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Spontaneous Coronary Artery Dissection and Fibromuscular Dysplasia: Vasculopathies With a Predilection for Women

Siiri E. Iismaa, PhD[a,b], **Stephanie Hesselson, PhD**[a], **Lucy McGrath-Cadell, MD**[b,c], **David W. Muller, MD**[a,b,c], **Diane Fatkin, MD**[a,b,c], **Eleni Giannoulatou, DPhil**[a,c], **Jason Kovacic, MD, PhD**[d], **Robert M. Graham, MD**[a,b,c,*]

[a]Molecular Cardiology and Biophysics Division, Victor Chang Cardiac Research Institute, Sydney, NSW, Australia

[b]St Vincent's Clinical School, St Vincent's Hospital, Sydney, NSW, Australia

[c]Faculty of Medicine, University of NSW, Sydney, NSW, Australia

[d]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Abstract

The burden of cardiovascular disease in women is being increasingly appreciated. Nevertheless, both clinicians and the general public are largely unaware that cardiovascular disease is the leading cause of death worldwide in women in all countries and that outcomes after a heart attack are worse for women than men. Of note, certain types of cardiovascular disease have a predilection for women, including spontaneous coronary artery dissection (SCAD) and fibromuscular dysplasia (FMD). Although uncommon, SCAD is being increasingly recognised as the cause of an acute coronary syndrome (ACS) and can recur. It is a potentially fatal, under-diagnosed condition that affects relatively young women, who often have few traditional risk factors, and is the commonest cause of a myocardial infarction associated with pregnancy. In contrast, FMD often remains silent but when manifested can also cause major sequelae, including renal infarction, stroke, cervical artery dissection and gut infarction. Here we provide an update on the diagnosis, aetiology and management of these important disorders that overwhelmingly affect women.

Keywords

Spontaneous coronary artery dissection; Fibromuscular dysplasia; Women; Heart disease

*Corresponding author at: Victor Chang Cardiac Research Institute, 405 Liverpool St, Darlinghurst, Sydney, NSW 2010 Australia; b.graham@victorchang.edu.au.

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Introduction

Cardiovascular disease (CVD, mainly coronary heart disease [CHD] and stroke) in women is under-recognised, under-appreciated and under-treated. Yet, CVD remains the leading cause of death in women worldwide, including in both developed and under-developed countries [1], outranking death due to breast cancer by seven-fold [2].

Historically, CVD has been seen as predominantly affecting men, partly because mortality rates for CHD are higher in men than women at all ages [3]. However, because women live longer, CVD events in women may outnumber those in men such that there is little difference between the sexes when the lifetime risk of CVD is considered [4]. Moreover, recurrent myocardial infarction and death within one year of an index event occur much more commonly in women than in men [5].

Of concern, is that not only the general public but also clinicians are unaware that CHD is the leading global cause of death in women [1]. Also, women are less likely than men to receive preventative therapies, such as aspirin, statins and lifestyle changes, despite the fact that there is good evidence that they are effective secondary prevention strategies not only in men but also in women. Furthermore, when prescribed medications, women are less likely to be treated aggressively to achieve desired target goals of blood pressure reduction, lipid lowering or glucose control in diabetics [1,6]. Perhaps most alarming is that female patients of male cardiologists have worse outcomes, that is higher mortality, than male patients, with no such gender differential when the treating cardiologist is female [7].

A further consideration with respect to CVD in women is the fact that in addition to traditional risk factors for CVD (age, smoking, diabetes, high blood pressure, dyslipidaemia, family history), there are also female-specific risk factors, including early menarche, early menopause, history of miscarriages, early age at first birth, history of still births, gestational diabetes, pre-eclampsia, etc. [8]. Moreover, certain forms of CVD have a predilection for women, including SCAD, FMD, Takotsubo cardiomyopathy (TC), heart failure with preserved ejection fraction (HFpEF), peripartum cardiomyopathy and myocardial infarction with non-obstructed coronary arteries (MINOCA). In this review we will consider recent advances in our understanding of both SCAD and FMD, two disorders that commonly co-exist.

Spontaneous Coronary Artery Dissection

Definition and Epidemiology

Spontaneous coronary artery dissection is a disease that affects the epicardial coronary arteries. It presents as an ACS (ST elevation myocardial infarct [STEMI], non-STEMI or unstable angina) or sudden death. It is due to a spontaneous bleed into the wall of a coronary artery leading to an intramural haematoma (IMH) [9,10]. The IMH causes the wall of the culprit vessel to bulge into the lumen thereby obstructing blood flow to the myocardium that is perfused by the affected artery (Figure 1).

SCAD predominantly affects women (>90% of cases), who are relatively young (45–52 years), often not overweight, with a low incidence of traditional risk factors but a higher prevalence of migraine, depression and anxiety [11,12]. It accounts for 2–4% of all cases of ACS, is the commonest cause of a myocardial infarction (MI) associated with pregnancy, occurring predominantly in the first post-partum week, and has been reported to cause 0.5% of sudden death at autopsy [13]. Although ≈60% of affected women are post-menopausal, it can also affect women in their twenties [2]. It is under-diagnosed, since a myocardial infarction is often not considered as a diagnosis in younger women presenting with chest pain or other ACS symptoms, or a diagnostic angiogram or a troponin level is not obtained.

Pathology – SCAD or "SCAB"?

Although detailed pathological studies of SCAD-affected vessels are limited, recent studies confirm older reports that the IMH forms either between the inner two-thirds and the outer third of the tunica media or between the media and adventitia [14–16]. The IMH is thought to form as a result of an intimal tear due to spontaneous disruption of the endothelium, which allows blood to track from the lumen into the vessel wall where it forms a false lumen. In this situation, the true and false lumens are contiguous. Angiographically, this lesion, classified as Type 1 (30% of cases; Figure 2) [12], is characterised by the appearance of an intimal flap, and given the contiguity of the true and false lumens, contrast material tracks freely into the false lumen causing vessel wall staining. Alternatively, an IMH is thought to result from disruption of vasa vasorum within the vessel wall, with no direct connectivity between the IMH and the true lumen, which precludes entry of contrast material into the vessel wall. Angiographically, these lesions, classified as Type 2 or 3 (≈67 and 3% of cases, respectively; Figure 2), are evident as coronary artery narrowing but without a flap or vessel wall staining. It remains unclear if the latter mechanism might be the initiating pathology, which then leads to intimal disruption as the IMH expands leading to intimal fissuring and a tear as the IMH progresses and increases pressure in the false lumen [17]. Optical coherence tomography (OCT) studies suggest that SCAD patients have a higher density of coronary adventitial vasa vasorum in the non-culprit segments adjacent to the coronary artery regions affected by the SCAD [18]. Rupture of these proliferative vasa vasorum could result in micro-haematomas between the media and adventitia leading to coronary artery dissection. However, it is unclear if this proliferation of vasa vasorum is causal or merely a reactive response to dissection in the adjacent culprit vessel segment.

Like atherosclerotic coronary artery disease (asCAD), myocardial infarction in SCAD patients is also due to obstruction of coronary blood flow, albeit primarily due to an IMH causing the vessel wall to bulge into the affected coronary artery lumen, rather than to plaque and thrombi. Given this obstruction to coronary blood flow, we would argue that SCAD is *not* a cause of MINOCA, despite suggestions to the contrary [19].

In contrast to asCAD, however, SCAD is primarily a *bleeding* disorder and not a thrombotic disorder. Although occlusion of the true lumen may be worsened by thrombi, OCT studies indicate that, compared to the IMH, thrombi play only a small role in impairing myocardial perfusion [20–23]. To remind ourselves of the primary haemorrhagic nature of the lesion, which then progresses to secondarily cause vessel wall dissection, SCAD should perhaps

more correctly be described as a "**spontaneous coronary artery bleed"** or **SCAB**. Nor is this merely a semantic issue—it has therapeutic implications as, at present, the management of SCAD largely mimics that of asCAD, with therapy (*vide infra*) being directed at a thrombotic, rather than a primary bleeding disorder, which may be detrimental [24,25].

Aetiology

The aetiology of SCAD is likely to be multifactorial, with a high proportion of cases being associated with predisposing vasculopathies, particularly FMD (found in 45–86% of cases) and migraine [11], and possibly even TC [26,27].

Familial clustering of SCAD has been reported [28], suggesting a potential genetic aetiology. In a recent study, we found that 23 of 235 SCAD cases (8.8%) showed familial clustering involving sister-sister pairs in six families, three first-degree cousins in one family (Figure 3), two first-degree cousins in two families, a mother-son pair, and a family with concordant monozygotic twins i.e. both twins having had SCAD [29].

Very little is known, however, about the genetic defects that predispose to SCAD. In a multi-centre study involving 1,055 SCAD cases and 7,190 controls, we recently identified a common variant (rs9349379-A) in the PHACTR1/EDN1 genetic locus as the first risk allele for SCAD. This variant has been previously been associated with FMD [30]. The association of rs9349379-A with SCAD was highly significant (OR 1.65; p=6.76 × 10e-21) and independent of FMD. Interesting, the minor allele at this locus, rs9349379-G, has been associated with asCAD [31].

In addition to these findings, rare variants in several genes have been identified in a small number of SCAD cases (<5% to 8%) [11,32]. Although it remains to be determined whether these variants are truly disease-causing, the association of the genes involved with other disorders points to possible biological pathways that might be involved in SCAD pathogenesis. These include polycystic kidney disease (*PKD1*, encoding polycystin 1), α_1-antitrypsin deficiency and inherited connective tissue disorders, such as vascular Ehlers Danlos syndrome (*COL3A1* mutations encoding type 3 collagen), Marfan's syndrome (*FBN1* mutations encoding fibrillin 1), Loeys-Dietz syndrome (*TGFBR-1* and *2* mutations encoding transforming growth factor beta receptor-1/2 mutations, and *SMAD3* mutations), and nail-patella syndrome (*LMX1B* mutations encoding LIM Homeobox Transcription Factor 1β). Other genes that have been suggested to be associated with SCAD include *F11R* (encoding the F11 receptor, a component of the intercellular tight junction [33]) and *TLN1* (encoding talin 1, a large protein of the integrin adhesion complex [34]).

Most studies reported to date involve predominantly Caucasian patients. Whether genetic associations and other features of SCAD differ in other ethnic groups is unclear, but it is of interest that a recent analysis of SCAD in patients of predominantly (>80%) Arabic ethnicity found a much higher incidence of SCAD (49%) in men, who were relatively young (44 years). This may indicate differing genetic influences or may reflect the high incidence of consanguinity in Arabic families. In addition, variants in *TSR1,* encoding a protein involved in ribosomal 40S assembly, have been associated with the development of SCAD in the Chinese Han population. However, this was an unusual population as only 18% of 85

patients studied were women and cases with atherosclerotic coronary artery disease were not excluded [35].

In addition to a genetic predisposition, environmental factors appear to be important risk factors and triggers of SCAD events, as suggested by our identification of a family in which monozygotic twins are discordant for SCAD [29]. Hormonal influences in the context of pregnancy or menopause may also be potential risk factors and SCAD can also occur in association with systemic inflammatory disorders (such as systemic lupus erythematosus, Crohn's disease and ulcerative colitis etc.). Other environmental factors include stressors that likely increase cardiocirculatory sheer stress, such as extreme physical effort (particularly isometric exercise), intense Valsalva-like activities (e.g. coughing, retching, childbirth) and severe emotional stress.

Taken together, it seems reasonable to postulate that SCAD pathogenesis involves a genetic predisposition, that is likely multi-genic, coupled with an environmental insult (e.g. increased thoracolumbar pressure or a catecholamine surge) that together precipitate an endothelial tear or vasa vasorum rupture. However, more clinical and experimental studies are needed to understand the complex pathogenesis of this disorder. Since coronary artery samples are not available from SCAD survivors, an alternative approach to understanding disease pathogenesis, which we are currently exploring [36], is to evaluate phenotypic differences between patients versus controls in blood vessel cells differentiated from induced pluripotent stems cells (iPSCs).

Clinical Presentation

In most cases the clinical presentation of SCAD is analogous to that of other causes of ACS (i.e. chest pain, radiation to the arm, nausea or vomiting, diaphoresis, dyspnoea etc.) and associated with elevated cardiac enzymes. Electrocardiograph (ECG) changes may be absent or show either a STEMI or NSTEMI, in approximately a 1:1 ratio. Complications include ventricular arrhythmias in up to 11% of cases, cardiogenic shock (<5% of cases) or sudden death (<1% of cases) [11,12]. Troponin elevations are generally less that those observed with MIs due to asCAD and left ventricular ejection fraction (LVEF) is relatively preserved. Patients with pregnancy-associated SCAD (PA-SCAD) have a higher incidence of complications, less well-preserved contractile function, and are more likely to have a history of infertility therapy, multiple childbirth and pre-eclampsia [37].

Diagnosis and Management

After identification of the clinical syndrome by ECG and a troponin blood test, diagnosis is by coronary angiography with or without intracoronary nitroglycerin administration. In addition, OCT and intravascular ultrasonography (IVUS) may be useful, particularly in diagnosing Type 3 SCAD lesions, which can be difficult to distinguish from asCAD. However, they involve large bore catheters and guidewire insertion, while OCT also involves an intra-coronary contrast injection at relatively high flow rate. All of these factors can cause extension of the dissection. In general, a hallmark of SCAD is that the unaffected coronaries are normal with little or no plaque, save for increased tortuosity that is four times more likely to be present than in matched controls [38]. Computed tomography (CT) coronary

angiography may be useful for evaluating vessel healing after a SCAD event, however, because of its lower resolution, is not recommended for initial diagnosis.

SCAD can affect any coronary artery, with the left anterior descending artery and its branches being most commonly involved (45–61% of cases), followed by the circumflex (15–45%), right coronary artery (10–39%) and left main (4%). Most often the distal regions of these vessels are involved, but dissections can be long and affect almost the entire length of a vessel. Multiple vessels can be affected simultaneously in 9–23% of cases [39–41], including even the simultaneous involvement of all three major coronary vessels, which resulted in sudden death [16].

Given the high prevalence of extra-coronary FMD in SCAD patients, routine screening for FMD by non-invasive head-to-pelvis CT angiography or magnetic resonance angiography is recommended [42].

Management of SCAD is generally conservative and supportive, since outcomes from percutaneous coronary interventions (PCIs) are much less favourable than for asCAD lesions [11]. Anticoagulation therapy, particularly with heparin and thrombolytics should be avoided to prevent further bleeding into the IMH, unless angiography and/or OCT or IVUS show an intraluminal thrombus. In contrast to the treatment of atherosclerotic coronary artery disease post-PCI, there is currently no consensus view on the use of dual antiplatelet therapy (DAPT) in patients with SCAD. We would argue, however, that given the inherent haemorrhagic, rather than thrombotic, nature of SCAD, DAPT should be reserved for those undergoing PCI, but otherwise should be avoided, particularly in those with a Type 2/3 lesion, where thrombus formation is not an issue. Similarly, there is no rationale for long-term aspirin therapy or for statins in the absence of coronary artery plaque or dyslipidaemia, unless there is evidence of endothelial dysfunction [43]. Coronary artery bypass grafting is reserved for those with persistent pain or major complications. In patients with migraine, vasoconstrictor therapies, such as triptans, should be avoided. Cardiac rehabilitation is recommended for all patients, although consideration must be given to younger female patients, who may feel uncomfortable undertaking such programs in front of a majority of older men.

Outcomes

Spontaneous healing of the dissected vessel is the norm and generally is complete within 35 days. In-hospital mortality is low (<5%), although major adverse cardiovascular events, particularly recurrent chest pain, occur in up to >50% of cases [37,44]. A retrospective registry suggests that progression of SCAD with clinical worsening plus evidence of new coronary artery obstruction occurs in ≈18% of cases. If progression occurs, in most cases (91%) it is observed within the first 6 days of the index event [45]. This is important for patient management as it suggests a timeframe for in-hospital cardiac monitoring. Factors associated with progression include Type 2/3 lesions, that is, an IMH without an intimal tear, multi-vessel involvement, presentation with a STEMI, more severe luminal artery stenosis or longer length of intimal tear, lower LVEF, or with FMD on screening. Recurrences occur in up to 30% of cases and almost always involve a different branch of the coronary tree than the index event. Up to five recurrences have been reported in a single patient, all involving

different coronary artery branches, with healing between episodes [46]. Only blood pressure control using standard therapies, such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, etc., and β-blocker therapy (and perhaps calcium channel blockers) have been shown in observational studies to reduce recurrences [47].

High Burden of Linked Morbidities

Recurrent chest pain can be a diagnostic and management challenge requiring repeated cardiac enzyme measurements as well as ECG and coronary angiographic evaluations. In peri-menopausal women it can be catamenial, i.e. occurring 1–2 days before the next menstrual cycle, due possibly to the fall in oestrogens at that time, which are vasodilatory. In addition, anxiety and depression as well as insomnia and even frank post-traumatic stress disorder [48], occur commonly. Contributing factors include the unexpected nature of SCAD, relatively high recurrence rates, lack of known treatments, uncertainty regarding when to return to exercise and how much can be performed safely, and lack of guidelines as to how much weight can be safely lifted after a SCAD event (an issue of particular significance for women who have had an episode of PA-SCAD and now have a young child to care for).

Rehabilitation programs tailored for SCAD patients, in which weight lifting is limited to <9 kg in women and <22 kg in men, and isometric exercise and extensive Valsalva manoeuvres are avoided, and heart rate is kept low, have been reported to be well-tolerated and beneficial [44,49]. Moreover, there is no data to indicate that moderate exercise should be restricted and, unless the SCAD event occurred during intense exercise, it may be particularly beneficial if it reduces emotional stress.

Fibromuscular Dysplasia

Definition and Epidemiology

Like SCAD, FMD (fibromuscular hyperplasia or fibromuscular fibroplasia) is a non-atherosclerotic, non-inflammatory vasculopathy with dysplastic growth of medium-sized arteries, that predominantly affects women (>90% of cases) with a mean age at diagnosis of 52 years, although it can affect children as young as 5 years. It most likely has a genetic component to its aetiology, although familial clustering is low (≈10%). It manifests as arterial stenoses, tortuosity, aneurysms, or dissection causing high blood pressure or infarction (renal artery involvement), or migraine, transient ischaemic attacks or stroke (cervical artery involvement).

The prevalence of FMD in the general population is not known, as many patients are asymptomatic. However, in a retrospective review of renal angiograms performed in >2,500 potential kidney donors, the prevalence of FMD was found to be between 3.8 and 6.6% [50].

Pathology

Although it can affect almost any vascular bed, the renal (80% of cases) and extracranial carotid arteries (74%) are the most commonly affected, with mesenteric and iliac arteries

being less commonly involved. Coronary artery FMD or involvement of veins has been reported but are both extremely rare [51,52].

There are various types of FMD. An older and now seldom used histopathological classification system was based on the dominant arterial wall layer involved, namely, intimal, medial, or adventitial (peri-medial). These accounted for 5, 85 and 10% of cases of renal artery FMD, respectively [53]. However, due to a change in management from surgery to catheter-based therapy (e.g. angioplasty), FMD vascular samples are now rarely obtained and FMD is now classified angiographically as focal or multi-focal. Multi-focal FMD is the most common form and appears angiographically as alternating stenoses caused by fibromuscular ridges due to excessive myofibroblast proliferation, and dilation caused by smooth muscle cell/fibroblast/matrix destruction and loss, giving a “string of beads” appearance (Figure 4). Focal FMD is less common and characterised by a discrete focal stenosis due to intimal fibroplasia or, uncommonly, to medial hyperplasia or adventitial fibroplasia, with collagen replacement of the fibrous adventitia. The presence of at least one focal or multi-focal arterial lesion is required to establish the diagnosis of FMD, whereas an aneurysm, dissection or vessel tortuosity, alone, is not. However, if a patient has a focal or multi-focal lesion in one vascular bed, the presence of an aneurysm, dissection or tortuosity in another is considered to be due to multi-vessel FMD involvement of all affected vascular beds [42].

Aetiology

Like SCAD, the cause of FMD is largely unknown but it appears almost certain to arise due to a combination of genetic and environmental factors. In addition, there is evidence that smoking, hormonal effects, mechanical stress and the paucity of vasa vasorum in the renal, extracranial carotid and external iliac arteries may play a role. Hormonal effects are suggested by the female predilection of FMD and by the known profound alterations in vascular wall smooth muscle and elastic tissue associated with pregnancy [54–58].

Renal artery traction due to ptotic kidneys (the right kidney, sitting below the liver with its longer artery, is more susceptible to FMD than the left; and, almost 80% of unilateral renal artery lesions occur on the right), internal carotid stretching over the upper cervical vertebrae, and tension in the superior mesenteric artery from the weight of the viscera, may be important mechanical factors contributing to FMD aetiology. In addition, excessive pulsatility of the tortuous arteries frequently observed in FMD vessels may contribute to FMD pathology by causing mural microtrauma.

Renal, extracranial carotids, and external iliac arteries have few vasa vasorum, which may predispose the vessel to mural ischaemia and, thus, the development of dysplastic lesions and, experimentally, an FMD-like lesion is observed with occlusion of the vasa vasorum [59].

As indicated, a genetic predisposition to FMD pathogenesis is very likely, although gene variants suggested to be involved, including those for angiotensin-converting enzyme, α1-antitrypsin, α-smooth muscle actin, collagen 3A, and transforming growth factors-β1 and -β2 genes, have not been replicated [50]. In addition, whole exome sequencing of 16 cases of

FMD failed to find any robust genetic variants [60]. At present, only a single FMD-associated genetic locus has been identified, this being the rs9349379-A risk allele in the PHACTR1/EDN1 genetic locus [30], as also described above for SCAD. However, Olin and colleagues [61] recently reported the identification of a unique proteogenomic signature in the plasma of women with multi-focal FMD. Combining these data with machine learning approaches allowed the development of a provisional blood-based diagnostic test for the disease.

Presentation

Clinically, FMD presentation varies depending on the arterial bed involved. Although many lesions are silent, hypertension is observed most often with renal artery involvement, while headaches, pulsatile tinnitus, dizziness or migraine and, less commonly, amaurosis fugax, Horner's syndrome or cranial nerve palsies, are observed with cervical artery FMD, and weight loss or mesenteric angina is observed with mesenteric artery stenosis. More severe phenotypes result from end-organ ischaemia, such as renal dissection and infarction, transient ischaemic attacks, subarachnoid haemorrhage, cervical artery dissection or stroke, myocardial infarction or gut infarction.

Diagnosis and Management

Given the lack of specific symptoms in many cases, early diagnosis is challenging and, not infrequently, FMD is found incidentally when angiography or Doppler studies are performed for some other indication e.g. evaluation of potential renal donor kidneys, or to evaluate a carotid or renal bruit, respectively. Hence, the need for a diagnostic test as is being developed by Olin et al. [61]. Both non-invasive tests (duplex ultrasonography, magnetic resonance angiography, CT angiography) and invasive tests (catheter angiography) are used to diagnose FMD. Catheter-based angiography, although invasive, remains the gold standard for identifying FMD stenoses, aneurysms and arterial dissections. However, in common use, CT angiography is perhaps the preferred methodology as it offers the greatest resolution and accuracy of the non-invasive modalities.

Unlike the recommendations for SCAD, in the absence of contraindications, antiplatelet therapy (i.e. aspirin 75–100 mg daily) is considered reasonable for patients with FMD to prevent thrombotic and thromboembolic complications [42]. For patients suffering from refractory hypertension resulting from renal FMD causing significant renal artery stenosis, catheter-based balloon angioplasty is an accepted and well-proven therapy. While much less common, intracerebral aneurysms are often also treated by catheter-based coil embolisation. Otherwise, there are currently no disease-specific treatments or drug therapies targeting the dysplastic vascular lesions of FMD. Other management varies depending on organ involvement and presentation, as considered in detail elsewhere [42,50,62].

Outcomes

Outcomes are variable, depending on organ involvement and sequelae (e.g. aneurysm rupture, dissection and infarction, etc.). Multi-focal lesions generally show little, if any, progression and in the absence of hypertension there is no good evidence that such lesions in renal arteries should be treated. Although predominantly a disease of women, men appear to

have a more aggressive course, with aneurysms and dissections occurring twice as often as in women [63]. Like SCAD, lack of specific treatments and uncertainty of outcomes lead to considerable anxiety in many patients that needs to be considered when treating patients with FMD, since very “dark” metaphorical analogies like “[Living with] A sword of Damocles” have been used to describe what it means to live with the disorder [64].

Conclusions

Spontaneous coronary artery dissection and FMD are important vasculopathies that both predominantly affect women. With the former, there is exclusive involvement of the muscular epicardial coronary arteries, whereas the latter can affect virtually any vascular bed but has a predilection for renal, extracranial carotid, mesenteric and iliac arteries. The mean age of presentation is similar for both disorders, although FMD can also occur in children. Both show familial clustering, although with a low prevalence, and both are associated with significant long-term morbidities due to the lack of specific therapies and the potential for recurrences or major sequelae. In addition, the identification of both disorders has increased dramatically, particularly for SCAD, with the development and application of high-resolution angiographic techniques.

Of interest, despite differences in the arterial beds involved, the findings that extra-coronary FMD is detected commonly in SCAD patients and that both have a genetic predisposition to their aetiology (the same genetic locus being associated with both disorders) suggest that they share at least some of the same molecular mechanisms underlying their pathophysiology.

Nevertheless, important differences between SCAD and FMD include the abrupt presentation of SCAD with a significant prevalence of associated major adverse cardiovascular events, including myocardial infarction and sudden death, whereas many cases of FMD are silent, with the disorder only being diagnosed incidentally when an unrelated diagnostic procedure is performed.

Progress in our understanding of their pathophysiology is hampered by the paucity of tissue available for histological evaluation and by the relatively small number of patients involved and, thus, available for clinical trials of various treatments and interventions. To obviate this issue requires multi-centre collaborative studies that allow pooling of cohorts and the use of social media platforms for patient identification—both of which have already been applied successfully, although much work remains if we are to significantly improve outcomes from these major vasculopathies.

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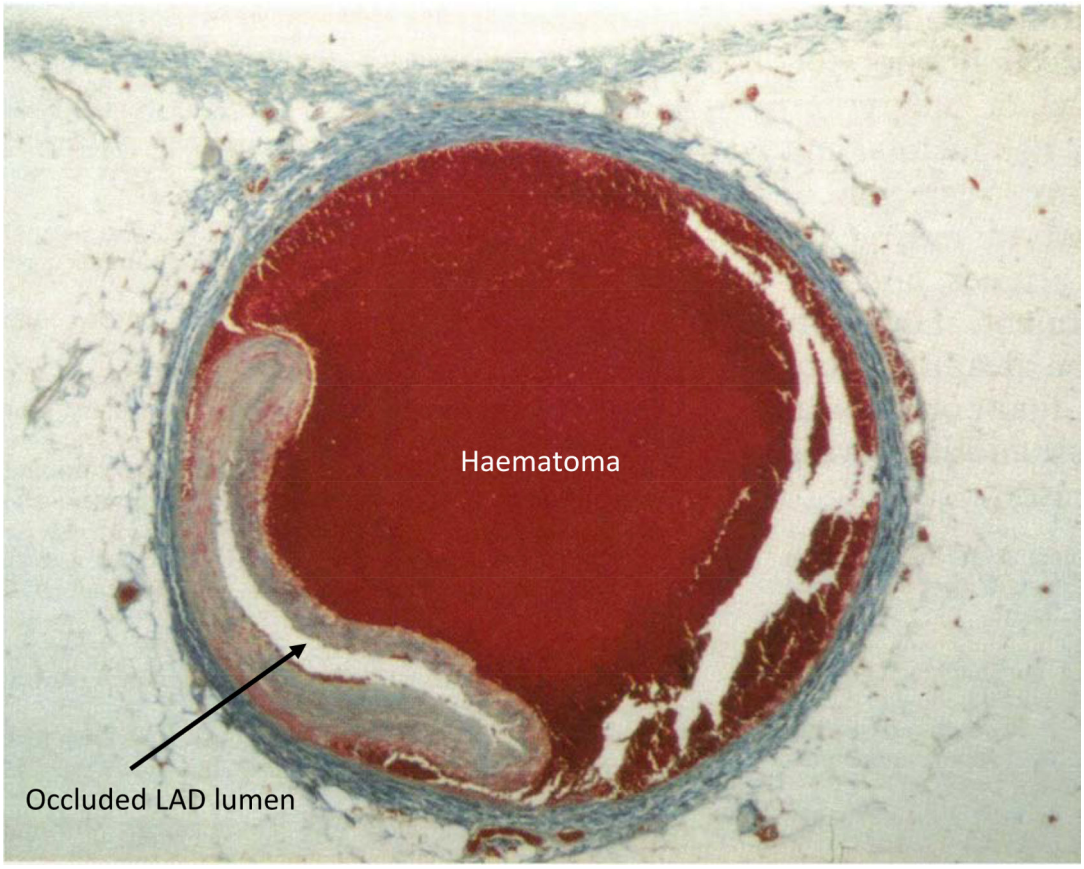

Figure 1:
Left anterior descending coronary artery occluded by a dissecting haematoma in a 43-year old woman, who died suddenly at rest. Azan-Mallory stain, 17.5 x magnification (from [15] with permission).
Abbreviation: LAD, left anterior descending

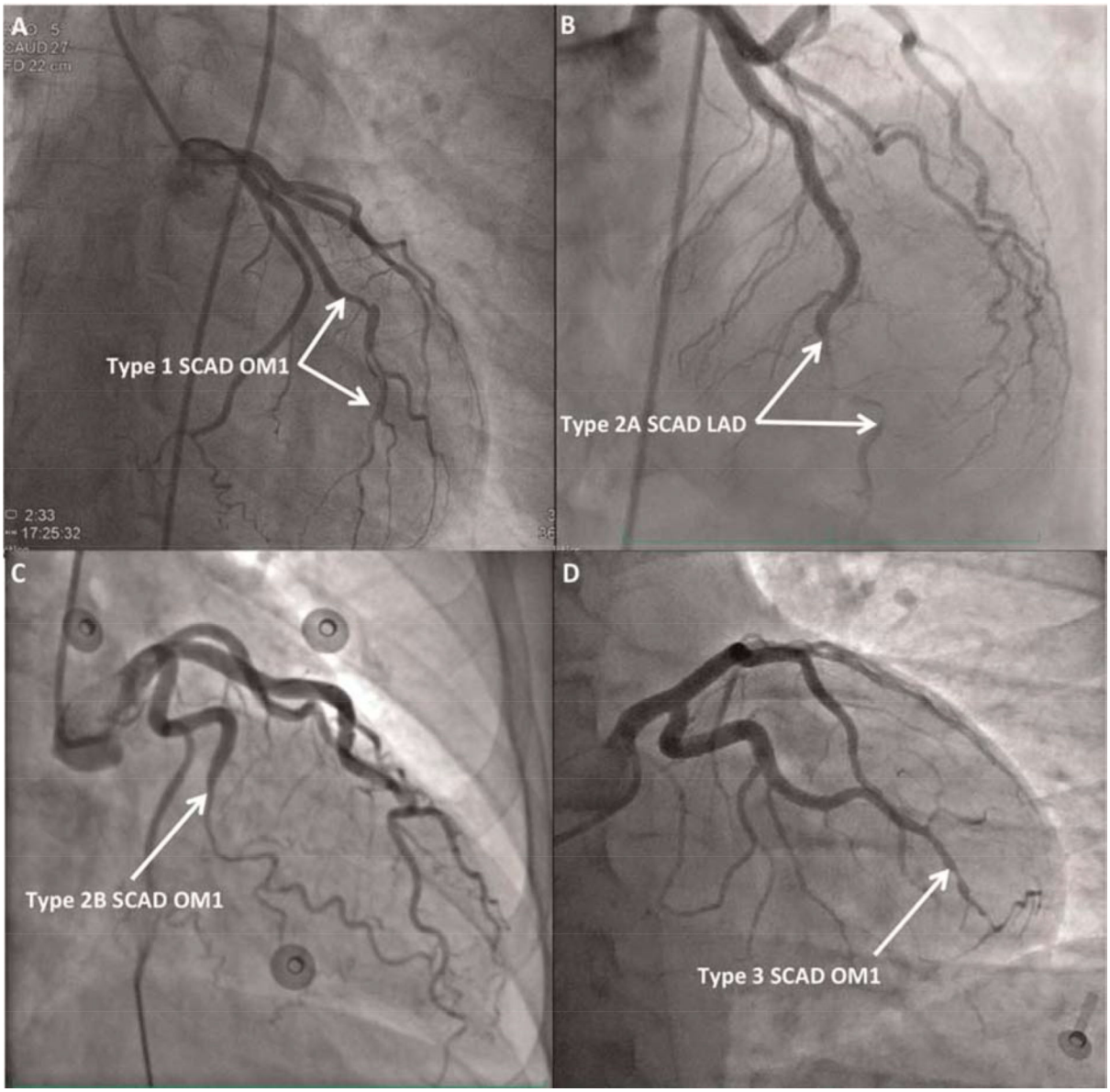

Figure 2:

Coronary angiograms showing different types of SCAD. (A) Arrows show a dissection flap in the obtuse marginal branch of the circumflex coronary artery consistent with type 1 SCAD. (B) Arrows show diffuse stenosis of the left anterior descending coronary artery consistent with type 2A SCAD. (C) Arrow shows diffuse stenosis to the apical tip of the obtuse marginal branch of the circumflex coronary artery consistent with type 2B SCAD. (D) Arrow shows focal tubular stenosis of the obtuse marginal branch of the circumflex coronary artery consistent with type 3 SCAD. This figure was published in Heart, Lung and Circulation, Vol 27, Graham RM, McGrath-Cadell L, Muller DWM, Holloway CJ, The Mystery and Enigma of Spontaneous Coronary Artery Dissection, pp 401–405, Copyright Elsevier (2018) [10].

Abbreviations: LAD, left anterior descending; SCAD, spontaneous coronary artery dissection

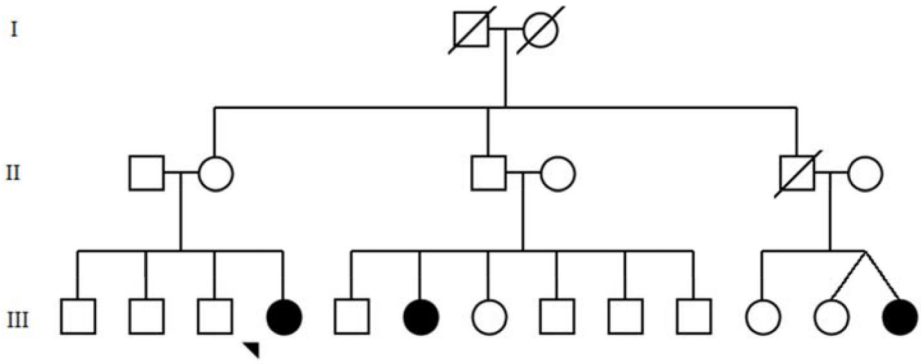

Figure 3:
Pedigree of a family in which three first cousins (generation III) had a spontaneous coronary artery dissection (SCAD) episode at age 40 (propositus; indicated by the arrowhead), 51 and 37 years.

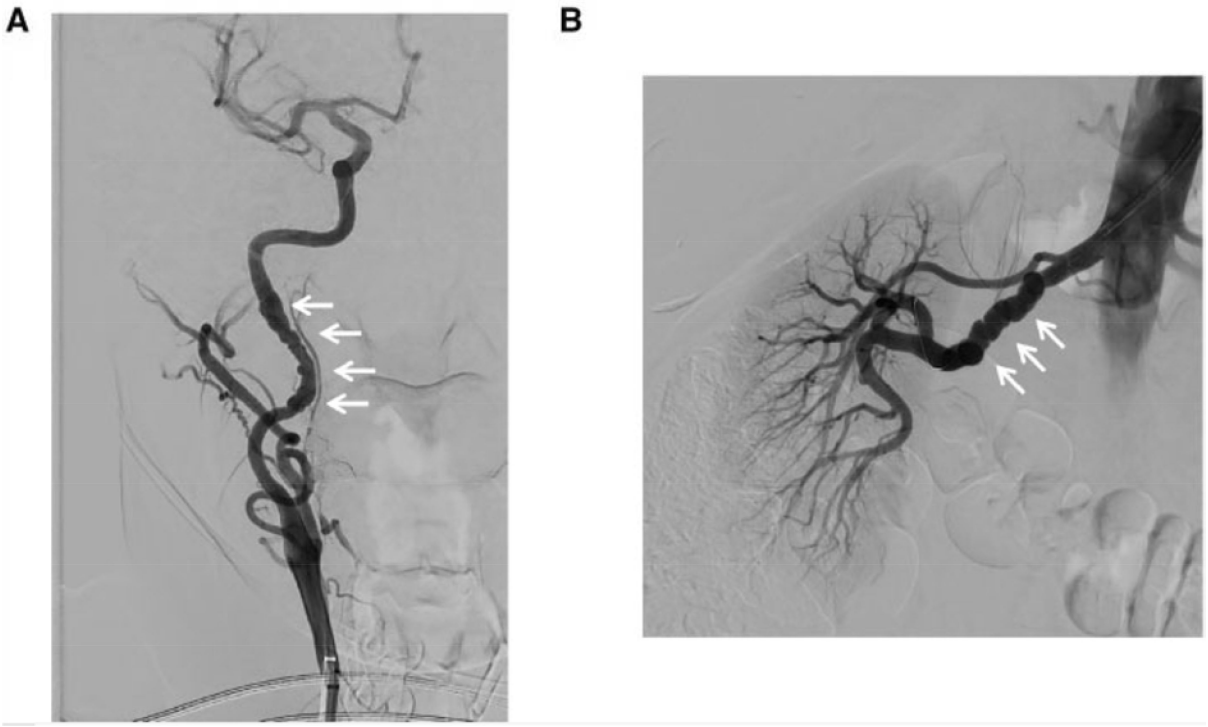

Figure 4:
Typical angiographic appearance of multi-focal fibromuscular dysplasia (FMD) (indicated by white arrows) affecting (A) carotid and (B) renal arteries (from [61] with permission).