An Introduction to Clinical Research

Mount Sinai Heart

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A Few Comments About Problem Solving

It's not that I'm so smart, it's just that I stay with problems longer.
Albert Einstein

Success consists of going from failure to failure without loss of enthusiasm.
Winston Churchill

If you're not failing every now and again, it's a sign you're not doing anything very innovative.
Woody Allen

Are you going to observe or experiment?

observational – cross sectional, case series, case-control studies, cohort studies
observe and record characteristics
look for associations

experimental – before and after studies, comparative trials (controlled or head to head), randomised trials (ditto)
identify participants
place in common context
intervene
observe/evaluate effects of intervention

The Problems Studying FMD are:

-- Most studies are very small:

---case reports

---small case series

---almost all involve less than 100 subjects

-- Therefore, we do not even know what questions to ask. That is why we are doing registry and not a randomized clinical trial.

United States Department of Health & Human Services

AHRQ Agency for Healthcare Research and Quality

Advancing Excellence in Health Care www.ahrq.gov

Registries for Evaluating Patient Outcomes: A User's Guide

Final Research Report published 16 May 2007

http://effectivehealthcare.ahrq.gov/reports/new_research.cfm

Definition of a Registry

AHRQ

Registries for Evaluating Patient Outcomes: A User's Guide

"A patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes."

In the U.S. FMD Registry we take the information recorded at your office visits. This includes the history, examination, results of all tests performed and documentation and results of any procedures. We capture this information in a central database and evaluate large numbers of patients for trends.

Benefits of Registries

- Obtain ‘real world’ therapeutic effectiveness and safety data
- Large patient numbers can detect rare adverse events
- Heterogeneity among numerous investigative sites
- Research collaboration with interactive communication & data reporting to investigators
- Usual diagnostic and follow-up procedures can be used rather than “research” procedures
- Can be conducted in any phase of product development

Benefits of Registries

- Flexible, multi-faceted, e.g., sub-studies
- Study subjects are heterogeneous
  - Various treatments
  - Concomitant meds
  - Co-morbidities
- Hypothesis generation when an a priori hypothesis is difficult to define
- Supportive data for label extensions
- Evidence-based medicine for outcomes & reimbursement
- Cost effective on a per patient basis

Limitations of Registries

- The FMD registry operates on a shoestring budget.
- For most research studies, coordinators and principal investigators get paid for their time. This helps to support their salary so their institutions allow them time to do the research.
- Every coordinator and PI participates in the registry with no compensation.
- All money goes to maintaining the database at the University of Michigan and they are giving us a huge discount on costs.
- For example a randomized controlled trial can cost up to 200 million dollars to run.
- The CORAL TRIAL with 940 patients cost about 30 million!

How is a Registry "different" from a RCT?

Registry

- Effectiveness
- Observational
- "Real world"
- Hypothesis generating
- Large "N"
- Flexible

RCT

- Efficacy
- Randomized
- Controlled / selection criteria
- Hypothesis driven
- Small "N"
- Powered

CORAL

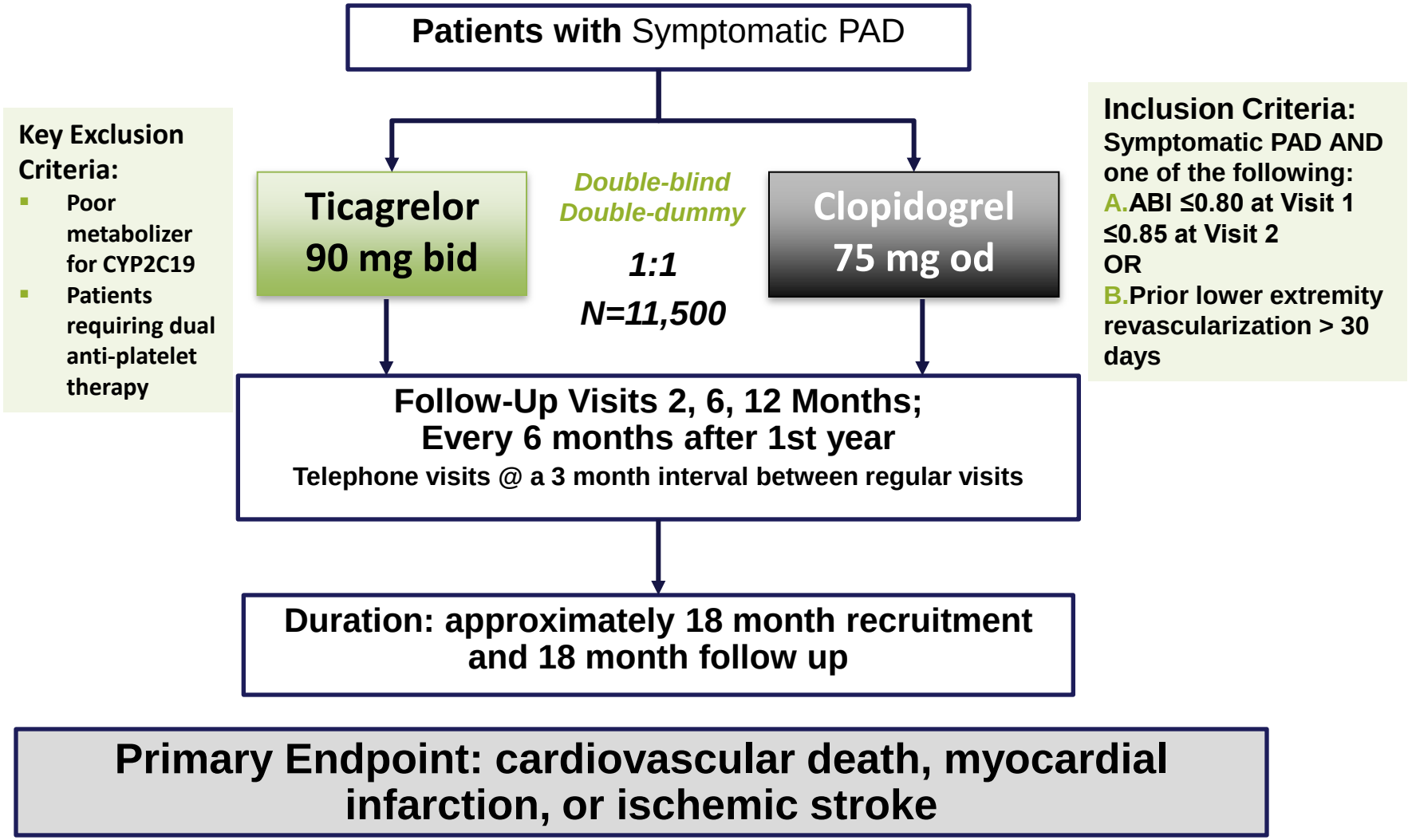
(Cardiovascular Outcomes in Renal Atherosclerotic Lesions)

- CORAL Trial
  - Multicenter, unblinded, randomized trial
  - The purpose of the CORAL study is to determine the best treatment for patients who have high blood pressure and blockage of the renal artery that supplies blood to the kidney.
  - As a patient in the study there are 2 courses of treatment.
    - One group will receive blood pressure medication only.
    - The second group will receive blood pressure medication plus stent, which is used to open the blockage.

EUCLID

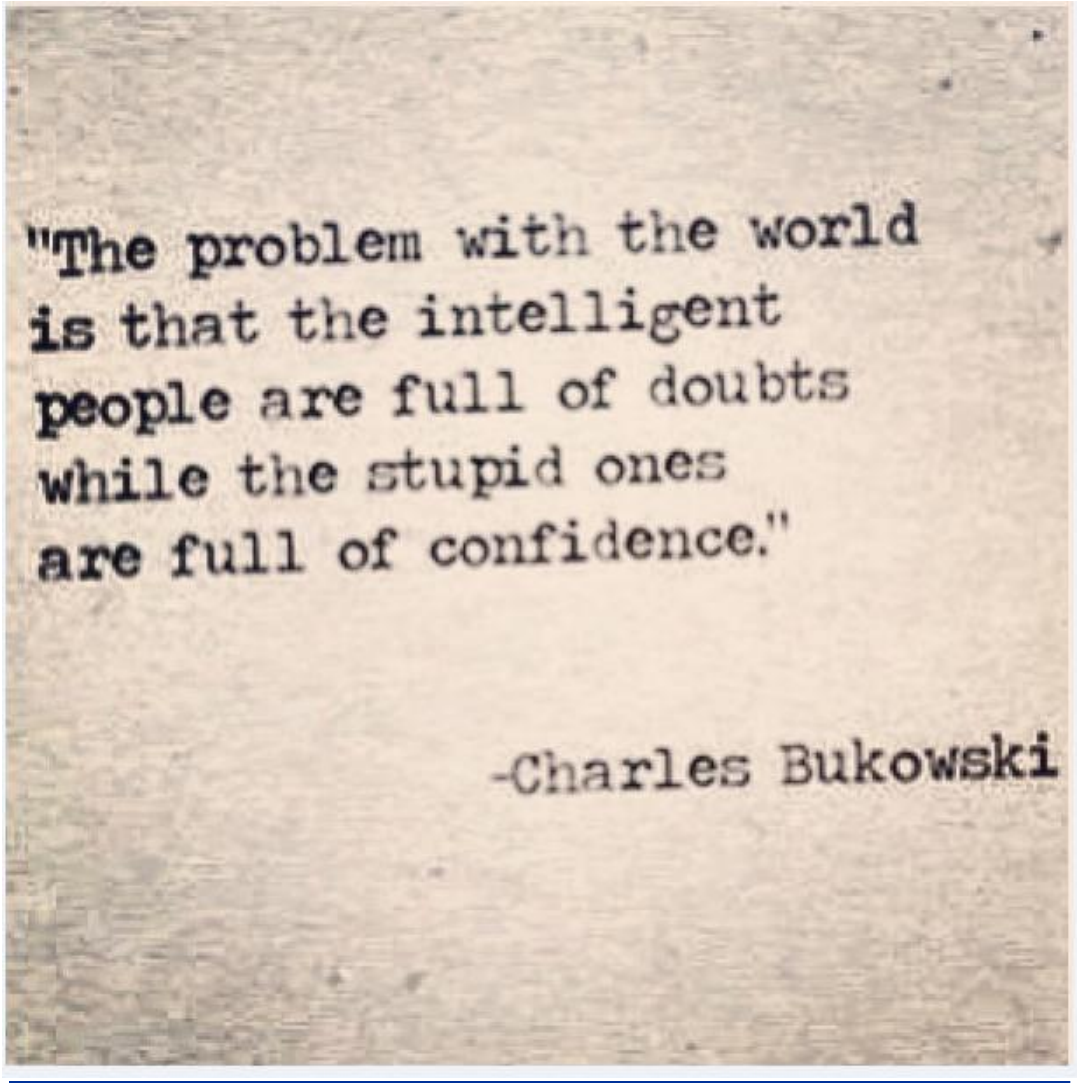
- Patients with peripheral artery disease die from heart attack, stroke and other cardiovascular deaths
- Clopidogrel is better than aspirin in preventing MI, stroke or CV death
- Preliminary studies with tricagrelor in the heart appear to be superior to clopidogril
- 11500 patients from 28 countries worldwide
- Randomized, double blind study

EUCLID Study Design



Center For Fibromuscular Dysplasia Care & Research

Mount Sinai *Heart*



Mount Sinai Heart
Center for Fibromuscular Care and Research

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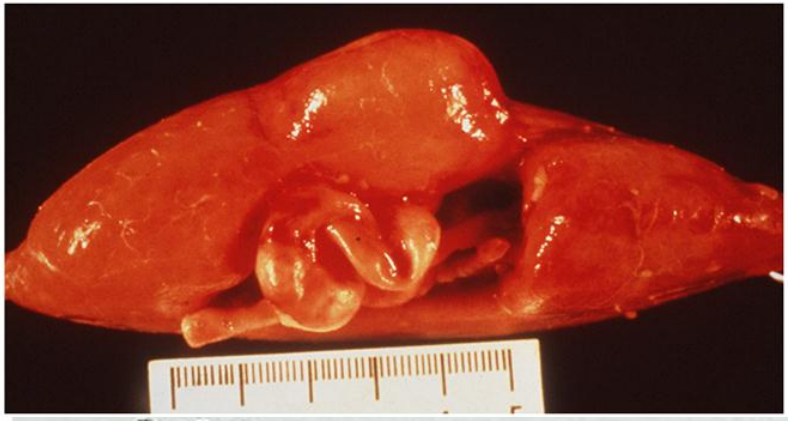
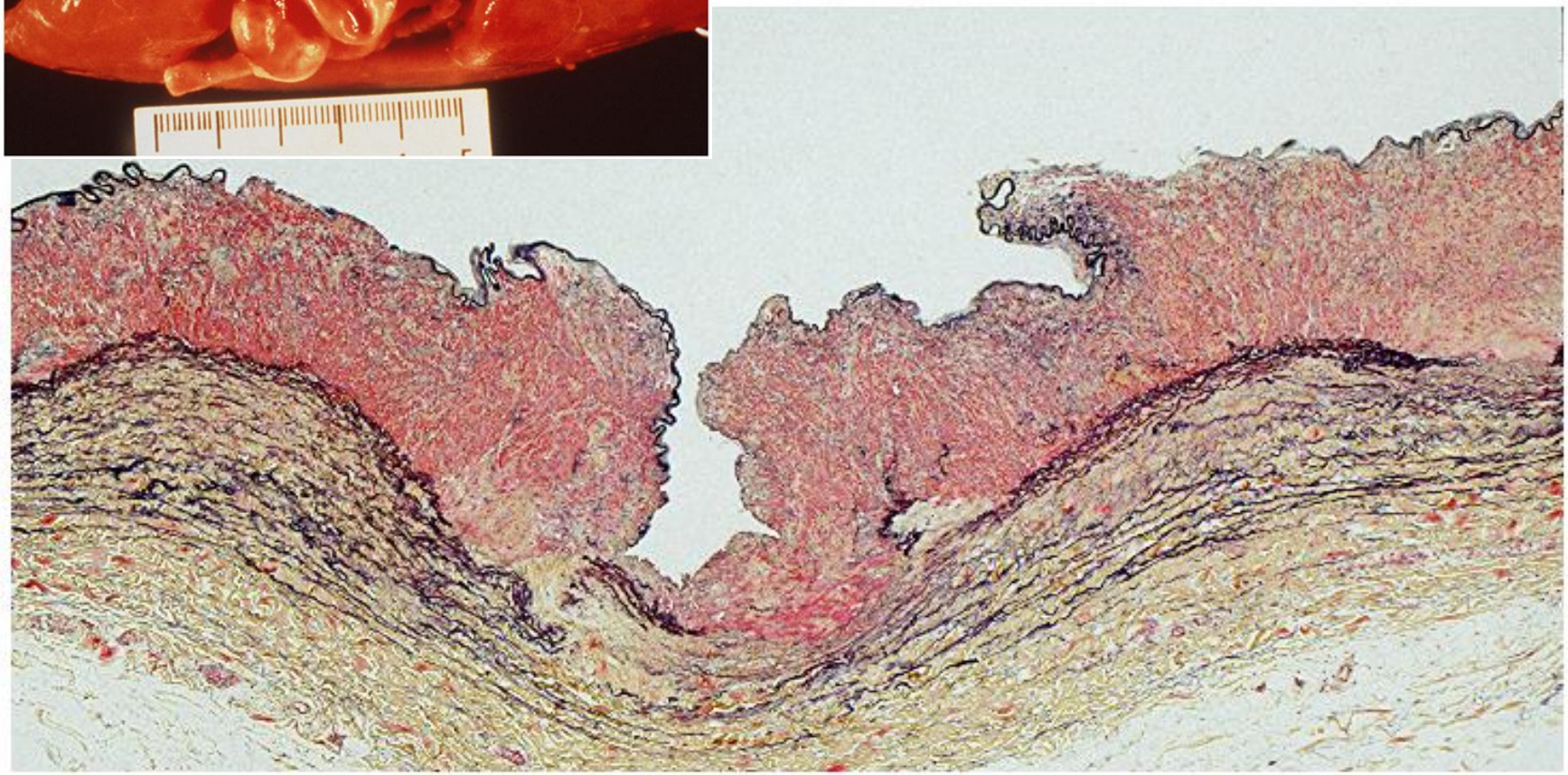
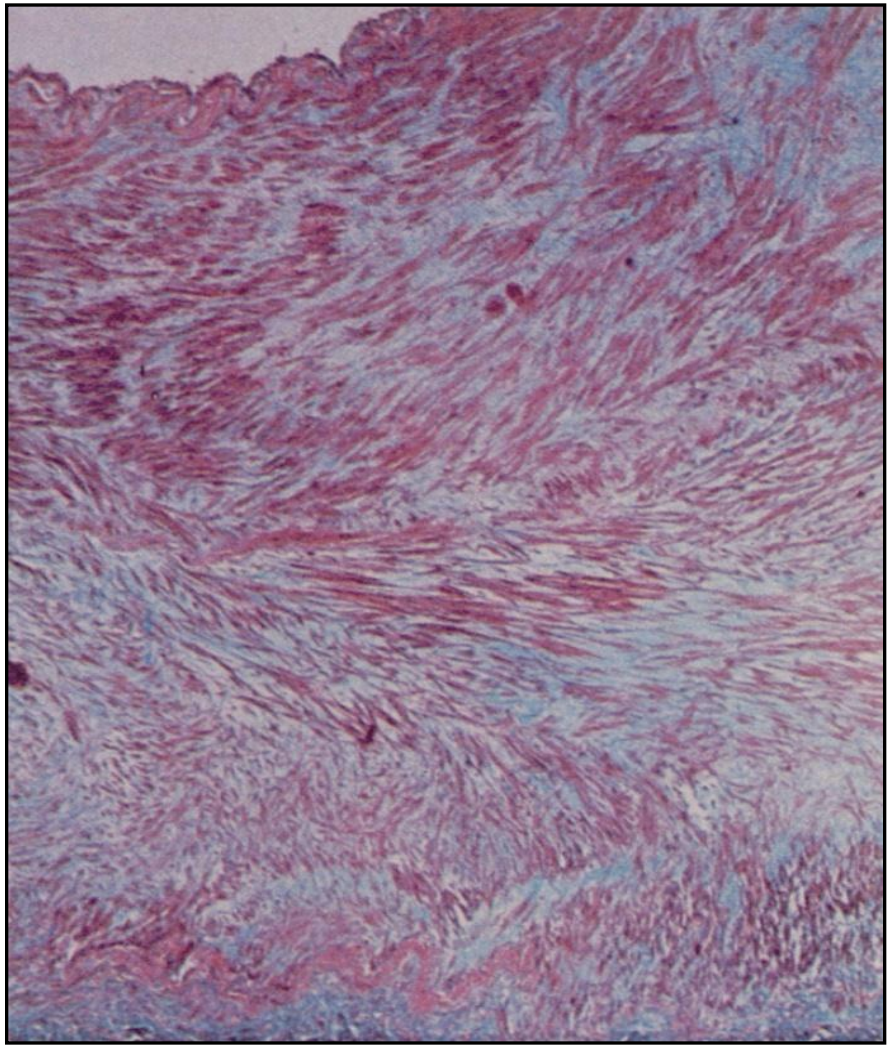
Valentin Fuster, M.D., Ph.D.- Director, Mount Sinai Heart

Medial fibromuscular dysplasia





Fibroblast cells and FMD

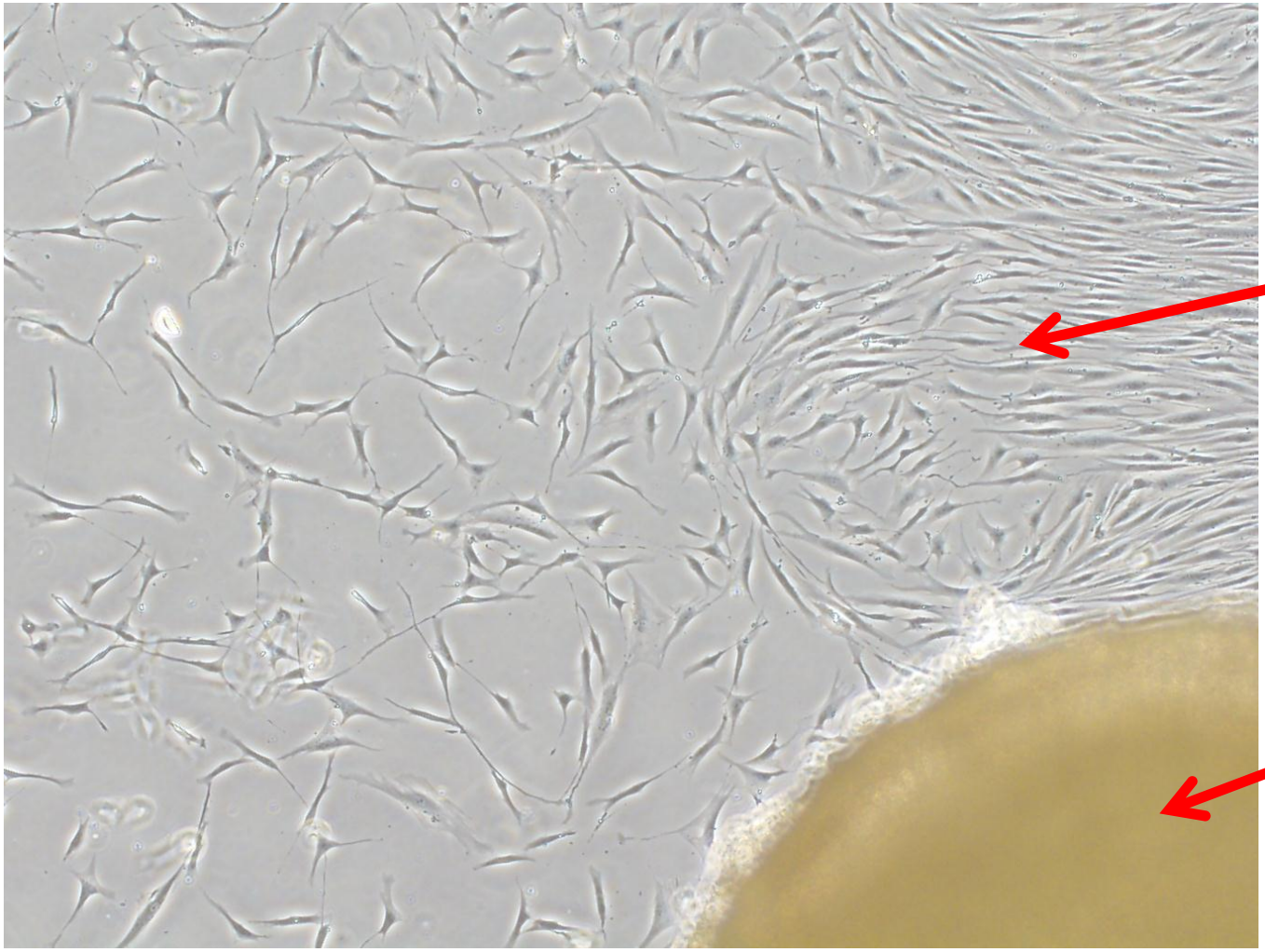


Fibromuscular Dysplasia (Masson stain) showing extensive fibrous tissue occupying the vessel wall.

Fibroblast cells appear to be the culprit in FMD.

Fibroblasts can easily be grown in the lab from a small 2-3mm skin biopsy.

Fibroblast cells can be grown in the laboratory



Fibroblasts growing out from skin biopsy

Small piece of skin biopsy from FMD patient

FMD Research Plan

Overall Objective: To establish the cellular and genetic basis of FMD.

- ***Specific Aim 1:*** *To establish a library of fibroblasts from patients with FMD and unaffected controls by skin biopsy and cell culture.*

  This library of fibroblasts from FMD patients will be an invaluable resource on which to base numerous future studies of this disease. We aim to recruit 200 patients and controls.

FMD Research Plan

- ***Specific Aim 2:*** *To compare the functional cell characteristics of fibroblasts from FMD patients and control family members.*

  Fibroblasts will be profiled according to standardized assays including proliferation, migration, resistance to oxidative stress and senescence.

  In this fashion, we will assess the characteristics of fibroblasts from FMD patients, and will make direct comparisons with cells from healthy persons without FMD.

  This should give important clues as to what is occurring at a cellular level in FMD patients.

FMD Research Plan

- ***Specific Aim 3:*** *To define the genetic profile of fibroblasts from FMD patients.*

  We will profile the gene expression pattern of fibroblasts from FMD and healthy control patients using state-of-the-art high-throughput Illumina and Affimetrix gene array platforms to identify the pattern of genes that are ‘turned on’ in FMD patients versus healthy control persons.

  This will provide key data about what is occurring at the genetic level in cells from patients with FMD.

FMD Research Plan

- ***Specific Aim 4:*** *To examine the cause of FMD at the genetic level using DNA samples collected from blood.*

  We will define the genetic DNA sequence of FMD patients and controls aiming to identify causative genetic variants for this disease. Potential findings at the DNA level will be linked back to the cellular fibroblast data to increase the likelihood of identifying the basis of this disease.

  Defining the cause of FMD is likely to be the first important step in working towards a specific therapy for this disease.

FMD Laboratory Research Plan

Potential Outcomes

Gain important insights into the disease process and begin to establish the cellular basis of FMD

Ultimate aim, though very challenging, is to define the cause of this condition.

What have We Learned About Fibromuscular Dysplasia

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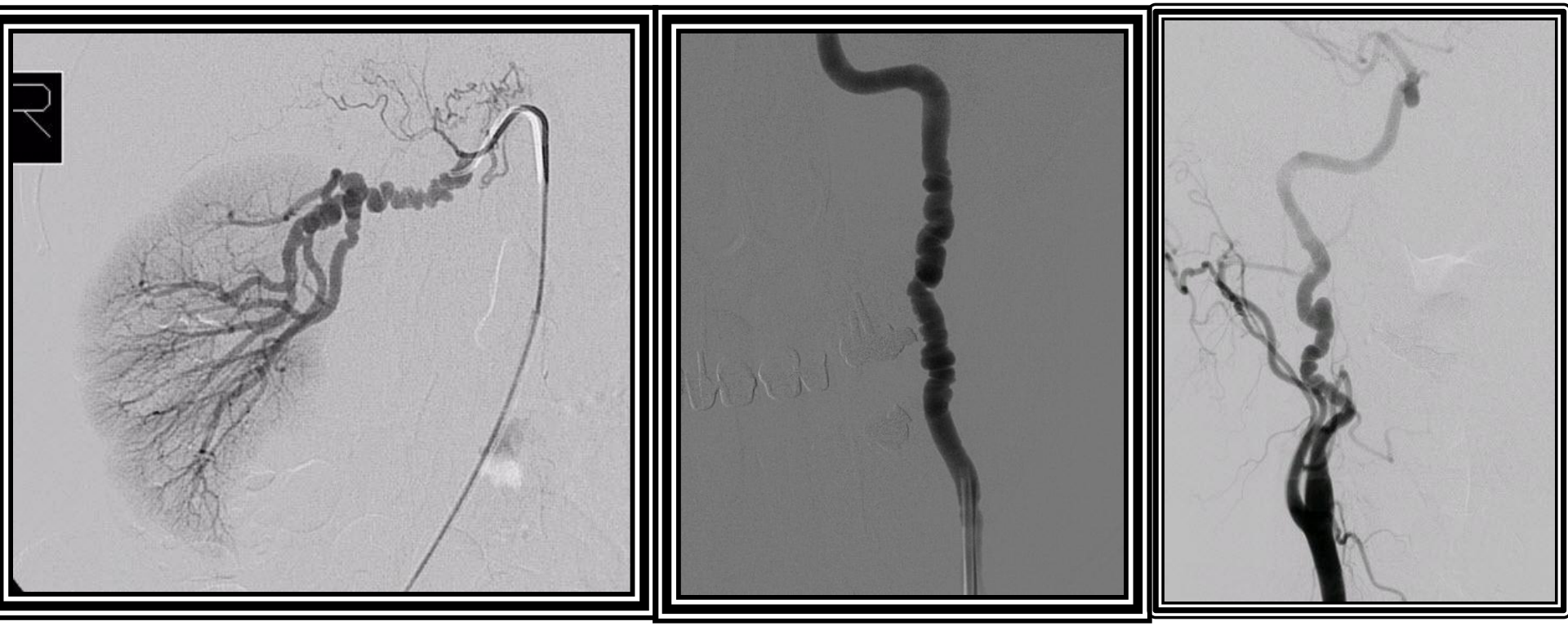
Medial Fibroplasia



Classification of Fibromuscular Dysplasia

Classification	Frequency	Pathology	Angiographic appearance
Medial dysplasia			
Medial fibroplasia			"String of beads" appearance where the diameter of the "beading" is larger than the diameter of the artery
Perimedial fibroplasia		the outer half of the media	"Beading" in which the "beads" are smaller than the diameter of the artery
Medial hyperplasia	1–2%	True smooth muscle cell hyperplasia without fibrosis	Concentric smooth stenosis (similar to intimal disease)
Intimal fibroplasia	<10%	eccentric depo- en in the intima matory component mina fragmented	Concentric focal band Long smooth narrowing
Adventitial (periarterial) fibroplasia	<1%	eplaces the f the adventitia and may extend into surrounding tissue	

Multifocal

Focal

Circulation
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Stroke

The United States Registry for Fibromuscular Dysplasia

Results in the First 447 Patients

Jeffrey W. Olin, DO; James Froehlich, MD; Xiaokui Gu, MA; J. Michael Bacharach, MD, MPH; Kim Eagle, MD; Bruce H. Gray, DO; Michael R. Jaff, DO; Esther S.H. Kim, MD, MPH; Pam Mace, RN; Alan H. Matsumoto, MD; Robert D. McBane, MD; Eva Kline-Rogers, MS, RN; Christopher J. White, MD; Heather L. Gornik, MD, MHS

Background—Fibromuscular dysplasia (FMD), a noninflammatory disease of medium-size arteries, may lead to stenosis, occlusion, dissection, and/or aneurysm. There has been little progress in understanding the epidemiology, pathogenesis, and outcomes since its first description in 1938.

Methods and Results—Clinical features, presenting symptoms, and vascular events are reviewed for the first 447 patients enrolled in a national FMD registry from 9 US sites. Vascular beds were imaged selectively based on clinical presentation and local practice. The majority of patients were female (91%) with a mean age at diagnosis of 51.9 (SD 13.4 years; range, 5–83 years). Hypertension, headache, and pulsatile tinnitus were the most common presenting symptoms of the disease. Self-reported family history of stroke (53.5%), aneurysm (23.5%), and sudden death (19.8%) were common, but FMD in first- or second-degree relatives was reported only in 7.3%. FMD was identified in the renal artery in 294 patients, extracranial carotid arteries in 251 patients, and vertebral arteries in 82 patients. A past or presenting history of vascular events were common: 19.2% of patients had a transient ischemic attack or stroke, 19.7% had experienced arterial dissection(s), and 17% of patients had an aneurysm(s). The most frequent indications for therapy were hypertension, aneurysm, and dissection.

Conclusions—In this registry, FMD occurred primarily in middle-aged women, although it presents across the lifespan. Cerebrovascular FMD occurred as frequently as renal FMD. Although a significant proportion of FMD patients may present with a serious vascular event, many present with nonspecific symptoms and a subsequent delay in diagnosis. (***Circulation*. 2012;125:3182-3190.**)

1 FMD is NOT only a disease of the young

Parameter	**Number (%)**
Demographics	
Age (mean±SD)	55.7 ± 13.1 years (range 18 – 86)
Age at first FMD-related symptom	47.2 ± 14.6
Age at diagnosis of FMD	51.9 ± 13.4 years (range 5-83)
Female	406/447(91)
Race	
White	395/414 (95.4)
Black	9/414 (2.2)
Hispanic	6/414 (1.5)
Asian	2/414 (0.5)
Other	2/414 (0.5)

Frequency of Presenting Symptoms and Clinical Signs of Fibromuscular Dysplasia*

Presenting Symptoms	N (%)
Hypertension	285 (63.8)
Headache	234 (52.4)
Pulsatile tinnitus	123 (27.5)
Dizziness	116 (26.0)
Cervical bruit	99 (22.2)
Flank/abdominal pain	70 (15.7)
Aneurysms	63 (14.1)
Cervical artery dissection	54 (12.1)

Olin JW et al. Circulation 2012;125:3182-3190

2 There is a Long Delay from the First Sign/Symptom of FMD

- U.S. Registry for FMD
  - Age at first symptom/sign 47 years old
  - Age at diagnosis of FMD 52 years old
  - 5 year delay
- French Study for FMD
  - Age at first symptom/sign 26 40
  - Age at diagnosis of FMD 30 49
  - 5 & 9 year delay

3 Doctors do not take patients symptoms seriously

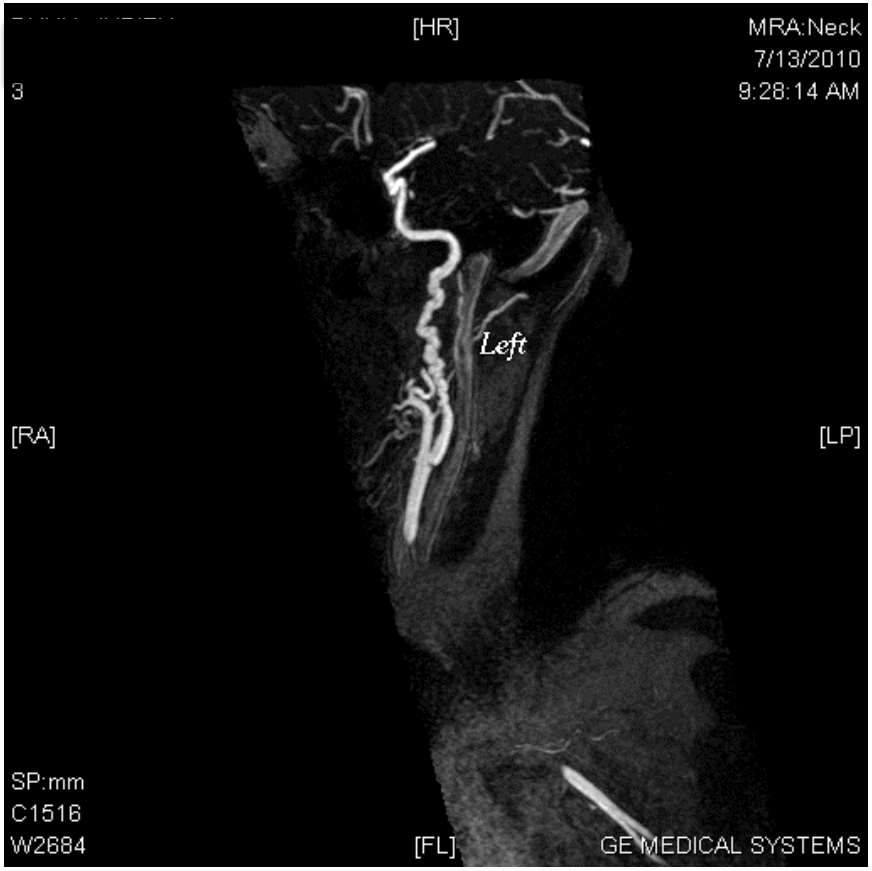
- Many of you have experience this
  - Pam: sent home from ER several times when she presented with carotid artery dissection
  - Rochelle: stent put in renal artery causing a tear in artery and loss of significant kidney function…she tried to tell the doctor not to put a stent in before the procedure.

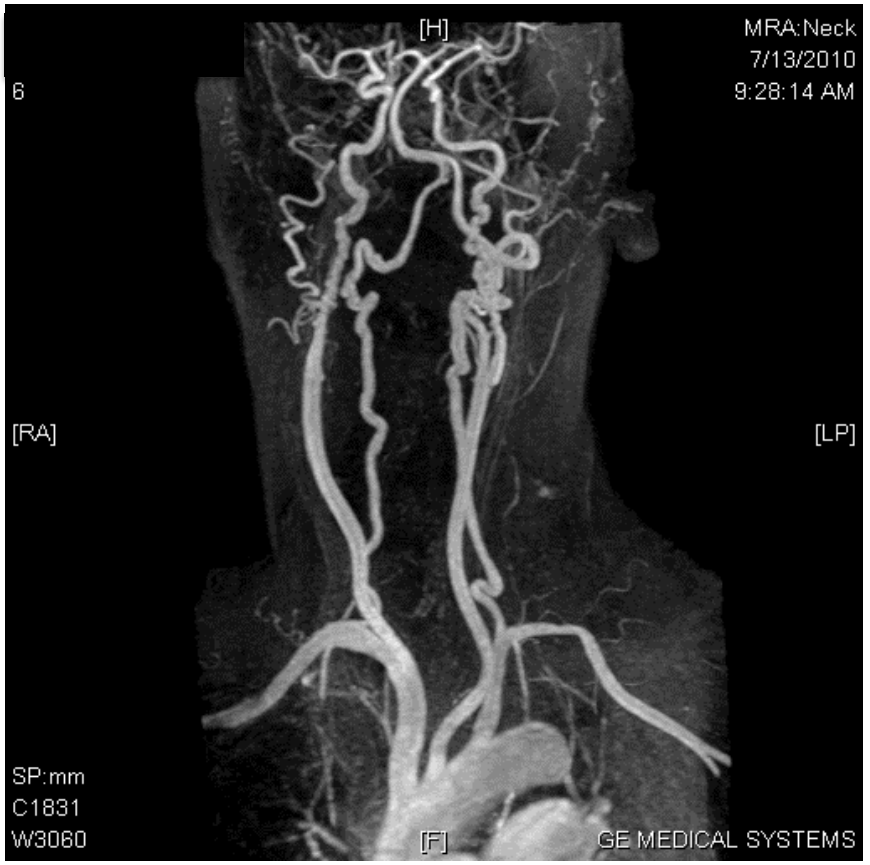
3 Doctors do not take patients symptoms seriously

- There are just some things we do not know:
  - Why do patients get dizzy?
  - Why do patients get headaches?
  - Why do many note fullness of the ears?
  - Why do patients get non-pulsatile tinnitus?
- BE HONEST! Just say I don't know why you are experiencing this.

4 Mutifocal FMD (string of beads, medial fibroplasia) does not progress

78 Year Old Woman: Angiograms in 1973 looked identical to the MRA performed 38 years later



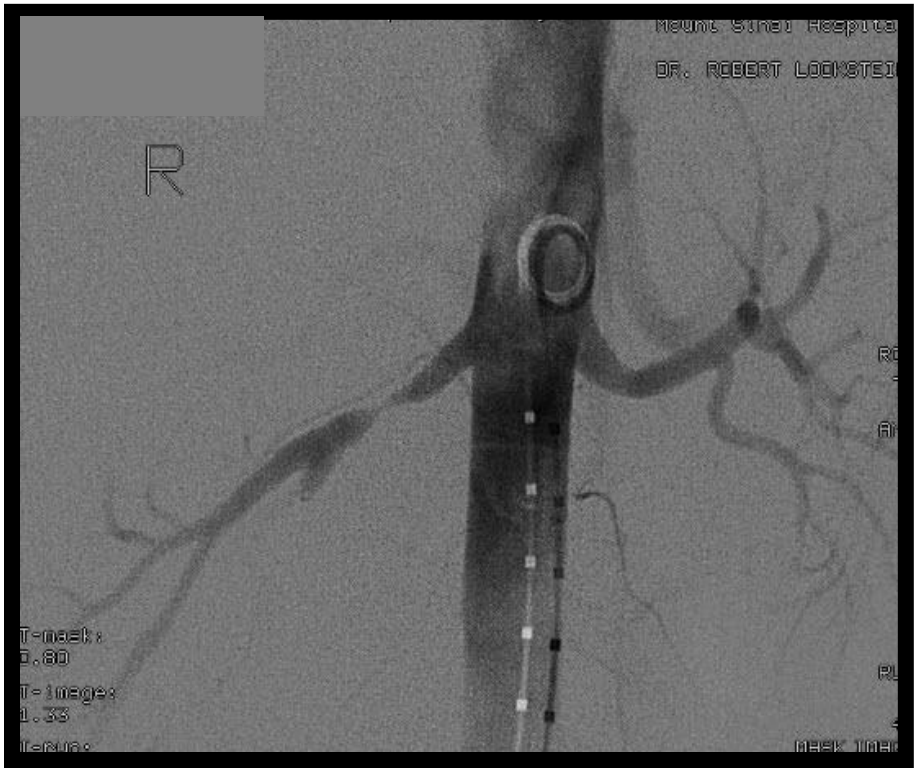


4 Mutifocal FMD (string of beads, medial fibroplasia) does not progress

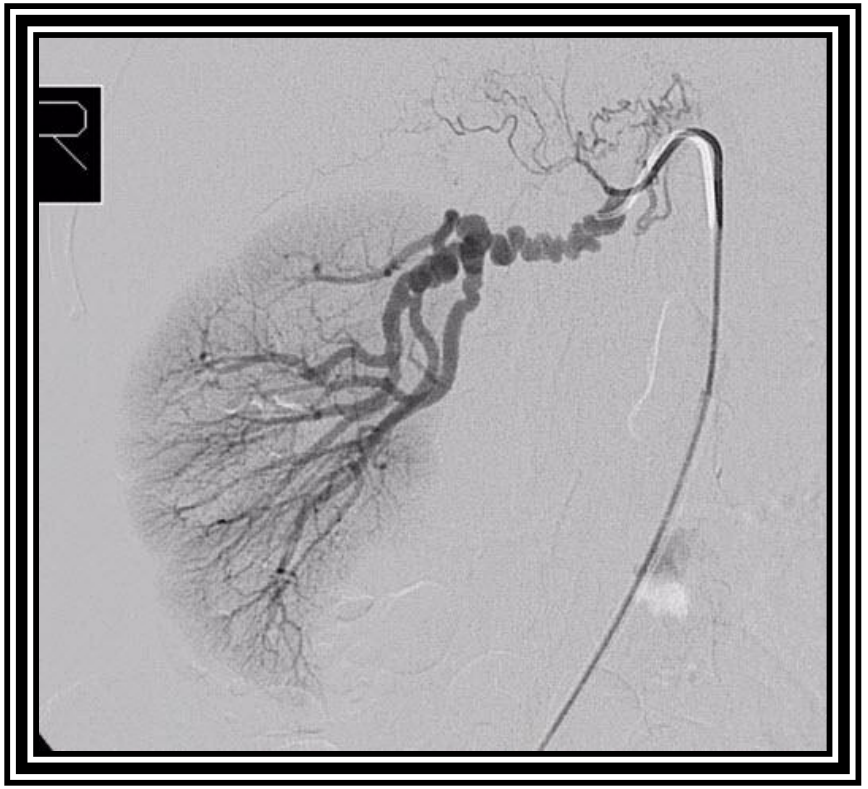
- We have now serial ultrasounds of the carotid and renal arteries on over 150 patients and have not seen progression, or the formation of an aneurysm in any patient.
- We are in the process of publishing this.

5 There are distinct differences based on the type of FMD

Unifocal



Multifocal



5 There are distinct differences based on the type of FMD

Vascular Medicine

Association Between 2 Angiographic Subtypes of Renal Artery Fibromuscular Dysplasia and Clinical Characteristics

Sébastien Savard, MD, MSc; Olivier Steichen, MD, MSc; Arshid Azarine, MD, MSc; Michel Azizi, MD, PhD; Xavier Jeunemaitre, MD, PhD; Pierre-François Plouin, MD

Background—Initially based on histology, the diagnosis of renal artery fibromuscular dysplasia (FMD) is now based mostly on angiographic appearance because arterial tissue samples are rarely available. This retrospective cross-sectional study aimed to assess the clinical relevance of a binary angiographic classification of FMD lesions (unifocal or multifocal) based on computed tomographic or magnetic resonance angiography.

Methods and Results—Adult patients diagnosed with FMD in a single tertiary care center for hypertension management were identified by screening of electronic files. FMD lesions were reviewed and classified according to computed tomography or magnetic resonance angiography as multifocal if there were at least 2 stenoses in the same arterial segment; otherwise, they were classified as unifocal. Of 337 patients with established renal artery FMD, 276 (82%) were classified as multifocal. Patients with unifocal and multifocal lesions differed significantly in median age at diagnosis of FMD (30 and 49 years) and hypertension (26 and 40 years), sex distribution (female:male ratio, 2:1 and 5:1), initial blood pressure (157/97 and 146/88 mm Hg), current smoking (50% and 26%), prevalence of unilateral renal artery lesions (79% and 38%), presence of kidney asymmetry (33% and 10%), renal revascularization procedures (90% and 35%), and hypertension cure rates in patients who underwent revascularization (54% and 26%).

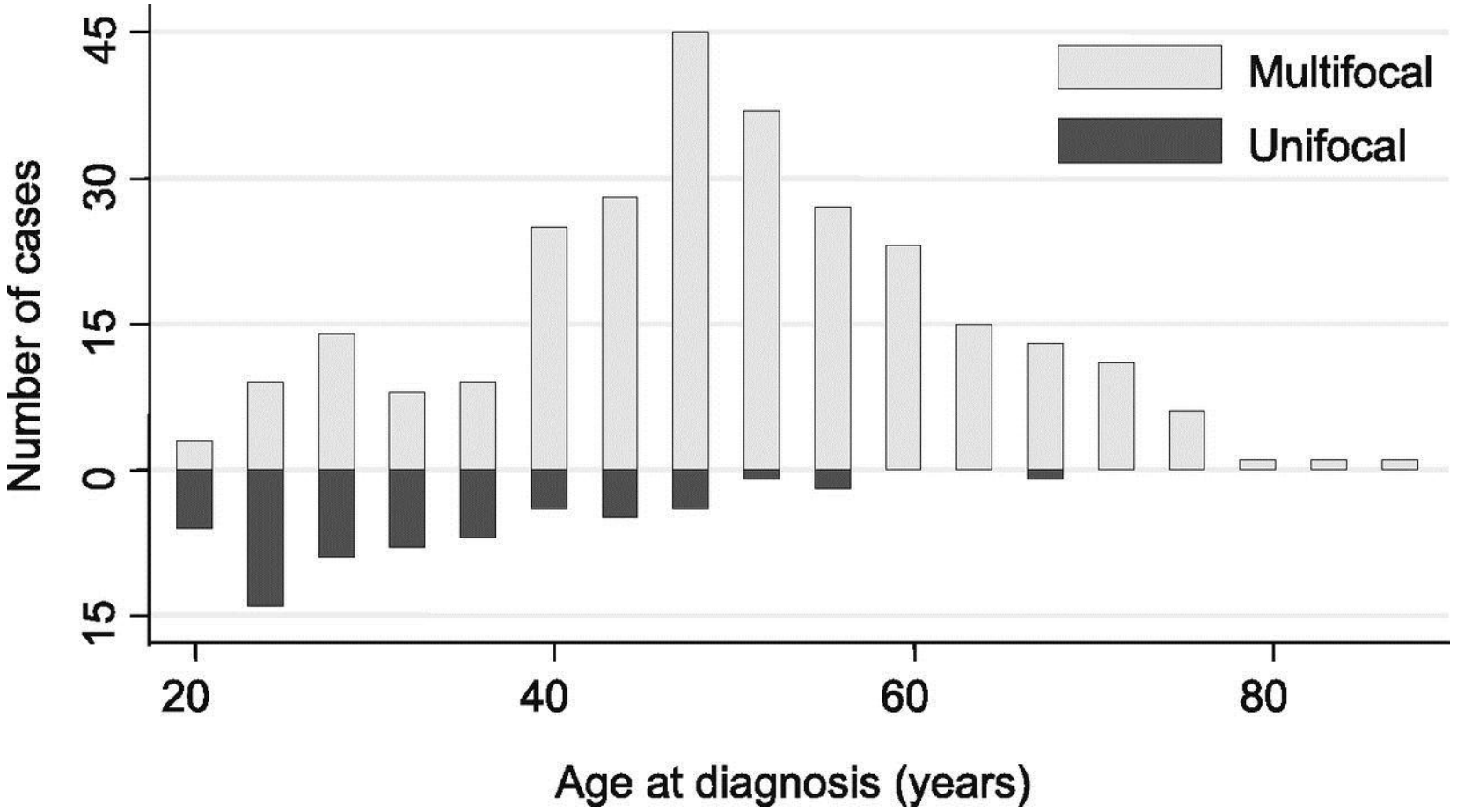
Conclusions—A binary angiographic classification into unifocal or multifocal renal artery FMD is straightforward and discriminates 2 groups of patients with different clinical phenotypes. ***(Circulation.* 2012;126:3062-3069.)**

Key Words: fibromuscular dysplasia ■ hypertension, renal ■ renal artery obstruction

Table 2. History and Characteristics at Diagnosis of Fibromuscular Dysplasia in Patients With Unifocal or Multifocal Renal Artery Lesions

	Unifocal FMD (n=61)		Multifocal FMD (n=276)		
	n*	Values	n*	Values	*P*
Male sex, n (%)	61	19 (31%)	276	47 (17%)	0.02
Personal history of hypertension, n (%)	61	60 (98%)	276	258 (93%)	0.22
Age at diagnosis of hypertension, y	60	26 (21, 36)	256	40 (32, 49)	<0.001
Age at diagnosis of FMD, y	61	30 (25, 39)	276	49 (42, 58)	<0.001
History of diabetes mellitus, n (%)	59	1 (2%)	269	12 (4%)	0.48
History of hypercholesterolemia, n (%)	59	10 (17%)	270	78 (29%)	0.07
Current smoker, n (%)	58	29 (50%)	268	69 (26%)	<0.001
Systolic blood pressure, mm Hg	55	157 (137, 174)	234	146 (128, 162)	0.006
Diastolic blood pressure, mm Hg	55	97 (87, 110)	234	88 (76, 100)	<0.001
Antihypertensive agents, n	55	1 (1, 2)	234	2 (1, 3)	0.74
Body mass index, kg/m^2	54	22 (20, 24)	232	23 (21, 27)	<0.001
Estimated creatinine clearance,† $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$	49	91 (83, 109)	218	86 (73, 100)	0.07
Renal asymmetry >20 mm, n (%)	48	16 (33%)	195	19 (10%)	<0.001
FMD site, n (%)					
Right, unilateral	61	29 (48%)	276	85 (31%)	<0.001
Left, unilateral	61	19 (31%)	276	20 (7%)	
Bilateral	61	13 (21%)	276	171 (62%)	
Median renal artery score	61	1 (1, 2)	276	3 (1, 3)	<0.001
Presence of renal artery aneurysms, n (%)	61	7 (11%)	276	31 (11%)	1
Presence of renal artery dissections, n (%)	61	4 (7%)	276	12 (4%)	0.50
Presence of cervical artery FMD, n (%)	24	6 (25%)	127	65 (51%)	0.03
Presence of iliofemoral artery FMD, n (%)	22	2 (9%)	123	30 (24%)	0.16
Presence of digestive artery FMD, n (%)	16	5 (31%)	97	50 (52%)	0.18

Age distribution at diagnosis of renal artery fibromuscular dysplasia.



Savard S et al. Circulation 2012;126:3062-3069

Table 3. Characteristics at Follow-Up >365 Days for Patients With Unifocal or Multifocal Renal Artery FMD With First Visit Before October 1, 2010

	Unifocal (n=52)		Multifocal (n=213)		
	n	Values	n	Values	*P*
Patients with clinical follow-up >365 d, n (%)	52	31 (60%)	213	141 (66%)	0.42
Follow-up duration, y	31	4 (2, 8)	141	4 (3, 9)	0.39
Renal artery intervention during follow-up, n (%)	31	28 (90%)	141	50 (35%)	<0.001
Current smoker, at last follow-up, n (%)	31	9 (29)	139	24 (17)	0.14
Body mass index at last follow-up, kg/m^2	30	23 (22, 26)	130	25 (22, 28)	0.25
Systolic blood pressure at last follow-up, mm Hg	31	123 (114, 130)	139	124 (114, 135)	0.54
Change in systolic blood pressure, mm Hg	31	−30 (−53, −14)	138	−20 (−37, −5)	0.03
Diastolic blood pressure at last follow-up, mm Hg	31	77 (74, 85)	139	74 (67, 82)	0.06
Change in diastolic blood pressure, mm Hg	31	−19 (−35, −3)	138	−14 (−27, −2)	0.14
Antihypertensive agents at last follow-up, n	31	0 (0, 1)	140	2 (1, 3)	<0.001
Change in number of antihypertensive agents, n	31	−1 (−1, 0)	139	0 (−1, 1)	0.006
Estimated creatinine clearance at last follow-up,* $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$	25	130 (109, 153)	106	124 (108, 146)	0.45
Change in estimated creatinine clearance,* $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$	25	42 (24, 53)	98	41 (27, 56)	0.96

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Editorial

Is Fibromuscular Dysplasia a Single Disease?

Jeffrey W. Olin, DO

Circulation. 2012;126:2925-2927

Well Now, Dr. Esther Kim Has Shown Us in What Ways We Are Different

Clinical Manifestations of Fibromuscular Dysplasia Vary by Patient Sex:

A Report of the United States Registry for FMD

Esther S.H. Kim[1], Jeffrey W. Olin[2], James B. Froehlich[3], Xiaokui Gu[3], J. Michael Bacharach[4], Bruce H. Gray[5], Michael R. Jaff[6], Barry T. Katzen[7], Eva Kline-Rogers[3], Pamela D. Mace[8], Alan H. Matsumoto[9], Robert D. McBane[10], Christopher J. White[11], Heather L. Gornik[1]

Presenting Symptoms	Total # of patients (%)	Male N (%)	Female N (%)	P-value
Abnormal Swooshing Sound in Ear (pulsatile)	168/503 (33.4)	4/44 (9.1)	164/459 (35.7)	0.0002
Cervical Bruit	123/496 (24.8)	2/44 (4.5)	121/452 (26.8)	0.0004
Flank/Abdominal Pain	85/494 (17.2)	21/48 (43.8)	64/446 (14.3)	<0.0001
Aneurysms	94/525 (17.9)	16/44 (36.4)	78/481 (16.2)	0.0031
Abdominal Bruit	53/491 (10.8)	0/43 (0)	53/448 (11.8)	0.009
Renal Artery Dissection	18/515 (3.5)	8/45 (17.8)	10/470 (2.1)	<0.0001
Azotemia/Renal Insufficiency	14/507 (2.8)	4/44 (9.1)	10/463 (2.2)	0.026
Myocardial Infarction	9/519 (1.7)	1/44 (2.3)	8/475 (1.7)	0.56

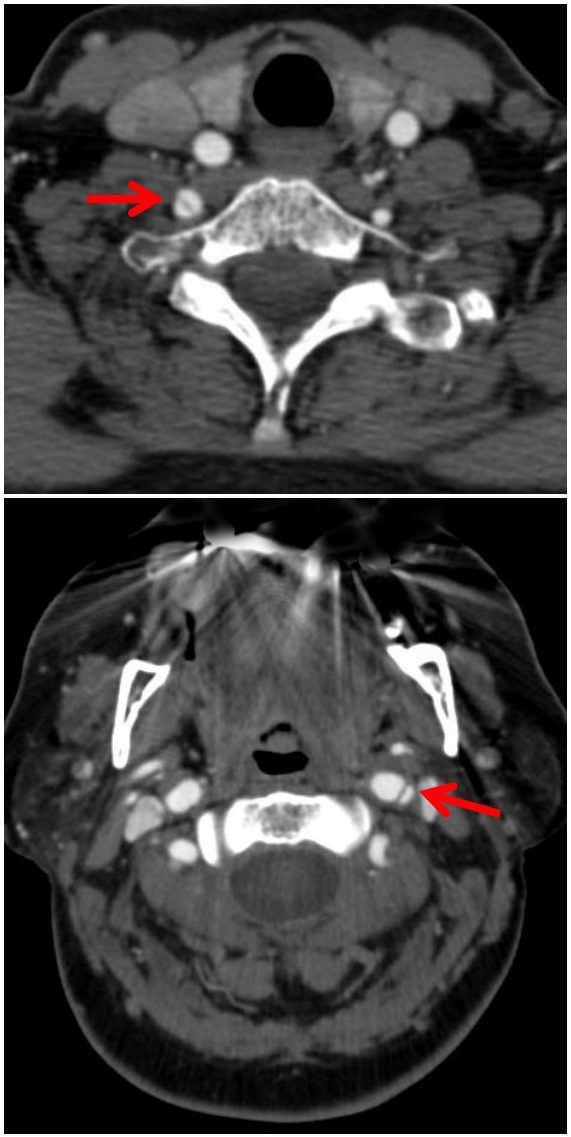
	All N=615 No. (%)*	Male N=52 No. (%)*	Female N=563 No. (%)*	P-value
Arterial Bed Involved				
Renal	382/507 (75.3)	35/39 (89.7)	347/468 (74.1)	0.032
Extracranial carotid	346/476 (72.7)	15/34 (44.1)	331/442 (74.9)	0.00043
Vascular complication	123/567 (21.7)	19/48 (39.6)	104/519 (20.0)	0.0031
Any arterial dissection				
Any arterial aneurysm	124/559 (22.2)	20/49 (40.8)	104/510 (20.4)	0.002

6 Silent FMD Occurs in Many Patients

57 Year Old Female

Presentation:

- Right Kidney Infarction from dissection
- Incidentally noted:
  - Left renal artery aneurysm
  - right vertebral artery dissection
  - left internal carotid artery dissection
  - right vertebral artery aneurysm
  - medial fibroplasia of bilateral internal carotid and vertebral arteries.



Distribution of Vascular Bed Involvement in Fibromuscular Dysplasia

Vascular Bed Involved	N	# of patients with imaging	%
Renal artery	294	369	79.7
Extracranial carotid artery	251	338	74.3
Vertebral artery	82	224	36.6
Mesenteric arteries	52	198	26.3
Lower extremity arteries	42	0	60.0
Intracranial carotid arteries*	35	206	17.0
Upper extremity arteries	10	63	15.
Aorta†	0	145	0

* Includes intracranial aneurysms

† While there were aneurysms in the aorta in 15 patients, there were no instances of typical radiographic findings of FMD in the aorta.

Olin JW et al. Circulation 2012;125:3182-90

FMD is More Common Than We Think

- 3 pieces of evidence:
  - Data from “Normal” Kidney Donors
  - Incidental Findings during imaging for other reasons
  - FMD discovered in patients who present for other reasons

Incidental FMD in Potential Renal Donors

- 1862 renal arteriograms[1]
  - 71 patients (3.8%) had FMD
    - 75% women
    - Mean age 51 years
- 3.9% of 101 CT angiograms[2]

If this information is correct, more than 5 million women in the U.S. have FMD

1. Cragg AH et al. Radiology 1989;172:145-7.
2. Blondin D et al. Eur J Radiol 2009;ePub ahead of print

7 String of Beads is not the only manifestation of FMD

- Family History
- Dissection
- Aneurysm
- Tortuosity

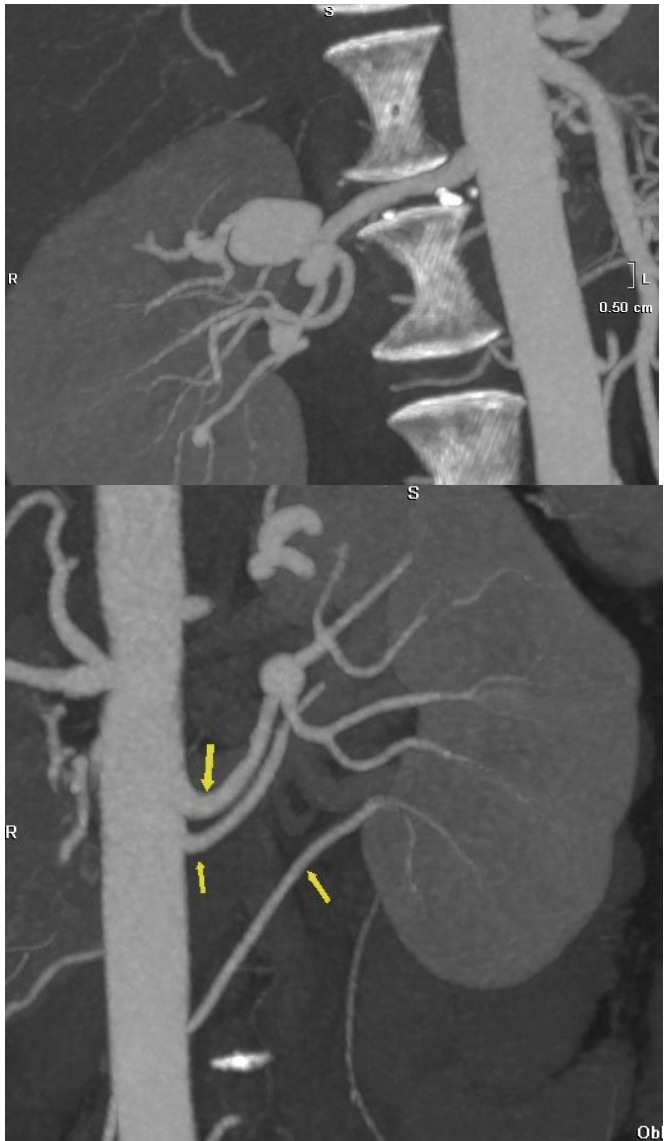
Self-Reported Family History of Vascular Disease or Risk Factors Among 1st and 2nd Degree Relatives of Fibromuscular Dysplasia Patients

Family History	N (%)
Hypertension	289/366 (79.0)
Hyperlipidemia	171/302 (56.6)
Stroke	175/327 (53.5)
Aneurysm	76/323 (23.5)
Sudden Death	60/303 (19.8)
FMD	26/354 (7.3)
Dissection	6/303 (2.0)
Neurofibromatosis	2/299 (0.7)
Ehlers-Danlos Syndrome	1/302 (0.3)

***Denominator of reported responses is reported as different than total cohort size of N=447 patients to account for missing data**

Olin JW et al. Circulation 2012;125:3182-3190

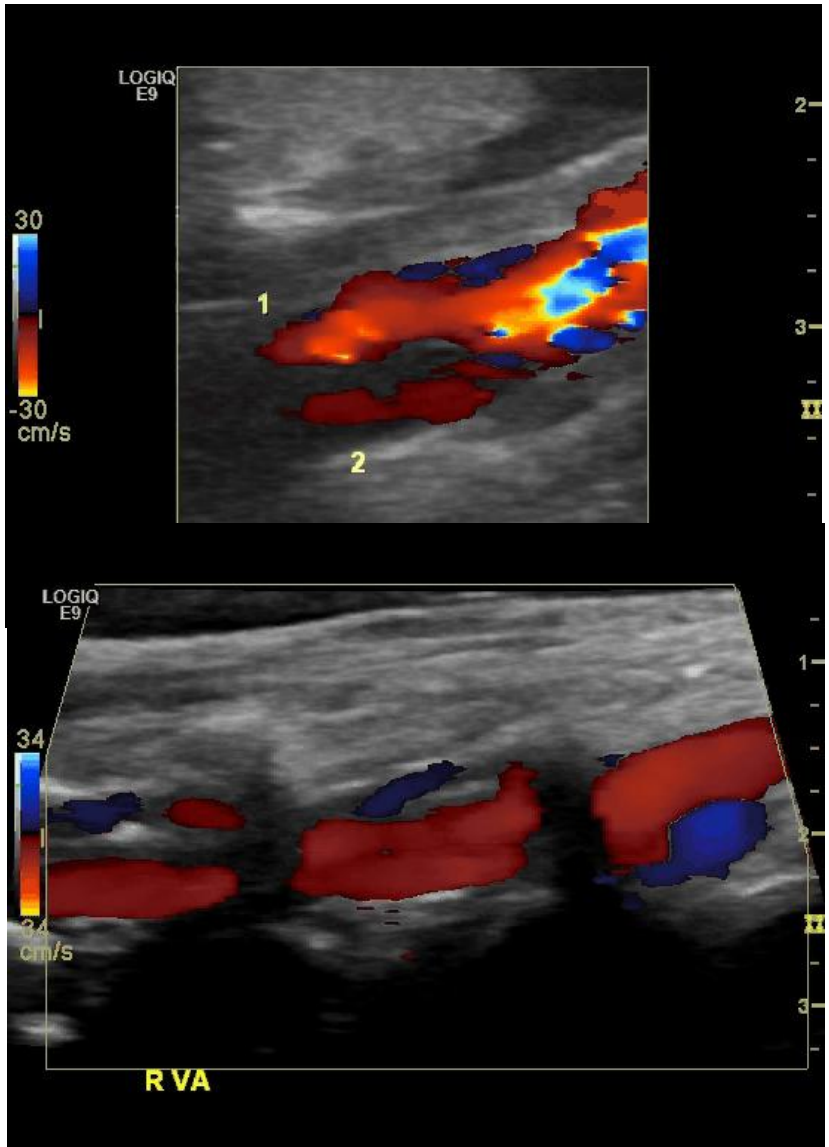
Prevalence and Vascular Distribution of Aneurysms in 447 FMD patients



Any aneurysm	**76 (17%)**
Renal artery	25 (33%)
Carotid artery	16 (21%)
Aorta	15 (20%)
Celiac artery	12 (16%)
Cerebral arteries	9 (12%)
Mesenteric	5 (6.6%)
Basilar	5 (6.6%)
Vertebral	2 (2.6%)

Olin JW et al. Circulation 2012;125:3182-3190

Prevalence and Vascular Distribution of Arterial Dissections in 447 FMD patients



Any dissection88 (19.7%)	
Carotid artery	68 (75%)
Renal artery	19 (22%)
Vertebral artery	15 (17%)
Mesenteric artery	4 (4.5%)
Coronary artery	3(3.4%)
Celiac artery	2(2.3%)
Iliac artery	2(2.3%)

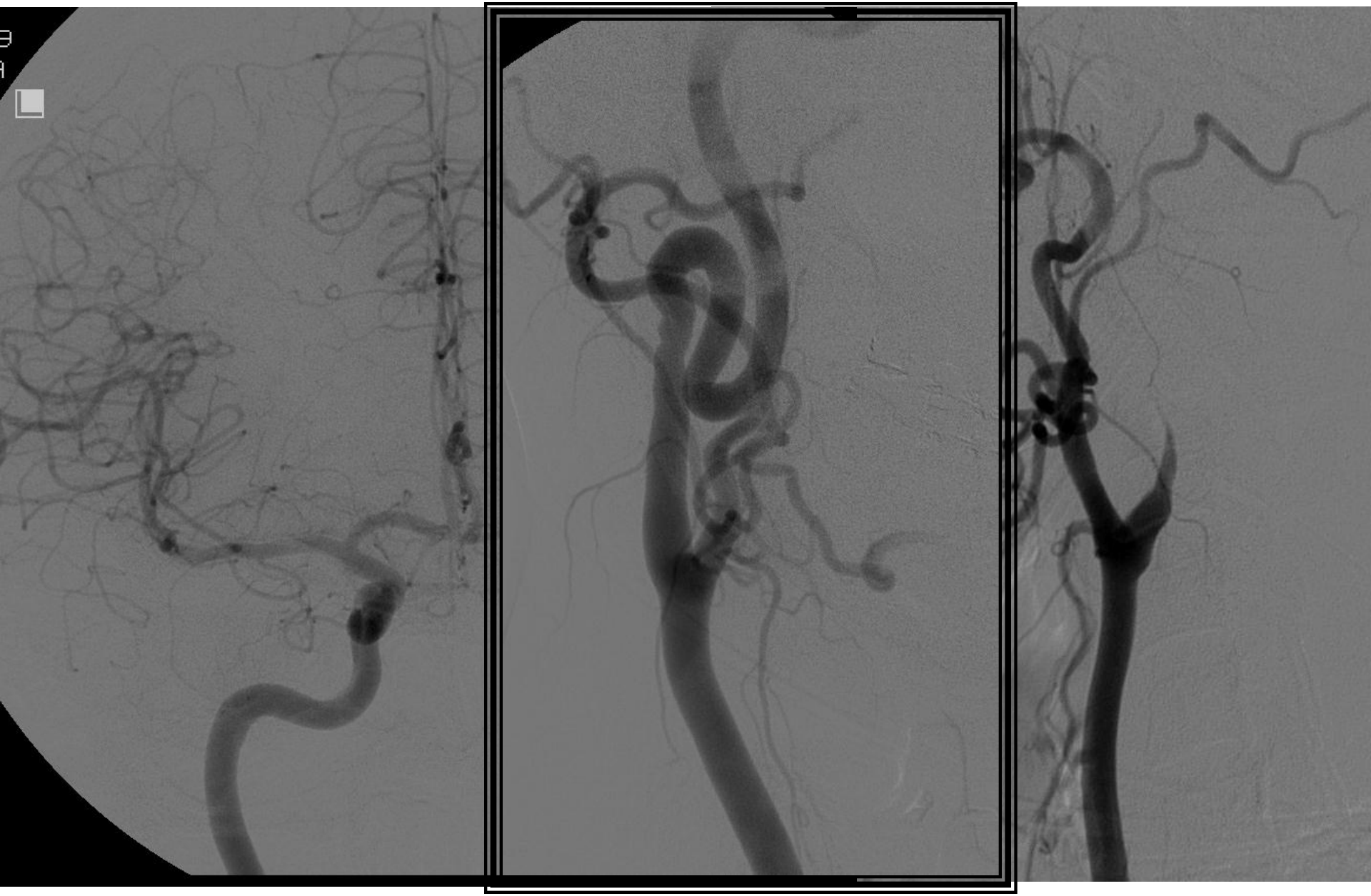
Parameter	Dissection N= 88	No Dissection N= 359	P Value
Age at time of enrollment	51.4±10.6	56.8±13.4	<0001
Age at Diagnosis	48.4±9.6	52.7±14.1	0.0012
Female	83%	93%	0.0033
Hypertension	58%	75.5%	0.0014
Age of onset	43.2±11.5	43.1±15.5	0.97
Headache	74.7%	56.1%	0.0036
Aneurysm other than aorta	15.9%	13.7%	0.61
Aortic aneurysm	4 (4.6%)	11 (3.1%)	0.51

Results

Neurologic Event	Dissection N= 88	No Dissection N= 359	P Value
Amaurosis Fugax	10.2%	3.9%	0.027
Hemispheric TIA	21.6%	10.6%	0.011
Horner's Syndrome	26%	2.5%	<0.0001
Stroke	21%	6%	<0.0001
Subarachnoid Hemorrhage	2.3	0.8	0.26

RIGHT CAROTID

LEFT CAROTID



The S Curve:

A Novel Morphological Finding in the Internal Carotid Artery in Patients with Fibromuscular Dysplasia

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Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY

BACKGROUND

Fibromuscular dysplasia (FMD) is a non-atherosclerotic vascular disease that is more frequent in woman and most commonly affects the renal and internal carotid arteries (ICA) leading to stenosis, occlusion, aneurysm and dissection. A previously unrecognized finding present in FMD patients is an elongation of the mid to distal ICA causing a distinct morphological appearance in the shape of an 'S'.

PURPOSE

1) Demonstrate that the "S Curve" morphology of the internal carotid artery occurs more frequently in FMD patients as compared to controls

2) Assess if there are differences in the prevalence of the "S Curve" in patients with FMD in various locations

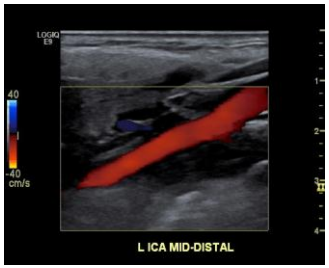
METHODS

Carotid artery duplex ultrasounds of 117 patients with FMD were reviewed in a retrospective case control study from 2009 - 2011. Patients were determined to have S Curves on ultrasound by two independent reviewers. There were 4 controls for each FMD patient with a S Curve divided equally into two groups: 1) Age and gender matched and; 2) Age >70 and gender matched. Chi Square statistical analysis was performed to generate odds ratios.

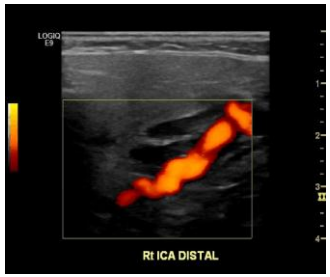
CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

Normal Distal Carotid Artery Ultrasound



'Typical" Ultrasound of Carotid FMD



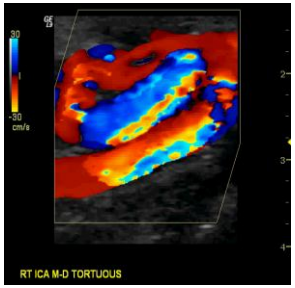
RESULTS

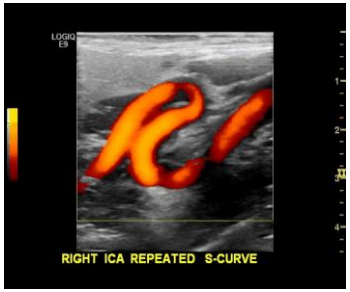
	FMD (No S Curve) (n= 80)	FMD (S Curve) (n=37)	P	Control 1 (age ± 2 y) (n=74)	P	Control 2 (age ≥70) (n=74)	P
Age (yrs)	50.3 ± 10	52.0 ± 12	0.17	52.3 ± 12	0.08	79.0 ± 6	<0.01
Female (n)	96% (77)	87% (32)	0.05	87% (64)	0.03	87% (64)	0.03

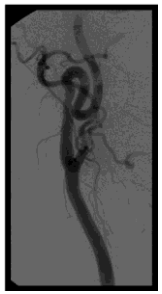
	S Curve		OR	95% CI	P
FMD	37/117	(31.6%)			
Control 1	2/74	(2.7%)	**16.65**	(3.87 - 71.55)	**<0.00001**
Control 2	12/74	(16.2%)	**2.39**	(1.15 - 4.96)	**0.018**

	S Curve (n=37)	No S Curve (n=80)	OR	95% CI	P
Male	5 (13.5%)	3 (3.8%)	**4.01**	(0.90 – 17.79)	.052
Carotid FMD only	9 (24.3%)	20 (25.0%)	**0.94**	(0.33 – 2.61)	0.90
Renal FMD only	13 (35.1%)	27 (33.8%)	**1.07**	(0.38 – 2.99)	0.90
Carotid & Renal FMD	15 (40.5%)	33 (41.2%)	**0.97**	(0.44 – 2.15)	0.94

The S Curve







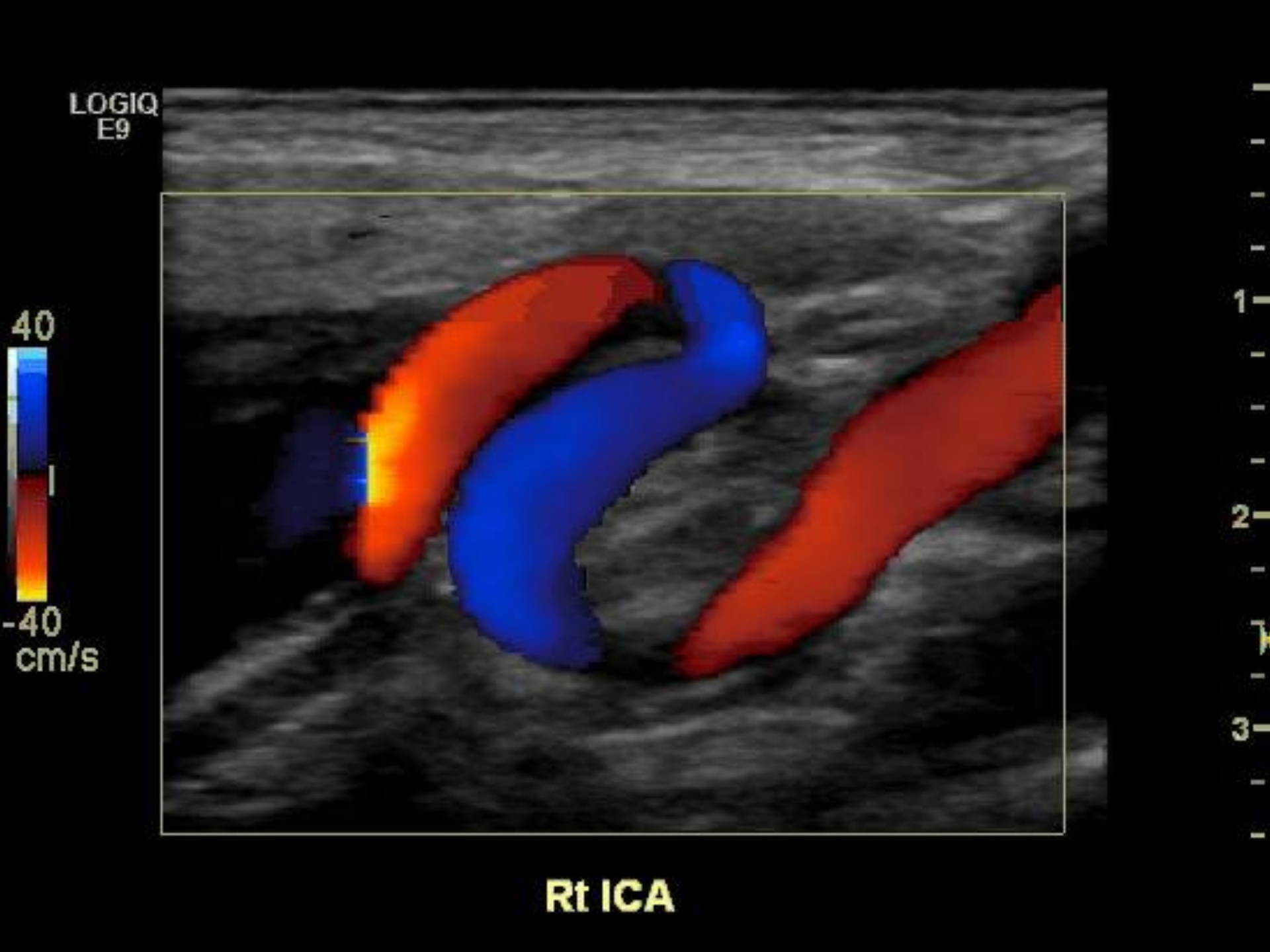
CONCLUSION

The S Curve is a novel morphological pattern visualized on duplex ultrasonography in the mid-distal ICA. There was a significantly higher prevalence of the S Curve in FMD patients as compared to both control groups. While the S Curve may not be specific to FMD, its presence in individuals < 70 years old should alert the clinician to the possibility that FMD is present.

Methods

- Setting
  - Vascular laboratory at an academic tertiary care referral center
- Study Design
  - Retrospective Case Control Study
  - Carotid duplex ultrasounds of 117 FMD patients
    - January 1, 2009 – November 1, 2011
  - S Curve patients were identified independently by two reviewers
  - Control Groups:
    - Two age/gender matched patients for each S curve patient
    - Two age $\geq$ 70 yrs old/gender matched patients for each S curve patient
    - Thus, 4 total control patients for every S curve patient

Mount Sinai HEART


LOGIQ
E9
40
-40
cm/s
1
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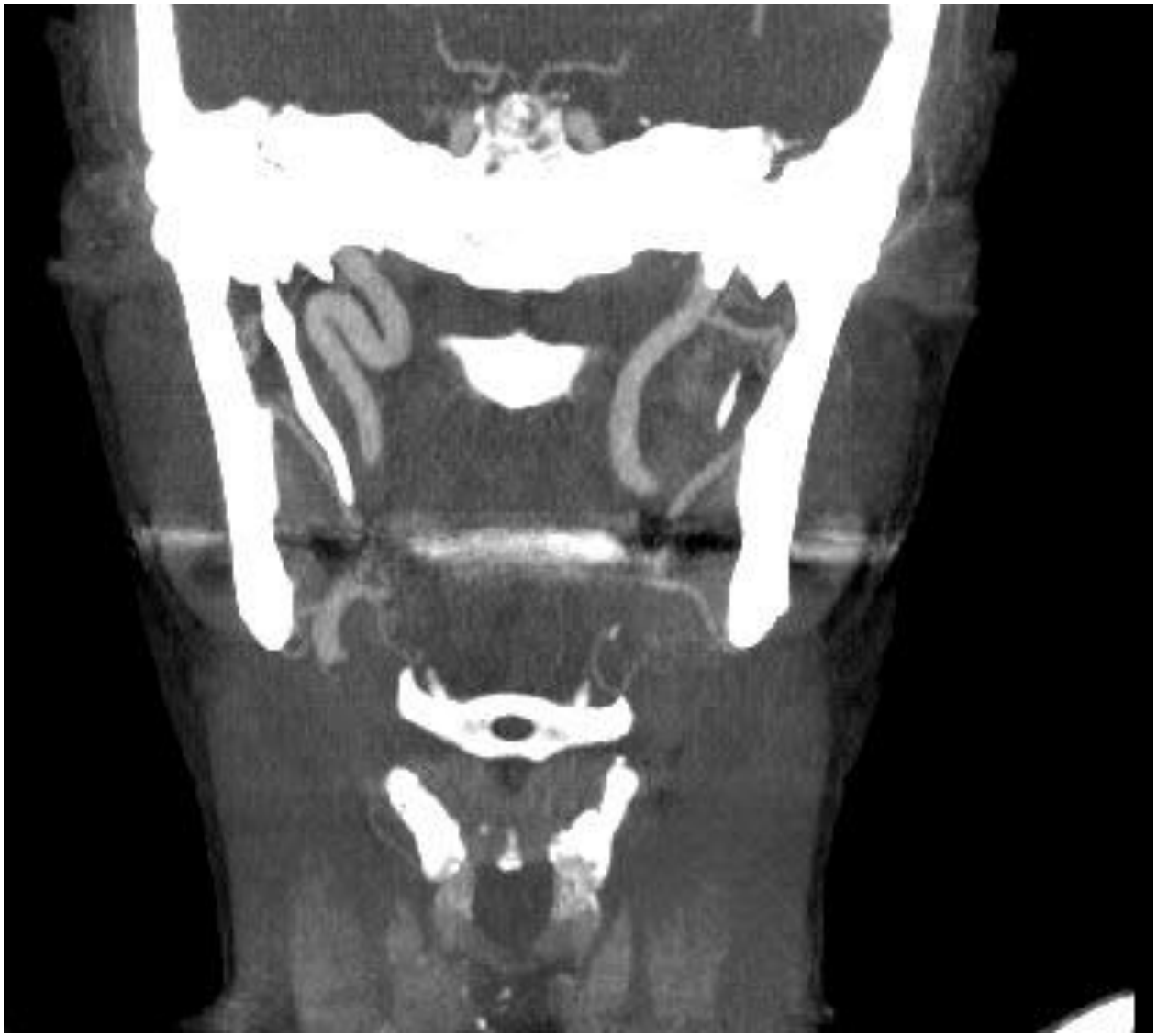

Results

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Control 2	12/74 (16.2%)	**2.39**	(1.15 - 4.96)	**0.018**

Conclusions

- The S Curve is a distinct morphologic pattern not previously studied in depth in patients with FMD.
- While it is not specific to patients with FMD, it occurs much more frequently in FMD patients compared to patients of similar age and gender or to elderly patients.
- The presence of an S Curve in a patient under 70 should alert the clinician to the possibility of FMD.

Consider the Diagnosis of FMD in the Following Circumstances

- Onset of hypertension under the age of 35
- Resistant hypertension (i.e, hypertension that cannot be controlled to goal despite at least 3 medications with different mechanisms of action and one of the medications being a diuretic)
- Epigastric bruit and high blood pressure
- Cervical bruit in a patient under the age of 60 years
- Pulsatile tinnitus [swooshing or whooshing sound in the ear(s)]
- Severe and recurrent headaches, especially migraine-type
- TIA or stroke in a patient under the age of 60
- Dissection of a peripheral artery (carotid, vertebral, renal)
- Aneurysm in a visceral or intracranial vessel
- Aortic aneurysm in a patient under the age of 60
- Subarachnoid hemorrhage
- Renal infarction