA branches	28.0%
rPDA	20.0%
Right posterolateral	8.0%
SCAD involving >1 coronary artery	12.0%
Separate coronary arteries involved	8.0%
Retrograde or antegrade extension	4.0%*

*One patient had retrograde dissection from mid left anterior descending (LAD) to left main and circumflex artery requiring coronary artery bypass graft surgery (CABG). One patient extended from mid LAD to distal LAD and third diagonal artery.

rPDA = right posterior descending coronary artery; SCAD = spontaneous coronary artery dissection.

patients had repeat coronary angiograms at a mean of 378.5 ± 243.8 days (median 398.5 days, range 34 to 795 days) after their SCAD presentations, all of which showed healing of the previously dissected segments (Figs. 1 and 4).

With regard to potential precipitating factors for SCAD, intense emotional stress was reported in 26.0% of patients preceding their event (e.g., death of family member, arguments, divorce), and 16.0% reported exercising before but not necessarily during their pain presentation. Only 2 patients were performing intense isometric exercises (lifting ≥50-pound weights) at the gymnasium around their chest pain onset. Another patient was lifting her 40-pound child when she developed pain. Other patients who reported exercising include skiing the day before, running 10 km 2 days before, sexual intercourse 30 min before, or doing routine light isometric and aerobic workouts in the gymnasium hours before their event.

With regard to potential predisposing conditions, 2 patients (4.0%) were pregnant within 1 year of the SCAD event. Only 1 patient had true postpartum SCAD (defined as within 6 weeks of delivery by the World Health Organization) (10), developing chest pain 9 days after vaginal delivery. The other patient was 11 months postpartum and still breastfeeding her child when she had SCAD, complicated by extensive retrograde dissection. With respect to systemic inflammatory conditions, only 2 patients (4.0%) had a prior history of ulcerative colitis but were inactive during their SCAD presentation. There were no other autoimmune conditions identified.

We were able to screen for FMD in at least 1 noncoronary territory in most of these SCAD patients. Renal artery screening was performed in 94.0% of patients (38 of 50, 76.0%, had angiographic screening), iliac artery screening was performed in 64.0% of patients, and cerebrovascular screening was performed in 66.0% of patients. Only 3 patients (6.0%) were not screened for FMD in any noncoronary territory. Fibromuscular dysplasia was identified in at least 1 noncoronary vascular territory (renal, iliac, or cerebrovascular) in 86.0% of patients, and 42.0% had more than 1 noncoronary vascular territory FMD (Table 4). There were 7 (14.0%) patients who were not diagnosed with FMD, of which 5 (10.0%) had not yet had complete screening of all 3 vascular territories, and 2 were negative upon complete screening (1 patient was the 11-month postpartum who had the extensive retrograde dissection and was screened with CTA or MRA for all 3 territories; 1 patient had negative renal and iliac angiograms and negative cerebrovascular CTA). Among patients diagnosed with FMD (n = 43), 25 (58.1%) had renal artery involvement, 21 (48.8%) had iliac artery involvement, and 19 (46.5%) had cerebrovascular involvement (of which 6 [14.0%] had cerebral aneurysm, and 1 [2.3%] had distal cervical carotid pseudoaneurysm).

Discussions

We have identified 50 patients with nonatherosclerotic SCAD over a 6-year period at Vancouver General Hospital. Given our previous discovery of the association between FMD and SCAD (5), we attempted to routinely screen for FMD in 3 noncoronary vascular territories and found that most (86.0%) patients with SCAD have concomitant FMD. Only 2 screened patients (4.0%) did not have concomitant FMD, and the remainder (5 patients, 10.0%) have not had complete screening. Only 1 patient was postpartum, 2 patients had prior history of ulcerative colitis, and 2 patients were doing intensive isometric exercises when they presented with SCAD. All patients survived their SCAD presentation.

This high prevalence of noncoronary FMD among SCAD patients is too high to be coincidental. Although the true prevalence of FMD in the general population is not known and was previously thought to be rare, studies that assessed the frequency of renal artery FMD on angiogram in kidney donors reported prevalence of 3.8% to 6.6% (11–13). Thus, FMD is also an under-diagnosed condition, much like SCAD; however, the reason for under-diagnosis of FMD is presumably because most patients are clinically silent. Nevertheless, such a high prevalence of association between FMD and SCAD would imply a potential causative link and would strengthen our hypothesis that underlying coronary FMD predisposed these patients to SCAD.

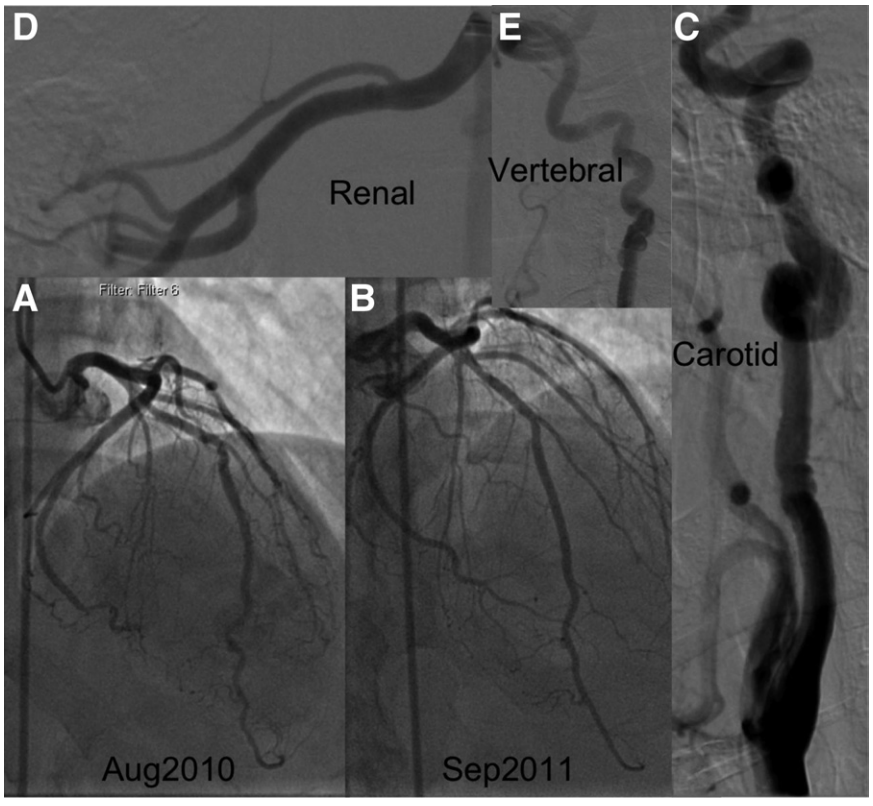

Figure 4. Dissection of Posterolateral Artery and Subsequent Healing in FMD Patient

(A) Coronary angiogram showing dissected left posterolateral artery in August 2010. **(B)** Coronary angiogram showing healed dissected left posterolateral artery in September 2011. **(C)** Right carotid angiogram showing string-of-beads with band-like stenosis in the mid extracranial carotid, and tortuosity of the distal carotid artery. **(D)** Right renal angiogram showing mild irregularity of the mid main right renal artery on digital subtraction angiography. **(E)** Right vertebral artery angiography showing string-of-beads with bands of stenosis in the distal cervical vertebral artery.

Definitive diagnosis of coronary FMD would require histological postmortem confirmation, which is obviously not available in our series, because all our patients survived. However, the concept of coronary FMD predisposing patients to SCAD is not novel, and there have been 3 published histological reports confirming this causative link.

Table 4. Involvement With Noncoronary FMD Among These Patients With SCAD (N = 50)

FMD in ≥1 noncoronary territories	86.0% (43)
FMD in ≥2 noncoronary territories	42.0% (21)
FMD not observed	14.0% (7)
Incomplete screening	10.0% (5)
Screened cerebral, renal, iliac	4.0% (2)
FMD vascular involvement (n = 43)	
Renal arteries	58.1% (25)
Iliac arteries	48.8% (21)
Cerebrovasculature	46.5% (19)
Cerebral aneurysm	16.3% (7)

Values are % (n).
FMD = fibromuscular dysplasia; SCAD = spontaneous coronary artery dissection.

The first was published in 1987, involving a 24-year-old white man who suffered multi-organ damage from colonic perforation, who subsequently had ventricular tachycardia and hypotension, and was found on autopsy to have SCAD of the RCA and LAD due to coronary FMD (14). The second involved a 29-year-old woman with MI due to multiple progressive SCAD 5 days postpartum and was found to have coronary FMD on her explanted heart for transplantation in 1994 (15). The third case, published in 2007, involved a 38-year-old woman who died of simultaneous ruptured anterior communicating artery aneurysm and SCAD of the RCA, and she had FMD of multiple vascular beds, including the coronary arteries on autopsy (16). The prevalence of SCD due to concomitant SCAD and coronary FMD seems rare, on the basis of these limited publications. In an autopsy series of 50 patients who had nonatherosclerotic SCD (accounting for 3% of all 1,647 SCD) by Hill et al. (17), they found 2 patients (0.1% of all SCD) who died of coronary FMD and 8 patients (0.4% of all SCD) who died of SCAD. In fact, there are more published reports of SCD (over 24 confirmed autopsies to

date) due to the obstructive obliterative forms of coronary FMD (without associated SCAD) causing critical coronary stenosis and probable ventricular arrhythmia, which can affect both small intramural or larger epicardial coronary arteries (17–24).

The first antemortem report of probable coronary FMD as a cause of MI was by Pate and Buller from our group (6). That report described 7 peri-menopausal women with nonfatal ST-segment elevation or non–ST-segment elevation MI, long-isolated obliterative lesions in the mid and distal segments of interventricular groove coronary arteries, and coincident renal FMD. They proposed coronary FMD (medial and intimal hyperplasia) as a potential cause of these ischemic events but also considered superimposed thrombus or dissection as contributing factors.

The histopathology of FMD has been categorized into intimal fibroplasia, medial fibroplasia, medial hyperplasia, peri-medial fibroplasia, and adventitial fibroplasia. Medial fibroplasia is the most commonly seen abnormality in 80% to 90% of FMD (25), with alternating areas of thinned and thickened medial collagen ridges as well as stenotic thin webs and post-stenotic dilation, causing the characteristic string-of-beads appearance (9). The other types of histopathology are less frequent (10% to 20% of cases) and might produce angiographic findings of concentric stenoses or tubular lesions that might be indistinguishable from atherosclerosis (9). In the first autopsy report of coronary FMD, affected segments were severely thickened by intimal and medial hyperplasia and fibrosis, along with adventitial proliferation of collagen, which caused severe obliteration of lumen (14). Smooth muscle fibers were extensively disorganized, running in oblique or longitudinal patterns rather than the normal circular manner, with varying intimal and medial collagen deposition. The internal elastic lamina can be disrupted, duplicated, or practically absent in severely affected coronary arteries. Different coronary segments had a myriad of abnormalities, due to disorganized hyperplasia of myofibroblasts in the intima and media. Another coronary FMD autopsy showed severe intimal thickening from subendothelial smooth muscle cells surrounded by fibrous connective tissue in the affected artery (21). These pathological abnormalities might manifest in the coronary arteries as the classic string-of-beads appearance (rare) (23) or as diffuse tubular stenosis in mid-distal vessels (might be due to obliterative disease, dissection, or healed dissection) (6,26,27), or more likely as "normal" (subsequently labeled as microvascular disease). These pathological arterial wall abnormalities can predispose the coronary arteries to dissection, thrombosis, aneurysm formation, or embolization, akin to arteries in other vascular territories affected by FMD.

Since our report describing the association of FMD and SCAD (5), there have been 2 further publications relating to this association. In the small series by Toggweiler et al. (28), they screened 12 SCAD patients with whole-body MRA and duplex sonography (of extra-cranial cerebral arteries and renal arteries) at a median 1,036 days after their SCAD events and found 25% with renal FMD. Our prevalence of FMD among SCAD patients was higher than this study. It is well-accepted that MRA and CTA might miss mild FMD abnormalities (13,29,30), which is a particular concern for renal donors. The limitations with these noninvasive imaging techniques reflect the poor spatial resolution, compared with standard digital subtraction angiography for visualizing segmental or accessory renal arteries and even for main renal arteries when the abnormalities are mild. Published studies that evaluated MRA in comparison with digital subtraction angiography typically assessed only significant stenoses (≥50% severity) and only in populations with hypertension where renal stenosis, if present, would tend to be more severe and more easily detected by MRA (31,32). For instance, in the study by Willoteaux et al. (32) that evaluated 25 hypertensive FMD patients, the sensitivity for evaluating ≥50% stenosis with MRA was only 68%, even when the radiologists knew that all these patients had renal FMD. Thus, it is understandable that mild FMD renal arteries could be missed with MRA or CTA, especially if the disease is in the mid to distal segments of the renal arteries, as is typically the case with FMD involvement (Fig. 3). Recognizing this limitation, 76% of our patients had renal artery catheter angiography (selective or nonselective). We have seen numerous examples of mild FMD missed on CTA or MRA in the renal, iliac. or cerebrovasculature, which were subsequently confirmed on standard catheter angiography (unreported).

More recently, another study by Tweet et al. (33) reported their retrospective series of 87 SCAD patients from the Mayo Clinic. They found that, among 16 patients who had iliofemoral angiogram for arteriotomy closure, 50% had incidental external iliac FMD. There were also 2 other patients with carotid dissections who were diagnosed with FMD on CTA. The remainder of their patients was not screened for FMD; furthermore, routine screening of other vascular territory for FMD was not done. The authors concluded that FMD is an important risk factor for SCAD and that the true prevalence of FMD was likely higher than identified in their study. Thus, the results from both Toggweiler and Tweet corroborate our findings of the association and potential causation of SCAD and FMD.

Study limitations. Our study is small and predominantly retrospective in the identification of patients with SCAD. However, this is the largest series where patients were screened for FMD involvement in other vascular territories. Moreover, we subsequently attempted to follow all these patients prospectively in our SCAD clinic and enrolled them in our non-atherosclerotic coronary artery disease registry. Only a few patients were not followed since their SCAD event, because they were from out-of-town or were lost to contact. Our study also excluded patients with atherosclerotic forms of

SCAD, which is presumably why women were disproportionately represented compared with prior studies. Furthermore, we do not have histology to confirm coronary FMD as the predisposing cause of SCAD in these patients, and this remains a hypothesis that should be further evaluated in autopsies of patients with prior SCAD.

Conclusions

Non-atherosclerotic SCAD predominantly affects women, and most of these patients have FMD involving at least 1 non-coronary territory. We suspect that these patients have underlying coronary FMD that predisposed them to SCAD, but this requires future confirmation with tissue histology. Adjunctive intracoronary imaging would also be useful in describing intimal and medial fibrotic and hyperplastic changes in patients who survive their SCAD event. Further studies are pertinent to evaluate the long-term outcome and prognosis of these patients.

Reprint requests and correspondence: Dr. Jacqueline Saw, Vancouver General Hospital, 2775 Laurel Street, 9th Floor, Vancouver, British Columbia, V5Z 1M9, Canada. E-mail: jsaw@mail.ubc.ca.

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