Journal of
Transcatheter Interventions
e-ISSN e-2595-4350

Spontaneous coronary artery dissection, a multifactorial disease: insights from a center experience

Dissecção espontânea da artéria coronária, uma doença multifatorial: perspectivas da experiência de um centro

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DOI: 10.31160/JOTCI202331A20220017

ABSTRACT – **Background**: Although it is a poorly known disease, spontaneous coronary artery dissection is an important and frequently underdiagnosed cause of non-atherosclerotic acute coronary syndrome, particularly in women. The objective of this study was to characterize a consecutive sample of patients diagnosed with spontaneous coronary artery dissection with respect to predisposing and precipitating factors; clinical and angiographic presentation; management; occurrence of adverse cardiac events; recurrence; and *de novo* spontaneous coronary artery dissection. **Methods**: Longitudinal, observational, retrospective, single-centre study, including patients diagnosed with spontaneous coronary artery dissection (n=60) admitted between January 2010 and December 2020. **Results**: Median age was 55 years, and 83% were women. Most patients (60%) presented without any or just one cardiovascular risk factor. Non-ST-segment elevation acute myocardial infarction accounted for 67% of clinical presentations. The most frequently affected coronary artery was the left anterior descending (47%). Most lesions (77%) appeared on angiography as type 2 spontaneous coronary artery dissection. Conservative management was chosen as the initial approach in most patients (72%). The overall incidence of *de novo* spontaneous coronary artery dissection was not significantly different among patients initially managed with revascularization as compared to conservative treatment (p=0.953). However, spontaneous coronary artery dissection recurrence occurred in the originally involved vessel in 3 of 15 patients initially managed with revascularization, as compared to only one among 43 patients treated conservatively (p<0.05). **Conclusion**: Spontaneous coronary artery dissection occurs more often in young women. Non-ST-segment elevation acute myocardial infarction was the most frequent clinical presentation involving mainly the left anterior descending artery. Revascularization did not protect from recurrence.

Keywords: Acute coronary syndrome; Angiography; Coronary artery dissection, spontaneous; Dissection; Vascular diseases; Cardiovascular diseases; Heart disease risk factors; Women

RESUMO – **Introdução**: Embora seja uma doença pouco conhecida, a dissecção espontânea da artéria coronária é uma causa importante e frequentemente subdiagnosticada da síndrome coronariana aguda não aterosclerótica, principalmente em mulheres. O objetivo deste estudo foi caracterizar uma amostra consecutiva de pacientes diagnosticados com dissecção espontânea da artéria coronária quanto a fatores predisponentes e desencadeadores; quadro clínico e angiográfico; abordagem terapêutica; ocorrência de eventos cardíacos adversos; recorrência e dissecção espontânea de artéria coronária *de novo*. **Métodos**: Estudo retrospectivo observacional longitudinal, unicêntrico, que incluiu pacientes diagnosticados com dissecção espontânea da artéria coronária (n=60) admitidos entre janeiro de 2010 e dezembro de 2020. **Resultados**: A mediana da idade foi de 55 anos, e 83% eram mulheres. A maioria dos pacientes (60%) não apresentava nenhum ou tinha apenas um fator de risco cardiovascular. O infarto agudo do miocárdio sem supradesnivelamento do segmento ST foi o quadro clínico em 67% dos casos. A artéria coronária mais frequentemente envolvida foi a descendente anterior (47%). A maioria das lesões (77%) aparecia na angiografia como dissecção espontânea da artéria coronária tipo 2. O tratamento conservador foi selecionado como abordagem inicial na maioria dos pacientes (72%). A incidência geral de dissecção espontânea da artéria coronária *de novo* não foi significativamente diferente entre os pacientes tratados primeiramente com revascularização, em comparação com os que receberam tratamento conservador (p=0,953). No entanto, a recidiva da dissecção espontânea da artéria coronária ocorreu no vaso originalmente envolvido em 3 dos 15 pacientes tratados com revascularização, em comparação com apenas um entre os 43 pacientes que foram tratados de

How to cite this article:
Oliveira CC, Vasconcelos N, Abreu G, Braga CG, Costa J, Marques J. Spontaneous coronary artery dissection, a multifactorial disease: insights from a center experience. J Transcat Intervent. 2023;31:eA20220017. https://doi.org/10.31160/JOTCI202331A20220017

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Received on:
Dec 6, 2022

Accepted on:
Feb 15, 23

forma conservadora (p<0,05). **Conclusão**: A dissecção espontânea da artéria coronária é mais frequente em mulheres jovens. O infarto agudo do miocárdio sem supradesnivelamento do segmento ST foi o quadro clínico mais observado, envolvendo principalmente a artéria descendente anterior. A revascularização não protegeu da recorrência.

Descritores: Síndrome coronariana aguda; Angiografia; Dissecção espontânea da artéria coronária; Dissecção; Doenças vasculares; Doenças cardiovasculares; Fatores de risco de doenças cardíacas; Mulheres

INTRODUCTION

Spontaneous coronary artery dissection (SCAD) is defined as a non-traumatic, non-iatrogenic, and non-atherosclerotic separation of the epicardial coronary artery layers due to intramural hemorrhage, which may occur with or without rupture of the intimal layer, leading to intraluminal narrowing and consequent decreased coronary blood flow.[1,2]

This is an underdiagnosed cause of non-atherosclerotic acute coronary syndrome (ACS), most commonly thought to affect young women with a low prevalence of classic cardiovascular risk factors.[3]

Currently, the prevalence of SCAD is estimated at approximately 4% of all patients presenting with ACS, and its true prevalence may be underestimated.[4] In fact, this prevalence increases significantly in women aged ≤50 years, and in this age group, SCAD may account for up to 35% of ACS presentations.[5,6] However, gender and age biases make it difficult to evaluate women with ACS, and thus, the diagnosis of diseases such as SCAD are often missed.[7]

Intracoronary imaging techniques, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT), have increasingly assumed an important role in the diagnosis of SCAD.[8-10] Spontaneous coronary artery dissection physiology is primarily distinguished by the presence or absence of intimal disruption and can be further classified based on angiographic criteria.[11,12] In our study, SCAD was categorized according to the Saw classification. Considering the coronary circulation, SCAD most often affects only one vessel, with the left anterior descending artery being the most affected, particularly in its medial or distal segments.[13-16]

It has become evident that multiple factors may predispose to this condition, namely fibromuscular dysplasia (FMD); connective tissue diseases (highlighting Marfan and Ehlers-Danlos syndrome); pregnancy and multiparity; systemic inflammatory diseases (including systemic lupus erythematosus, inflammatory bowel disease, polyarteritis nodosa, and sarcoidosis), as well as exogenous hormones (oral contraceptives and hormone replacement therapy).[17]

More recently, Adlam et al. described the first genetic variant associated with SCAD. This study reported that rs9348379 is the first genetic risk locus for SCAD, and that this common variant is further associated with FMD and other vascular disorders, providing a genetic explanation for the clinical association among these disorders.[18] Nevertheless, the exact etiology of this disease remains unknown. Additionally, it is often associated with precipitating events, such as emotional stress, physical stress (Valsalva maneuvers or intense exercise), or recreational drug use.[19]

The most common clinical presentation is an ACS, usually with chest pain associated with elevated levels of cardiac enzymes.[20] Treatment depends mainly on severity of the clinical presentation, hemodynamic status, topography of the dissection, number of arteries affected, and distal coronary flow, ranging from conservative treatment to coronary artery bypass graft surgery.[21,22] Its correct and prompt diagnosis is essential since the treatment modality may differ based on it. Thus, unlike atherosclerotic disease, a conservative strategy is most often adopted in patients with low-risk SCAD, given its favorable evolution, with spontaneous healing of the intramural hematoma occurring in most patients (>95% in 30 days).[23] Nevertheless, it should be considered that conservative therapy may not be the preferred approach to high-risk patients, such as those with ongoing ischemia, left main artery dissection, or hemodynamic instability. In such cases, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) should be considered to restore blood flow.

Although mortality associated with this disease is low, there is a high risk of recurrence of adverse cardiac events, including recurrence of SCAD. In a series of observational studies with a follow-up of 4 to 10 years, the recurrence rate of SCAD reached up to 30% of patients.[6,15,19,24] Several factors associated with the risk of recurrence have been identified, including coronary artery tortuosity, FMD, history of hypertension, and migraine.[25-27]

In this study, we aimed to characterize and establish the factors related to SCAD and its management.

METHODS

A single-centre, longitudinal observational retrospective study, of consecutive patients (n=60) admitted between January 2010 and December 2020, with a diagnosis of ACS due to SCAD. All coronary angiographies were jointly reviewed by two experts. Tortuosity was defined by the presence of one of two criteria: ≥3 consecutive curvatures of 90º to 180º, measured at end-diastole in a major epicardial coronary artery ≥2mm in diameter, or ≥2 consecutive curvatures of ≥180º in a major epicardial coronary artery ≥2mm in diameter.[25]

The decision about treatment was made by the interventional cardiologist based on clinical presentation, coronary anatomy, and other clinical factors. In general, pa-

tients with a flow-limiting dissection in a large vessel and evidence of ongoing ischemia were revascularized using PCI. Patients without evidence of ongoing ischemia and without flow limiting dissection of a major coronary vessel were treated conservatively. Conservative treatment included dual antiplatelet therapy (acetylsalicylic acid [ASA] + adenosine-diphosphate [ADP] receptor antagonist), statins, betablockers (BB), and angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), depending on left ventricular function and blood pressure.

Ethical statement

The study was approved by the Ethics Committee. All study procedures were carried out in accordance with the rules of Ethical Conduct and Good Practice, following the principles of the Declaration of Helsinki and the Convention on Human Rights and Biomedicine.

Study sample

Data from consecutive patients diagnosed with SCAD, admitted between January 2010 and December 2020, were included in the study (n=60).

Inclusion criteria

Spontaneous coronary artery dissection diagnosis according to the Saw classification: SCAD was diagnosed and classified as into type 1 (evident arterial wall stain with multiple radiolucent lumens), type 2 (diffuse smooth stenosis of varying severity), and type 3 lesions (focal or tubular stenosis mimicking atherosclerosis).

Exclusion criteria

Patients with non-cardiac comorbidities responsible for mean expected life span <1 year, documented prior to initiation of treatment; atherosclerotic, traumatic, or iatrogenic SCAD; age less than 18 years.

Study design

Clinical, analytical, and imaging data were obtained from medical records of hospital stay and subsequent consultations. Spontaneous coronary artery dissection was diagnosed based on the presence of angiographic characteristics on coronary angiography and subsequently categorized according to Saw's classification.[11]

Statistical analysis

The data collected was stored in Microsoft Excel format. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 27. The normality of distribution of continuous variables was tested by one-sample Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented as mean ± standard deviation (SD); non-normal variables were reported as median [interquartile range – IQR]. Categorical variables were presented as relative frequency (percentage). Spontaneous coronary artery dissection recurrence in patients initially managed with revascularization by PCI and conservative therapy was compared using the Student's *t* test for independent samples. A value of $p<0.05$ was considered significant.

RESULTS

Patient characteristics

We studied 60 patients with SCAD (Table 1). The median age of the cohort was 55±12 years (minimum 28 and maximum 82), and the patients were predominantly female (Figure 1).

Hypertension (43%; n=26) and dyslipidemia (35%; n=21) were the most prevalent cardiovascular risk factors. Furthermore, obesity (22%; n=13) and overweight (45%; n=27) were also highly predominant (Table 2). Most patients (60%; n=36) presented without any or just one cardiovascular risk factor. However, 38% of patients (n=23) presented with two or three cardiovascular risk factors (Figure 2).

Predisposing and precipitating factors

Predisposing and precipitating factors were identified in several patients. Multiparity (≥3 births) was present in 25% of patients (n=15). A small proportion of patients had other predisposing factors, such as hormone treatment (13%; n=8) or autoimmune diseases (10%; n=6). Furthermore, several patients had comorbidities which have been previously linked to an increased risk of SCAD, such as depressive syndrome (22%; n=13) or previous myocardial infarction (12%; n=7). Possible triggers for SCAD (physical or emotional stress, Valsalva maneuver, and drugs) were identified in a total of eight patients.

Clinical presentation

Non-ST segment elevation myocardial infarction (NSTEMI) was the most common presentation on admission (67%; n=40), followed by ST segment elevation myocardial infarction (STEMI) (28%; n=17). Sudden cardiac arrest (3%; n=2) or stable angina (2%; n=1) were uncommon presentations (Table 3). During hospital stay, the mean troponin I peak was 16,6 (8,2 to 40,9) ng/mL. A significant number of patients had left ventricular systolic dysfunction (30%; n=18).

Angiographic characteristics and coronary anatomy

There were 55 patients (92%) with dissection in one vessel, and five patients (8%) with more than one affected vessel, all of which involved contiguous arteries.

Table 1. Patient characteristics, presentation, treatment, and follow-up (n=60)

Patient	Gender	Age	Predisposing	Triggering	Presentation	Peak troponin I (ng/dL)	Territory	SCAD	Intracoronary	Coronary tortuosity	Treatment	Recurrence	*De novo* SCAD	Reinfarction*
1	F	56	Absent	Absent	NSTEMI	34.6	LCX	2	No	Yes	Conservative	No	Yes (LAD)	Yes
2	F	65	MP	VM	NSTEMI	6.87	RCA	2	No	†	PCI	No	No	No
3	F	44	AID, MP	Absent	STEMI	65,0	LAD	2	No	No	Conservative	No	Yes (RCA)	No
4	F	57	CTD, MP	VM	NSTEMI	13.4	LAD	2	No	Yes	Conservative	No	No	Yes
5	F	39	MP	Absent	NSTEMI	31.7	RCA	1	Yes	No	Conservative	No	No	Yes
6	F	52	MP	Absent	STEMI	2.83	LAD	1	No	Yes	Conservative	No	Yes (LCX)	Yes
7	F	38	MP	Absent	NSTEMI	1.14	LCX	2	No	No	Conservative	No	Yes (LAD)	Yes
8	F	35	HT	Absent	STEMI	111,0	LAD	1	No	No	PCI	No	No	No
9	F	51	MP	Absent	STEMI	71,0	LAD	2	No	No	PCI	No	Yes (RCA)	Yes
10	F	53	Absent	Absent	NSTEMI	0.88	LCX	2	Yes	Yes	PCI	No	No	No
11	F	54	MP	Absent	STEMI	40.9	RCA	2	No	No	PCI	No	No	No
12	M	67	AID	Absent	NSTEMI	14.3	LCX	2	No	No	PCI	Yes	No	Yes
13	F	70	AID	Absent	STEMI	21,0	LCX	2	No	Yes	PCI	Yes	No	Yes
14	F	65	AID	Absent	STEMI	26,0	RCA	1	No	No	Conservative	No	No	Yes
15	F	61	Absent	Absent	NSTEMI	10.9	LAD	1	No	No	PCI	Yes	No	Yes
16	F	35	HT, MP	Absent	NSTEMI	43,0	LAD	1	No	No	PCI	No	No	No
17	M	49	Absent	Absent	STEMI	48.4	LAD	2	No	Yes	PCI	No	No	No
18	F	63	Absent	Absent	SCA	15.3	LAD	2	No	Yes	Conservative	No	No	No
19	M	52	Absent	Absent	STEMI	39.9	LAD	2	No	No	Conservative	No	No	No
20	F	64	Absent	Absent	NSTEMI	68,0	LCX	2	No	Yes	Conservative	No	No	No
21	F	59	HT, MP	Absent	SCA	79.2	LAD	1	No	No	PCI	No	No	No
22	F	52	MP	Absent	NSTEMI	20.3	RCA	2	No	Yes	Conservative	No	No	No
23	M	82	Absent	Absent	NSTEMI	47.9	LCX	1	No	No	Conservative	No	No	No
24	F	56	Absent	Absent	NSTEMI	0.23	LAD	2	No	No	PCI‡	Yes	No	Yes
25	F	65	Absent	Absent	NSTEMI	11.3	LCX	2	No	Yes	Conservative	No	No	No
26	M	49	Absent	PH Stress	NSTEMI	14.4	LCX	1	Yes	No	PCI‡	Yes	No	Yes
27	F	71	MP	Absent	NSTEMI	19.5	LAD	2	No	No	Conservative	No	No	Yes
28	M	63	Absent	Absent	NSTEMI	71.2	LCX	1	No	No	Conservative	No	No	No
29	F	54	Absent	Absent	NSTEMI	30.2	LCX	2	No	Yes	Conservative	No	No	No
30	F	53	Absent	Absent	NSTEMI	27.4	LAD	2	No	No	PCI	No	No	No
31	F	60	AID, HT	Absent	NSTEMI	2.56	RCA	2	No	Yes	Conservative	No	No	No
32	F	52	Absent	Absent	STEMI	11.4	LAD	1	No	No	Conservative	No	No	No
33	M	46	Absent	Drugs	NSTEMI	23.5	RCA	2	No	No	Conservative	Yes	No	Yes
34	F	42	Absent	Absent	NSTEMI	6.67	LAD	2	No	Yes	Conservative	No	No	No
35	M	44	Absent	Absent	NSTEMI	78.3	LCX	2	Yes	No	Conservative	No	No	No
36	F	68	Absent	Absent	NSTEMI	7.47	LAD, LCX	2	No	Yes	Conservative	No	No	No
37	M	28	Absent	Drugs	STEMI	212,0	LAD, LCX	2	No	No	PCI	No	No	No
38	F	70	Absent	Absent	STEMI	19.2	LAD	2	No	Yes	Conservative	No	No	No
39	F	58	HT	Absent	NSTEMI	5.21	LAD,LCX	1,2	No	No	PCI	No	No	No
40	F	60	Absent	Absent	NSTEMI	5.22	LAD	2	No	Yes	Conservative	No	No	No
41	F	49	Absent	Absent	STEMI	77.4	RCA	2	No	No	Conservative	No	No	No
42	F	77	Absent	Absent	STEMI	11.2	LAD	2	No	Yes	Conservative	No	No	No
43	M	79	Absent	Absent	NSTEMI	28,0	RCA	2	No	Yes	Conservative	No	No	No
44	F	54	Absent	Absent	NSTEMI	1.53	LCX	2	No	Yes	Conservative	No	No	No
45	F	54	Absent	Absent	NSTEMI	28.4	LCX	2	No	No	Conservative	No	No	No
46	F	63	Absent	PH Stress	NSTEMI	8.33	LAD	2	No	Yes	Conservative	No	No	No
47	M	41	Absent	Emotional stress	NSTEMI	14.5	LAD	1	No	No	Conservative	No	No	No
48	F	59	Absent	Emotional stress	NSTEMI	3.4	LAD	2	No	No	Conservative	No	Yes (LMCA)	No
49	F	62	Absent	Absent	Stable angina		LAD	2	No	No	Conservative	No	No	No
50	F	56	Absent	Absent	NSTEMI	51.8	LAD	2	No	Yes	Conservative	No	Yes (RCA)	Yes
51	F	37	Absent	Absent	NSTEMI	8.83	LCX	2	No	No	Conservative	No	No	No
52	F	34	HT	Absent	STEMI	11.7	LAD, LCX	1,2	No	No	Conservative	No	No	No
53	F	60	Absent	Absent	NSTEMI	20.1	RCA	2	No	Yes	Conservative	No	No	No
54	F	64	MP	Absent	STEMI	13,0	RCA	2	No	Yes	Conservative	No	No	No
55	F	56	MP	Absent	STEMI	71,0	LAD	2	No	No	PCI	No	Yes (RCA)	Yes
56	F	63	Absent	Absent	NSTEMI	8.2	RCA	2	No	Yes	Conservative	No	No	No
57	F	30	HT	Absent	NSTEMI	16629,0	LCX	2	No	No	Conservative	No	No	No
58	F	46	AID	Absent	NSTEMI	9.3	LCX	2	No	No	Conservative	No	No	No
59	F	50	Absent	Absent	NSTEMI	6.9	LAD	2	No	No	Conservative	No	No	No
60	F	36	HT, MP, PP	Absent	NSTEMI	4.44	LMCA	2	Yes	No	Conservative	No	No	No

* In-hospital and long-term; † data not available; ‡ patients were managed by PCI after recurrence of SCAD.

SCAD: spontaneous coronary artery dissection; F: female; NSTEMI: non-ST segment elevation myocardial infarction; LCX: left circumflex artery; LAD: left anterior descending artery; MP: multiparity; VM: Valsalva maneuver type activity; RCA: right coronary artery; PCI: percutaneous coronary intervention; AID: autoimmune disease; STEMI: ST segment elevation myocardial infarction; CTD: connective tissue disease; HT: hormone therapy; M: male; SCA: sudden cardiac arrest; LMCA: left main coronary artery; PP: peripartum.

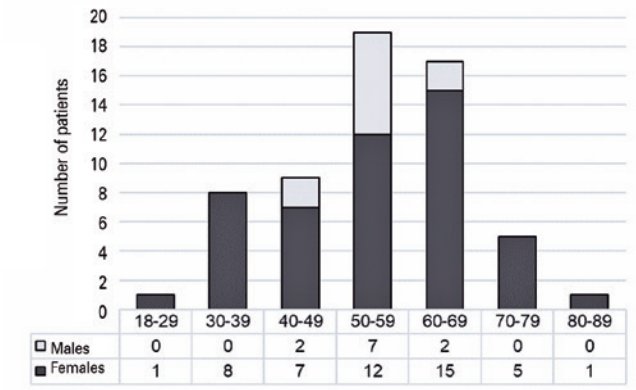


Figure 1. Age and sex distribution (n=60).

Table 2. Baseline characteristics (n=60)

Age, years	55±12
Female gender	49 (83)
BMI	26.3 (24.3-29.4)
Traditional cardiovascular risk factors	
Hypertension	26 (43)
Smoking	11 (18)
Diabetes	6 (10)
Dyslipidemia	21 (35)
Obesity (BMI ≥30.0)	13 (22)
Overweight (BMI 25.0-29.9)	27 (45)
Comorbidities	
Cerebrovascular disease	4 (7)
History of coronary artery disease	2 (3)
Previous myocardial infarction	7 (12)
Chronic kidney disease	1 (2)
Thyroid disease	5 (8)
Depressive syndrome	13 (22)
Predisposing factors	
Autoimmune disease	6 (10)
Connective tissue disorder	1 (2)
Multiparity ≥3	15 (25)
Peripartum	1 (2)
Hormone treatment	8 (13)
Precipitating factors	
Physical stress	2 (3)
Emotional stress	2 (3)
Valsalva maneuver	2 (3)
Drugs	2 (3)

Results expressed as mean ± standard deviation, n (%), or median (interquartile range).
BMI: body mass index.

The most common artery territory dissected was the left anterior descending artery (47% of all patients with single vessel SCAD; n=26), followed by the left circumflex artery (31% of all patients with single vessel SCAD; n=17) and the right coronary artery (22% of all patients with single vessel SCAD; n=12).

Of all the dissections, more than two-thirds had type 2 angiographic SCAD (77%; n=46), 20% (n=12) had type 1, and 3% (n=2) had both type 1 and 2 dissections. Figure 3 shows coronary angiography of two patients displaying type 1 (Figure 3A) and type 2 (Figure 3B) SCAD.

Treatment and adverse events

Most patients were treated conservatively/medically (72%; n=43). This included dual antiplatelet therapy, BB, ACEI/ARB, and statins. Only 17 patients (28%) underwent angioplasty with drug-eluting stents. Two of these patients were not initially treated with PCI but later required angioplasty because of SCAD recurrence. None of the patients required CABG (Table 4).

At discharge, most patients maintained dual antiplatelet therapy with aspirin (95%; n=57) and an ADP antagonist (72%; n=43), statins (93%; n=56), BB (88%; n=53), and ACEI/ARB (72%; n=43).

Spontaneous coronary artery dissection recurrence (dissection in the same vessel) occurred in six patients (10%), and mostly happened early on in time (5±2 days). *De novo* SCAD, defined as a dissection event in a different vessel, occurred in eight patients (13%) over a higher spam of time (1,291±914 days).

Figure 4 compares the rate of recurrent SCAD between patients initially managed with revascularization by PCI and conservative therapy (patients who were not initially treated with PCI but later required angioplasty because of SCAD recurrence were not included, n=2). The overall incidence of *de novo* SCAD was not significantly different between the two groups (revascularization, 13% *versus* conservative treatment, 14%; p=0.953). However, 20% of the revascularization group (3 of 15 patients), developed recurrent SCAD in the originally involved PCI-treated vessel, compared to just one patient (2%) in the conservative treatment group (p<0.05).

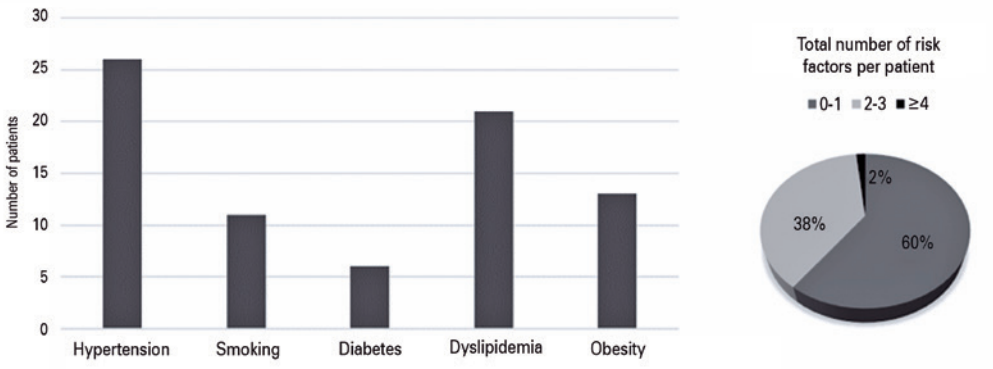


Figure 2. Frequency of conventional cardiovascular disease risk factors (n=60).

Table 3. Clinical presentation and angiographic characteristics (n=60)

Presentation			
SCA	2 (3)		
STEMI	17 (28)		
NSTEMI	40 (67)		
Stable angina	1 (2)		
Ejection fraction*			
Ejection fraction <50%	18 (30)		
Ejection fraction, %	54	(46-58)	
Peak troponin I, ng/mL*	16.6	(8,2-40,9)	
Hemoglobin, g/dL	13.1 ± 1.2		
Serum creatinin (mg/dl)	0.7		
Territory and number of arteries involved			
SCAD involving 1 artery	55 (92)		
LAD	26 (47)		of all patients with single-vessel SCAD
Proximal	1		
Mid	8		
Distal	12		
First diagonal branch	4		
Second diagonal branch	1		
LCX	17 (31)		of all patients with single-vessel SCAD
Distal	5		
First obtuse marginal branch	8		
Second obtuse marginal branch	2		
Intermediate branch	2		
RCA	12 (22)		of all patients with single-vessel SCAD
Proximal RCA	2		
Mid RCA	2		
Posterolateral branch	4		
Posterior descending branch	4		
SCAD involving >1 artery	5 (8)		of all patients with single-vessel SCAD
One dissection extending from main to side branch	1		
Left main coronary artery and proximal LAD	1		
Proximal LAD and first obtuse marginal branch	1		
Mid LAD and proximal circumflex artery	1		
Mid LAD and first obtuse marginal branch	1		
Mid LAD and second obtuse marginal branch			
Angiographic type of SCAD			
1	12 (20)		
2	46 (77)		
1 e 2	2 (3)		
Initial TIMI flow			
0	3 (5)		
1	18 (30)		
2	9 (15)		
3	30 (50)		
Killip class			
I	56 (93)		
II	2 (3)		
III	2 (3)		
Coronary tortuosity*	24 (41)		
Intracoronary imaging	5 (8)		

*n=59.

SCA: sudden cardiac arrest; STEMI: ST segment elevation myocardial infarction; NSTEMI: non-ST segment elevation myocardial infarction; SCAD: spontaneous coronary artery dissection; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; TIMI: Thrombolysis In Myocardial Infarction.

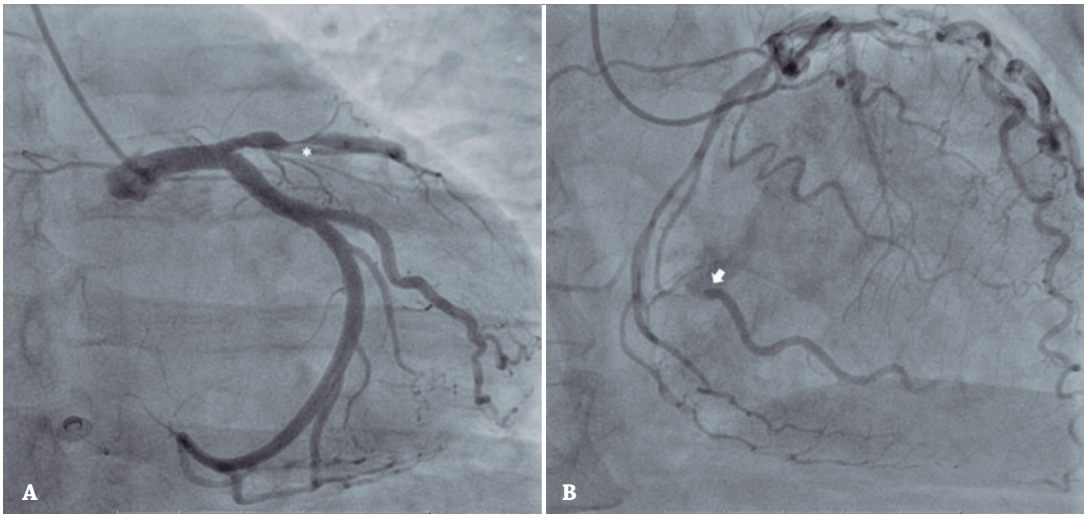
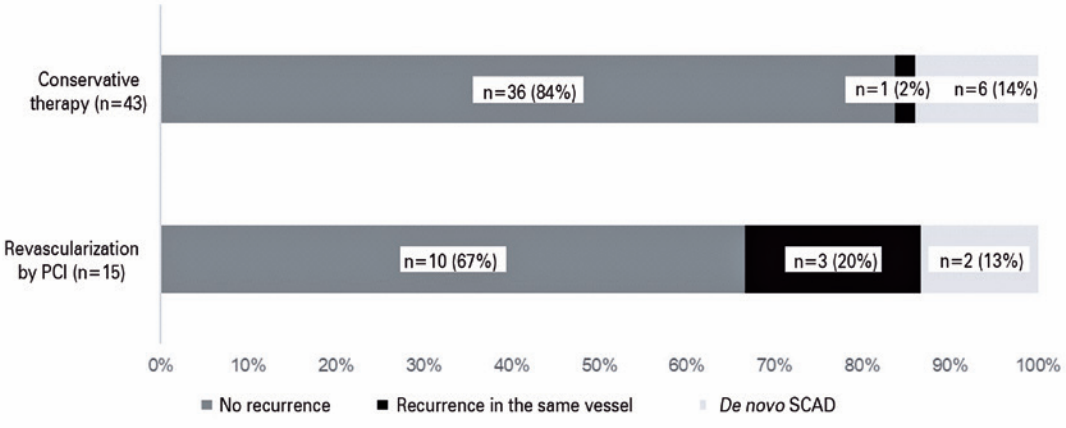


Figure 3. Coronary angiography documenting type 1 and 2 spontaneous coronary artery dissection. (A) Type 1 and 2 spontaneous coronary artery dissection in the left anterior descending artery. The asterisk indicates intimal tear separating the true lumen from the false lumen. (B) Type 2 spontaneous coronary artery dissection in the left circumflex artery, showing a narrowing of artery caliber, bordered distally by normal artery segment (arrow).

Tabela 4. Treatment, medication at discharge, and adverse events (n=60)

Treatment		
Conservative	43 (72)	
PCI*	17 (28)	
Medication at discharge		
Aspirin	57 (95)	
ADP antagonist	43 (72)	
Beta-blocker	53 (88)	
Statin	56 (93)	
ACE inhibitor/ARB	43 (72)	
Adverse events		
SCAD recurrence (same vessel)	6 (10)	(5±2 days)
De novo SCAD (different vessel)	8 (13)	(1.291±914 days)
Miocardial infarction	17 (28)	
Heart failure	6 (10)	

Results expressed as n (%) or mean ± standard deviation.
* Two patients were managed by PCI after recurrence of SCAD.
PCI: percutaneous coronary intervention; ADP: adenosine diphosphate; ACE: angiotensin-converting enzyme; ARB: angiotensin-receptor blocker; SCAD: spontaneous coronary artery dissection.



PCI: percutaneous coronary intervention; SCAD: spontaneous coronary artery dissection.
Figure 4. Comparison of spontaneous coronary artery dissection recurrence events in coronary vessels in patients initially managed by coronary revascularization (percutaneous coronary intervention) or conservative treatment (n=58).

DISCUSSION

Spontaneous coronary artery dissection is an important but often undiagnosed cause of ACS leading to myocardial infarction, predominantly in young to middle-aged women, although it can affect both sexes across the lifespan.[28,29] The underlying mechanism of non-atherosclerotic SCAD has not been fully understood.[30] The primary event can be either an intimal tear, leading to separation of coronary wall layers and to a double lumen, or alternatively, rupture of the *vasa vasorum*, resulting in a secondary intramural hemorrhage and formation of an intramural hematoma (without a distinct intimal rupture), which causes luminal compression and ultimately coronary obstruction.[31,32]

Precipitating stressors, such as physical and emotional stress, maneuvers that increase intraabdominal pressure (eg. Valsalva) or drugs, increase cardiocirculatory stress, and can provoke the acute SCAD event. In fact, recent studies reported over 50% of patients experienced precipitating stressors preceding SCAD.[19,26] Our study found multiparity to be the most frequent predisposing factor. However, a weak association between precipitant stressors and SCAD, with only eight patients referring a possible trigger.

Pregnancy has also been frequently associated with SCAD. In fact, numerous studies report a high prevalence of SCAD during the peripartum period. Hormonal and hemodynamic changes have been hypothesized as contributing to weakening the coronary arterial wall.[33,34] However, in our study this was not the case, as only one of our female patients presented with SCAD during pregnancy or the peripartum. Since SCAD disproportionately affects women, the role of hormones should not be discarded. Exposure to recurrent and chronic hormone changes may further increase SCAD risks in women. In our study, almost a third of our patients either presented with multiparity or were on hormone treatment.

Although the cause of SCAD is unknown, it probably includes factors related to patient vulnerabilities, such as FMD, autoimmune diseases, and connective tissue disorders. Because patients with SCAD present with a high prevalence of extracoronary vascular abnormalities, the most import one being FMD, it has been hypothesized that SCAD is an initial presentation of an underlying arterial disorder.[35,36] In fact, a study of 168 patients with SCAD, screened all patients with invasive or noninvasive angiography of the cerebral, iliac, or renal circulations, and FMD was diagnosed in 72% of patients, in one or more territories.[19] This highlights the importance of systemic vascular imaging in all patients presenting with SCAD, as well as screening for inflammatory/immunologic markers. Unfortunately, in our center we only recently began to routinely screen for extracoronary vascular abnormalities and an association with FMD, and therefore this data is lacking in our study.

Several studies suggest that the prevalence of conventional cardiovascular risk factors is lower among patients that suffer from SCAD when compared to those who had a myocardial infarction from atherosclerotic disease.[15,19,37,38] However, in our study we found that risk factors, such as hypertension and dyslipidemia, are frequent, with up to 38% of patients presenting with two or three risk factors. Similarly, Saw et al. reported that although most patients (69.7%) had one or no cardiovascular risk factors, baseline hypertension was present in 36.4% and 25.7% of participants, respectively.[26] Also, recent data from a prospective national SCAD registry in Spain reported that classic cardiovascular risk factors are common in women with SCAD.[33] Moreover, there is a high proportion of either obese (22%) or overweight (41%) patients in our study. Recently, it has been suggested that sex-dependent perivascular adipose tissue-mediated mechanisms may be implicated in the pathogenesis of SCAD.[39,40] Cessation of endogenous estrogen production following menopause leads to perivascular adipose tissue expansion and adipocyte hypertrophy, increasing vascular tone and inflammation, particularly in patients with obesity and associated conditions such as hypertension and diabetes.[41]

In most patients SCAD manifests as ACS. The clinical signs are undistinguishable from those of ACS due to coronary atherosclerosis. The proportion of patients with SCAD presenting as STEMI *versus* NSTEMI significantly differs between diverse series (26 to 49%), while other clinical presentations, such as ventricular fibrillation or SCA are infrequent.[20,21,42] In our study, an overwhelming percentage of patients presented with NSTEMI (67%), whereas STEMI was the initial presentation in 28% of patients.

An accurate SCAD diagnosis is crucial, and a high degree of clinical suspicion is often necessary. Coronary angiography is currently the first-line diagnostic tool; nevertheless, it does not come without risks and iatrogenic dissection might occur.[43] Most SCAD can be readily distinguished angiographically from other causes of ACS; however misdiagnoses are still common. Intracoronary imaging (IVUS/OCT) has theoretical advantages over coronary angiography; nonetheless, a large coronary imaging series confirmed a small number of complications (5 of 63 cases) directly attributable to intracoronary imaging, resulting in either false lumen propagation, impaired flow, or iatrogenic dissection.[44,45] When compared to OCT, imaging with IVUS does not require high-pressure injection of contrast and presents with a safer diagnostic profile. However, its lower spatial resolution makes it challenging to distinguish SCAD from lipid-rich atheroma (a key differential diagnosis).[46] Because of this, routine imaging is not recommended and should only be considered if angiography alone is not enough to make a diagnosis (*e.g.* type 3 or unclear lesions).[17,21] In our center, because of this high

risk of complications, the use of intracoronary imaging is reserved only for the most challenging diagnostic cases, and consequently intracoronary imaging in the present study was not often employed.

Left ventricular function after SCAD-related ACS is often preserved.[19] Similarly, in our study, only 30% of patients presented with an ejection fraction less than 50%. Also, consistently with other studies, we observed that all of our patients had elevated cardiac biomarkers (troponin I) consistent with myocardial infarction (normal level <0.045 ng/mL).[15]

At the time of coronary angiography, most patients presented with a single affected artery, while multivessel involvement of contiguous coronary segments was infrequent. As in other studies, the left anterior descending artery was the most frequently affected vessel, and the most common angiographic type of SCAD was type 2 (diffuse long and smooth stenosis, which can vary in severity from mild stenosis to complete occlusion).[15,19,32] Also, a significant percentage of our patients (41%) had coronary tortuosity. Eleid et al. described an association between recurrence and increased coronary tortuosity. However, it is unclear whether tortuosity is a marker of underlying vasculopathy, since it is often associated with FMD, or if it provides by itself a mechanism for arterial injury.[20,25,47]

In most SCAD patients, conservative therapy is the preferred strategy.[20,24] In line with this, a large percentage of our patients (72%) were treated conservatively/medically.

Two recent meta-analysis found that long-term risk of death, recurrent SCAD, and repeat revascularization did not significantly differ among patients with SCAD medically treated, as compared to those treated with invasive therapy, suggesting that randomized controlled trials are needed to confirm these findings.[48] Nevertheless, current consensus favors a conservative treatment strategy, unless patients have high-risk features, such as ongoing ischemia, recurrent chest pains, left main coronary artery dissection, ventricular arrhythmias, or hemodynamic instability.[17,21]

Given the good results of conservative treatment, at our center, there was a greater tendency over time towards conservative treatment and less towards revascularization. Early on, several patients were treated with PCI, however, in recent years the preferred approach was conservative treatment in most patients, except for those presenting with hemodynamic instability. It is also noteworthy that in our series, patients initially managed by PCI ended up having more SCAD recurrence events in the same vessel. On the other hand, in the specific case of SCAD, percutaneous intervention is often associated with a lower percentage of success and occurrence of complications, when compared to percutaneous intervention in atherosclerotic disease. SCAD recurrence has been also described as associated with hypertension in other studies.[26]

Anticoagulation and dual antiplatelet therapy are generally initiated before SCAD is diagnosed. However, anticoagulation should be discontinued after SCAD has been confirmed on angiography owing to risk of dissection extension due to worsening of intramural bleeding.[17,21] Most patients are managed with long-term aspirin, BB, ACEI/ARB, and short-term clopidogrel, with the addition of statins in patients with dyslipidemia.[1] These approaches are largely based on expert opinions derived from the clinical experience as randomized controlled trials lack to support an evidence-based approach. Beta-blockers may have an additional benefit of preventing the recurrence of SCAD,[26] which is common and occurs in 7% of patients over midterm follow-up. Close monitoring is also important after a SCAD-event since adverse cardiovascular events post-SCAD are frequent. Nonetheless, to date, no clear risk factors have been demonstrated that can be associated with a higher recurrence rate. Severe coronary artery tortuosity has been proposed as a risk factor for recurrence, but further studies are required to corroborate this association.[25]

Care of SCAD patients will often include cardiac rehabilitation (a supervised exercise and education program) to aid in the recovery process, both physically and emotionally. However, a study found that up to 67% of women suffering from SCAD did not participate in cardiac rehabilitation due to lack of medical referral, mostly because of the belief that precipitating stressors, such as exercise, may predispose patients to recurrent SCAD. But cardiac rehabilitation is a key recommendation for all persons following myocardial infarction. In fact, excessive restrictions on physical activity may be even more damaging by subjecting the individual to risks of other health problems, such as depression, obesity, diabetes, and osteoporosis. Therefore, aiming for moderate-intensity physical activity should be a priority for patients that have suffered from SCAD. Unfortunately, this is not yet our reality, and the number of patients that are referred to cardiac rehabilitation in our center is still quite low. This is one aspect that should be urgently improved for the benefit of our patients.

Although SCAD remains an uncommon cause of myocardial infarction overall, its role in myocardial infarctions among women is considerable, and it is still often overlooked and misdiagnosed as atherosclerotic disease. Our study sheds some light on the characteristics and clinical course of patients with SCAD in Portugal. In fact, to the best of our knowledge, this is the largest series of patients with SCAD reported to date in our country. This study also aims to bring attention of our medical community to the significant number of patients presenting with SCAD, reinforcing the need for a high clinical suspicion of this condition, particularly in young women with few conventional atherosclerotic risk factors, to obtain an early and proper diagnosis, which is critical for saving lives.

CONCLUSION

In our center, most patients with coronary artery dissection were treated conservatively with a good prognosis. Patients initially managed by percutaneous coronary intervention ended up having more spontaneous coronary artery dissection recurrence events in the same vessel. A high index of suspicion is necessary to make a spontaneous coronary artery dissection diagnosis. It is important that clinicians recognize relevant clinical features, particularly in young women without conventional cardiovascular risk factors presenting with acute coronary syndrome, since spontaneous coronary artery dissection diagnosis has specific long-term prognostic and therapeutic implications.

SOURCE OF FINANCING

None.

CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

CONTRIBUTION OF AUTHORS

Conception and design of the study: CCO, GA and CGB; data collection: CCO, GA, NV and CGB; data interpretation: CCO, NV, GA, CGB, JC and JM; text writing: CCO, GA and NV; approval of the final version to be published: CCO, NV, GA, CGB, JC and JM.

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