Considering as differential diagnosis in patients with an atypical presentation of ACS

MINOCA and spontaneous dissection: diagnosis and therapy

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Myocardial infarction with non-obstructive coronary arteries (MINOCA)

Myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA) is defined as MI according to the fourth universal definition of MI [1] without coronary stenosis ≥50% on coronary angiography, and without a specific alternate diagnosis for the acute presentation [2, 3]. MINOCA is present in approximately 5–6% of patients with acute myocardial infarction [2, 3], and frequently affects women (up to 50%) [3]. MINOCA patients are usually younger (mean age 58 years [3]), and have a lower prevalence of traditional cardiovascular risk factors [4–7] compared with patients with obstructive coronary artery disease [4]. Black, Maori, Pacific race, or Hispanic ethnicities are more frequently affected [3].

MINOCA can be caused by a variety of underlying aetiologies, which need to be specifically screened for [2, 3, 8]. Primary coronary causes are plaque rupture, plaque erosion, spontaneous coronary artery dissection (SCAD), coronary artery spasm and microvascular dysfunction. Extracoronary causes include secondary coronary thromboembolism from intra- and extracardiac sources, such as left atrial appendage or valve thrombosis, thrombophilia disorders, paradoxical embolism in the context of a persistent foramen ovale (PFO), or rarely, other sources of emboli such as vegetations, tumours or complex aortic plaques [2, 3]. The frequency of these underlying aetiologies is insufficiently assessed, as studies incorporating a full aetiological work-up for the detection of all of these pathologies are scarce [2, 3].

The typical presentation is similar to atherosclerotic acute coronary syndrome (ACS), with chest pain and evidence of myocardial ischaemia [1]. However, as the coronary arteries are by definition not occluded, MINOCA patients infrequently present with ST-segment deviations and have smaller degrees of troponin elevation compared with patients with obstructive coronary artery disease [3].

The main differential diagnoses of MINOCA include myocarditis, takotsubo cardiomyopathy, other cardiomyopathies, and type 2 MI (i.e., demand-supply mismatch) [1–3].

Diagnostic algorithm

A diagnostic algorithm for MINOCA is presented in figure 1, C (adapted from [3, 8]).

In patients with a clinical presentation of MI [1], but absence of ≥50% stenosis on coronary angiography (fig. 1, A), the working diagnosis of MINOCA can be established. As a first step, other causes for troponin elevation and the acute presentation need to be excluded by a careful review of all medical records, 12-lead ECG and clinical reasoning [2, 3] (fig. 1, C).

The coronary angiogram should be carefully reviewed for potential culprit lesions. In the event of any angiographic ambiguity consistent with a potential culprit lesion for the MI, and/or in the case of wall motion abnormalities or ECG changes pointing to a potential infarct-related vessel, intracoronary imaging of the suspected infarct vessel using optical coherence tomography (OCT) should be performed. OCT is considered the gold standard imaging technique, as it is the only technique that is able to detect small thrombi with high precision. Intracoronary findings may include small plaque ruptures, erosions, ostial sidebranch occlusions, local or systemic emboli (i.e., thrombi in the absence of plaque), type 2 or 3 SCAD or plaques responsible for spasm (fig. 1, C) [2, 3, 8]. In a recent prospective study, detection of a culprit lesion with OCT in MINOCA patients was reportedly facilitated in up to 46% of patients [9]. With the integration of OCT early in the diagnostic process, unnecessary further tests and treatments can be avoided following coronary angiography.

All patients with an established working diagnosis of MINOCA but without angiographic/intracoronary imaging evidence of a coronary culprit lesion should undergo cardiac magnetic resonance imaging (CMR), which is the key diagnostic tool in MINOCA [2, 3]. CMR was reported to identify the underlying cause in 87% of patients with a working diagnosis of MINOCA [10]. A

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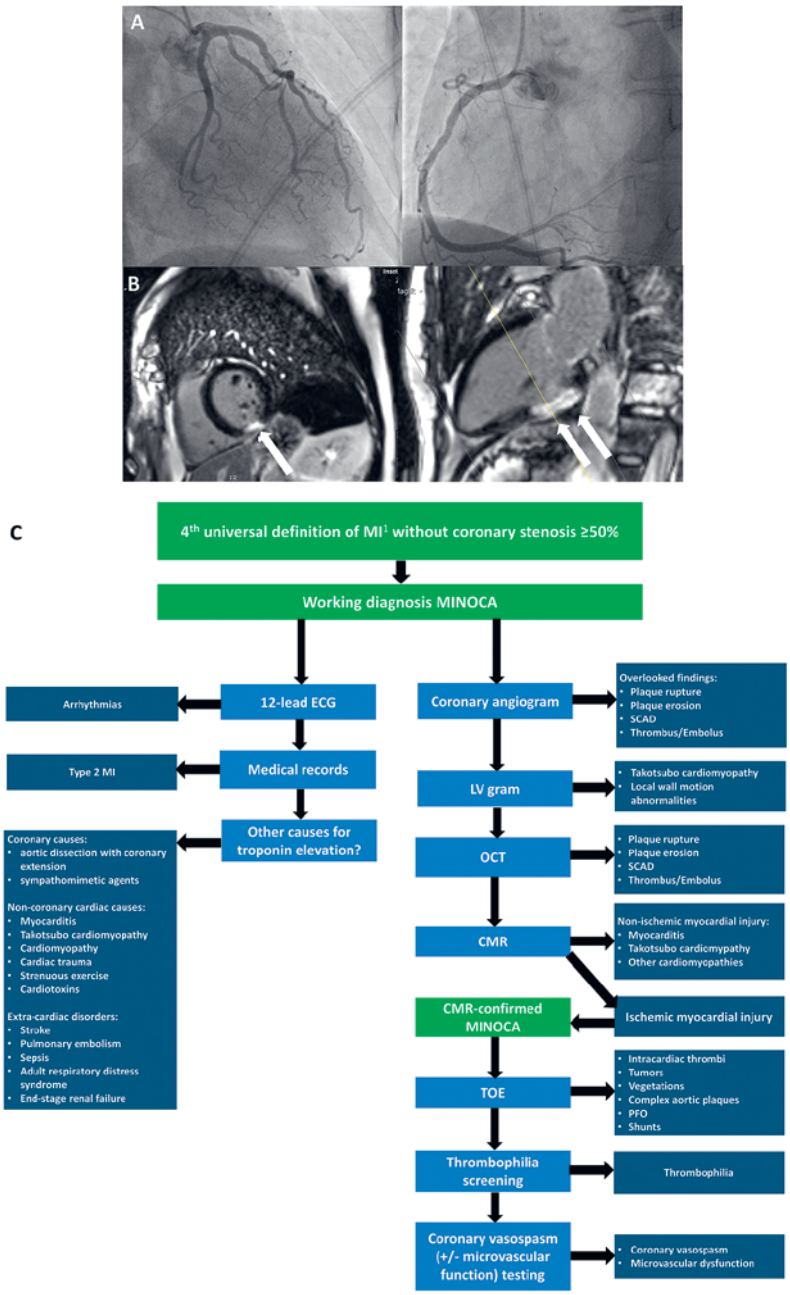

Figure 1:: MINOCA: Case example and diagnostic algorithm. A) Non-obstructive coronary arteries in a 62-year old woman with NSTEMI. B) Transmural inferior basal to mid-ventricular LGE on CMR (white arrows). C) Diagnostic algorithm for MINOCA. CMR = cardiac magnetic resonance imaging, ECG = electrocardiogram, LGE = late gadolinum enhancement, LV = left ventricle, MI = myocardial infarction, MINOCA = myocardial infarction with non-obstructive coronary arteries, NSTEMI = non-ST-elevation myocardial infarction, OCT = optical coherence tomography, PFO = persistent foramen ovale, SCAD = spontaneous coronary artery dissection, TOE = transoesophageal echocardiography.

subendocardial or transmural distribution of myocardial necrosis along the vessel wall, as reflected by late gadolinium enhancement (LGE) (fig. 1, B), is consistent with an ischaemic cause, and thus confirms the diagnosis of MINOCA. Further work-up to detect its underlying pathology should follow (fig. 1, C) [2, 3]. In contrast, mid-wall or subepicardial myocardial LGE is consistent with myocarditis, takotsubo cardiomyopathy, or other cardiomyopathies, and excludes the diagnosis of MINOCA.

Further work-up after MINOCA

Further aetiological work up consists of screening for intra- or extracardiac sources of thrombi and emboli, coronary epicardial spasm and microvascular dysfunction [2, 3]. This includes transoesophageal echocardiography (TOE) to evaluate the presence of intracardiac thrombi, tumours, vegetations, complex aortic plaques, shunts and, specifically, a PFO. Screening for atrial fibrillation from 12-lead ECG and patient history is recommended by current position papers [2, 3]; however, owing to the paroxysmal nature of this arrhythmia, prolonged rhythm monitoring might be considered. Screening for inherited or acquired thrombophilias is advisable. In patients with a high clinical suspicion of coronary vasospasm or microvascular dysfunction, invasive vasospasm testing and/or assessment of coronary flow reserve and microvascular resistance should be performed (fig. 1, C).

Therapy

Therapeutic concepts are based on the underlying aetiology [2, 3, 8].

Plaque rupture should be treated as any other atherosclerotic ACS with revascularisation followed by secondary preventive medication including antiplatelet therapy, high-intensity statin, beta-blockers and angiotensin-converting-enzyme inhibitors / angiotensin-II-receptor blockers [8, 11].

In plaque erosion, non-stenting techniques with aggressive standard secondary preventive medication after ACS are currently discussed and can be advised if there is a large residual lumen and a relatively low thrombus burden, but data is still too limited to provide specific recommendations [12]. Therefore, erosion may be treated in the same way as other atherosclerotic ACS [8, 11].

Coronary epicardial spasm or microvascular dysfunction should be treated with calcium channel blockers, nitrates or other antispastic agents [13]. However, if a clear plaque can be identified as a trigger for spasm, it might be treated with a stent [14].

Thromboembolic conditions are treated with antiplatelet or anticoagulant therapy, dependent on the specific aetiology. If a PFO is detected and presumed causal for MINOCA, closure is warranted [2, 3].

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If no underlying cause of MINOCA can be established after a comprehensive work-up, current guidelines give a class IIbC recommendation to treat patients in a similar way to obstructive coronary artery disease [8].

Follow-up and prognosis

Follow-up is largely guided by the underlying pathology, but should include assessment of left ventricular function and optimisation of disease-specific secondary preventive medication in all patients [2, 3].

The prognosis after MINOCA is better than for patients with AMI [4, 15, 16], but worse than for healthy age- and sex-matched patients without cardiovascular disease [5]. Five-year mortality rates of up to 10–16% have been reported after MINOCA [17]. Despite lower rates of recurrent MI and unplanned revascularisation, non-cardiac mortality was reported to be significantly higher compared with patients with obstructive coronary artery disease [18]. This points to significant comorbidity among MINOCA patients and highlights the need for a proper aetiological work-up to unravel the underlying pathology.

Table 1: SCAD: Predisposing and precipitating factos [19].

Predisposing factors	Precipitating factors
Fibromuscular dysplasia	Coronary spasm
Coronary tortuosity and ectasia	Intense exercise (isometric, aerobic)
Pregnancy (antepartum, postpartum, multiple pregnancies)	Emotional stress or sleep deprivation
Connective tissue disorders • Marfan syndrome • Loeys-Dietz syndrome • Vascular Ehler Danlos syndrome • Neurofibromatosis type I • Cystic medical necrosis • Lysyl oxidase deficiency • Alpha-1-antitrypsin deficiency • Alport syndrome • Polycystic kidney disease • Pseudoxanthoma elasticum	Valsalva type activities • Sexual activity • Vomiting • Cough
Hormonal imbalance/therapy • Menstruation • Oral contraception • Oestrogen replacement therapy • Clomiphene • β-human chorionic gonadotropin • Testosterone • Polycystic ovary syndrome	Recreational drugs • Cocaine • Amphetamines
Systemic diseases· • Systemic lupus erythematosus • Inflammatory bowel disease • Polyarteritis nodosa • Sarcoidosis • Churgh-Strauss syndrome • Granulomatosis with polyangiitis (Wegener) • Rheumatoid arthritis • Takayasu arteritis • Hypothyroidism • Celiac disease • Polycythaemia vera • Behcets disease • Cryoglobulinaemia	Drugs • Calcineurin inhibitors • 5-Fluorouracil • Fenfluramine • Corticosteroids • Methylphenidate • Ergotamine • Sumatriptan • Dobutamine

Spontaneous coronary artery dissection (SCAD)

Spontaneous coronary artery dissection (SCAD) is defined as a non-atherosclerotic, non-traumatic or iatrogenic separation of the coronary arterial tunics secondary to vasa vasorum haemorrhage or intimal tear, which creates a false lumen, coronary compression and downstream myocardial ischaemia [8, 19, 20]. The available evidence reports SCAD in 2–4% of angiograms performed for ACS, but SCAD is responsible for 23–36% of ACS in women <60 years of age [19]. Among these women, pregnancy- or peripartum-related SCAD represents only a minority (~10%) of the cases, and thus SCAD should no longer be considered a primarily peripartum condition [19]. The mean age of affected patients is 44–53 years, affecting 90% women, without ethnic variation [19]. Male SCAD patients differ from female cases, being slightly younger (mean –4 years) with higher rates of preceding isometric exercise and lower rates of prior emotional stress [21].

Two distinct pathophysiological mechanisms have been proposed: 1) The "inside-out" model, where an endothelial and intimal tear allows the blood to enter the media, and 2) the "outside-in" model, where a primary disruption of vasa vasorum micro-vessels leads to direct haemorrhage into the media. In both cases, blood propagates axially along the vessel, leading to an extension of the false and compression of the true lumen [19, 20].

SCAD results from a combination of predisposing factors and precipitating factors acting as acute triggers [19, 20] (table 1).

The most common presentation of SCAD is chest discomfort with elevation of cardiac biomarkers [8]. Chest pain may be more common in SCAD (i.e., 60–90%) than in atherosclerotic ACS, as the dissection itself is inherently painful and adds to the pain of myocardial ischaemia [22]. ST-segment elevation myocardial infarction (STEMI) on ECG is reported in 26–55% of patients [19].

The main differential diagnosis of SCAD include atherosclerotic ACS, coronary spasm, Takotsubo cardiomyopathy, coronary thromboembolism and MINOCA [19, 20].

SCAD is classified into three main types [23] (fig. 2, A): *Type 1* (29–48%) shows the classical angiographic radiolucent flap and linear double lumen often associated with contrast hold-up, which is relatively easy to detect. *Type 2* (52–67%) consists of a long diffuse and smooth stenosis. *Type 3* (0–3.9%) exhibits focal stenosis, which is angiographically indistinguishable from focal atherosclerotic stenosis. Both type 2 and type 3

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SCAD may be challenging to detect angiographically and require a high level of expertise.

Diagnostic algorithm

A diagnostic algorithm for SCAD is shown in figure 2, D (adapted from [8]).

The principal tool for the diagnosis of SCAD is coronary angiography. Owing to the limited spatial resolution, coronary computed tomography angiography (CCTA) has currently no major role in the initial diagnosis of SCAD, but can be used as a follow-up imaging modality when the site of dissection is already known [8, 19, 20].

In the case of diagnostic uncertainty (type 2 or 3 SCAD), intracoronary imaging with intravascular ultrasound (IVUS) or OCT should be used [8, 19, 20, 24] (fig. 2, D). Intracoronary imaging may even play a pivotal role in the diagnosis of SCAD, as the typical angiographic features of iatrogenic coronary dissections familiar to the interventional cardiologist (radiolucent flap, dual lumen and contrast hold-up), are present in only a minority of SCAD angiograms [19].

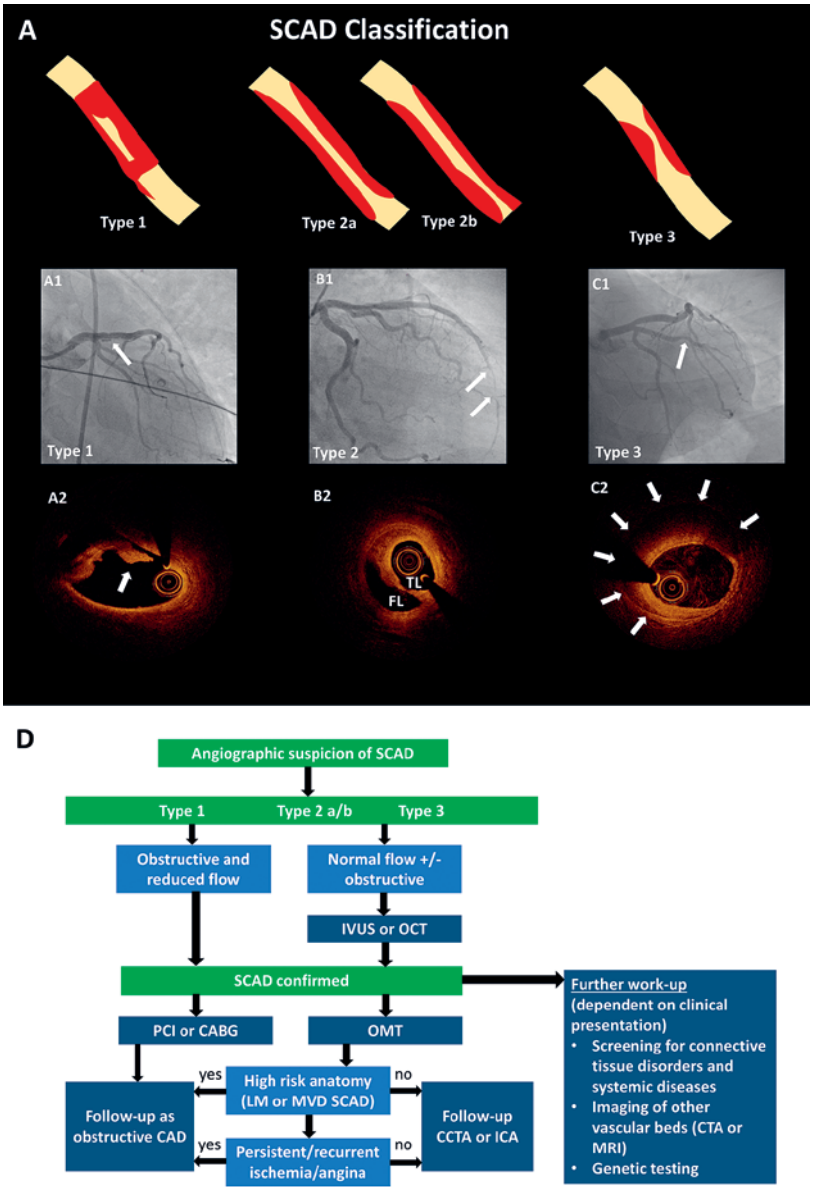

Figure 2: SCAD: Classification and Diagnostic algorithm. A) SCAD classification. A1) Type 1 SCAD with typical double lumen contour on angiography and intimal flap on OCT (A2). B1) Type 2b SCAD with visualization of the true lumen (TL) and false lumen (FL) on OCT (B2). C1) Type 3 SCAD with intramural hematoma on OCT (B3). D) Diagnostic algorithm for SCAD. CABG = coronary artery bypass grafting, CAD = coronary artery disease, CCTA = coronary computed tomography angiography, CTA = computed tomography angiography, ICA = invasive coronary angiography, IVUS = intravascular ultrasound, LM = left main, MRI = magnetic resonance imaging, MVD = multivessel disease, OCT = optical coherence tomography, OMT = optimal medical therapy, PCI = percutaneous coronary intervention, SCAD = spontaneous coronary artery dissection.

Further work-up after SCAD

In the majority of patients, SCAD is not an isolated event, but reflects an underlying vascular, genetic or autoimmune/inflammatory condition [19, 20]. A careful assessment of the personal and family history, and concomitant symptoms is warranted [19, 20] and further diagnostic tests to detect, for example, connective tissue disorders or systemic diseases, should be tailored to the individual risk constellation. Owing to the association between SCAD, fibromuscular dysplasia and other extra-coronary vascular abnormalities, imaging of other vascular beds is advised [19, 20], such as with low-dose computed tomography angiography from neck to pelvis [25] or magnetic resonance angiography [26]. The yield from routine genetic testing without a suggestive personal or family history or physical examination is low [27]. Genetic testing should therefore be restricted to patients with a suspected genetic condition and generally be performed in expert centres [19, 20] (fig. 2, D).

Therapy

Owing to the disrupted and friable coronary vessel wall, revascularisation is challenging and percutaneous coronary intervention (PCI) is consistently reported to lead to worse outcomes than in atherosclerotic coronary artery disease [8, 19, 20]. Specific risks of PCI in SCAD include secondary iatrogenic dissection, guidewire passage into the false lumen, proximal and/or distal false lumen propagation during stent deployment, persistent distal dissection and major side branch restriction or occlusion by propagation of haematoma [19].

Coronary artery bypass grafting (CABG) represents only a bail-out strategy for patients with failure of PCI, ongoing ischaemia in a significant myocardial territo-

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ry, or because the anatomical complexity exceeds the possibilities of PCI.

Collectively, revascularisation should only be attempted in the presence of haemodynamic instability or ongoing ischaemia (e.g., persistent ST-elevation, chest pain refractory to analgesics and nitroglycerin) and anatomical feasibility. Whenever this is not fulfilled, a conservative strategy is generally favoured, as most SCAD heal spontaneously within a few weeks. In the absence of revascularisation, in-hospital surveillance may be prolonged in order to minimise the risk of SCAD progression [8, 19, 20].

Controversy exists regarding intensity and duration of antiplatelet therapy, but generally it should be restricted to invasively treated patients, following current ACS guidelines [8, 11]. In medically managed patients, antiplatelet therapy cannot be routinely recommended. Acutely, it may even worsen intramural bleeding [8, 19, 20].

They mainstay of treatment is aggressive blood pressure control, as elevated blood pressure is an independent predictor of recurrent SCAD [28]. Beta-blockers have been shown to reduce the risk of recurrence in observational studies [28], and should be the preferred antihypertensive agent [8, 19, 20].

Current data do not support the routine use of statins without another clinical conditions mandating such treatment [19, 20].

Follow-up and prognosis

Follow-up of SCAD includes assessment of left ventricular ejection fraction, clinical symptoms, blood pressure control and treatment of the underlying condition (if present/identified). Imaging follow-up may be performed with coronary angiography or CCTA (fig. 2, D). Even though not suitable for initial diagnosis, CCTA may represent a valuable non-invasive option for follow-up imaging, when the site of dissection is already known [8, 19, 20].

SCAD is associated with increased long-term major adverse cardiac events rates ranging from 15–47%, depending on the population studied and follow-up duration [19]. This is driven by high rates of recurrent dissections (4.5–29.4%) [19]. SCAD recurrence frequently affects de novo territories and stenting at the index event does not seem to be protective [19]. Dedicated research is needed to deepen the understanding of SCAD and to help improve prognosis.

Key points

- MINOCA and SCAD present as acute ACS and should be considered as differential diagnosis in patients with an atypical presentation of ACS (i.e., no atherosclerotic risk factors, no overt culprit lesion on coronary angiography).
- Intracoronary imaging plays a pivotal role in the diagnosis of MINOCA and SCAD types 2 and 3.
- Confirmation of MINOCA by CMR and an aetiological work-up to determine its underlying pathology is warranted to establish the diagnosis and guide therapy.
- In the absence of haemodynamic compromise or ongoing ischaemia, SCAD should be managed conservatively with blood pressure control using beta-blockers, whenever clinically feasible.

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Conflicts of interest
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