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Acute coronary syndrome with spontaneous coronary artery dissection: which therapeutic option for a different pathophysiology?

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Spontaneous coronary artery dissection (SCAD) has been recognized as an emergent cause of acute coronary syndrome (ACS), myocardial infarction, and sudden death. Patients mostly affected by SCAD are individuals without or with few cardiovascular risk factors, particularly young women, thus suggesting a clearly different pathophysiology than the more common atherosclerosis. Present research efforts outlined an improved characterization of the prevalence, natural history, and clinical outcome of SCAD. Intracoronary imaging has been an important asset in this condition, providing an improved diagnostic and therapeutic understanding. Current evidences suggest not only that this condition is more common than previously thought but also that the clinical management could be distinctly different from ACS secondary to atherosclerosis. Both medical and interventional treatment should consider the different cause of ACS, as well as the clinical stability of the patient, taking into account that the risk of recurrence is particularly high, predominantly during the first few days after the acute event. Stemming from new scientific evidences in terms of pathophysiology, clinical approach, therapy strategies, and follow-up of SCAD, it is important to identify spontaneous coronary dissection in the differential diagnosis of ACS.

Introduction

Spontaneous dissection of an epicardial coronary artery (SCAD), i.e.—not linked to atherosclerotic, iatrogenic, or traumatic cause—is a clinical condition that leads to the formation of an intramural haematoma (IMH), or false lumen, which compresses the true lumen causing narrowing of the affected artery with potential clinical sequelae (e.g. acute or chronic coronary syndromes).[1,2] According to histopathological and intracoronary imaging studies, dissection usually occurs at the level of the external third of the middle tunic, with the resulting formation of IMH due to a lesion of continuity with the true lumen or, more likely, as confirmed by optical coherence tomography (OCT) studies, due to Haemorrhage of the vasa vasorum.[1,2]

The pathogenesis of SCAD is multifactorial, attributable to genetic causes (e.g. Marfan or Ehlers–Danlos syndromes), hormonal imbalances, underlying arteriopathies or other precipitating factors that can act as triggers for the onset of dissection (e.g. systemic inflammation, intense physical exercise, etc.).[1-3] Specifically, SCAD is associated primarily with two conditions such as peripartum and fibromuscular dysplasia. Coronary dissection is in fact the most common cause of acute myocardial infarction (AMI) associated with pregnancy (43%) and occurs more often in the last trimester or in the immediate peripartum.[4,5] Hormonal imbalances related to gestation would seem to represent its cause main, leading to changes in the vascular connective tissue. Oestrogen and progesterone (both endogenous and exogenous, as in the case of leuprorelin[6]) could in fact favour structural alterations inside the vessel wall, causing their progressive weakening. It should be emphasized that peripartum SCADs are associated with more proximal

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dissections, larger AMIs, worse left ventricle dysfunction and poorer prognosis than non-SCAD AMIs.[1,2]

Fibromuscular dysplasia is instead a non-atherosclerotic non-inflammatory vascular disease, which can affect any artery in the body (most often the renal artery), causing stenosis, aneurysms, or dissections. The association between the two conditions is now well known, so much so that many authors consider SCAD as the cardiac manifestation of fibromuscular dysplasia.[1,2]

SCAD, which represents between 1% and 4% of the causes of acute coronary syndrome (ACS), is more common in women under 60 years of age, who often have few or none cardiovascular risk factors.[7] The arteries are most affected in middle and distal tracts, while the most involved vessel is usually the left anterior descending artery, with consequent segmental anomalies of the left ventricular wall motion on the echocardiogram. In most cases, coronary dissections occur in the form of ACS with increased levels of markers of myocardial necrosis, electrocardiographic changes (both ST-segment elevation and ST-segment depression), and typical chest pain.[1,2,4] (*Table 1*).

Diagnosis

In the case of SCAD, an accurate diagnosis is fundamental to allow a correct management of the patient, as the treatment can vary if compared to the typical AMI from atherosclerotic cause.[1,4] Coronary angiography remains the first diagnostic examination, even if, being a two-dimensional method, it does not provide a clear view of the vessel wall. Traditionally, the pathognomonic angiographic aspect of SCAD provides for the presence of multiple lumens with extra-luminal impregnation of contrast medium, evidence now downgraded by recent studies.[8] In fact, the use of intravascular imaging has allowed to obtain a better understanding of the angiographic variants of the SCAD.

Saw[9] have proposed a classification of SCAD that is widely accepted and used nowadays. SCAD type 1 (*Figure 1*) refers to the classic aspect described above (e.g. multiple radiolucent lumens or impregnation with contrast within the vessel wall). Type 2 SCAD indicates the presence of diffuse stenosis which may have different severity and length (usually >20 mm): variant 2A concerns a diffuse arterial narrowing preceded and succeeded by healthy sections; the variant 2B (*Figure 2*) extends to the periphery of the vessel;[8] the SCAD type 3 is a tubular or focal stenosis, usually <20 mm, which mimics an atherosclerotic lesion; in this case, intra-coronary imaging is crucial to visualize the IMH and to make a correct differential diagnosis,[1,8,9] as suggested by recent consensus documents on the

Table 1 Presentation symptoms in the context of SCADs with acute clinical presentation

Presenting symptoms in acute SCAD	Frequency (%)
Chest pain	95.9
Arm irradiation	51.5
Nausea and vomiting	23.7
Neck irradiation	22.2
Sweating	21.1
Dyspnoea	19.6
Back pain	13.9
Dizziness	8.8
VT or VF	7.2
Astenia	5.2
Headache	1.5
Syncope	0.5

Data from ref.[1]
VF, ventricular fibrillation; VT, ventricular tachycardia.

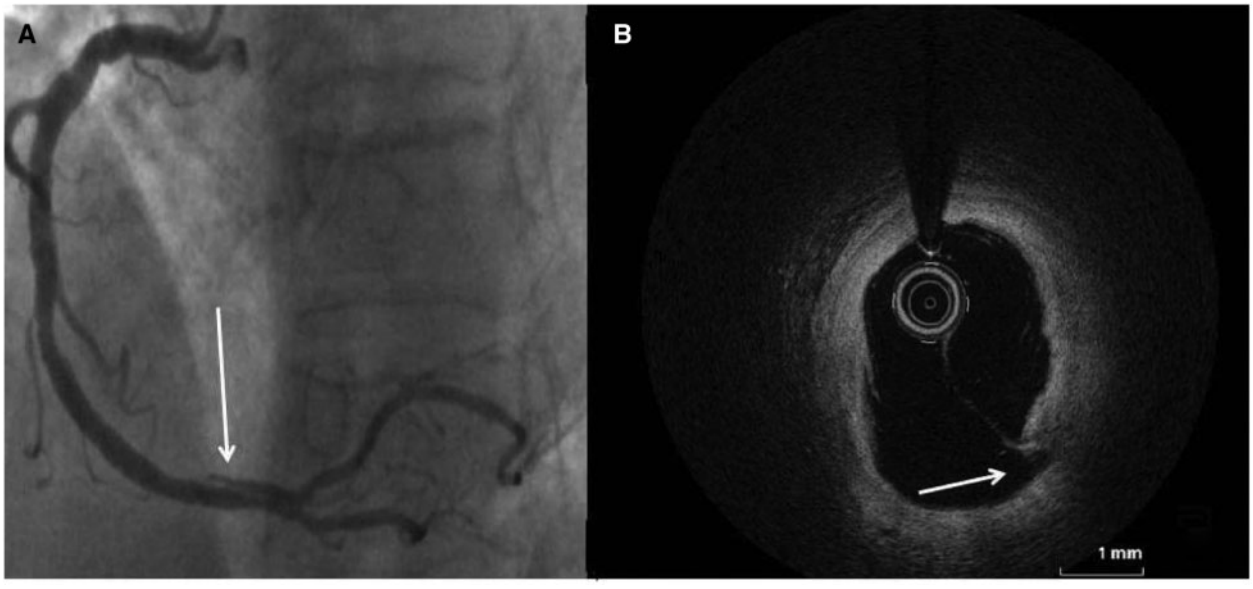

Figure 1 (*A*) Right coronary angiography in patient with acute coronary syndrome (inferior NSTEMI), with evidence of spontaneous coronary dissection type 1 in the distal tract before the crux, with the characteristic double contour aspect. (*B*) OCT of the same lesion that highlights the intimal flap in the proximal section of the dissection.

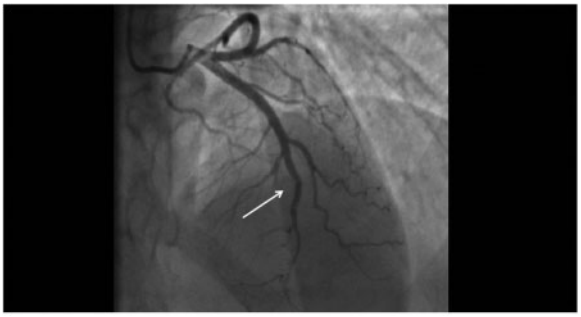

Figure 2 Spontaneous coronary dissection in a 34-year-old patient who has recently given birth in the last trimester of pregnancy. The examination was performed in an urgent regime in a symptomatic but haemodynamically stable patient with anterior ST-segment elevation. The dissection extends from the middle segment to the distal tract of the left anterior descending coronary artery (type 2B).

subject.[1,10] In 2017, Al-Hussaini and Adlam[11] have proposed a further variant (SCAD type 4), i.e. a distal coronary occlusion (non-embolic in nature) with subsequent evidence of spontaneous healing, as expected from the natural history of SCAD.

During the last decade, intra-coronary imaging represented a decisive turning point for diagnosing SCAD, especially in doubtful cases (e.g. SCAD type 3).[11] Both intravascular ultrasound (IVUS) and OCT can be used to visualize the vessel wall, to identify the intimal rupture, the false lumen or the IMH.[1–3] Although both methods are useful, the OCT is preferable to the IVUS because of the higher spatial resolution (10–20 μm vs. 150 μm), and the greater sensitivity in identifying SCAD-associated lesions.

Theoretically, cardiac computed tomography could also be useful in the differential diagnosis of SCAD in patients at moderate-low risk, since it is a non-invasive technique that allows both the visualization of the wall and the vessel lumen. However, this examination is characterized by a lower spatial and temporal resolution than coronary angiography, which determines a lower sensitivity and an increased risk of false negatives.[2] For this reason, current consensus documents do not suggest the use of cardiac computed tomography as first-line examination in the context of SCAD with acute presentation.[1,10] Computed tomography may instead be useful during the follow-up of these patients, especially in SCAD involving large-caliber coronary arteries affected in their proximal segments.

Therapy and management

While the usefulness of revascularization of atherosclerotic ACS through coronary angioplasty (percutaneous coronary intervention, PCI) is well established, there are still no randomized studies that support its effectiveness in the context of SCAD. In contrast, observational studies have shown an increased risk of coronary complications during PCI in patients with SCAD, especially in haemodynamically stable presentations.[2,4,12]

Recent studies suggest that in patients with no signs of ischaemia and haemodynamically stable, a conservative approach is associated with better outcomes.[1,2] In the Mayo Clinic cohort, 73% of patients with SCAD had undergone complete coronary healing during a median follow-up of 876 days.[4] Similarly, in a cohort of 79 subjects with SCAD form Vancouver, all of the patients underwent spontaneous healing during a median follow-up of 161 days.[12] It should be noted that the early complications of SCAD are usually observed within the first 5–7 days after the index event and are often related to the extension of the dissection. For this reason, compared to common ACSs, a longer period of hospital observation is required, to be able to promptly treat patients with recurrences of SCAD.

With the regards of drug medications, the use of antithrombotic agents is still a matter of controversy since SCAD is considered as a result of the formation of an IMH. The risk of antithrombotic therapy is related to possible further bleeding within the vessel wall that may lead to an increased extension of dissection and higher risk of coronary artery rupture and cardiac tamponade, as already demonstrated with the use of thrombolytics, drugs now contraindicated in the context of SCAD.[1,2,10] Few data about anticoagulants agents, whose use must be well thought out, considering the potential risks of dissection progression. Also antiplatelet therapy appears controversial: according to the guidelines of the 2014 American College of Cardiology and American Heart Association, patients undergoing PCI in the event of SCAD should receive dual antiplatelet therapy (DAPT).[2] However, there are no randomized comparison studies between DAPT and aspirin monotherapy, neither in patients with SCAD treated with PCI nor in those treated conservatively. Some experts recommend the use of aspirin alone for at least 1 year after the acute event, even if the decision regarding the use of any antithrombotic strategy must always consider individual risk.[1,10]

Beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers can be used in SCAD context (with particular attention to ACE inhibitors in women of childbearing age, since they are teratogenic), if their use is necessary to act on arrhythmias, ventricular dysfunctions, and arterial hypertension.[1,2,10] The use of statins is not generally recommended by current consensus documents but remains controversial. A harmful effect of statins was observed in a retrospective study of 87 cases, but this evidence has not been confirmed by a larger cohort of 327 patients.[1,2] To clarify this topic a clinical trial is underway to investigate the safety of statins and ACE inhibitors in patients with SCAD. This study is called SAFER-SCAD and its results are expected around June 2021.[2] The treatment of SCAD with coronary angioplasty is often associated with suboptimal results.[1,10] In fact, Affected arteries are more damaged and fragile in their architecture with greater risk of iatrogenic damage. Furthermore, reabsorption of the IMH can lead to malapposition of the stent struts, favouring a greater predisposition to intra-stent thrombosis.[13] A procedural failure occurred in 53% of 189 patients of the Mayo Clinic cohort and in 36% of the 168 patients from the Vancouver cohort.[4,12] The radial approach can be linked to a higher catheter-induced coronary dissection rate than the femoral approach. Iatrogenic dissections in SCAD context often involve other coronaries than those affected by the acute episode, indicating an extreme fragility of the vessel walls, which are very susceptible to dissection. With radial approach, the greatest

risk may be related to a deep and non-coaxial cannulation of the coronary ostium and to a more aggressive manipulation of the catheter, conditions associated to a greater tortuosity of the subclavian and brachiocephalic vascular tree.[1,12] According to these considerations, even if extrapolated from retrospective observational studies, it is clear that conservative management is preferable in the first instance in the case of patients with haemodynamically stable SCAD.[1,2,10]

However, in case of clinical instability, coronary angioplasty may represent the life-saving treatment for the patient. A recent observational study, the largest on the subject, compared coronary revascularization in patients with atherosclerotic ST elevation myocardial infarction (STEMI-ATH) and ST elevation myocardial infarction from coronary dissection (STEMI-SCAD).[14] In this study, conducted from 2003 to 2017, coronary artery dissection represented 1% of total ACS (female in 93% of cases). It should be noted that the presentation with cardiogenic shock was twice frequent in STEMI-SCAD patients compared to STEMI-ATH. Revascularization rate was lower in SCAD presentation (70% vs. 97%). In STEMI-SCAD, the left main coronary artery was involved in seven patients (13%, each of whom suffered cardiogenic shock), while procedural success was obtained in 91% of cases. However, overall 3-year survival was higher in patients with STEMI-SCAD (98% vs. 84%), indicating the good efficacy of PCI in an emergency settings.[14]

Finally, coronary artery bypass graft represents a valid, urgent, option for unstable patients in whom coronary angioplasty is contraindicated, unsuccessful or not feasible.[1,2] The retrospective Mayo Clinic study reported a 94% procedure success rate and 100% intra-hospital survival.[4] However, at 16 months angiographic follow-up, few grafts were still patent, most likely due to spontaneous healing and reabsorption of the IMH, with restoration of the normal flow of the native vessel.[1,2,4]

Follow-up: prognosis and recurrence risk

Major adverse cardiovascular events (MACE) are relatively common after a SCAD episode, often related to recurrence of the dissection, with a MACE rate of 8.8% after 30 days (according to a recent North American registry), between 10% and 30% at 2–3 years, and approximately 50% in over 10 years of follow-up.[1,2,7,15] Mortality is however low, as shown by Tweet *et al.*,[15] who reported a 10-year survival of 92% with the Kaplan–Meier method. The high rate of MACE is usually associated with recurrent SCAD, even if it's important to note that, in 80% of cases, dissection occurs in a new site of the coronary tree; this shows that stenting the primary lesion does not significantly reduce the risk of recurrence.[2,15] To date, no clear risk factors have been demonstrated that can be associated with a higher recurrence rate; some authors suggest an association with the severe tortuosity of the coronary arteries, although this hypothesis must still be demonstrated.[2]

Future directions and problems to solve

Despite the risk factors, the clinical setting and the angiographic aspect of coronary dissections are now better characterized than in the past, there is still a strong uncertainty about the real incidence, natural history or ideal treatment of SCAD. To date, there are at least five ongoing clinical studies that will help answer some of these questions.[2] However, there is a need to conduct randomized controlled trials to better investigate possible therapeutic regimens with beta-blockers or anti-platelet drugs, or, even more, which invasive strategy may be preferred.[2]

Discussion and conclusions

SCAD is a clinical entity that commonly occurs in the form of ACS. In most cases, it affects patients with no particular cardiovascular risk factors: either young women or patients with various associated comorbidities, such as arterial connective tissue diseases or systemic inflammatory diseases.[1,2] The recent introduction of a diagnostic angiographic classification, associated with a greater use of intra-coronary imaging has revolutionized the diagnostic performance of operators, leading to a better understanding of the incidence and pathogenesis of SCAD. However, from an angiographic point of view, coronary dissection mimics atherosclerotic disease, with consequent misdiagnosis and uncertainty about the real incidence of this clinical condition.[1,2] Therefore, this may lead to an erroneous assessment of the real cause underlying the ACS, followed by an incorrect treatment. In fact, while the usefulness of interventional therapy is well established in atherosclerotic disease, its role in SCAD aetiology is still matter of debate, especially in clinically stable patients; in fact, in these subjects, PCI is related with a higher rate of spontaneous healing and high percentages of procedural failure if compared to PCI from atherosclerotic disease.[1,2,10] Therefore, research should aim to establish the real incidence of the disease and the best therapeutic iter for this kind of patients (both from an interventional and pharmacological aspect), taking into account the clinical setting and the possible risk factors. Finally, it is fundamental that all cardiologists (interventional and non-interventional) are informed and aware of this particular clinical condition, as guidelines, treatment and prognosis, totally differ from the 'common' atherosclerotic ACS.[1,2,14]

Conflict of interest: none declared.

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