Spontaneous coronary artery dissection (SCAD) is a rare clinical entity of unknown cause that classically is thought to occur in young women without traditional coronary risk factors. An intimal rupture, leading to 2 separate coronary lumens, or an intramural hematoma without an intimal tear, constitutes the underlying pathological substrate. Pressure-driven expansion of the false lumen or bleeding-induced enlargement of the intramural hematoma induce axial propagation of the disease and true lumen compression eventually resulting in myocardial ischemia. Coronary angiography remains the most widely used diagnostic tool and the presence of a radiolucent intimal flap with contrast staining has been classically considered the hallmark of this disease. Systemic connective tissue disorders, inflammatory/immunologic diseases, the peripartum period and, more recently, fibromuscular dysplasia (FMD) have all been associated with SCAD. These conditions might induce arterial fragility and provide the underlying substrate of a vulnerable coronary vessel wall. Most patients with SCAD present with an acute myocardial infarction. However, after the acute event clinical stabilization frequently ensues and, eventually, most patients have a favorable long-term prognosis. Actually, recent reports suggest that a conservative initial management strategy seems indicated in most patients with SCAD. Nevertheless, patients with ongoing or recurrent ischemia may require urgent coronary revascularization. Revascularization, however, is particularly challenging and demanding in this setting because of the underlying disrupted coronary vessel wall. Finally, the use of intracoronary diagnostic techniques (intravascular ultrasound or optical coherence tomography [OCT]), able to provide an accurate tomographic visualization of the coronary vessel wall, has been recently proposed as instrumental to enhance diagnostic accuracy.

However, until recently, our understanding of this unique condition has been restricted to the limited and probably biased evidence stemming from a myriad of case reports and relatively small and retrospective series of patients lacking adequate long-term clinical follow-up. Therefore, 8 decades after its original pathological description and with <800 cases reported, currently the diagnosis and management of patients with SCAD remains not only elusive but also challenging. In this regard, the 2 large series of patients with SCAD published in this issue of the journal are of paramount clinical relevance. Altogether, data on >400 patients with SCAD are presented. These 2 studies provide novel insights that certainly consolidate and advance our knowledge on this elusive clinical entity.

In the first study, Saw et al, from the Vancouver General Hospital, prospectively evaluated the baseline characteristics, predisposing conditions, precipitating factors, and clinical outcome of 168 patients with nonatherosclerotic SCAD. Most patients were prospectively studied and followed up although ≤30% of cases were retrospectively identified. Mean age was 52 years and 92% of patients were women, mostly postmenopausal. Interestingly, a precipitating physical or emotional stress was detected in 56% of patients. A diffuse angiographic lumen narrowing (rather than the classical dissection flap) was found in the majority (67%) of cases. Most patients (80%) were treated conservatively with a favorable clinical outcome. However, one third of patients in whom revascularization was attempted had unsuccessful procedures or experienced procedural-related complications. Ultimately, only one third of all patients undergoing percutaneous coronary interventions had successful and durable long-term results. Importantly, patients were also routinely screened for extracoronary vascular findings because the original description of the association of SCAD with FMD was previously made by these investigators. Noteworthy, in this large series, the incidence of associated FMD was 72%. Furthermore, spontaneous coronary healing (single lumen and a residual narrowing <50%) was noticed in all patients who had a repeat angiogram >1 month from diagnosis. Finally, in the group of patients prospectively identified the cumulative event-rate at 2 years was only 10%, mainly derived from episodes of recurrent SCAD.

The results of this large series of patients with SCAD are of major clinical interest considering the rarity of the condition although many findings were confirmatory in nature. Nevertheless, the high prevalence of precipitating factors (exercise or stress related) represents a valuable novel finding that emerged from the use of a dedicated predefined questionnaire. Likewise, the confirmation of an association with FMD in most patients using a systematic vascular screening is also highly relevant. The only potential limitation of this study remains the possibility of overdiagnosis because most patients did not show a radiolucent flap, and intracoronary diagnostic techniques were not systematically used to confirm the presence of the disease in cases with diffuse coronary narrowing. However, all angiograms were centrally reviewed by these experienced investigators who took special care to rule out conventional
atherosclerosis as the culprit disease. Accordingly, the risk of significant overdiagnosis seems negligible.\textsuperscript{15}

The second study comes from the Mayo Clinic and currently represents the largest series of patients with SCAD reported to date. Eleid et al\textsuperscript{16} specifically sought to assess the prevalence of coronary tortuosity in this disease and its pathophysiological and clinical implications. In a case-control study, patients with SCAD ($n$=246; mean age, 45 years; 96\% women) were compared with 300 control patients (matched by age and sex), without overt coronary artery disease. The presence and extent of coronary tortuosity were exhaustively analyzed, and a new tortuosity score was devised. Tortuosity was significantly more prevalent among patients presenting with SCAD (78\% versus 17\% in controls; tortuosity score, 4.4 versus 2.4 in controls). Importantly, severe tortuosity (≥2 consecutive curvatures ≥180°) was associated with a higher risk of recurrent SCAD. Tortuosity frequently involved the circumflex coronary artery and nonculprit arteries. Interestingly, among patients with SCAD tortuosity was more frequently found in those with hypertension and was less common in those with peripartum status. Furthermore, although screening for noncoronary vasculopathy was not routinely performed, 70\% of screened patients eventually demonstrated associated extracoronary vasculopathy (mainly FMD) as an incidental finding. Of interest, some angiographic markers of tortuosity, including corkscrew appearance and multivessel symmetrical tortuosity, were associated with FMD. Recurrences occurred in 40 patients (16\%), frequently in segments with tortuosity, especially at bifurcations or hinge points.\textsuperscript{16}

Although coming from a retrospective analysis, we should acknowledge that the information provided by this large study is novel, methodologically sound, and clinically relevant. Reassuringly, despite the complexity of the analysis involved, intra- and interobserver reproducibility for degrees of tortuosity, the tortuosity score, and the symmetry and corkscrew sign were all excellent. However, authors noted that a subtle luminal irregularity resembling FMD was observed in 48\% of patients at follow-up at the segment with previous SCAD. Nevertheless, currently, the diagnosis of coronary FMD remains speculative and, therefore, it is difficult to understand how this could be recognized in a healed vessel segment. In addition, although in this study the presence of either a noniatrogenic dissection plane or the presence of an intramural hematoma confirmed by OCT was required for the diagnosis, eventually half of the cases actually presented with an intramural hematoma. It remains unclear whether the diagnosis in all cases without an angiographic intimal flap was confirmed by OCT or, as in the study of Saw et al,\textsuperscript{15} in some cases it was only supported by a characteristic angiographic pattern. Finally, the high prevalence of FMD found in this study is consistent with previous reports and confirms the importance of this intriguing association.\textsuperscript{9-13}

Coronary tortuosity has been classically considered to present more frequent in women and has been associated with hypertension and related to the myocardial mass.\textsuperscript{17} In the study of Eleid et al,\textsuperscript{16} age, female sex, and hypertension were associated with coronary tortuosity in patients with SCAD. From a physiopathological stand point, elastin plays a crucial role in the vessel wall and its deficiency results in significant vessel alterations including elongation and tortuosity.\textsuperscript{17} Interestingly, vessel tortuosity is a characteristic feature of FMD. The present study confirms the association of coronary tortuosity with noncoronary FMD but fails to find an association with systemic connective tissue disorders. Severe coronary tortuosity may cause turbulent coronary flow leading to increased shear stress on the vessel wall. Experimental models demonstrate that regions with low and oscillatory shear stress form at the inner wall downstream of major (>120°) bends. It has been suggested that tortuosity-induced flow alterations may lead to a reduction of distal coronary pressure leading to ischemia.\textsuperscript{18} Likewise, when compared with other coronary segments, the flow resistance during exercise increases by 92\% in tortuous segments.\textsuperscript{18}

**Final Remarks**

In both studies, only cases of pure isolated SCAD were included.\textsuperscript{15,16} Other previous reports, however, demonstrated that SCAD may also occur in patients with associated atherosclerotic coronary artery disease.\textsuperscript{7} In those patients, age of presentation is significantly older. In this regard, it is of interest that most patients in these 2 series were relatively old, including a high prevalence of postmenopausal women when compared with classical studies of isolated SCAD. Interestingly, age of presentation and the prevalence of female sex were identical in a recent large US registry on FMD.\textsuperscript{19} The association between SCAD and FMD in other large arteries was previously described by the Canadian group.\textsuperscript{5,10-13} The current 2 new studies confirm this association and provide more robust epidemiological evidence.\textsuperscript{15,16} FMD may present as vessel tortuosity and tends to be discovered incidentally in asymptomatic individuals who may have a family history.\textsuperscript{19} Considering the rarity of both conditions, it is clear that we are facing a new syndrome that until now has not been properly characterized. Therefore, additional research efforts should be implemented to ascertain the pathophysiological implications of this intriguing, recently described, association and, eventually, to demonstrate causality. It is clear that we are in the down of a new era, where genetic studies focused on genes encoding proteins relevant to the pathophysiology of the vessel wall will soon clarify the existence of underlying ultrastructural changes and, ultimately, the molecular basis of this elusive clinical entity. It seems clear that this syndrome presents with different phenotypic manifestations that may affect several vascular territories. However, the potential implications of the different phenotypic manifestations remain unclear. At the coronary level, for instance, we still do not know whether patients presenting with intramural hematoma have a different prognosis from those displaying a classical intimal flap. Moreover, until now, the diagnosis of FMD in the coronary arteries was only possible a posteriori, once acute coronary complications (classical dissection or intramural hematoma) had occurred. The diagnosis of noncomplicated coronary FMD remains to be defined because currently the anatomic substrate accounting for a vulnerable coronary vessel wall remains unsettled. This is surprising considering the widespread use of sophisticated imaging techniques, and in particular OCT with its nearly histological axial resolution, in patients presenting with acute coronary syndromes. Moreover, routine late angiography has not been systematically used in most studies yet this could be of clinical value in patients with SCAD. Indeed, this may be
required to ensure complete vessel healing because noninvasive techniques (namely CT angiography) currently have a limited role in selected patients with involvement of proximal coronary segments.20

We strongly believe that the use of OCT or intravascular ultrasound should be systematically considered in cases where the characteristic angiographic intimal flap is not detected and also in cases requiring coronary interventions to guide these procedures14 (Figure). In these patients, we previously demonstrated that OCT is able to disclose the extent and severity of the disease readily. In patients with classical SCAD, the presence of the 2 lumens, the location extent and thickness of the intimomedial membrane and the intimal tear can be readily visualized.14 The occurrence of an intramural hematoma should be suspected when a diffuse stenosis, especially if depicting a broken line appearance, is detected in a winding smooth vessel. In these patients, the presence of intramural hematoma and the characteristics of the false lumen can be nicely disclosed by OCT. Importantly, in patients with an acute coronary syndrome and completely normal vessels on angiography, this technique may also unravel the presence of an intramural hematoma.14 Conversely, the disease can be discarded in other patients despite a strong clinical suspicion and a suggestive angiography. Finally, at follow-up, only the near-histological resolution provided by OCT may confirm the presence of a complete healing with a restitutio ad integrum of the coronary vessel wall.14 It is clear, therefore, that a major paradigm shift has occurred in the diagnosis of this entity.14 The only limitation for OCT remains imaging in small vessels with diffuse disease because the imaging catheter tends to be occlusive preventing adequate blood clearance. Likewise, experience and caution are required when imaging patients with previously disrupted vessels, especially considering that, in most cases, a coronary intervention is not required. Intravascular imaging (particularly intravascular ultrasound) might also provide important diagnostic clues on large extracardiac arteries although evidence in this regard is more limited. In most patients with FMD, the string of beds sign, characteristic of the multifocal pattern of medial fibroplasia, is readily recognized. In others patients, more subtle abnormalities, such as those not only generated by the focal appearance of intimal fibroplasia but also as a result of conventional atherosclerotic disease, may pose major diagnostic dilemmas.19 The clinical value of a comprehensive tomographic assessment of these vessels warrants prospective assessment.20

Last but not least, the results of the study from Saw et al15 and another previous study from the Mayo Clinic8 suggest that coronary revascularization is challenging in these patients and may be associated with acute failure or complications. Coronary stenting may cause axial propagation of the hematoma and side-branch loss. Moreover, only one third of percutaneous procedures maintain adequate long-term vessel patency, and the fate of most surgical grafts is also poor in this condition.9,15 The latter may be a result of clinically unrecognized initial technical failure or, as provocative suggested by some authors, because of competitive flow resulting from native coronary vessel healing.9,15 This information together with the accumulating evidence demonstrating that complete spontaneous vessel healing is part of the natural history of the disease reinforces the value of our previous proposal of selecting a conservative initial approach in most patients presenting with SCAD.7,14 Reserving revascularization for patients with ongoing or recurrent ischemia despite optimal medical therapy seems reasonable based on currently available evidence. However, the high recurrence rate found in these 2 large series15,16 is of concern and suggests that these patients require close clinical surveillance. The use of β-blockers (able to reduce systolic pressure, heart rate, and shear stress) has been suggested in patients with SCAD.2–5 β-blockers blunt the response to brisk catecholamine surges and might emerge as an attractive means to prevent recurrences, especially in patients with severe coronary tortuosity and perhaps also in those with FMD. However, more data are eagerly awaited before we can recommend this time-honored drug as an effective, evidence-based, prophylactic therapy.

Figure. Diffuse angiographic narrowing of the left anterior descending coronary artery (middle) in a patient presenting with an acute coronary syndrome. A healthy mildly tortuous marginal branch is also visualized. 1–5, Optical coherence tomography images obtained at different sites of the left anterior coronary artery disclosing the presence of a long intramural hematoma. *Wire artifact.
Disclosures

None.

References


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