Association of Spontaneous Coronary Artery Dissection With Atrial Arrhythmias

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The co-morbidities and long-term complications of spontaneous coronary artery dissection (SCAD) are incompletely understood. This study investigated the association of atrial arrhythmias (AA), defined as atrial fibrillation and atrial flutter, with SCAD in a patient registry and population-based cohort. This observational study was performed in 2 parts. The first was a retrospective study reviewing patients diagnosed with AA in the Mayo Clinic SCAD Registry. The second was a population-based, case-control study to assess AA in patients with SCAD compared with age- and gender-matched controls. Of 1,214 patients in the Mayo Clinic SCAD Registry, 45 patients (3.7%) with SCAD were identified with an AA. A total of 8 of those patients (17.8%) had a pre-SCAD AA; 20 (44.4%) had a peri-SCAD AA; and 17 (37.8%) had a post-SCAD AA. The univariate analysis did not reveal significant associations with traditional cardiovascular risk factors. In the population-based cohort, 5 patients with SCAD (4%) and 4 controls (1%) developed an AA before the date of SCAD for each patient (odds ratio 4.5, 95% confidence interval [CI] 1.05 to 19.0, p = 0.04). A total of 5 patients with SCAD (4%) and 3 controls (1%) developed an AA in the 10 years after SCAD (hazard ratio 6.3, 95% CI 1.2 to 32.8, p = 0.03). A subgroup of patients with SCAD experienced AA before and after SCAD. Patients with a history of SCAD were more likely to develop AA in the next 10 years than were age- and gender-matched healthy controls. **(Am J Cardiol 2023;186:203−208)**

Spontaneous coronary artery dissection (SCAD) is an increasingly recognized cause of acute coronary syndrome, occurring predominantly in young women. SCAD is due to a nonatherosclerotic abrupt separation between the layers of the coronary arterial wall, resulting in intramural hematoma or intimal flap causing ischemia and/or infarction. In contrast to risk factors for atherosclerotic heart disease, currently identified factors associated with SCAD include female gender and systemic arteriopathies such as fibromuscular dysplasia (FMD).[1] Despite growing knowledge and recognition of SCAD, understanding its predictors and long-term complications remains incomplete. Atrial fibrillation (AF) and atrial flutter are mentioned in a small number of case reports describing several clinical presentations of SCAD accompanied by tamponade,[2] chest pain,[3] cardiac arrest,[4] and Takotsubo cardiomyopathy.[5] More recently, an observational study reported that 0.9% of patients with SCAD had new-onset AF within 30 days of their SCAD event.[6] Another observational study described AF as an independent predictor of in-hospital mortality in patients with SCAD, although more than a third of these patients were male and the diagnosis of SCAD was based on medical codes rather than angiographic confirmation.[7] Given the significant co-morbidity and long-term implications attributed to atrial arrhythmia (AA), a retrospective review was performed of clinical data from the Mayo Clinic SCAD Registry (MCSR) and a population-based, case-control study of patients with and without SCAD in the Upper Midwest.

Methods

Patients with angiographically confirmed, nonatherosclerotic SCAD who are consenting participants in the MCSR were included in part 1. Participant data provide detailed phenotypes using questionnaires, medical history, ancillary clinical information, imaging, and prospective follow-up. This study included patients enrolled between August 20, 2011 and February 10, 2020. The index date was defined as the patient's first SCAD event.

The diagnosis of an AA, including AF and atrial flutter, was queried in patients enrolled in the MCSR using 2 different methods (Figure 1). First, patients in the MSCR were identified by medical record number and investigated using a hospital-wide data repository using diagnostic codes and free text in the clinical records. The diagnostic codes and

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See page 207 for disclosure information.

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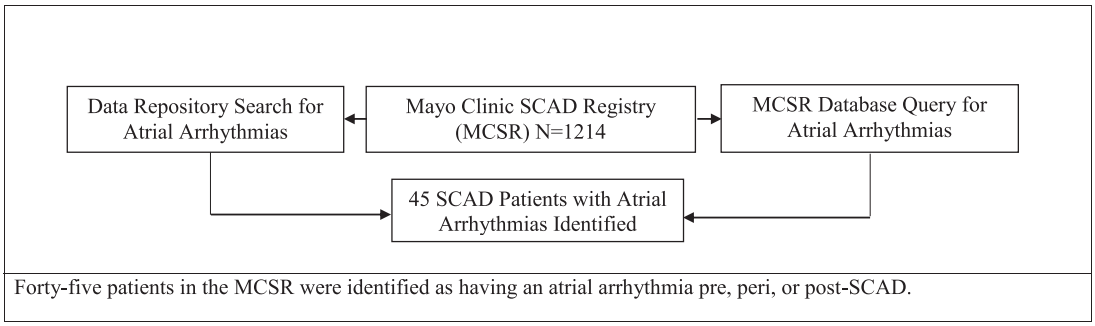


Figure 1. A total of 45 patients in the MCSR were identified as having an atrial arrhythmia pre-, peri, or post-SCAD.

free text searches performed in that data repository were comprehensive for AA (Supplementary Table 1). These same text terms were then searched within the MCSR clinical database to identify other potential patients with AA with confirmed self-reports on intake. Follow-up AA surveys were also included.

All patients with AA identified with these methods were manually verified using available records. All patients with AA without sufficient supporting data in the electronic medical record or the MCSR, such as a diagnostic electrocardiogram, a consultative visit for the AA, a clearly described history of an AA, a procedural history such as ablation or cardioversion, and/or medical management of these diagnoses, were not included. A total of 87 patients were not counted because of insufficient supporting information. A total of 45 patients were identified as meeting the criteria.

Details regarding the timing of the AA related to index SCAD event, demographic information, and medical co-morbidities were recorded. Pre-SCAD AA was defined as an AA before the initial SCAD; peri-SCAD was defined as an AA that occurred during initial hospitalization; and post-SCAD was defined as an AA after hospital discharge.

Variables were summarized as mean (SD) or median (interquartile range) for continuous and frequency (percentage) for discrete variables. Differences between those with and without pre-SCAD AA were tested for continuous variables using a one-way analysis of variance or Kruskal-Wallis rank sum test for non-normal variables. For discrete variables, Pearson's chi-square test was used. Univariate cause-specific Cox proportional hazards models were used to predict the time to initial AA after SCAD in the presence of the competing risk of mortality. Patients with a previous AA were excluded from this analysis. The classic cardiovascular risk factors used as independent predictors included hypertension (HTN), tobacco history (current and former smoking), hyperlipidemia (HLD), and diabetes mellitus (DM). In addition, pericoronary or postcoronary artery bypass graft was fit as a time dependent predictor of AA. The hazard ratio (HR) and 95% confidence intervals (CIs) were reported. All analyses were conducted using SAS (version 9.4, SAS Institute, Carey, North Carolina).

Patients with angiographically confirmed SCAD from a larger population-cohort were included in part 2.

The Rochester Epidemiology Project (REP) is a population-based medical records-linkage system of subjects who lived in Olmsted County from 1966 to the present;[8] the Expanded REP (E-REP) includes adults living in 1 of 26 neighboring counties in Southeastern Minnesota or Western Wisconsin from 2010 to the present.[9] A cohort of patients with SCAD and controls were identified using these databases as previously described.[10]

Potential SCAD cases occurring between January 1, 1995 and January 1, 2020 were identified using coronary artery dissection diagnosis codes (Supplementary Table 1). Each patient was angiographically verified by dedicated interventional cardiologists and met the criteria for SCAD, defined as the presence of an intramural hematoma and/or a dissection plane. Patients with traumatic or iatrogenic coronary artery injury and atherosclerotic plaque were excluded. Previously identified and verified cases within the study time window were also included.[11] Three control subjects for each patient with SCAD were identified on the basis of the absence of SCAD diagnosis codes and matched on the basis of age (±3 years), gender, county of residence, and time frame of available medical records before the index date of the corresponding SCAD case.[10] Details regarding the timing of the AA, demographic information, and medical co-morbidities were recorded.

Variables were summarized as mean (SD) for continuous or frequency (percentage) for discrete variables. Cumulative incidence curves and cause-specific Cox proportional hazards models were used to predict the time to first AA in the presence of the competing risk of mortality. Differences between curves were tested using Gray's test, and the HRs and 95% CIs were reported from the Cox models. The significance threshold was a 2-sided $p < 0.05$. All analyses were prespecified in a protocol and performed using SAS version 9.4 (SAS Institute Inc.).[10]

Parts 1 and 2 of this study received Institutional Review Board approval from the Mayo and Olmsted Institutional Review Boards (20-001533; 015-OMC-20).

Results

A total of 1,214 patients from the MCSR were initially identified, with SCAD index dates ranging from May 1, 1986 to November 11, 2019. The mean age at SCAD was 46.6 ± 9.9 years (range 17.5 to 76.8 years), and 1,165 patients were female (96%). A total of 45 patients with SCAD (3.7%) were identified as having an AA. Of those, 8 patients (17.8%) had a pre-SCAD AA; 20 (44.4%) had a peri-SCAD AA; and 17 (37.8%) had a post-SCAD AA (Table 1). Over a median follow-up of 1.74 years (0.66 to

Table 1
Baseline characteristics of Mayo Clinic SCAD Registry patients with SCAD

	Total SCAD (1214)	Atrial arrhythmia negative (1169/1214)	Atrial arrhythmia positive (45/1214)	Atrial arrhythmia pre-SCAD (8/45)	Atrial Arrhythmia Peri-SCAD (20/45)	Atrial arrhythmia post-SCAD (17/45)	Hazard ratio (95% confidence interval)	p-value*
Female (%)	1165 (96)	1125 (96.2)	40 (88.9)	7 (87.5)	20 (100)	13 (76.5)	0.33 (0.12, 0.93)	0.04
Caucasian (%)	1121 (93.3) 1201†	1078 (92.2)	43 (96)	8 (100)	19 (95)	16 (94.1)	1.08 (0.26, 4.50)	0.92
Mean age in years initial SCAD [SD]	46.6 [9.9]	46.5 [9.9]	51.5 [11.5]	47.1 [14.6]	49.3 [10.8]	56.7 [9.1]	1.05 (1.01, 1.09)	0.006

Spontaneous coronary artery dissection (SCAD) generally affects young, female patients. This is also true in patients with concomitant Atrial Arrhythmias (AA).
* The P values listed represent the results of a univariate competing risk Cox proportional hazard analysis where atrial arrhythmia was the outcome.
† Total n excluding incomplete data.

4.70), the univariate analyses did not reveal significant associations with traditional cardiovascular risk factors. Specifically, 15 of 45 patients (33.3%) with AA had a history of HTN compared with 373 of 1,168 patients (31.9%) with SCAD without AA (HR 1.00, 95% CI 0.50 to 2.00, p = 0.993); 12 of 45 patients (26.6%) with AA had a history of tobacco use compared with 309 of 1,160 (26.7%) without AA (HR 0.90, 95% CI 0.42 to 1.92, p = 0.79); 17 of 45 patients (37.8%) with AA had a history of HLD compared with 386 of 1,143 (33.8%) without AA (HR 0.77, 95% CI 0.38 to 1.58, p = 0.48); 2 of 45 patients (4.4%) with AA had a history of DM compared with 35 of 1,169 (2.88%) without AA (HR 0.97, 95% CI 0.13 to 7.11, p = 0.98) (Table 2). Peri- and post-SCAD AA were not associated with coronary artery bypass graft performed for SCAD during or at some point after their initial hospitalization when viewed as a time dependent predictor (HR 0.44, 95% CI 0.06 to 3.31, p = 0.48). Moreover, there was no association between previously diagnosed heart failure and the development of AA in patients with a pre-SCAD (p = 0.32) or post-SCAD arrhythmia (HR 1.16, 95% CI 0.37 to 3.62, p = 0.80).

A total of 114 patients with SCAD and 342 controls were identified within the 27-county region of the REP and E-REP, with index dates between 1995 and 2018 and a median follow-up of 3.9 (2.1 to 6.3) years. The mean age at SCAD was 51 ± 11 years (range 31 to 86 years); 102 patients (90%) were female; and index dates were defined as the date of the SCAD event in SCAD cases and date when non-SCAD medical care was sought in the controls ±3 years. Baseline characteristics of the SCAD cases and their controls were similar except that diagnosis codes of HTN, HLD, and FMD were more prevalent in the SCAD cases. In contrast, DM and tobacco diagnosis codes were more prevalent in the controls (Table 3).

AA occurred more frequently both before and after SCAD than in the control group. A total of 5 SCAD cases (4%) and 4 controls (1%) developed an AA before the index date (p = 0.04). A total of 5 SCAD cases (4%) and 3 controls (1%) developed an AA after the index date, which was found to be significant in the cumulative incidence curves (Figure 2; p = 0.01). The cause-specific hazard models reinforced this association, showing the SCAD group had a sixfold higher risk than did the non-SCAD matches (HR 6.26, 95% CI 1.19 to 32.85, p = 0.03).

Discussion

This study reveals a higher-than-expected incidence of AA in the MCSR and an association between SCAD and AA in the REP/E-REP population-based cohorts. There was no association of AA with traditional cardiovascular risk factors such as HTN, tobacco history, or HLD in the MCSR cohort. In the population-based cohort, the association of AA with SCAD was statistically significant even when controlling for those traditional risk factors. In addition, patients with a history of SCAD events were at 6 times higher risk of developing an AA than were age- and gender-matched healthy controls over a median of 3.9 years of follow-up.

Mechanistically, AA is associated with myocardial fibrosis caused by chronic inflammation related to prominent

Table 2
Traditional cardiovascular risk factors of Mayo Clinic SCAD Registry patients with SCAD

	Total SCAD (1214)	Atrial arrhythmia negative (1169/1214)	Atrial arrhythmia positive (45/1214)	Atrial arrhythmia pre-SCAD (8/45)	Atrial arrhythmia peri-SCAD (20/45)	Atrial arrhythmia post-SCAD (17/45)	Hazard ratio (95% confidence interval)
Hypertension (%)	388 (32.0) 1212*	373 (31.9)	15 (33.3)	3 (37.5)	5 (25)	7 (41.2)	1.00 (0.50, 2.00)
Dyslipidemia (%)	402 (33.1) 1187*	385 (32.9)	17 (3.8)	4 (50)	4 (20)	9 (52.9)	0.89 (0.45, 1.75)
Tobacco (%)	320 (26.4) 1204*	308 (26.3)	12 (26.7)	2 (25)	4 (20)	6 (35.3)	0.94 (0.45, 1.95)
Diabetes Mellitus (%)	36 (3.0) 1213*	34 (3.0)	2 (4.4)	0	1 (5)	1 (5.9)	1.83 (0.44, 7.61)

The positive association between spontaneous coronary artery dissection (SCAD) and the development of an atrial arrhythmia pre, peri, or post-SCAD was independent of traditional cardiovascular risk factors.

* Total n excluding incomplete data.

epicardial fat,[12] microRNA,[13] and reactive oxygen species,[14] with consequent atrial remodeling, dilation, and scarring.[15] It is possible that the AA observed in patients with SCAD may be a manifestation of the myocardial changes because of ischemia and infarction rather than being directly associated with SCAD. For example, the prevalence of AF in acute myocardial infarction is 6% to 21% and as high as 35% after cardiac surgery.[16,17] However, the risk of AA associated with myocardial infarction is strongly linked to the male gender, preexisting heart failure, and age >55 years, with the most significant association after age 70 years. This strongly contrasts to the SCAD demographic, which is women with a mean age of 46 and 51 years in the MCSR and population-based cohorts, respectively. Perhaps the underlying aspects that predispose to SCAD—but are not fully understood—may also predispose to risk of AA; however, there are not enough data to support this hypothesis.

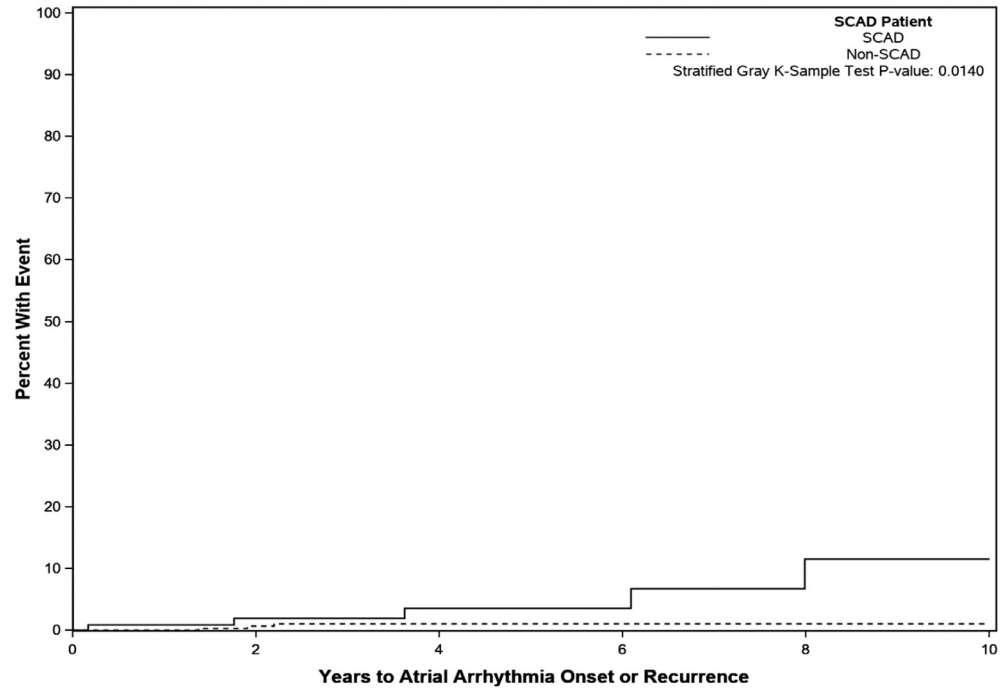
Both SCAD and FMD, an arteriopathy strongly associated with SCAD, are generally considered noninflammatory conditions.[1] However, recent research suggests a newfound recognition of inflammation in early FMD given the arterial fibrosis seen in advanced FMD.[18] This is supported by an association with inflammatory cytokines,[19] deposition of inflammatory proteins in the walls of affected vessels,[20] and features associated with vascular inflammation on optical coherence tomography.[21] Although these are preliminary findings, inflammation beyond that occurring with myocardial injury may be hypothesized as an underlying mechanism for predisposition to SCAD and AA.

This study indicates that AA is associated with SCAD compared with matched controls, although the absolute number of affected patients was relatively small. From a clinical perspective, treatment for AA in patients with SCAD should be consistent with the usual standard of care because there are no data to suggest otherwise. Although this has not been replicated, 1 large observational study found lower SCAD recurrence rates associated with ongoing β-blocker therapy.[22] As such, it is reasonable to prefer β-blockers as the rate control agent for the treatment of AA in the setting of SCAD. The potential use of β-blockers may also help with migraine headaches[23] and post-SCAD chest pain,[1] blood pressure control, and shear stress reduction in tortuous vessels.[24]

Table 3
REP and E-REP population characteristics

Variable	REP and E-REP SCAD n = 114	REP and E-REP CONTROLS n = 342	p-Value
Male	12 (11%)	36 (11%)	>0.99
Female	102 (89%)	306 (89%)	>0.99
Mean age in years (SD)	51.1 (11.5)	51.1 (11.4)	0.79
Caucasian	108 (95%)	316 (92%)	0.52
Body mass index (SD)	29.1 (6.9)	30.1 (7.0)	0.21
Prior hypertension	44 (39%)	95 (28%)	0.022
No tobacco history	53 (52%)	119 (43%)	0.018
Former smoker	37 (36%)	90 (33%)	0.018
Current smoker	12 (12%)	66 (24%)	0.018
Prior diabetes mellitus	5 (4%)	41 (12%)	0.021
Hyperlipidemia	60 (53%)	127 (37%)	0.002
OSA	12 (11%)	23 (7%)	0.19
Prior heart failure	1 (1%)	5 (1%)	0.64
Prior CVA	2 (2%)	7 (2%)	0.80
Prior MI up to 90 days post-index	6 (5%)	5 (1%)	.034
Prior FMD up to 90 days post-index	24 (21%)	1 (0%)	<.001
Prior atrial arrhythmia (AA)	5 (4%)	4 (1%)	0.043
Mean age at first AA	60.2 (19.3)	57.6 (12.3)	0.99

Hypertension, hyperlipidemia, and fibromuscular dysplasia were more prevalent in the spontaneous coronary artery dissection cases, whereas diabetes mellitus and a tobacco history were more prevalent in the controls.



The incidence of atrial arrhythmia increased more over the 10 years following spontaneous coronary artery dissection than that of the controls.

Figure 2. The incidence of atrial arrhythmia increased more over the 10 years following spontaneous coronary artery dissection than that of the controls.

Careful attention should also be given to the modifiable risk factors and downstream complications of AF that might have clinical implications in SCAD. These include obesity, HTN, DM, obstructive sleep apnea, and alcohol consumption.[25] The population-based SCAD cohort had a higher prevalence of HTN than did the controls, and history of HTN has been associated with SCAD recurrence.[22] Therefore, blood pressure management is crucial for patients with SCAD and HTN.

This study does have several strengths and limitations. The MCSR inevitably has selection bias because patients with more severe presentations and long-term complications of SCAD may seek out the registry and tertiary care. The population-based cohort overcomes such bias but consists of patients in the Upper Midwest and may not be generalizable to the entire population. In addition, the data repository interprets the absence of data of AA as negative data, meaning patients who received negative screening results may have shown positive results for AA, particularly if they are enrolled in the MCSR and receive their care elsewhere. Hence, the number of patients with concomitant SCAD and AA may be underestimated. Finally, the sixfold increase in the risk of development of AA in the population-based group with SCAD is statistically significant, but this was for a small group of patients with relatively few events.

In summary, AA was present and more common in patients with SCAD than in age- and gender-matched controls, regardless of co-morbidities. This finding emphasizes the importance of evaluating and treating AA in patients with SCAD with suggestive symptoms.

In conclusion, we report that patients who have a history of SCAD may be at 6 times higher risk of developing an AA than are age- and gender-matched healthy controls in the year after SCAD. Additional prospective studies are necessary to determine the disease connection and the optimal management of SCAD and AA.

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Disclosures

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.09.032

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