Spontaneous Coronary Artery Dissection: New Insights from the Tip of the Iceberg?

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Spontaneous coronary artery dissection (SCAD) is a rare clinical entity of unknown etiology that typically affects young women without coronary risk factors\textsuperscript{1-5}. Initial reports were scarce and based on autopsy findings after episodes of sudden cardiac death suggesting that the condition had a dismal prognosis\textsuperscript{1,2}. An intimal tear was seldom found in autopsy series and, therefore, primary disruption with bleeding of \textit{vasa vasorum} and intramedial hemorrhage was proposed as the underlying mechanism\textsuperscript{1,2}. Alternatively, an intimal tear may lead to separation of coronary wall layers and, eventually, to a double lumen. Pressure-driven expansion of the false lumen induces axial propagation of the disease and true lumen compression resulting in myocardial ischemia\textsuperscript{2-4}. In some patients, weakening of the arterial wall (hormonal changes, cystic medial necrosis, proteolytic enzymes from periadventitial eosinophils)\textsuperscript{2}, may provide an underlying “\textit{vulnerable coronary wall}”.

Coronary angiography is widely used in the diagnosis of SCAD, being the classical “\textit{intimal flap}” the hallmark of this disease. Most patients present with an acute coronary syndrome but have a favorable prognosis\textsuperscript{2-5}. However, available evidence on this condition is limited to multiple case-reports and small retrospective case-series with short follow-up\textsuperscript{1-5}. Therefore, 8 decades after its first pathologic description\textsuperscript{1} the diagnosis and management of SCAD remains elusive.

**Present Study**

In this issue of the journal, Tweet\textsuperscript{6} present the characteristics, management and outcome of a uniquely large cohort of patients with SCAD seen at the Mayo Clinic during the last 3 decades. Eighty-seven consecutive patients with SCAD were included. In all cases a “dissection plane” was visible on angiography but associated atherosclerosis was absent. Mean age was 43 years and 82\% were female. Predisposing conditions included extreme exertion (44\% of males) and
postpartum status (18% of females). Half of the patients presented with ST-segment elevation myocardial infarction and 14% with life-threatening ventricular arrhythmias. Two-thirds of patients underwent revascularization during hospitalization but acute results of coronary interventions and long-term results of surgery were relatively poor. The estimated 10-year mortality was 7.7% but the rate of major adverse events was 47%. Interestingly, mortality was lower but the event-rate was similar to that seen in a large -carefully matched- patient population with atherosclerotic coronary artery disease and acute coronary syndromes. Moreover, at 4 years SCAD recurred in 15 patients (all female). Last but not least, fibromuscular dysplasia (FMD) was incidentally found in 50% of patients with available femoral angiograms and the authors dare to suggest that FMD may represent a potentially causative factor.

Due to the absence of large series of patients with SCAD, the current report represents a milestone in our understanding of this entity and provides novel insights for clinical decision making. This series represents -by far- the largest study ever performed on this exceedingly rare disease. In addition, although retrospective in design, the methodological requirements were superior to those used in previous studies. Patients with concomitant atherosclerosis were excluded. Most previous registries, however, lumped together patients with “isolated” SCAD and those with SCAD associated with atherosclerotic lesions. Patients with associated atherosclerosis tend to be older, more frequently male, and have a higher prevalence of coronary risk factors but their prognosis appears similar to that seen in isolated SCAD. However, it is likely that most of those patients actually present atherosclerotic plaque disruption as the underlying pathologic substrate and, therefore, a different condition.

Sixty-three patients (72%) received initial care at a referring institution. In this regard it would have been of interest to know whether the initial management also included
revascularization procedures and also the time interval from initial presentation to evaluation at
the Mayo Clinic. It remains possible that preferential referral of complex patients and those
already having experienced complications would have caused a selection bias and a high-risk
patient cohort. This might explain the relatively poor acute and long-term clinical outcome of the
present series as compared with some prior studies that, alternatively, may have suffered from
publication bias2-5.

In the current study medical management is described in detail but its potential influence
on clinical outcome remained unsettled. Before diagnosis, most patients with SCAD are
managed as conventional acute coronary syndromes with aggressive antithrombotic and
antiplatelet therapies and some (15% in the present series) receive fibrinolytics (classically
contraindicated in this scenario)2-5. Most investigators suggest the maintenance of antiplatelet
agents to avoid progressive thrombus formation and vessel occlusion2-4. However, these drugs
may act as a double-edged sword preventing vessel healing and facilitating the extension of the
disease. Alternatively, on theoretical grounds, the use of beta-blockers would be perceived as the
mainstay of therapy to induce a favorable hemodynamic status and reduce local shear-stress with
potential benefit in the acute setting but also to prevent recurrences2-4. However, the real clinical
value of this therapy remains unsettled.

Results of revascularization were suboptimal6. However, revascularization strategies were
performed along 3 decades. Due to continuous technological advances and the accumulated
clinical experience it remains likely that results improved overtime. Of interest, the definition of
intervention success only required any improvement in blood flow (for occluded arteries) or the
“maintenance” of a TIMI 2/3 flow. These broad criteria appear justified considering that some
coronary segments with significant stenosis were intentionally left untreated. Nevertheless,
technical success was only obtained in 28 of 43 procedures (65%), and this included interventions complicated by hematoma propagation and requiring the unplanned implantation of multiple stents. The main reason for failure was the inability to negotiate the guidewire into the distal true lumen. Surprisingly, target vessel revascularization was not included in the combined clinical endpoint. However, this information together with data on late restenosis would have been of major clinical interest.

Revascularization was also the preferred therapy in most previous case-series. This strategy has been selected not only in unstable patients but also in stabilized patients when anatomy seemed favorable. Restricting treatment to the most severe or proximal coronary segment is usually indicated. Surprisingly, in many studies there is a striking dissociation between the systematic words of caution regarding these interventions and the good results reported after stenting. Axial propagation of the hematoma and side-branch loss, remain major concerns. Likewise, in the present series early results of coronary surgery appeared favorable but 11 of 15 bypass grafts undergoing late angiographic assessment were occluded. Studies specifically addressing results of coronary surgery in SCAD patients are lacking but most reports emphasize potential hazards at the anastomosis site. Therefore, the current study provides robust evidence demonstrating that results of revascularization in this challenging setting are poorer than previously thought and suggest that this strategy should be reserved for high-risk patients.

In this series and in most previous reports a very good prognosis was reported in patients managed conservatively. It remains possible, however, that only highly selected patients received medical therapy alone and this might explain their favorable outcome. We prospectively followed-up 45 consecutive patients with SCAD that were initially managed with a “conservative therapeutic strategy” where revascularization (35% during admission) was
restricted to patients with ongoing/recurrent ischemia\textsuperscript{5}. At follow-up, only 1 patient died from congestive heart failure and 2 required revascularization, but no patient had recurrent SCAD, suffered a myocardial infarction, or died suddenly. After discharge, the 3-year event-free survival was 92%. Interestingly, spontaneous disappearance of the SCAD image was demonstrated at follow-up in half of our patients\textsuperscript{5}, in close agreement with data from the current study\textsuperscript{6} and previous reports\textsuperscript{4}. Notably, this evolution mimics the fate of most iatrogenic residual dissections after coronary interventions\textsuperscript{7}. Although the natural history of SCAD remains ill-defined, the possibility of spontaneous healing provides yet another strong argument in favour of a conservative strategy in these patients\textsuperscript{5}.

\textbf{Fibromuscular Dysplasia}

The suggestion by Tweet et al\textsuperscript{6} of underlying FMD as a potentially “causative” factor was provocative indeed although only based on findings obtained in 10 patients. Interestingly, although FMD has been previously associated with SCAD\textsuperscript{8} its potential relevance remained buried within the never-ending list of predisposing conditions\textsuperscript{2-4,8}. FMD is a nonatherosclerotic, noninflammatory, vascular disease of unknown etiology that frequently affects young females and may lead to arterial stenosis, dissection, or aneurysm formation\textsuperscript{8-10}. Medial fibroplasia is characterized by the classic “string of beads” sign, most often affecting renal and carotid arteries. However, FMD of the coronary arteries has only been rarely described pathologically in small vessels or causing myocardial infarction and sudden death\textsuperscript{8}. Pate et al\textsuperscript{9} described 7 young females with acute coronary syndromes and a diffuse disease at mid coronary segments with a characteristic abrupt transition from a normal proximal segment. Incidental renal or cerebrovascular FMD was detected in all of them leading to the suggestion that this angiographic pattern was the result of “coronary” FMD\textsuperscript{9}. Recently, the same group used optical coherence...
tomography (OCT) to demonstrate that in patients with associated FMD this finding was caused
by unrecognized SCAD\textsuperscript{10}. Further studies, involving a systematic and comprehensive vascular
screening are eagerly awaited to fully ascertain the true prevalence and implications of this likely
overlooked association, potentially responsible for a vulnerable coronary wall.

**Insights From Tomographic Imaging Techniques**

Tweet at al\textsuperscript{6} indicated that their annual incidence results (0.26/100,000 persons) were likely
underestimated. They suggested that presentation as sudden death, under-referral in otherwise
healthy women, and under-recognition by angiography, remain potential factors. In our
experience, the latter represents a major cause for misdiagnosis\textsuperscript{5}. As occurs in aortic dissection,
SCAD ultimately remains a disease of the vessel wall\textsuperscript{11,12} which is poorly characterized by
angiography. Actually, the narrowing caused by an intramural hematoma impinging into the
lumen is frequently misinterpreted as atherosclerotic disease\textsuperscript{11,12}.

Intracoronary diagnostic techniques provide tomographic, high-resolution images of the
vessel wall\textsuperscript{11,12}. Intravascular ultrasound (IVUS) (resolution 150\textmu m) and OCT (resolution 15\textmu m)
clearly recognize the normal vessel wall and atherosclerotic involvement. The intimomedial flap,
its circumferential and longitudinal spatial distribution, the true and false lumens, and the take-off of related side-branches, are readily depicted. Moreover, the presence of an intramural
hematoma is nicely visualized. IVUS allows a complete assessment of the external elastic lamina
and depicts the full extent of the disease even in large vessels\textsuperscript{11}. Due to its shallow penetration
OCT frequently fails to provide a complete picture of the vessel but, due to its superb resolution,
is ideally suited to identify the intimal tear and to depict subtle morphologic features close to the
lumen\textsuperscript{12}. Interestingly, during interventions sealing the “entry door” appears indicated to ensure
favorable results. OCT also provides unsurpassed visualization of the “intimomedial” membrane
(intima and most inner layers of the media) facilitating accurate measurements\textsuperscript{12}(Figure 1). Although indirect angiographic data suggested that SCAD may resolve during follow-up only OCT provides reassuring information of a “restitution ad integrum” of the coronary wall\textsuperscript{12}. Current OCT systems allow a faster interrogation of the target segment but remain limited by the requirement of a blood-free lumen (problematic in vessels with severe stenoses) and by the shadowing caused by red thrombus. Both techniques recognize the position of the guide-wire within the true lumen which remains critical when coronary interventions are planned. Although intracoronary techniques provide striking images they should be used with great care in these patients to avoid further vessel injury in the already disrupted coronary wall\textsuperscript{12}.

Invasive imaging appears instrumental to unravel, for the first time, the “\textit{dark side of the moon}” in this condition\textsuperscript{11,12}. In all cases additional comprehensive information of the underlying pathology is obtained (Figure 1). Furthermore, intracoronary imaging may disclose the presence of an intramural hematoma at sites with lumen narrowing and also at angiographically normal segments (Figure 2). In our experience, intramural hematomas should be suspected in patients with otherwise completely smooth vessels (typically with curly or even corkscrew appearance) at segments showing a diffuse lumen narrowing that causes straitening of the vessel or a characteristic “\textit{broken-line}” appearance. Thinking “outside the box” remains critical during the interpretation of subtle angiographic features, especially in young patients with otherwise normal vessels.

Finally, the value of multislice-CT in this condition has been demonstrated. This non-invasive technique appears ideally suited for follow-up purposes to gain a clearer picture of this dynamic entity\textsuperscript{2}. 
Final Remarks

This uniquely large, high-quality, registry on SCAD provides novel important insights that advance our knowledge and help to improve current diagnostic and therapeutic algorithms. In most patients prognosis appears favorable after initial stabilization. Revascularization remains challenging and, therefore, should be restricted to patients with ongoing/recurrent ischemia and suitable anatomy. Some patients remain at risk for late events, including recurrent SCAD, supporting the need of a close clinical surveillance. The diagnosis also remains very challenging, especially in patients presenting with an intramural hematoma were the value of intracoronary imaging cannot be overemphasized. Whether or not the prognosis of this cohort differs from that of classical SCAD remains unknown. Further prospective multicenter studies are required to fully ascertain the wide morphological and prognostic spectrum of this unique condition.

However, to obtain the adequate perspective we should always keep in mind the possibility of non-coronary vascular involvement and also the limited insights gained from the tip of an iceberg.

Conflict of Interest Disclosures: None.

References:


**Figure Legends:**

**Figure 1.** OCT findings in a patient with "classical" SCAD. A) longitudinal view unraveling the entry tear (arrow). The intimomedial membrane is readily recognized along the vessel length separating the true (TL) from the false lumen (FL). B) Cross-sectional image depicting the
compressed TL and the larger FL. * wire artefact. Modified from reference 7 (with permission from the Journal of the American College of Cardiology).

**Figure 2.** Coronary intramural hematoma. **A)** Diffuse lesion in the mid left anterior coronary artery (arrows). Notice the sudden reduction in lumen caliber and a "broken line" appearance. **B)** OCT depicting a relatively homogeneous intramural hematoma without an intimal rupture. The external elastic lamina is poorly detected from 12 to 4 o’clock. **C)** IVUS disclosing a characteristic three-layered appearance of the intimomedial membrane and a small, elliptic, true lumen. The large false lumen has heterogenous content. (*) = wire artefact.
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