Prevalence of Coronary Vasospasm Using Coronary Reactivity Testing in Patients With Spontaneous Coronary Artery Dissection

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Spontaneous coronary artery dissection (SCAD) is an important cause of myocardial infarction and sudden cardiac death, particularly in young to middle-aged women. Coronary vasospasm is another condition believed to be associated with SCAD; however, this has only been shown in isolated case reports to date. We sought to examine the association of SCAD and coronary vasospasm by reporting the experience of coronary vasospasm testing in patients with a history of previous SCAD in a large, tertiary referral center. We conducted a single-center retrospective review of patients with history of SCAD confirmed by angiography who received provocative testing using ergonovine in the Cleveland Clinic cardiac catheterization lab from January 1990 to December 2016. Positive vasospasm was defined as: (1) total or subtotal occlusion of at least 1 major coronary artery induced by administration of ergonovine and (2) resolution of said occlusion with the administration of nitrates. Patients with history of strong trauma to the chest and iatrogenic dissection (e.g., catheter-induced) were excluded from the study. We identified 11 patients who satisfied all inclusion criteria. All participants were women and the mean age was 47 years: 73% received screening for fibromuscular dysplasia and of those, 38% were found to have the diagnosis. Only 1 of 11 patients had a positive vasospasm test in the setting of ergonovine administration in the catheterization lab. In conclusion, we found a low prevalence of coronary vasospasm in individuals with confirmed previous SCAD. **(Am J Cardiol 2019;123:1812−1815)**

Spontaneous coronary artery dissection (SCAD) is defined as a spontaneous separation of the coronary artery wall that is not iatrogenic or related to trauma. Although once believed to be a rare condition, it is now believed that 1.7% to 4% of patients presenting with acute coronary syndromes have SCAD, with a prevalence that increases to 8.7% in women under the age of 50.[1,2] Despite improved recognition and diagnosis, the etiology of SCAD remains unclear.

Coronary vasospasm is a condition believed to be associated with SCAD; however, this has only been shown in isolated case reports to date.[3−9] The ergonovine maleate provocative test for coronary arterial spasm, introduced by Dr. Heupler in 1972,[10] is highly sensitive and specific for identifying symptomatic vasospasm and has previously been shown to induce vasospasm at the site of a previous healed spontaneous dissection.[6] We sought to examine the association of SCAD and coronary vasospasm by reporting the experience of coronary vasospasm testing in patients with a history of SCAD in a tertiary referral center.

Methods

The medical records of all patients who received provocative testing using ergonovine in our catheterization lab from January 1, 1990 to December 31, 2016 were reviewed for history of SCAD. Patients with a history of at least 1 SCAD event confirmed by angiography who subsequently underwent coronary reactivity testing were included in the study, whereas those with history of trauma or iatrogenic dissection were excluded. Provocative testing was performed at a discretely different time period after the SCAD event, when clinically indicated.

This study was approved by the Cleveland Clinic Institutional Review Board. All of the coronary angiograms were reviewed by Dr. Frederick Heupler. The classification of the lesions was determined by consensus of 2 cardiologists with proficiency in diagnosing SCAD. Provocation of vasospasm was undertaken with ergonovine administered as either 0.2 or 0.3 mg by intravenous bolus over 30 seconds. Twelve-lead electrocardiograms (ECGs) were recorded every minute for 5 minutes. Repeat coronary angiograms were performed after 5 minutes or sooner if the patient had angina and/or ischemic changes on ECG. The diagnosis of vasospasm was defined as: (1) total or subtotal occlusion of at least 1 major coronary artery induced by administration of ergonovine and (2) resolution of said occlusion with administration of nitrates.[11]

Baseline demographic and clinical data were obtained by chart review from the electronic medical record. Presenting symptoms at the time of prior acute SCAD was reported. Patients were defined as having hypertension if it was reported in the medical chart or if they had a systolic blood pressure of ≥140 mm Hg and/or a diastolic blood pressure of ≥90 mm Hg on 2 or more separate occasions before ergonovine testing. Patients were reported as having

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history of diabetes mellitus (i.e., type 1, type 2, or gestational) if it was reported in the medical chart or they were taking antidiabetic medications. Patients were classified as having coronary atherosclerotic disease if they had known obstructive disease of ≥50% stenosis by coronary angiography that could not be attributed to a previous dissection.

Results

Of the 185 unique patients who received ergonovine testing in the cardiac catheterization laboratories at Cleveland Clinic from January 1990 to December 2016, 14 had reported findings of coronary dissection. Three were excluded for iatrogenic dissection. Eleven patients met the inclusion criteria. The characteristics of these patients are presented in Table 1. All patients were women and the majority were Caucasian (91%). The mean age was 47 years. The most common presenting symptom at the time of initial infarction due to SCAD was chest pain. Although hypertension was common among this cohort, other coronary artery disease risk factors including hyperlipidemia, tobacco smoking, and diabetes were not. In addition, none of the patients had obstructive atherosclerosis of ≥50% stenosis by coronary angiography. Eight of 11 patients in our study were screened for fibromuscular dysplasia (FMD) in other arterial beds. Of the 8 patients who received some form of screening, 3 were found to have FMD present in the extracranial arteries.

The mean time from most recent SCAD event confirmed by coronary angiogram to ergonovine testing was 20 months with a range from 1 to 56 months. In all cases, patients received repeat catheterization with coronary reactivity testing due to persistent angina despite medical management of previous dissection. The left anterior descending artery (LAD) was the most common vessel to be affected by SCAD. The vast majority of the cases were treated medically at the time of initial SCAD event and all dissections subsequently healed based on coronary angiography imaging performed at the time of the coronary reactivity testing. Only 2 patients received intervention in setting of acute SCAD. One patient had a 2.6 × 13 mm drug eluting stent (DES) placed in the LAD upon initial presentation. Her subsequent coronary angiogram showed a healed dissection with a widely patent stent in the LAD and a negative response to ergonovine.

One of 11 patients had a positive vasospasm response in the setting of ergonovine administration in the catheterization lab. She initially presented to the hospital with chest pain, diaphoresis, nausea, and emesis and was diagnosed with an acute myocardial infarction in the setting of significantly elevated cardiac enzymes. She was taken urgently for cardiac catheterization where she was found to have SCAD in the left main trunk extending to the mid LAD. Given the extent of her dissection, she underwent emergent coronary artery bypass graft (CABG) ×3 with a left internal mammary artery to the obtuse marginal, and saphenous vein graft sequential to the LAD and diagonal branches. Six months later, she received ergonovine testing in the setting of persistent angina occurring on a daily basis. She experienced chest pain during the test but no ECG changes and was found to have severe coronary vasospasm of the LAD provoked by ergonovine that was immediately relieved with intracoronary nitroglycerin. Images from this patient's left heart catheterization are shown in Figure 1.

Discussion

The association between coronary vasospasm and prior SCAD has been reported, but only in case report format.[3–9] SCAD is an uncommon phenomenon and case reports may overestimate the actual prevalence of coronary vasospasm in these individuals.[12] We did not find a high prevalence of coronary vasospasm after SCAD in our series. On the contrary, only 1 of the 11 patients had a positive vasospasm test when challenged with ergonovine in the cardiac catheterization laboratory. One of the strengths of our case series is that the sample population consists of patients referred to a large, tertiary care center.

There was an association with FMD in our study although the prevalence was not as high as in other studies. It has been previously reported that women with SCAD have a high prevalence of FMD, as high as 72% in 1 large series.[2] Our

Table 1
Characteristics of 11 SCAD patients with ergonovine testing

Age	HTN	DM	Smoker	FMD present	Vessel(s) affected by SCAD	Time from initial SCAD to vasospasm testing	PCI	CABG	Positive vasospasm response
38	No	No	Never	N/A*	LMT, LAD	6 months	No	Yes	Yes (LAD)
38	Yes	No	Never	No	LAD	10 months	No	No	No
38	Yes	No	Never	No	LAD, LCX, RCA	27 months	No	No	No
43	Yes	No	Former	No	LAD, RCA	1 month	No	No	No
46	No	No	Never	Yes	LAD	7 months	No	No	No
46	No	No	Never	N/A*	LAD	56 months	Yes	No	No
48	No	Yes	Never	No	LAD	51 months	No	No	No
50	Yes	No	Never	Yes	LMT, LCX	3 months	No	No	No
53	No	No	Former	N/A*	LCX	26 months	No	No	No
56	Yes	No	Never	Yes	LAD, LCX	24 months	No	No	No
57	Yes	No	Never	No	LAD, LCX	9 months	No	No	No

CABG = coronary artery bypass graft; DM = diabetes mellitus; HTN = hypertension; LAD = left anterior descending; LCX = left circumflex; LMT = left main trunk; PCI = percutaneous coronary intervention; RCA = right coronary artery.

* Indicates screening for FMD not performed.

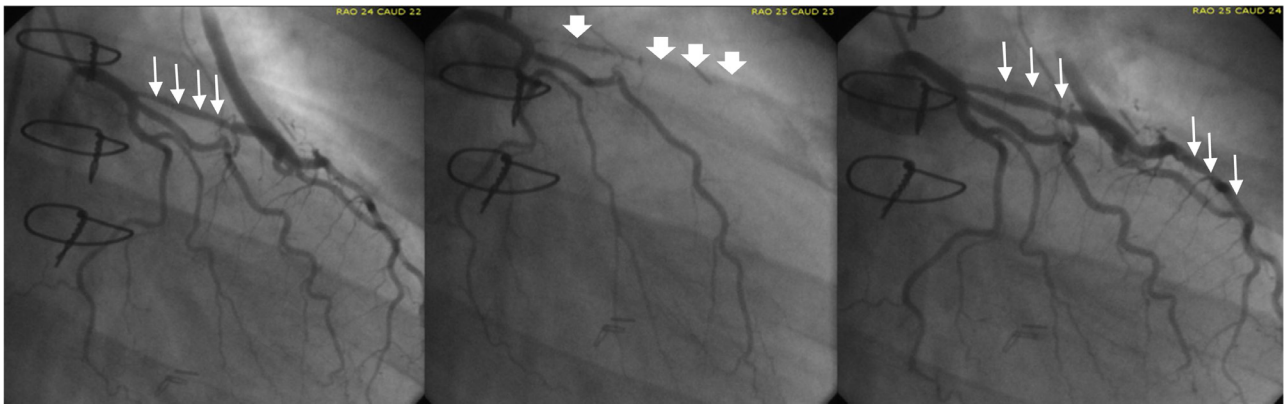

Figure 1. Coronary angiogram from Case 1 showing residual dissection from previous SCAD visualized in proximal LAD before methylergonovine administration (arrows). Subsequent total obstruction of the proximal LAD due to vasospasm provoked by administration of 0.2 mg of intravenous methylergonovine (arrowheads). Complete resolution of the vasospasm after administration of 200 mcg of intracoronary nitroglycerin (arrows).

sample had a much lower than expected prevalence of FMD, particularly in nonextracranial arterial beds, with no patients showing evidence of FMD in the renal, mesenteric, or extremity arteries. We suspect the prevalence is lower than expected because ultrasound was the primary modality used in this retrospective study dating back to nearly 3 decades ago. The current practice of head-to-pelvis computed tomography angiography (CTA) as recommended by the American Heart Association (AHA) consensus statement was not yet routine practice.[13] Although patients with SCAD frequently present with acute myocardial infarction, they do not tend to have the typical coronary risk factors which likely reflects a distinct etiology from other acute coronary syndromes. The etiology appears more closely related to a noninflammatory arteriopathy which also supports the predominance of FMD in these patients. Routine management for all SCAD patients should include screening for FMD in the extracranial, renal, mesenteric, and extremity vascular beds.

The study is limited by the small sample size and retrospective design. However, it still remains the largest study in the United States to examine the prevalence of vasospasm among patients with history of SCAD using coronary reactivity testing in the catheterization laboratory. These findings corroborate a recent study which found a low prevalence of vasospasm among patients after acetylcholine reactivity testing.[14] The results are subject to the limitations inherent in a retrospective design. Consequently, the causal association between vasospasm and SCAD cannot be determined. Lastly, because patients were included in the study retrospectively, there may be inherent selection bias in the sample. It is possible that the patients who underwent coronary reactivity testing were healthier (thus, presumed safe to undergo ergonovine testing) or sicker (because all participants had ongoing, severe angina after initial SCAD requiring at least one subsequent cardiac catheterization) than a representative sample of SCAD patients. However, the demographics are representative of known affected patients with SCAD and, indeed, are very similar to those reported in previous large case series.[15,16]

There are several important implications of this study for the clinical management of patients with SCAD. All patients had SCAD lesions healed by the time of presentation for the coronary reactivity testing. In 1 patient with medically managed SCAD and multiple diagnostic catheterizations, there was no resolution of initial event after 2 weeks, but complete resolution after 6 months. Thus, there is an amount of time, possibly greater than 2 weeks and up to a few months, required for healing of the lesion to occur. This is consistent with previous data which showed time dependency for SCAD lesions with residual dissections before 35 days from index event, but all cases healed after 35 days.[17] Given this observation, the "less is more" approach seems prudent as intervention may increase the risk of future complications. The current recommendation for management of acute SCAD according to the AHA consensus panel is conservative therapy in clinically stable patients, consideration of CABG in patients with complex anatomy (including left main disease), and percutaneous coronary intervention or urgent CABG in setting of ongoing ischemia and hemodynamic instability.[18] Interestingly, the patient who did test positive for vasospasm is only 1 of 2 patients in our series who received an intervention. However, the time between intervention and subsequent testing (6 months) makes it less likely that the intervention itself (in this case, CABG) accounted for the increased reactivity of the vessel. Still, little is known about the effect of intervention on coronary reactivity in this population. Although our cohort had a low prevalence of coronary vasospasm, future prospective studies are needed to more definitively establish whether or not an association between coronary vasospasm and SCAD exists.

Disclosures

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1. Saw J, Mancini J, Humphries KH. Contemporary review on spontaneous coronary artery dissection. *J Amer Coll Cardiol* 2016;68:297–312.
2. Vanzetto G, Berger-Coz E, Barone-Rochette G, Chavanon O, Bouvaist H, Hacini R, Blin D, Machecourt J. Prevalence, therapeutic management and medium-term prognosis of spontaneous coronary artery dissection: results from a database of 11,605 patients. *Eur J Cardiothorac Surg* 2009;35:250–254.
3. Mark DB, Kong Y, Whalen RE. Variant angina and spontaneous coronary artery dissection. *Am J Cardiol* 1985;56:485–486.
4. Nishikawa H, Nakanishi S, Nishiyama S, Nishimura S, Seki A, Yamaguchi H. Primary coronary artery dissection observed at coronary angiography. *Am J Cardiol* 1988;61:645–648.

5. Osaki J, Hirasawa K, Tateda K, Shibata J, Miyamoto N, Shishido T, Yamashita H, Onodera S. Spontaneous coronary artery dissection after a natural course for 10 years: a case report. *Jpn Circ J* 1992;56:955–959.
6. Slavich M, Ballarotto C, Margonato D, Peretto G, Giannini F, Spoladore R, Benincasa S, Cera M, Maranta F, Pappalardo F, Oppizzi M, Margonato A. Coronary reactivity testing in vasospastic angina leading to cardiac arrest and coronary dissection. *Int J Cardiol* 2016;210: 10–13.
7. Imamura M, Tsuchiya Y, Tahara H, Nii T, Nakashima Y, Arakawa K. Acute myocardial infarction in patient with primary coronary dissection and severe coronary vasospasm: a case report. *Angiology* 1995;46: 951–955.
8. Tsujita K, Miyazaki T, Kaikita K, Chitose T, Takaoka N, Soejima H, Tayama S, Hokimoto S, Sugiyama S, Ogawa H. Premenopausal woman with acute myocardial infarction caused by spontaneous coronary artery dissection and potential association with coronary vasospasm. Cardiovasc Interv Ther 2012;27:121–126.
9. Takatsu F, Takemoto K. Spontaneous coronary dissection as an expression of CAD: correlation with vasospasm. Clin Med Res 2015; 4:21–26.
10. Heupler F. Syndrome of symptomatic coronary arterial spasm with nearly normal coronary arteriograms. *Am J Cardiol* 1980;45:873–881.
11. Heupler F. Provocative testing for coronary arterial spasm: risk, method and rationale. *Am J Cardiol* 1980;46:335–337.
12. Buccheri D, Piraino D, Silva Orrego P, Cortese B. Is vasospasm overestimated in acute coronary syndromes presenting with non-obstructive coronary artery disease? The case for intravascular imaging. *Int J Cardiol* 2016;203:1125–1126.
13. Olin JW, Gornik HL, Bacharach JM, Biller J, Fine LJ, Gray BH, Gray WA, Gupta R, Hamburg NM, Katzen BT, Lookstein RA, Lumsden AB, Newburger JW, Rundek T, Sperati CJ, Stanley JC. Fibromusculr dysplasia: state of the science and critical unanswered questions: a scientific statement from the American Heart Association. *Circulation* 2014;129:1048–1078.
14. Waterbury TM, Tweet MS, Hayes SN, Prasad A, Lerman A, Gulati R. Coronary endothelial function and spontaneous coronary artery dissection. *Eur Heart J Acute Cardiov Care* 2018. https://doi.org/10.117/2048872618795255.
15. Saw J, Ricci D, Starovoytov A, Fox R, Buller CE. Spontaneous coronary artery dissection: prevalence of predisposing conditions including fibromuscular dysplasia in a tertiary center cohort. *JACC Cardiovasc Interv* 2013;6:44–52.
16. Tweet MS, Hayes SN, Pitta SR, Simari RD, Lerman A, Lennon RJ, Gersh BJ, Khambatta S, Best PJ, Rihal CS, Gulati R. Clinical features, management, and prognosis of spontaneous coronary artery dissection. *Circulation* 2012;126:579–588.
17. Prakash R, Starovoytov A, Heydari M, Mancini GB, Saw J. Catheter-induced iatrogenic coronary artery dissection in patients with spontaneous coronary artery dissection. *JACC Cardiovasc Interv* 2016;9: 1851–1853.
18. Hayes SN, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, Ganesh SK, Gulati R, Lindsay ME, Mieres JH, Naderi S, Shah S, Thaler DE, Tweet MS, Wood MJ. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. *Circulation* 2018;137:e523–e557. https://doi.org/10.1161/CIR.0000000000000564.