

Risk Factors, Imaging Findings, and Sex Differences in Spontaneous Coronary Artery Dissection



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Spontaneous coronary artery dissection (SCAD) is increasingly being recognized. However, data supporting diagnosis and management are scarce. We analyze a contemporary and comprehensive SCAD registry to advance the understanding of SCAD risk factors, angiographic appearance, and gender differences. This is a retrospective analysis of a prospectively populated database of SCAD patients seen at the Massachusetts General Hospital (MGH) between June 2013 and October 2017. Core laboratory analysis of both coronary angiograms and computerized tomographic (CT) angiography of the extracoronary vessels was performed. Of the 113 patients, 87% were female and mean age was 47 ± 10 years. Traditional cardiovascular risk factors including hypertension, hyperlipidemia, and smoking were present in 27%, 14%, and 22% of patients. Among females, 14%, 8%, and 9% had a history of gestational hypertension, pre-eclampsia, and gestational diabetes, respectively. Fifteen percent had used fertility treatment and 47% of postmenopausal women had used hormone replacement therapy. Angiography showed multivessel SCAD in 42%, severe coronary artery tortuosity in 59%, and extracoronary vascular abnormalities in 100% of patients with complete CT angiographic imaging. Gender differences revealed a self-reported depression and anxiety prevalence of 20% and 32%, respectively, in women compared with 0% in men. Type 1 SCAD was more commonly diagnosed in men than women (71% vs 29%, $p < 0.01$). In conclusion, we highlight under-recognized features of SCAD including (1) relation with pregnancy complications and exposure to hormonal therapy; (2) diffuse, multivessel process in tortuous coronaries on a background of extracoronary arterial abnormalities; and (3) gender differences highlighting the role of mental health as well as potential underdiagnoses in men.

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Spontaneous coronary artery dissection (SCAD) was first identified in 1931. It occurs when there is a tear in the intima or bleeding into the vasovasorum of the media, leading to the formation of a true and false lumen, which can eventually result in an intramural hematoma and myocardial infarction (MI).¹ Only over the last decade has SCAD gained increased recognition, predominantly as a result of efforts at academic medical centers^{2–4} to study and disseminate observations about SCAD patients, advances in imaging modalities in the cardiac catheterization lab, and grassroots efforts among patients to raise awareness. These efforts have led to the realization that the prevalence of SCAD was previously far under-recognized. SCAD is now

estimated to be the cause of approximately 1% to 4% of acute coronary syndrome (ACS) cases overall, but is the cause of ACS in up to 43% and 35% of pregnant women and women ≤ 50 years old, respectively.⁵ With increased awareness of SCAD, gaps in our knowledge pertaining to risk factors, diagnosis, management, and surveillance have become evident and an urgent research need. In this study, we advance the understanding of SCAD by sharing the findings of the Massachusetts General Hospital (MGH) SCAD registry. We focus on risk factors, imaging, and gender differences in SCAD. This contemporary and comprehensive registry provides a unique perspective on SCAD, elaborating on key observations mentioned in the literature, and challenging some of our current assumptions about SCAD.

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Methods

This study was approved by the Partners Human Research Committee (PHRC). Subjects were identified by their treating physicians within the division of cardiology and vascular medicine at the MGH. Subjects either presented to MGH with SCAD, were transferred after their SCAD event from another hospital, or came to our clinic at MGH for a second opinion after their SCAD occurrence. Data were collected prospectively thereafter. Inclusion

criteria were patients aged ≥ 18 years with a compatible clinical history and imaging evidence of SCAD. Detailed angiographic analysis of deidentified coronary angiograms was performed by the PERFUSE angiographic core laboratory. Reviewers were blinded to patient characteristics but were aware that they were reviewing angiograms of patients diagnosed with SCAD. All patients provided written informed consent and were sequentially enrolled in the MGH SCAD registry beginning July 2013. For the purpose of this analysis, data were collected through October 2017.

Each patient's medical record was used to collect details of their SCAD hospitalization (provider documentation of presentation, hospital course, and management), laboratory data, imaging results (electrocardiogram, echocardiogram, CT, MRI, stress testing), cardiac catheterization reports, and follow-up studies (extracoronary vascular imaging, genetic testing). Additionally, patients completed questionnaires asking about demographics, current symptoms, SCAD history, past medical history, reproductive health, medications, allergies, social history, nutrition, and physical activity.

As noted above, coronary angiograms for all SCAD patients were carefully analyzed by PERFUSE study group core angiographic team. The angiographic diagnosis of SCAD was made if a noniatrogenic dissection plane was identified in the absence of coronary atherosclerosis. SCAD type was characterized using the angiographic classification scheme proposed by Saw.⁶ A Type 1 dissection is defined as an arterial wall with multiple radiolucent lumens. A Type 2 dissection is defined as an abrupt change in arterial caliber leading to a diffuse (typically >20 mm) and smooth stenosis. A Type 3 dissection often mimics atherosclerosis in appearance, but can be distinguished by lack of atherosclerosis in other coronary arteries and length/appearance of stenoses.⁶ Coronary vessels involved, ejection fraction, and wall motion abnormalities were documented. Coronary tortuosity was evaluated using a simplified definition — tortuosity was defined as at least one change in vessel direction by $\geq 90^\circ$ and was subsequently classified as mild (isolated to 1 major coronary artery or 2 branch vessels) or severe (greater than 1 major coronary artery). For all patients with complete CTA head, neck, abdomen, and pelvis imaging available, a core laboratory radiologist over-read all images to evaluate for vascular abnormalities including beading, dissection, ectasia, aneurysm, or tortuosity.

Continuous variables were reported as mean $\pm$ standard deviation (SD) and categorical variables as absolute frequencies and percentages. Differences between genders were analyzed using the unequal variance *t* test for continuous variables and the Fisher's exact test for categorical variables. All statistical tests were two-sided and *p* values <0.05 were considered significant. Analyses were performed with Stata/SE 14.1 (College Station, TX: StataCorp LP).

Results

At the time of analysis, the MGH SCAD registry had 113 patients. Mean age of the population was 47 ± 10 years. Baseline characteristics are presented in Table 1. The reproductive health characteristics of the women in this registry are presented in Table 2 and compared with previously published data in SCAD and in non-SCAD women.⁷

Table 1

Baseline characteristics (n = 113)*

Variable	n
Female	98 (87%)
Male	15 (13%)
Asian	3 (3%)
Black	4 (4%)
White	84 (74%)
Other/not reported	22 (20%)
Hypertension	31 (27%)
Hyperlipidemia	16 (14%)
Diabetes mellitus	3 (3%)
Smoker	25 (22%)
Obesity	15 (13%)
Migraines	32 (28%)
Depression	20 (18%)
Anxiety	31 (27%)
Premature coronary artery disease in family	17 (16%)

* Percentages are out of available data per characteristic.

With regard to the initial SCAD presentation, 43% of patients reported symptom onset without any precipitating event, 26% during or after exercise, and 31% during or after a stressful emotional event. The most commonly reported symptom was chest pain/discomfort ($>90\%$) followed by nausea/vomiting (20%) and dyspnea (18%). All patients presented with ACS, 57% with a NSTEMI and 43% with a STEMI. The SCAD event was complicated by cardiac arrest in 13 cases (12%) of which 4 (4%) were out of hospital cardiac arrests.

Coronary angiogram findings are displayed in Table 3. Examples of Type 1 and 2 dissections are shown in Figure 1. Thirty-four patients had complete (head, neck, abdomen, and pelvis) CT angiographic imaging available for review. Classic beading typically associated with fibromuscular dysplasia (FMD) was present in 18 patients (53%). However, 100% of patients were found to have some vascular abnormality including beading, dissection, ectasia, aneurysm, or tortuosity. The affected arteries were iliac (82%), renal (74%), celiac (53%), superior mesenteric (35%), cervical or cerebral (29%), and splenic (9%).

We found that 75 patients (66%) underwent conservative medical management, 36 patients (32%) underwent percutaneous coronary intervention (PCI), and 2 patients (2%) had coronary artery bypass grafting surgery. In our sample, 98 patients (87%) were women and 15 patients (13%) were men. Notable differences between genders are shown in Table 4.

Discussion

In this study, we report observations from the MGH SCAD registry and highlight the following salient findings: (1) patients affected by SCAD have a higher burden of traditional cardiovascular risk factors than previously suggested and a higher prevalence of pregnancy complications, fertility treatment, and hormone replacement therapy than national averages; (2) SCAD may present in multiple arteries. Other coronary and systemic arterial abnormalities are

Table 2
Reproductive health history (n = 98)*

Variable	MGH cohort	Tweet et al ⁸ SCAD cohort	National estimates
Premenopausal	55%	NA	NA
Postmenopausal	45%	NA	NA
Ever used hormone replacement therapy	47%	NA	28% ¹⁸
Hormone replacement therapy at time of SCAD	16%	NA	9% ^{1,18}
Pregnancy-associated SCAD [†]	9%	17%	NA
Ever used birth Control	83%	87%	82% ¹⁹
Gestational hypertension	14%	12%	7% ²⁰
Pre-eclampsia	8%	7%	4% ¹⁴
Eclampsia	1%	0%	<0.1% ¹⁶
Gestational diabetes	9%	5%	6% ²⁰
Miscarriage	33%	NA	15% ¹⁵
Previous fertility treatment	16%	18%	3-4% ¹⁷

* Percentages are out of available data per characteristic.

[†] SCAD within 1 year of pregnancy.

[‡] Postmenopausal women using hormone replacement therapy at any given time.

common; (3) gender differences in SCAD exist particularly related to mental health and angiographic findings.

We found that a portion of our SCAD patients had traditional cardiovascular risk factors including hypertension, hyperlipidemia, smoking, and obesity. Other SCAD registries have shown similar co-morbid cardiovascular condition prevalence⁸ but SCAD is often described as affecting patients “with few or no traditional cardiovascular risk factors.”⁵ The basis of this description likely originates from observations that SCAD patients have a lower prevalence of traditional cardiovascular risk factors than the national, age-matched average.^{9–13} However, it is important to note that these risk factors are not absent and some risk factors such as hypertension are on par with age-matched national prevalence.¹⁰ Whether traditional atherosclerotic risk factors such as hypertension contribute to SCAD in the same way, they contribute to aortic dissection

Table 3
Coronary angiographic characteristics (n = 113)*

Variable	n
Left main artery dissection	0 (0%)
Proximal left anterior descending artery dissection	13 (12%)
Mid left anterior descending artery dissection	32 (29%)
Distal left anterior descending artery dissection	34 (31%)
Diagonal branch 1 artery dissection	12 (11%)
Diagonal branch 2 artery dissection	11 (10%)
Left circumflex artery dissection	8 (7%)
Obtuse marginal 1 artery dissection	28 (26%)
Distal right coronary artery dissection	14 (13%)
Posterior descending artery dissection	17 (16%)
Single artery dissected	64 (58%)
Multiple arteries dissected	46 (42%)
SCAD Type 1 dissection	37 (34%)
SCAD Type 2 dissection	81 (75%)
SCAD Type 3 dissection	1 (1%)
No vessel tortuosity	12 (11%)
Mild vessel tortuosity	32 (30%)
Severe vessel tortuosity	63 (59%)

* Percentages are out of available data per characteristic.

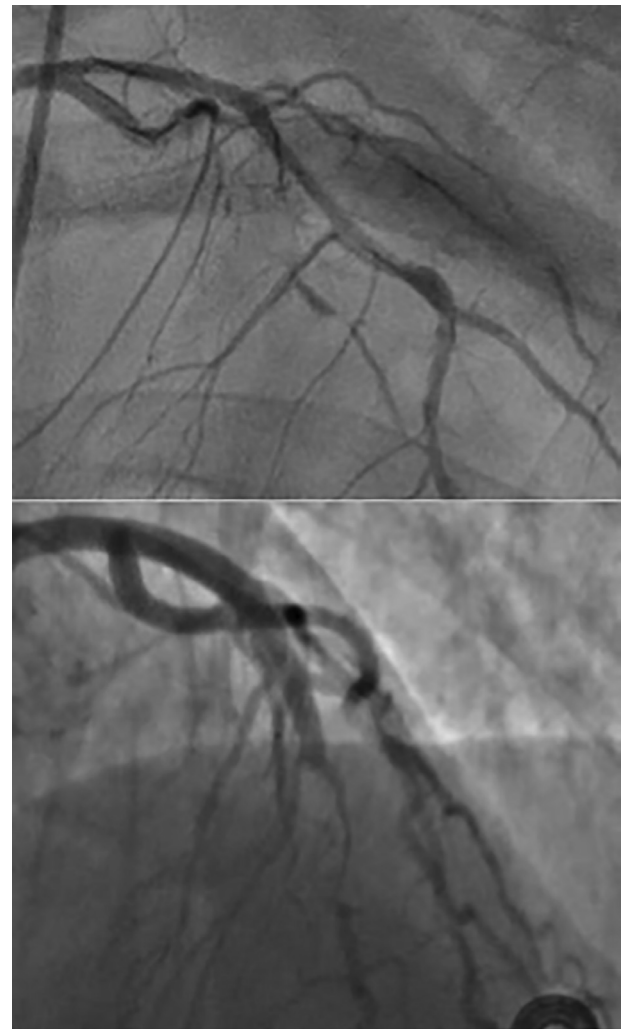


Figure 1. Example of Type 1 (top) and Type 2 (bottom) dissection.

Table 4

Sex differences in SCAD (n = 113)*

Variable	Females (n = 98)	Males (n = 15)	p Value
Past medical history: migraines	31 (32%)	1 (7%)	0.06
Past medical history: depression	20 (20%)	0 (0%)	0.07
Past medical history: anxiety	31 (32%)	0 (0%)	0.01
Symptom onset during exercise	22 (22%)	8 (53%)	<0.05
Symptom onset during emotional stress	31 (32%)	4 (22%)	0.8
Symptom onset during rest	52 (53%)	6 (40%)	0.48
Angiography: multi-vessel SCAD	43 (45%)	3 (20%)	0.09
Angiography: Type 1 SCAD	27 (29%)	10 (71%)	<0.01
Angiography: Type 2 SCAD	78 (83%)	3 (21%)	<0.01

* Percentages are out of available data per characteristic.

remains unclear. SCAD should be considered in the differential diagnosis of young men and women who present with ACS even in the presence of traditional risk factors.

Among women, the relation between hormone therapy and SCAD is recurrently noted but poorly understood. Tweet et al reported findings that patients with pregnancy-associated SCAD often had a more severe clinical presentation and a history notable for multiparity, fertility treatment, and pregnancy complications such as pre-eclampsia compared with nonpregnancy-associated SCAD.⁷ In our registry of all women with SCAD, we observed postmenopausal HRT utilization, pregnancy complications including gestational hypertension, pre-eclampsia, and miscarriage, and history of fertility treatment at rates notably higher than national averages.^{14–20} Further investigation into the relation between hormones, pregnancy complications, and SCAD may help us better understand the underlying pathophysiology of SCAD, mitigate risk, and guide recommendations in women at different reproductive stages.

We found that arterial abnormalities exist in SCAD patients beyond the dissection. In order to improve recognition of coronary tortuosity in clinical practice, we developed a simplified method for describing tortuosity. We noted coronary vessel tortuosity was frequently present, with most cases demonstrating severe tortuosity. Similar to previously published cohorts, extracoronary FMD was present in slightly over 50% of patients.^{2,21–23} Even among patients without the classic beading of FMD, no patient had completely normal vasculature. These observations suggest that vessel fragility may play a role in the pathogenesis of SCAD.

Another notable finding was the presence of multivessel SCAD in over 40% of patients. SCAD has classically been viewed as a predominantly single-vessel disorder most commonly affecting the left anterior descending artery. It is possible that the higher prevalence of multivessel SCAD is due to the careful review of all coronary arteries done in the present study. Dissections in small, distal, and branch vessels may be overlooked when angiographers focus only on the obvious infarct-related artery. Furthermore, this finding may reflect the better appreciation of SCAD, especially Type 2, over time.

SCAD seems to present differently in men and women. One of the most significant differences we noted relates to

the association between mental health and heart disease. We found a higher self-reported prevalence of anxiety and depression preceding SCAD in women compared with men. Psychiatric conditions are increasingly being recognized as independent risk factors for adverse cardiovascular events.^{24,25} Psychiatric conditions are hypothesized to result in varying degrees of stress-induced physiologic responses. Women may have more dramatic responses or may be more susceptible to these responses, which in SCAD cases, has been postulated to increase coronary artery shear stress and hence risk of dissection.⁵

A final notable difference was that men were more likely to have Type 1 than Type 2 SCAD despite the higher prevalence of Type 2 dissection in the overall SCAD population, both in our series and consistently in other registries. Although more common, Type 2 SCAD is more difficult to diagnose and its appearance is unknown to many angiographers.²⁶ Therefore, the higher prevalence of Type 1 SCAD in men may have resulted from SCAD only being diagnosed when the dissection was clearly evident. Given the scarcity of SCAD cases in men, many angiographers may not think about and hence diagnose Type 2 SCAD in men. Alternatively, biological differences may predispose men to more Type 1 SCAD and women to Type 2 SCAD. This finding raises the question of whether under-recognition of Type 2 lesions in men is resulting in a disproportionate underdiagnosis of SCAD in men.

Our study has limitations. First, it is a single-center registry. However, this did allow us to adhere to a strict protocol in creating and analyzing our SCAD cohort and to utilize stringent criteria including core-laboratory adjudication. Although the cohort is small, our study population was intentionally recruited over the span of only several years to reflect contemporary practice. To overcome widespread limitations in single-center biases and sample size, we urge for the creation of a collaborative registry to better understand this uncommon condition. Obviously, our cohort was dependent on the diagnosis of SCAD being made. Thus, it is inherently affected by selection bias. Unfortunately, these patients may only represent a subset of the whole SCAD population, assuming some are not diagnosed upon presentation with ACS.

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