

Fibromuscular Dysplasia and other Arteriopathies associated with Spontaneous Coronary Artery Dissection

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Ohio
CHAPTER

Disclosures

- No disclosures.

Overview

- Brief introduction to Spontaneous Coronary Artery Dissection (SCAD)
- How I approach the diagnostic evaluation of a patient with a SCAD event
- Identifying Fibromuscular Dysplasia (FMD) and other arterial disorders associated with SCAD
 - FMD
 - Select collagen vascular disorders

Spontaneous Coronary Artery Dissection (SCAD)

- Refers to spontaneous tear of the coronary artery that is NOT iatrogenic or traumatic, generally in the absence of atherosclerotic disease
- Increasing recognition of SCAD as a cause of MI
 - Predominantly female patients
 - Young
 - “Healthy” – paucity of traditional cardiovascular risk factors
 - Peripartum/postpartum MI
- Increasing detection of SCAD is the result of...
 - Improved intracoronary imaging: OCT + IVUS
 - Increased clinical suspicion + better pattern recognition

Why is it important to identify SCAD?

•Atherosclerosis

- Immediate management of MI
- Medication management of post-MI patient
- Whole body disease / panvascular

•SCAD

- Immediate management of MI
 - How do you treat the dissection?
- Medication management of post-MI patient
 - Differs from traditional atherosclerotic disease
- Whole body disease / panvascular
- Disorder of young patients
 - Lifestyle: exercise / activity limitations
 - Impact on family planning
 - Genetic basis: need for family screening?
 - One time event (hopefully) but impact across the continuum of life

Post-Acute Evaluation

History	Physical Exam	Testing
<ul style="list-style-type: none"> • Physical activity prior to or during onset of symptoms; stressful or emotional triggers during onset of symptoms • Prior episodes of symptoms; other episodes suggesting vascular events (ie TIA) • Details of other medical history or symptoms: headaches/migraines, tinnitus, vision impairment / abnormalities of lens, bowel perforations, pneumothorax, difficulty healing, easy bruising/bleeding, polycystic kidney/liver disease, autoimmune disorder, episodic BP elevations, substance abuse, herbal medications, Rx meds associated with dissection (triptans, stimulants) • Family history: known SCAD, other dissections, aneurysms, MI/stroke, sudden cardiac death, autoimmune disorders 	<ul style="list-style-type: none"> • Cardiopulmonary exam, Peripheral pulse exam, Neuro exam, Abdominal exam • Face exam <ul style="list-style-type: none"> • Spacing of eyes (hypertelorism), anisocoria -> Horner's syndrome, blue sclera, palpebral fissure abnormalities (large or protruding eyes); abnormalities of uvula (wide, long/narrow, bifid); dental crowding; abnormalities of hard palate or jaw; narrow nasal bridge; malar hypoplasia; micrognathia, short chin or narrow chin; small ear pinnae ("elfish" features) • Skin <ul style="list-style-type: none"> • Abnormal scars (not keloids—"cigarette paper" atrophic scars, impaired healing), striae, velvety texture, translucent/increased visible vascularity, laxity/elasticity • Skeletal/joint exam <ul style="list-style-type: none"> • Large or small joint laxity; scoliosis; dislocations • Pectus deformity (excavatum or carinatum) • Height, long digits, short neck (Turner syndrome) 	<ul style="list-style-type: none"> • Carotid artery ultrasound, renal artery ultrasound • Head to pelvis angiography (MRA or CTA head/neck, CTA chest/abd/pelvis) • Referral to Genetic Counselor and genetic arteriopathy panel

Arteriopathies

- **Non-inflammatory, non-atherogenic conditions which affect the fragility of vessels**
 - These conditions are not vasculitis; vasculitis is rarely implicated in dissection

- **Fibromuscular Dysplasia**
 - Multifocal vs unifocal

- **Heritable Connective Tissue Disorders (HCTD) or Collagen Vascular Disorders**
 - Syndromes affecting connective tissue of many organ systems: cardiovascular, skin, skeletal, eyes, lungs
 - Most typically recognized:
 - Marfan syndrome
 - Ehlers-Danlos syndrome
 - Loeys-Dietz syndrome

Fibromuscular Dysplasia (FMD)

- **Non-inflammatory, non-atherosclerotic disorder of medium-sized arteries**
 - Extracranial cerebrovascular circulation (carotid and vertebral arteries) involved in ~75% of cases.
 - Renal arteries involved in 75-80% of cases; 65% of patients with renal FMD also have carotid/vertebral involvement (and vice versa)
 - Additionally: visceral arteries, external iliac arteries, coronaries, brachial, radial, ulnar, superficial femoral arteries can all be involved. Association with aneurysms (intracranial, splanchnic).

- **Disease presentation is dependent on arterial segment involved**
 - Important cause of TIA, stroke. Can present as dissection, aneurysm, stenosis, occlusion, beading, tortuosity.
 - Accounts for 5-10% of cases of renovascular HTN in adult patients <60yo; however, many patients with renal involvement do not have renovascular HTN (do not have hemodynamically significant renal stenosis)
 - Accounts for 35-50% of renovascular HTN in children
 - Due to increasing imaging in the population –and practice of screening other arterial beds when FMD is identified in one vessel— asymptomatic disease is increasingly detected

Fibromuscular Dysplasia

- **Approximately 90% (or more) cases are reported in women**
- **Prevalence is likely higher than we once thought**
 - Review of angiographic data in asymptomatic potential kidney donors: 4.4% prevalence
 - Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial: known FMD was exclusion criterion, incident renal FMD dx in 5.7% of total study participants (8.8% of females who were enrolled)
- **Previously described as disease of young women, however, FMD is being identified in older patients with increasing frequency**
 - United States FMD Registry: mean age at diagnosis 52yo
 - Recent data suggesting elderly patients >65yo may have milder disease course



Olin JW et al. The United States Registry for Fibromuscular Dysplasia: results in the first 447 patients. *Circulation*. 2012;125(25):3182.
 Gornik HL et al. First international consensus on the diagnosis and management of fibromuscular dysplasia. *J Hypertens*. 2019;37(2):229.
 Shivapour DM et al. Epidemiology of fibromuscular dysplasia: A review of the literature. *Vasc Med*. 2016;21(4):376.

Fibromuscular Dysplasia

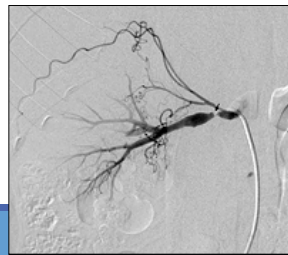
- **Etiology is unknown:** genetic basis + hormonal/environmental factors
 - Suspected hormonal influences as majority of patients are women of childbearing age
 - Studies have suggested autosomal inheritance with variable penetrance
- **Recent data: association between FMD and a single nucleotide variant in the PHACTR1 gene (phosphatase and actin regulator 1 gene, rs9349379-A allele)**
 - Also a risk locus for coronary artery disease (rs9349379-G), migraine headache and cervical artery dissection (rs9349379-A)
 - Recent data in 2019 now showing association of PHACTR1 with SCAD (rs9349379-A)

Perdu et al. Inheritance of arterial lesions in renal fibromuscular dysplasia. *J Hum Hypertens*. 2007;21(5):393.
 Kiando SR et al. PHACTR1 Is a Genetic Susceptibility Locus for Fibromuscular Dysplasia Supporting Its Complex Genetic Pattern of Inheritance. *PLoS Genet*. 2016;12(10):e1006367.
 DeBette S et al. Common variation in PHACTR1 is associated with susceptibility to cervical artery dissection. *Nat Genet*. 2015 Jan;47(1):78-83.
 Adlam D et al. Association of the PHACTR1/EDN1 Genetic Locus With Spontaneous Coronary Artery Dissection. *J Am Coll Cardiol* 2019;73:58-66.

Fibromuscular Dysplasia

• **FMD types: classification is by angiographic appearance** (simplified from former histologic classification scheme)

- **Multifocal FMD: classic “string of beads.”** Most common type (>80% cases), correlates to histologic medial fibroplasia
- Appearance is due to alternating fibromuscular webs and areas of dilatation. The internal elastic lamina is absent at areas of dilatation.
- **Focal FMD: circumferential or tubular stenosis.** Not frequently seen/recognized. Appearance is associated with histologic types: intimal fibroplasia, medial hyperplasia, periarterial hyperplasia.
- Some question of whether this represents a different disease.



Fibromuscular Dysplasia Case 1: Mrs. M

52yo white female referred for SCAD with STEMI 9/25/2018, with prior hx of STEMI 4/9/2017

○ **4/9/2017: STEMI, unknown mechanism**

- Woke at 4am from sleep with chest pain; presented to ER
- EKG: ST elevations in inferior/posterior leads and anterior/lateral leads, with ST depression in leads 1 and aVL
- Positive troponins
- LHC: reported as normal coronaries, apical WMA, LVEF 40%
- Transthoracic echo the following day: LVEF 55-60%
- Course complicated by AV fistula at left radial access site, surgically repaired
- Original event attributed to “stress”
- Mother suffering from terminal IPF; taking care of longtime HHC patient with ALS

○ **9/25/2018: recurrent STEMI**

- Returned home from evening walk with her husband, developed increasing chest and jaw pain; presented to ER
- EKG: ST elevations in anterior leads
- Positive troponins
- LHC: normal coronaries (no ASO), identified dissection in LAD, LVEF 35%
- Transthoracic echo the following day: LVEF 45-50% with anterior and apical WMA
- Medical management:
 - aspirin 81mg QD, clopidogrel 75mg QD, metoprolol succinate 75mg QD
 - Cardiac rehab
- 11/2018 appointment: currently asymptomatic

Case 1: Mrs. M

• Additional PMH:

- Hx of mild dyslipidemia, improved lipid profile with diet changes (Esselstyn plant based diet)
- Migraine headaches (does not use triptans)
- Anxiety
- Insomnia (zolpidem, clonazepam, melatonin)
- Never smoker; rare etoh. UTD cancer screenings. GOPO.

• Past surgical hx:

- L wrist AVF repair; none.

• FHx:

- Father with DM and ?-rheumatoid arthritis.
- No hx of aortic aneurysm, arterial aneurysm or dissection, MI, stroke/TIA, sudden cardiac death, known FMD, or connective tissue disorders.

• Physical Exam → NORMAL!

- BP [R] 113/66, [L] 115/57 | HR 76 | Wt 55.7kg | Ht 5' 7.5" | BMI 18.9
- Gen: Cooperative, in no acute distress, alert.
- Skin: Normal with no rashes or lesions. Warm and dry.
- HEENT: Anicteric sclera, PERRLA, EOMI. No oropharyngeal ulcers. No bifid uvula.
- Neck: Supple, no cervical adenopathy, thyroid symmetric without nodules, no carotid bruits, no JVD elevation.
- Heart: RRR, normal S1 and S2; no murmur, gallop or rubs.
- Lungs: CTA bilat; no rhonchi, rales, or wheezing.
- Abdomen: Abdomen soft, non-tender, BS normal, no palpable masses or organomegaly. No bruit.
- Upper extremities: Normal exam of the upper extremities.
- Lower extremities: Normal exam. No edema. Feet and toes warm.
- Peripheral pulses: Bilateral femoral=2/2, popliteal=2/2, dorsalis pedis=2/2, posterior tibial=2/2, brachial =2/2, radial = 2/2, ulnar= 2/2
- Neuro: CN II-XII intact. DTR 3/5 bilateral knee, ankles, triceps, biceps. Strength 5/5 bilateral upper and lower extremities.
- Musculoskeletal: Normal chest wall and back. Beighton hypermobility score 0

Case 1: Mrs. M

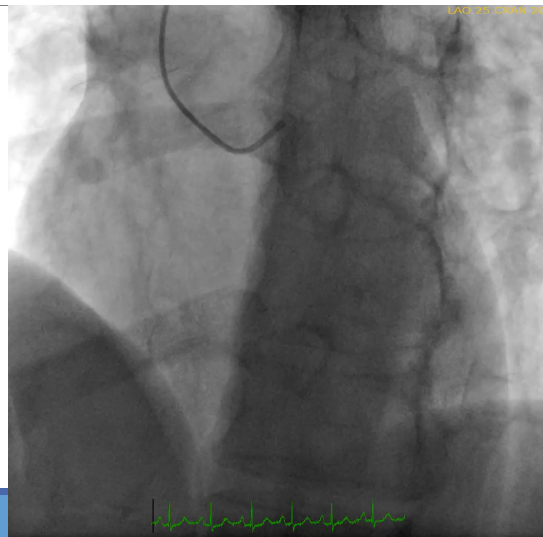
• 4/9/2017 LHC

- reviewed, likely dissections: distal RCA to PDA, distal branches of LCx and likely distal LAD vs diagonal branches

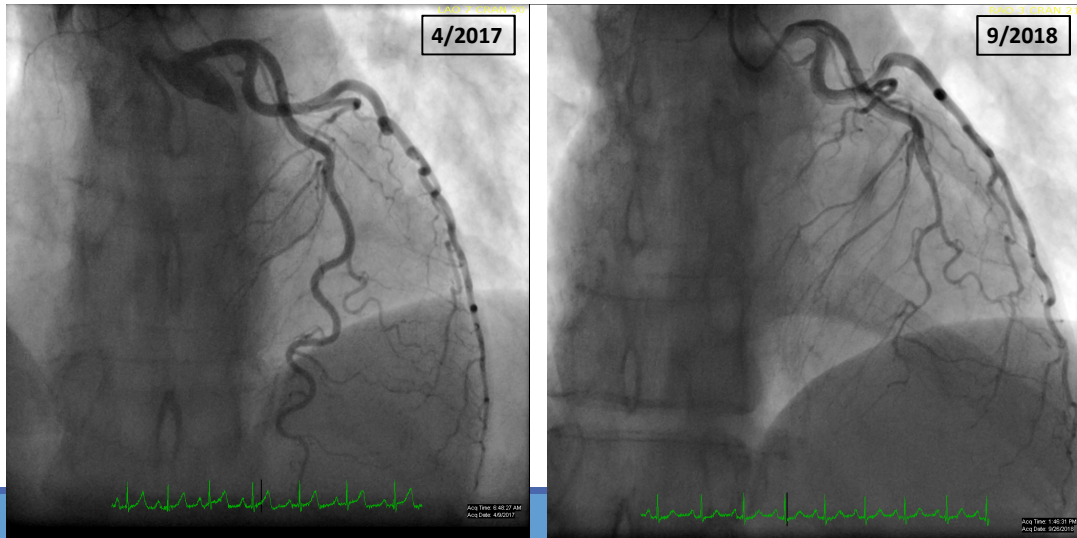
• 9/26/2018 LHC (shown at right)

- LAD dissection at mid with very slow flow to apex; RCA/PDA lesion did recannulate, LCx branches did not

- Both studies notable for very tortuous coronary arteries

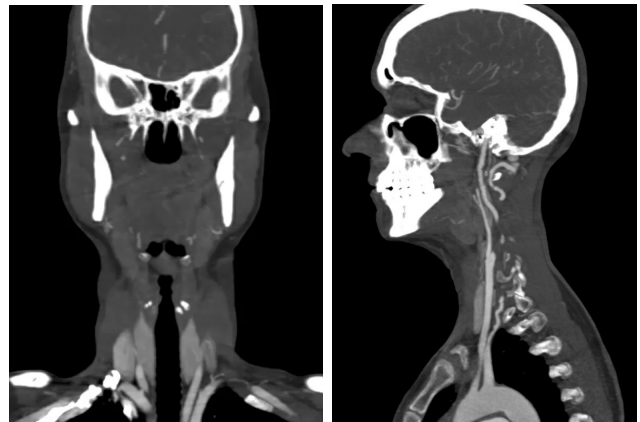


Case 1: Mrs. M



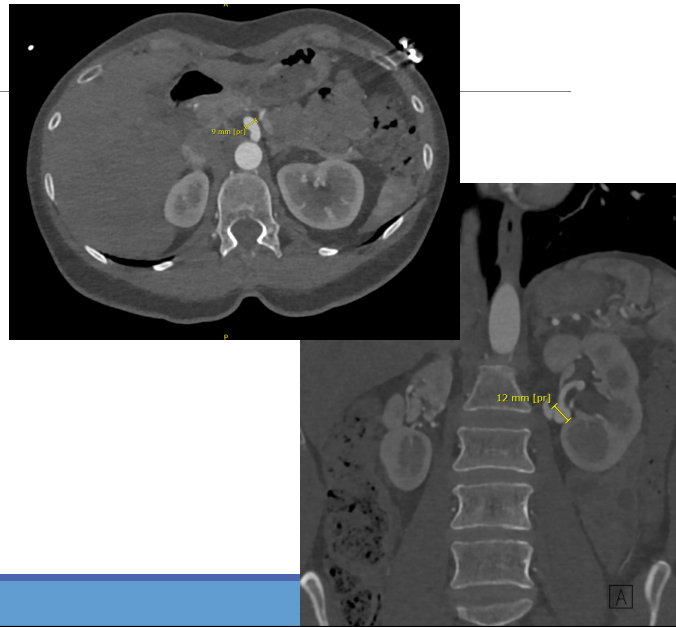
Case 1: Mrs. M

- Carotid artery duplex ultrasound
 - Elevated velocities and turbulent flow at distal internal carotid arteries bilaterally
- CTA head/neck
 - Irregularity and beading of the distal cervical ICA bilaterally
 - Mild irregularity of the bilateral vertebral arteries
 - Normal intracranial circulation
- Imaging consistent with fibromuscular dysplasia (FMD), multifocal type



Case 1: Mrs. M

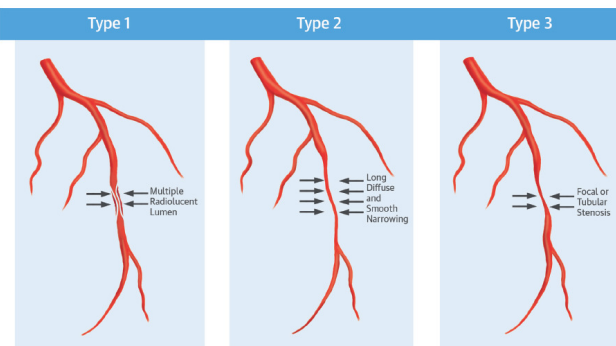
- Renal and mesenteric artery ultrasound
 - Normal
- CTA chest/abd/pelvis
 - Ectasia of proximal celiac artery, 9mm
 - Aneurysm of the distal left renal artery, 12 x 10mm
 - Normal aortic course and caliber throughout
- Given SCAD in addition to carotid artery beading and focal ectasia of visceral arteries (including renal involvement), felt to be most consistent with FMD
- Genetic panel: normal/negative



Coronary findings for FMD-associated SCAD

- **FMD is the most commonly reported arteriopathy associated with SCAD**
 - 62% of 327 patients with SCAD at one center found to have FMD
 - Estimate is a little high...but FMD is the most prevalent of the arteriopathies so agree that it would be most represented (inter-observer differences in diagnosis of FMD)
- **Lesion recognition important for dx of SCAD**
 - 3 types of dissection patterns (for SCAD due to any cause)
 - Can be hard to appreciate on tortuous arteries or small vessels!
- **Coronary artery beading is rare; few case reports**
- **Most typical finding is significant coronary tortuosity**
 - Attempts being made to standardize some measure of tortuosity
 - S-curve if seen in other arterial beds is not pathognomonic but is associated with FMD (and other arteriopathies)
 - Particularly useful finding in YOUNG patients; increasing frequency of finding tortuous or redundant vessels in elderly

CENTRAL ILLUSTRATION SCAD Classification



Saw, J. et al. J Am Coll Cardiol. 2017;70(9):1148-58.

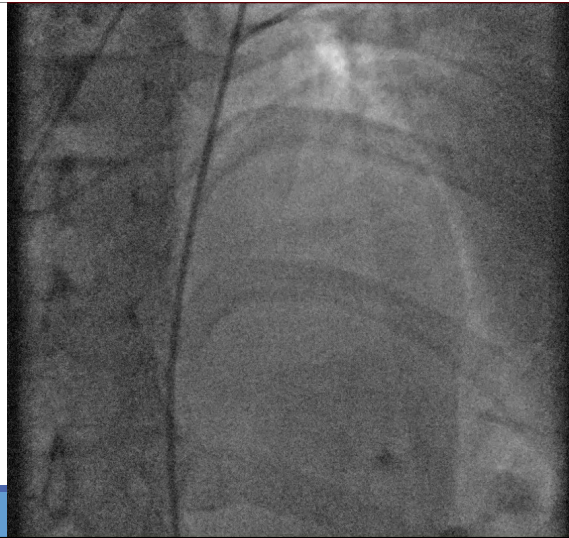
Saw J et al. Spontaneous Coronary Artery Dissection; Clinical Outcomes and Risk of Recurrence. J Am Coll Cardiol 2017;70:1148-58.

Coronary Tortuosity Case 1.5: Ms. H

• Many patients seen in clinic for SCAD have angiographically similar arteries as patient in Case 1: note coronary tortuosity again

49yo white female with hx of STEMI

- Seen for 2nd opinion for ?-SCAD after female paternal cousin was diagnosed with SCAD
- PMHx: migraines, never smoker, BMI 21
- FHx: Cousin-SCAD, father-cardiac arrest age 66
- 10/4/2017 STEMI
 - LHC: LAD reported as "30-40% mid stenosis and diffuse distal narrowing of up to 70%"
 - LCx and RCA appear normal



Case 1.5: Ms. H



- Renal artery and superior mesenteric artery angiography showed normal vessels (above)
- Carotid, renal artery, and mesenteric artery duplex ultrasound with normal results.
- Patient declined additional imaging screening (MRA or CTA) at this time
- Pursuing genetic testing; has 2 daughters

Vessel tortuosity: Intersection of Fluid Dynamics and Arterial Physiology

• Arterial tortuosity

- Most commonly associated with HTN, smoking, aging -> degeneration and fragmentation of structural components of extracellular matrix (ECM) of arterial wall and surrounding supportive connective tissue -> lose axial tension of vessel
- Or ECM with dysfunctional or deficient elastin/collagen due to genetic cause

• Subsequent reduced axial tension on vessel -> elongation of vessels -> vessel tortuosity

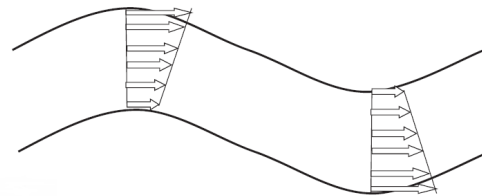
• Tortuosity increases vascular resistance, changes flow velocities (and *vorticity* = velocity + spin)

• Induces alterations in lumen shear force and wall stress

- Mechanical stress: regulates normal function of vascular endothelium and can induce injury/remodeling

• Tortuosity: vessel has increased sensitivity to low and high pressure states

- “Collapsible tube model:” lumen collapses or kinks if lumen pressure too low
- Long vessel segments under pressure become unstable when lumen pressure exceeds a critical value
- Shown: imbalanced wall stress distribution of flow through two deflection points



Modified from Han. *Twisted Blood Vessels: Symptoms, Etiology and Biomechanical Mechanisms.* J Vasc Research. 2012; 49: p190 Figure 4

Vessel tortuosity: Intersection of Fluid Dynamics and Arterial Physiology

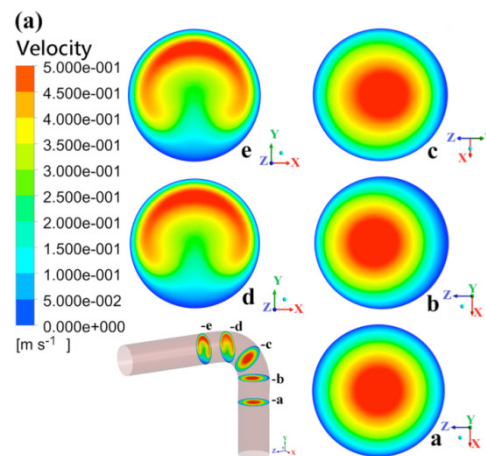
• Effects of Artery Curvature

- Velocity is skewed towards the outer bend
- Skewness becomes more prominent as curvature increases
- Curvature influences flow through the bend, but also the final output

• Model of 90 degree bend in artery: velocity skew in “hoof” like shape within the lumen

• Loss of Laminar Flow

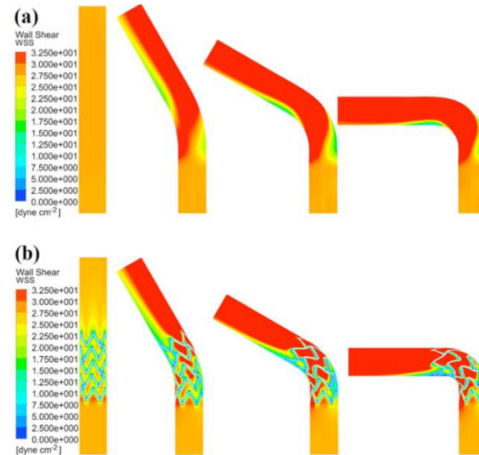
Image modified from Hsiao HM et al. *Hemodynamic Behavior of Coronary Stents in Straight and Curved Arteries.* Current Nanoscience. 2014(10)2, p4 Figure 5.



Vessel tortuosity: Intersection of Fluid Dynamics and Arterial Physiology

- Loss of **Laminar Flow** -> velocity shifts, turbulence
- Increases with increasing vessel curvature
- **High velocity**-> **Increased wall shear forces**
 - Shown in **Red**: outer bend
- **Low velocity**-> **Low wall shear forces**
 - Shown in **Blue**: inner bend, outer wall just distal to bend; backside of struts particularly at “crowns” (most curved area of strut)
 - Low wall shear forces -> slow or disturbed flow, associated with areas of atherosclerotic plaque development and greatest neointimal thickening in previously stented arteries

Image modified from Hsiao HM et al. *Hemodynamic Behavior of Coronary Stents in Straight and Curved Arteries*. *Current Nanoscience*. 2014(10)2, p4 Figure7.

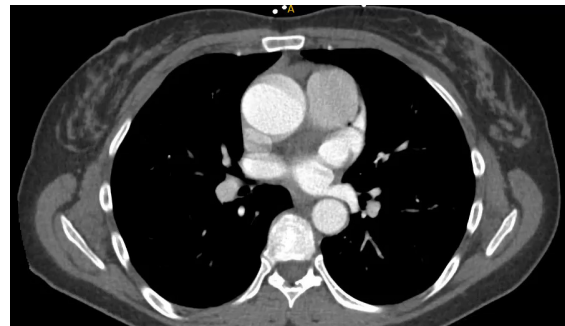


Arteriopathy Mimicry Case 2: Mrs. S

39 yo white female, referred for hypercoagulable state with limb ischemia. Never-smoker, BMI 26.

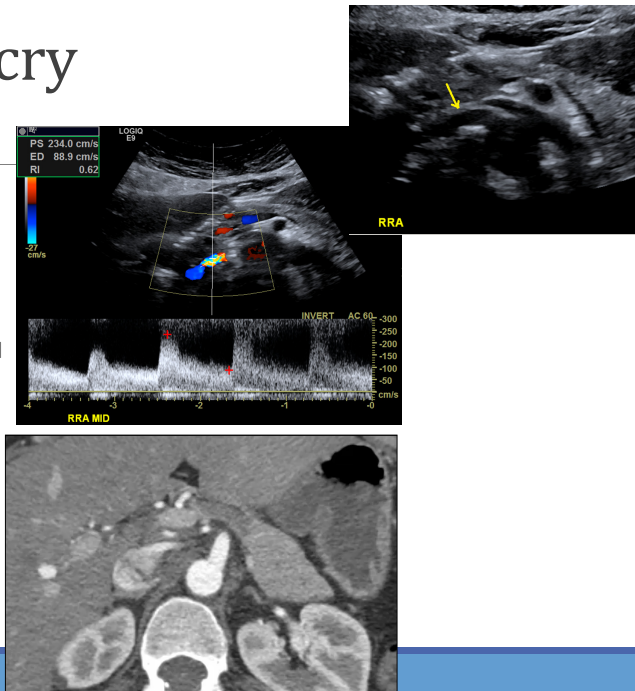
- 2001: Spontaneous pneumothorax
- 2004: Miscarriage at EGA 12wks
- 2006: Left cerebellar infarct with left vertebral artery occlusion; attributed to post-partum dissection
- 7/2017: Acute limb ischemia of left foot
 - PT, peroneal, AT arteries all with short segment occlusions
 - Mural thrombus at descending thoracic aortic arch
- Extensive hypercoag testing including bone marrow biopsy is unrevealing

○ Consider: what if primary issue is not thrombophilia, but instead aortic dissection leading to thromboembolism?



Arteriopathy Mimicry Case 2: Mrs. S

- Carotid duplex ultrasound
 - Normal results except known L vert occlusion
- Renal artery duplex ultrasound
 - Bilateral renal arteries with velocity shifts and turbulence at mid vessels, suggesting FMD
 - Close review of prior CTA confirmed beading of renal arteries (right more clearly than left)
- FMD is not strongly associated with aortic dissection, what is going on here?
- Genetics: confirmed FBN1 mutation -> Marfans
 - Paternal grandmother with aortic dissection
 - Father recently dx dislocated lens when he presented for cataract surgery -> confirmed FBN1
 - Son is negative for mutation



Marfan Syndrome (MFS)

- Heterozygous mutations in FBN1, coding for the extracellular matrix (ECM) protein fibrillin-1
 - Cardiovascular, ocular, and skeletal manifestations
 - Most common cardiovascular phenotype involves aortic aneurysm and particularly aortic root; risk for dissection at the sinuses of Valsalva
- If arteries other than or in addition to the aorta are involved (medium-sized vessels), consider Ehler-Danlos or Loays-Dietz syndrome
 - Pursue genetic testing to confirm diagnosis
- Case reports of FMD (beading) being a feature of underlying Heritable Connective Tissue Disorders

Ehler-Danlos Syndrome (EDS)

- **EDS:** a group of clinically and genetically heterogeneous connective tissue disorders
 - **Currently 13 subtypes;** many overlapping features -> molecular/genetic testing is key for suspected vascular involvement
 - **Typical features:** joint hypermobility with abnormalities of the ligaments and joint structure; dislocations/subluxation; skin hyperextensibility; easy bruising, thin skin; bowel rupture; and complications in childbirth or after childbirth including uterine rupture
- **Heterozygous mutation in COL3A1 gene = Vascular EDS = Type IV EDS = “vEDS”**
 - ~25% will have aortic aneurysmal disease on evaluation; also can involve medium to smaller sized arteries (truly panvascular)
 - **Very heterogenous in terms of severity.** May be milder forms of vEDS, however, it is unknown how to stratify/identify those at lower risk. Therefore all individuals with mutations in COL3A1 are currently managed similarly as high risk vascular patients.
 - Some patients with COL5A1/2 mutations can have aortic involvement

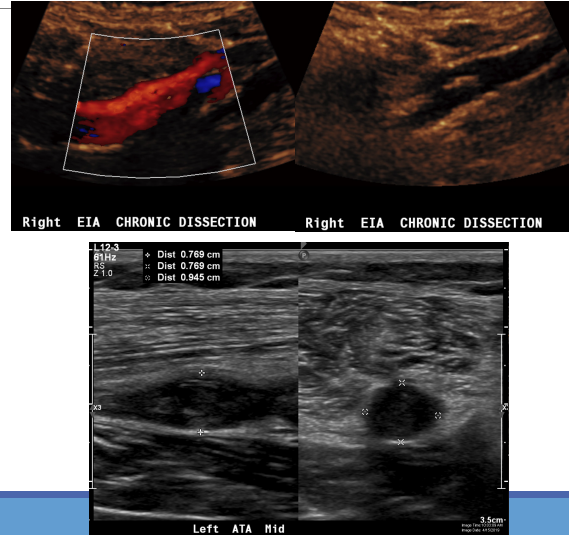
Ehler-Danlos Syndrome

- **Management:**
 - Periodic imaging screening/surveillance from head to pelvis. However, rupture of arteries can occur without any prior dilation of the artery.
 - Surgery is discouraged unless absolutely necessary due to tissue fragility and impaired healing. However, better outcomes are associated with diagnosis being made prior to surgical interventions.
 - EDS Hypermobility Types: referral to Orthopedics and/or Pain Management for complications related to joint subluxation, scoliosis, etc

Ehler-Danlos with Panvascular Involvement Case 3: Mrs. B

58yo white female seen for follow up last week

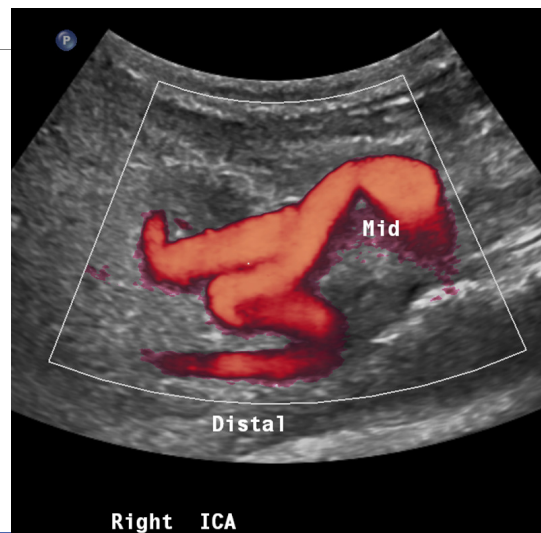
- 2001: inferior wall MI, initially attributed to vasospasm
 - Retrospectively determined to be SCAD
- 1/2009: presented with pain related to hepatic artery aneurysm
 - Found aneurysmal dilation of celiac artery, hepatic artery, and SMA, left renal artery, and evidence of chronic dissection of the right and left external iliac arteries
- 2009: evaluation
 - Screening imaging: cavernous right internal carotid artery with evidence of prior carotid and vertebral dissections
 - FHx: father deceased from thoracic aorta dissection(47); brother with iliac dissection (31); niece with vertebral dissection (24)
 - Gene testing: COL3A1 gene positive -> vEDS
- 3/2015: splenic artery rupture with emergent splenectomy
- 10/2017: first of many tibial artery aneurysm/dissections detected
- 4/2019: stable imaging including normal ABI
 - on BB + ARB + aspirin 81mg



Case 4: Mr. D

70yo white male seen regarding carotid stenosis, tortuosity, and syncope

- Seizure disorder dx age 6
- 1994: (age 45) Left-sided stroke
 - due to L ICA 100% occlusion, was told this was L ICA dissection
- 2016: increasing frequency of episodic dizziness
- 7/2018: speech difficulties and flashes of light in vision field, resolved in an hour
 - Became hypertensive while in ER -> chest pain
 - Heart catheterization "normal" -> ?-SCAD
- 12/2018: Syncope vs seizure while turning head over left shoulder to back out car down driveway.
 - Was found to have low phenobarbital level due to drug interaction with recently started statin



Symptomatic cervical vessel tortuosity Case 4: Mr. D



•Physical exam:

- Overall normal except short neck and retrognathia, mild hypertelorism and malar flattening, slightly protruding pointed ear pinnae. No bifid uvula or dental abnormalities.
- No hyperflexibility or skin abnormalities.

•CTA head/neck

- Significant tortuosity of bilateral cervical ICA
 - Fusiform dilation of the proximal right ICA
 - 11 mm pseudoaneurysm and long segment fusiform dilation involving the mid and distal left ICA (shown)
- Normal intracranial circulation; vertebral arteries patent; no significant atherosclerosis

•CTA chest/abdomen/pelvis

- No aortic aneurysm. Tortuosity of subclavian and iliac arteries.
- Focal dissection of the celiac trunk; stenosis of the hepatic artery at origin with post-stenotic dilation; tortuous SMA; tortuous left renal artery

•Genetic testing: TGF β 3 variant of unknown significance (VUS), probable Loeys-Dietz spectrum given facies and arterial involvement

- Considering pipeline stent of carotid vs resection

Loeys-Dietz Syndrome (LDS)

- Autosomal dominant mutations in TGBR1/2, SMAD2/3, or TGF β 2/3: code for components of the TGF β -signaling pathway
 - First identified in 2005: severe aneurysms and birth defects
 - Now recognized as large spectrum associated with this condition, ranging from people with aneurysms at very young ages and birth defects to those with aneurysm but little or no other connective tissue problems
- Mutations in TGFBR1 and TGFBR2 (TGFBR1/2) account for 5-10% of hereditary aneurysms
- LDS can be distinguished from Marfan by unique features:
 - Facial features: hypertelorism (eye spacing), bifid uvula or cleft palate, retrognathia, malar hypoplasia
 - Club feet, or contractures in rare cases
 - Widespread aortic and peripheral arterial aneurysm and tortuosity
 - No association is reported between LDS and the presence of ectopia lentis, a distinguishing feature of MFS
 - Overlapping features between MFS and LDS include scoliosis, pes planus, anterior chest deformity, spontaneous pneumothorax, and dural ectasia

Loeys-Dietz Syndrome (LDS)

Early Surgical Experience With Loeys-Dietz: A New Syndrome of Aggressive Thoracic Aortic Aneurysm Disease

Jason A. Williams, MD, Bart L. Loeys, MD, Lois U. Nwakanma, MD,
Harry C. Dietz, MD, Philip J. Spevak, MD, Nishant D. Patel, BA, Katrien François, MD,
Julie DeBacker, MD, Vincent L. Gott, MD, Luca A. Vricella, MD, and
Duke E. Cameron, MD

Division of Cardiac Surgery, McKusick-Nathans Institute of Genetic Medicine, Division of Pediatric Cardiology, and Howard
Hughes Medical Institute, The Johns Hopkins Medical Institutions, Baltimore, Maryland; and the Department of Cardiac Surgery
and Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium

“Clinical criteria and genotyping were used to identify 71 patients. Before surgical intervention, 6 patients (9%) died from aneurysm rupture or dissection, which occurred in several patients with aortic diameters of less than 4.5 cm and as early as 6 months of age.”



Williams et al. Ann Thorac Surg 2007;83:5757– 63

Loeys-Dietz Syndrome (LDS)

- Compared to Marfans, LDS cardiovascular manifestations tend to be more severe
 - Recommend screening/surveillance from head to pelvis at initial presentation and then 6mo later for interval comparison; if stable, should undergo annual screening
- Recommend surgical intervention on aneurysms at smaller diameters due to high rupture risk.
 - Guidelines suggest surgical intervention for thoracic aorta be considered at 4.2 cm for patients with LDS (Hiratzka et. al. 2010 Am Coll Cardiol).

Examples of facial features and extra-vascular features of LDS in a cohort of patients with TGF β 3 mutation.

Modified from Bertoli-Avella AM et al. Mutations in a TGF- β Ligand, TGF β 3, Cause Syndromic Aortic Aneurysms and Dissections. J Am Coll Cardiol. 2015;65:1324–36



Summary: Genetic Testing

Panel: ACTA2, CBS, COL3A1, COL5A1, COL5A2, EFEMP2, FBN1, FBN2, FLNA, FOXE3, MED12, MYH11, MYLK, NOTCH1, PLOD1, PRKG1,SKI, SLC2A10, SMAD3, SMAD4, TGFB2, TGFB3, TGFB1, TGFB2

Ehler-Danlos

COL3A1	Mutation associated with Vascular Ehlers Danlos syndrome (EDS type IV or vEDS) – can have panvascular involvement.
COL5A1 and COL5A2	Mutations associated with classic form of Ehlers Danlos syndrome (EDS) connective tissue disease that generally affects the skin and joints. Rarely, those with mutations in COL5A1 or COL5A2 develop aneurysms or dilations of the aorta, but the majority will not have cardiovascular involvement.

Loeys-Dietz Spectrum

TGFB1 and TGFB2	Loeys Dietz syndrome; accounts for 5-10% of hereditary aneurysms. Generally some features of a connective. Large spectrum associated with this condition, ranging from people with aneurysms at very young ages and birth defects to those with aneurysm but little or no other connective tissue problems.
TGFB2	Generally aortic involvement, overlap with individuals with Loeys Dietz presentation.
TGFB3	Features overlapping with Loeys-Dietz spectrum and Marfan syndrome; aneurysm and dissections involving aorta and other arteries. Associations with cardiomyopathy; case reports of congenital contractures, hypotonia, bifid uvula.
SMAD3	Clinical presentation overlaps Loeys-Dietz syndrome. Aneurysms reported throughout aorta, iliac arteries, intracranial arteries. Connective tissue findings present in many individuals. Notable early-onset osteoarthritis.

How to interpret the Variant of Unknown Significance (VUS) Result

- Patients with aortic dissections but no family history or overt syndromic features have an increased burden of rare genetic variants of unknown significance (VUS) in genes known to cause heritable thoracic aortic disease (HTAD) -> and other arterial abnormalities
- In a patient with known dissection or other vascular abnormality, there is greater likelihood that the VUS is clinically significant (high pre-test probability)
- In a patient with no known vascular events and no apparent abnormalities on imaging, a VUS is truly Unknown Significance
- Use your Genetic Counselor as a resource!
 - Results of panels are interpreted/reported by a board-certified clinical molecular geneticist or molecular genetic pathologist
 - Reports use of specific standard terminology- "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" to describe variants
 - Counselor can assist with interpreting significance of results and pulling data about the VUS
 - Patient should periodically check in for updated information about the VUS or testing updates

Kwartler CS et al. Variants of Unknown Significance in Genes Associated with Heritable Thoracic Aortic Disease Can Be Low Penetrant Risk Variants. American Journal of Human Genetics. 2018 July; 103: 138–143.

Richards S et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-24

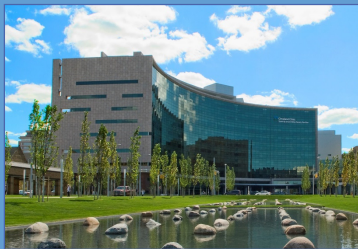
Clinical Genetics of SCAD

- MGH SCAD registry 7/2013-9/2017: 107 patients enrolled, 73 with cardiovascular genetics evaluation
 - Six patients (8.2%) had identifiable genetically triggered vascular disease. None of these 6 had radiographic evidence of FMD. Patients with positive gene testing were noted to be younger at time of first SCAD event.
 - 3 with vascular Ehlers-Danlos syndrome (*COL3A1*)
 - 1 with Nail-patella syndrome (*LMX1B*)
 - 1 with autosomal dominant polycystic kidney disease (*PKD1*)
 - 1 with Loey-Dietz syndrome (*SMAD3*)
 - Additional 12 patients with Variant of Unknown Significance (VUS) in one of the following genes: CBS, COL3A1, COL5A1, COL5A1, FBN2, FLNA, MYH11, NOTCH1, PKD1, PKD2

Kaadan MI et al. Prospective Cardiovascular Genetics Evaluation in Spontaneous Coronary Artery Dissection. *Circulation: Genomic and Precision Medicine*. 2018;11:e001933.

Fibromuscular Dysplasia and other Arteriopathies associated with Spontaneous Coronary Artery Dissection

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- Spontaneous Coronary Artery Dissection (SCAD) is a sentinel event which is frequently associated with an underlying arterial disorder
 - Maintain a high degree of suspicion for FMD and collagen vascular disorders, particularly in patients who are young, female, and have paucity of cardiovascular risk factors
 - High risk for recurrent events due to underlying arteriopathy, and due to injury at site of prior dissection
- Diagnostic evaluation of a patient with a SCAD event
 - Expert review of catheterization images
 - Exam sensitive to findings of connective tissue disorders (skin, joints, face)
 - High quality head to pelvis imaging to aid in diagnosis of underlying condition, and evaluate for other occult lesions (aneurysms, pseudoaneurysms/dissections, severe arterial tortuosity/kinks, stenosis)
 - Low threshold for Genetic Counseling and testing due to implications for future surveillance, risk estimates, and screening of other family members

- Online resources for providers and patients:

www.scadalliance.org
www.fmdsa.org
www.marfan.org
www.loeydietz.org
www.johnritterfoundation.org
www.ednf.org



Ohio
CHAPTER