Vascular function and structure in renal fibromuscular dysplasia: the MEDYA study

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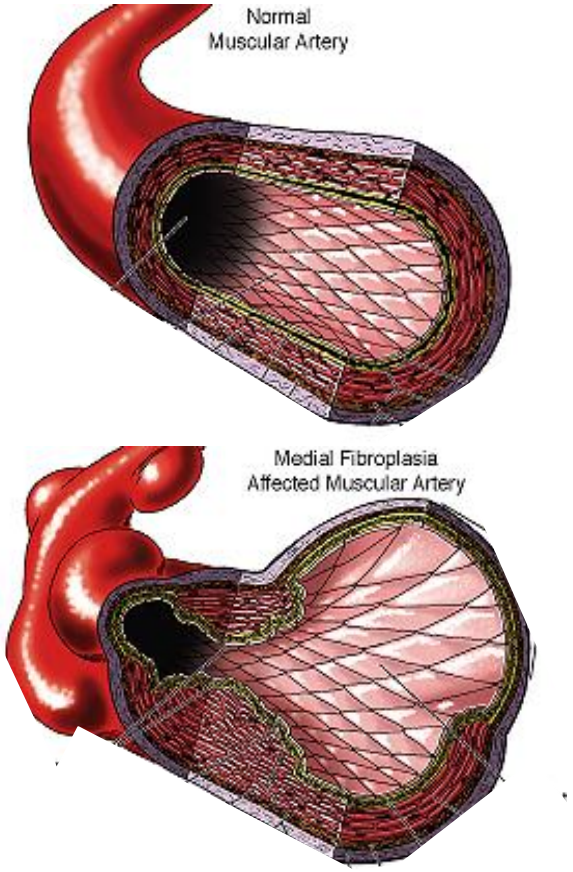
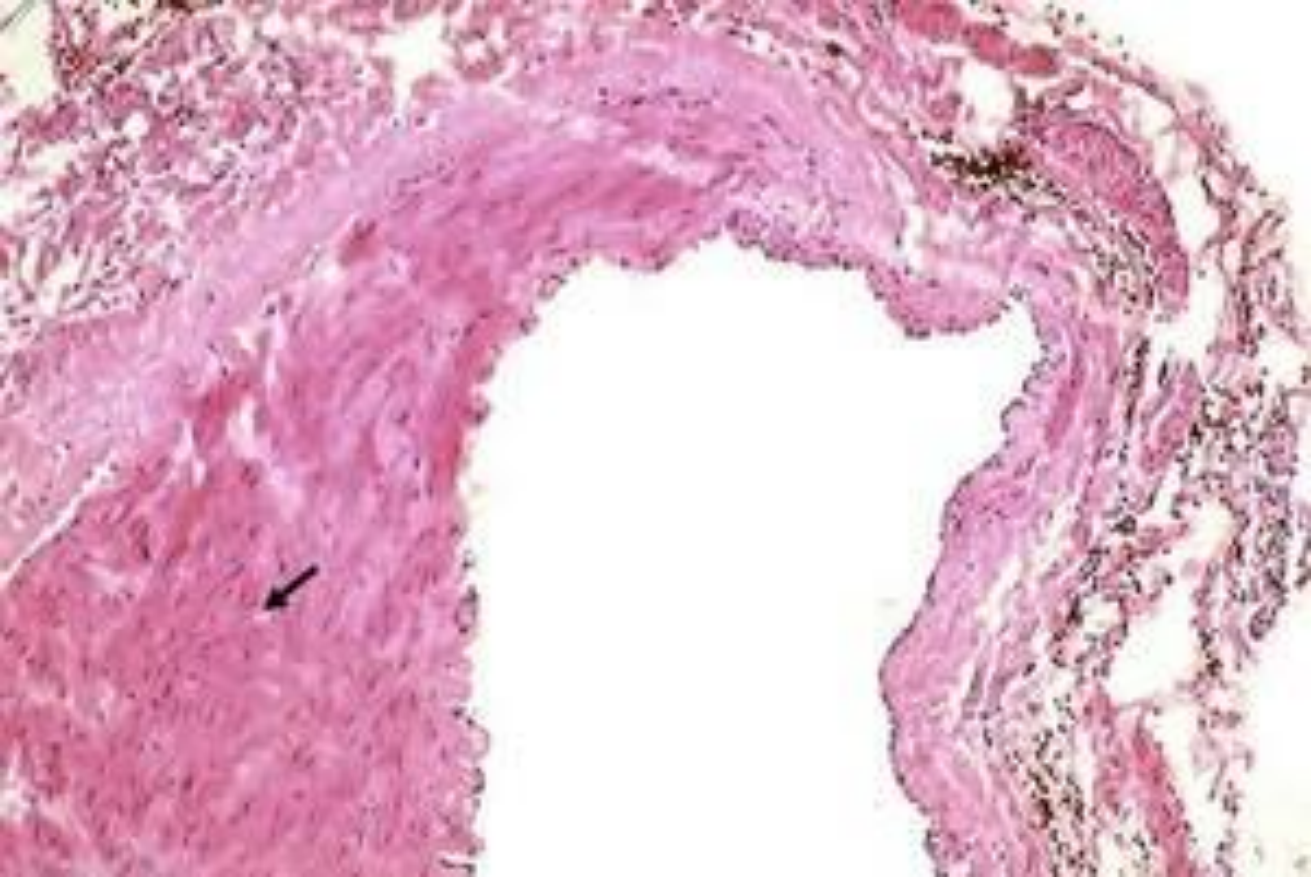
Fibromuscular dysplasia: definition

- FMD is an idiopathic, systemic, non-atherosclerotic, non-inflammatory vascular disease leading to stenosis, aneurysms, dissections and occlusion of small and medium-sized arteries.
- The diagnosis of FMD requires exclusion of artery spasm, arterial diseases of monogenic origin, and inflammatory arterial diseases.
- Renal and carotid arteries are more often involved
- FMD may lead to life-threatening complications such as cerebral hemorrhage or ischemia, accelerated and renovascular hypertension.



Persu et al. J Hypertens. 2014;32:1367-78.

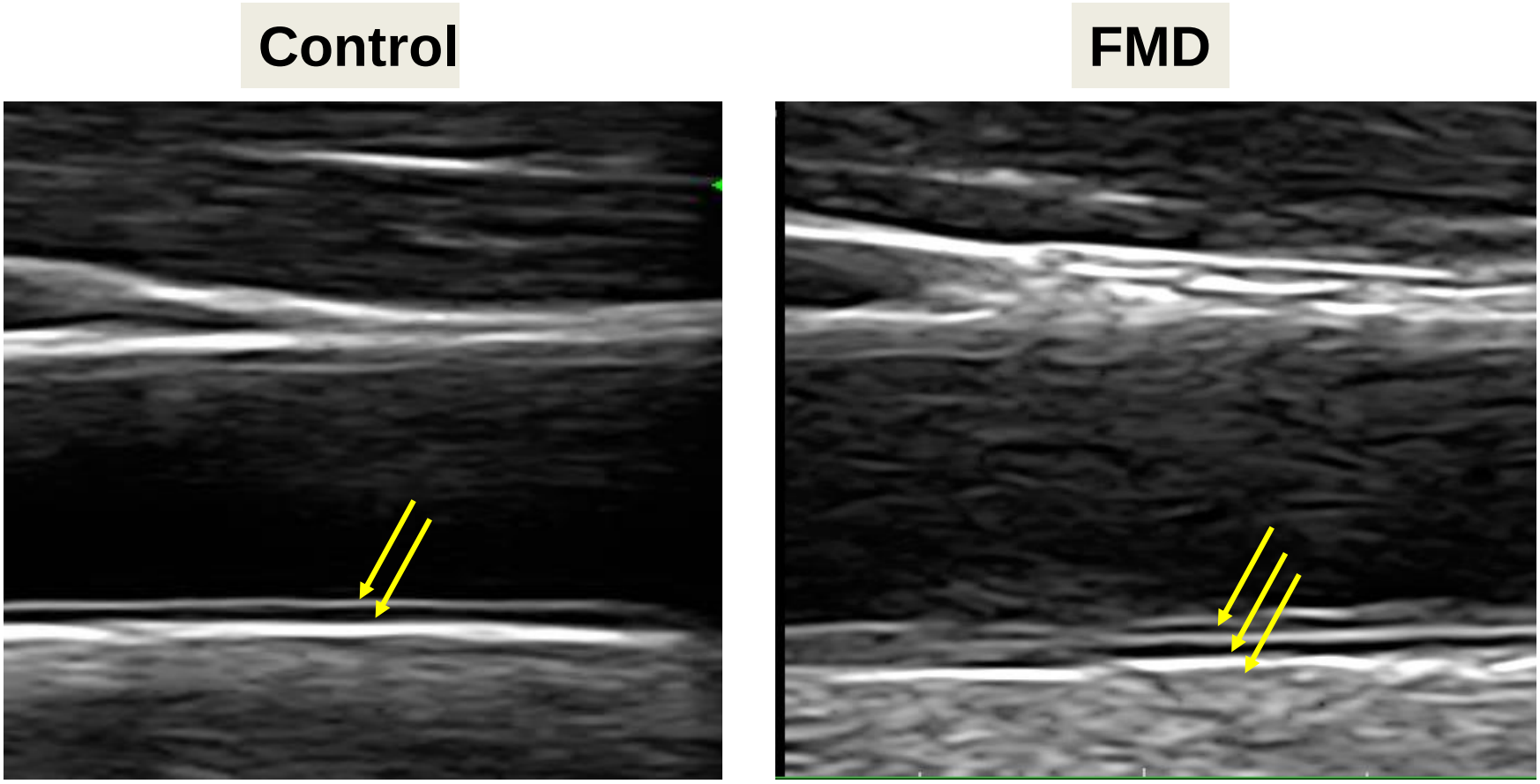


Medial fibroplasia:

- Thickened media alternating with thinned media → aneurysmal dilatations – “String of beads”
- Thickened media is replaced by collagen
- Internal elastic lamina may be thinned or fragmented → May lead to macroaneurysm formation

What about non-affected districts?

Carotid artery wall subclinical lesions in patients with renal fibromuscular dysplasia: the triple signal



Boutouyrie P et al. J Hypertens. 2003;21:2287–2295

MECANISMES PHYSIOPATHOLOGIQUES DE LA DYSPLASIE FIBROMUSCULAIRE ARTERIELLE: The MEDYA study

Aim

- to identify functional and structural alterations in non-affected arterial segments of individuals with multifocal FMD by means of a deep image-based vascular phenotyping, including:
  - endothelium-dependent and –independent dilation (EDD and EID respectively) of the brachial artery (BA)
  - aortic and carotid stiffness
  - triple signal (TS) at the common carotid level
  - carotid mechanical properties

- to investigate whether the presence of TS is associated with a different pattern of vascular alterations (exploratory aim).

Study design and population

Study design:

- case-control, cross-sectional

Study population:

- 50 individuals with renal multifocal fibromuscular dysplasia (FMD)
- 50 individuals with primary hypertension (PH)
- 50 healthy subjects (HS)

Methods: Endothelial function and smooth muscle function

Endothelium-dependent dilation - EDD (Flow-mediated dilation)

- Brachial artery diameter (BAD)
  → EDD = % BAD increase above baseline
  → Corrected EDD: BAD change allometrically corrected for baseline BAD
- Hyperemic stimulus
  → beat-to-beat flow velocity recording
  → baseline and hyperemic shear stress (SS)

- **Endothelium-independent vasodilation - EID (sublingual GTN administration, 150 μg)**

Allometric scaling for EDD and EID:

- Baseline and peak BAD logarithmically transformed and their difference (lnDiff) calculated
- Differences between groups in lnDiff analysed by ANCOVA model, with ln baseline BAD as covariate
- "corrected FMD" = [exp (Dbase-adjusted lnDiff) – 1] *100

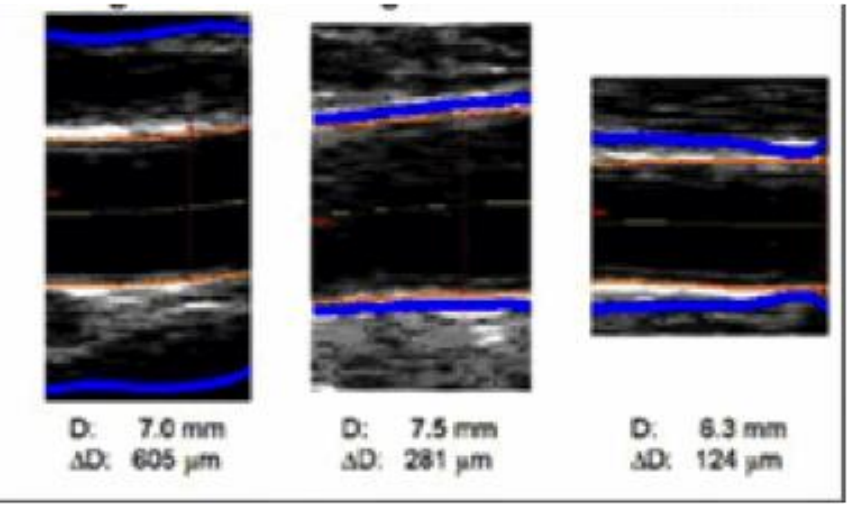
Atkinson G et al. Atherosclerosis 2013

Methods: Aortic and carotid stiffness

Carotid-femoral pulse wave velocity (PWV) and central pressures

- Applanation tonometry (Sphygmocor, Atcor Medical, Sydney, Australia)
- Carotid-femoral PWV

- Radial pressure waveform → aortic BP
- Augmentation Index (Aix): AP/PP
- Carotid pressure waveform → carotid BP



Carotid IMT and stiffness

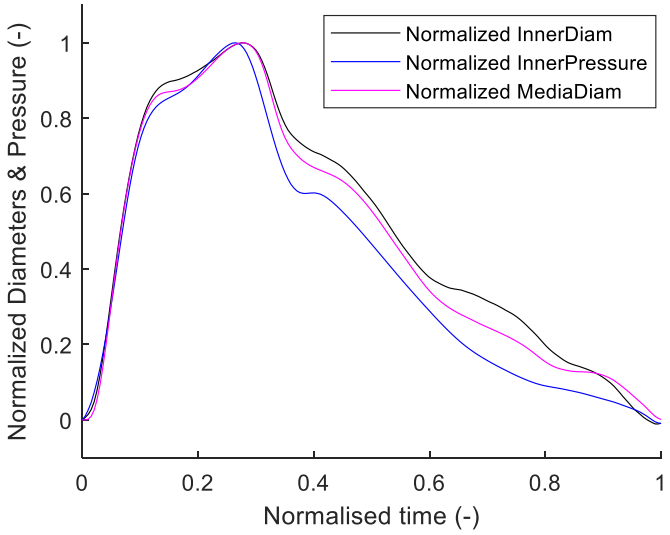
- Automated image-analysis
- High resolution echotracking device (ArtLab, ESAOTE; Maastricht, Netherlands)
- 128 RF line multiarray applied over a 4-cm arterial segment
- Right and left common carotid scans

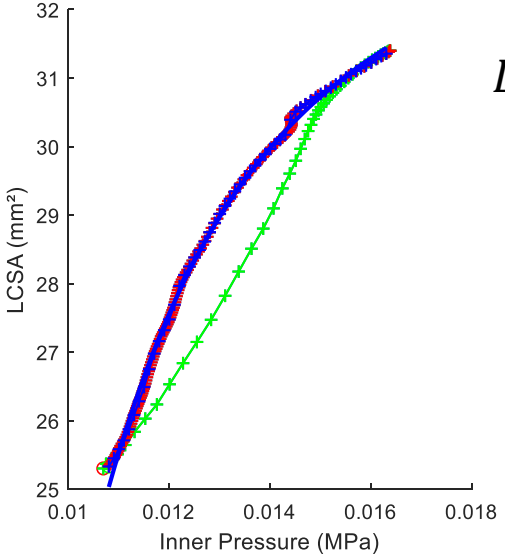
- cIMT / medial diameter
- Cross-sectional distensibility coefficient, DC): $\Delta A / (A \times \Delta P)$ (kPa^{-1})
- Carotid stiffness (CS, m/s) =$[(\Delta A / A \cdot PP) \cdot r)]^{-1/2}$

r= blood density

Intrinsic stiffness of the carotid wall at a given stress

- Right common carotid diameter and BP curves were synchronized
- Einc was calculated using the formula ([3(1+LCSA/WCSA)]/DC), but expressing LCSA, WCSA and DC as functions of BP
- The Einc-circStress curves were calculated within the diastolic-systolic BP range and compared between groups by mixed model analysis, and in particular for CWS = 80 KPa.





$$LCSA = \alpha\left[\frac{\pi}{2} + \tan^{-1}\left(\frac{P-\beta}{\gamma}\right)\right]$$

$$E_{inc} = \frac{3\left(1 + \frac{LCSA(P)}{meanWCSA}\right)}{Dist(P)}$$

$$\sigma_{circ} = \frac{P.D_i(P)}{D_e(P) - D_i(P)}$$

Laurent et al. Hypertension 1994, Bussy et al. Hypertension 2000

Clinical characteristics of the study population

	FMD (n=50)	PH (n=50)	HS (n=50)	p value
Age (years)	52.3±9.0	51.9±9.5	51.8±8.9	0.954
Female sex (n,%)	42 (88.0)	43 (86.0)	43 (86.0)	0.948
Caucasians (n,%)	40 (80.0)	41 (82.0)	43 (86.0)	0.722
BMI (Kg/m^2)	23 (21-25)	24 (23-26)	23 (21-26)	0.170
Hypertension duration (years)	6 (2-12)	4 (1-10)	-	0.214
Smoking:				0.467
Ex-smoker	14 (28.0)	8 (16.0)	10 (20.0)	
Never smoked	32 (64.0)	37 (74.0)	36 (76.0)	
Current smoker	4 (8.0)	5 (10.0)	2 (4.0)	
Hypercholesterolemia (n,%)	5 (10.0)	8 (16.0)	1 (2.0)	0.054
Type 2 diabetes (n,%)	0 (0.0)	0 (0.0)	0 (0.0)	-
Brachial systolic BP (mmHg)	129.9±15.2*	127.2±14.7*	117.6±11.4	<0.001
Brachial diastolic BP (mmHg)	71.5±10.5*	73.0±10.1*	66.9±7.5	0.004
Mean BP (mmHg)	95.6±12.0*	96.0±12.3*	88.4±9.9	0.002
Brachial PP (mmHg)	58.4±11.1*#	54.2±9.2	50.8±7.0	<0.001
Heart rate (bpm)	64.5±7.9	65.4±9.1	63.7±8.1	0.571

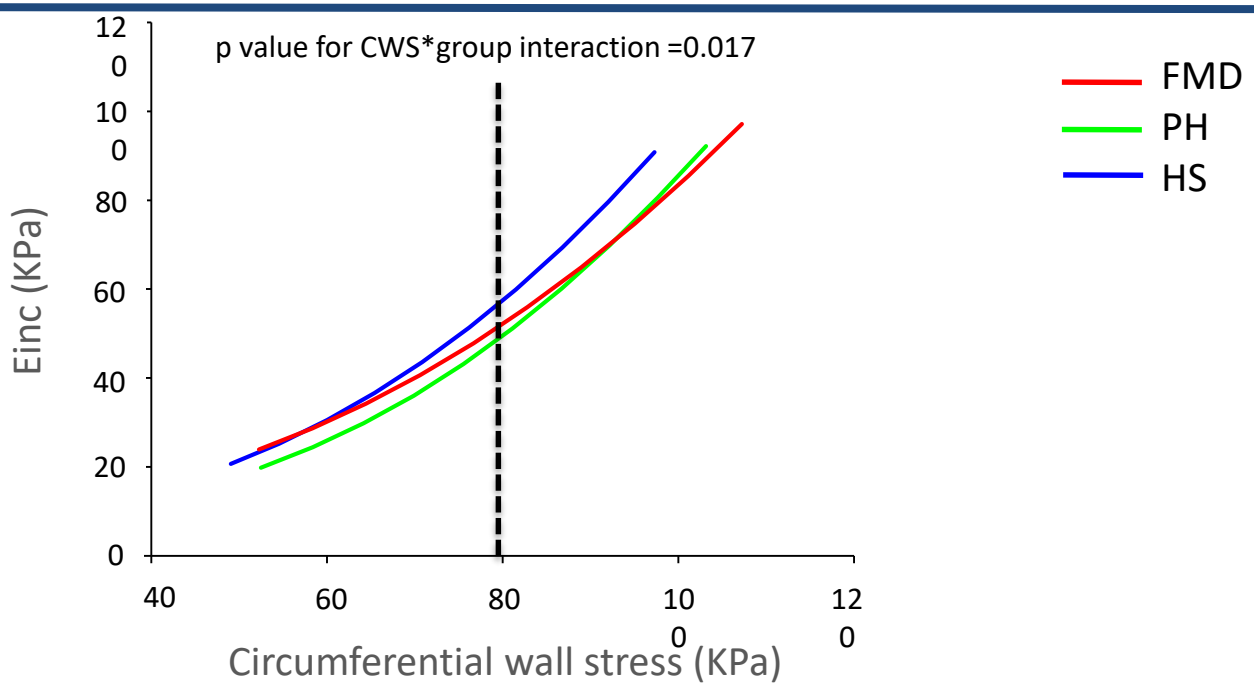
*: $p<0.05$ vs HS; #: $p<0.05$ vs PH

Results: endothelial function and applanation tonometry

	FMD (n=50)	PH (n=50)	HS (n=50)	p value
Endothelium-dependent dilation				
Baseline BA diameter (µm)	3867±710#	4172±628	4034±647	0.021
Maximum BA diameter (µm)	3957±721#	4289±628	4158±619	0.019
Baseline SS (dyne/cm^2 *10^{-2})	143 (54-423)	96 (31-216)	62 (22-152)	0.053
Peak SS (dyne/cm^2 *10^{-2})	1157 (935-1394)	1019 (815-1296)	1074 (886-1356)	0.171
EDD (%)	2.43 (0.30-4.75)	2.85 (-0.02-6.13)	2.75 (0.07-5.76)	0.651
Corrected EDD (%)	2.06 (1.10-3.02)	3.10 (1.05-5.15)	3.25 (1.10-5.39)	0.311
Endothelium-independent dilation				
Baseline BA diameter (µm)	3887±665#	4219±673	4022±660	0.020
Maximum BA diameter (µm)	4455±702#*	4817±611	4747±709	0.013
EID (%)	14.6 (8.9-19.9)*	15.3 (10.3-19.0)*	18.4 (12.8-21.4)	0.028
Corrected EID (%)	13.9 (9.5-18.4)*	15.6 (8.8-22.3)	18.2 (9.9-26.6)	0.008
Applanation tonometry				
PWV (m/s)	10.8±1.9*	11.2±2.0*	10.0±1.7	0.009
Aortic PP (mmHg)	45.6±10.2*	43.4±9.6	39.2±8.9	0.006

*: $p<0.05$ vs HS; #: $p<0.05$ vs PH

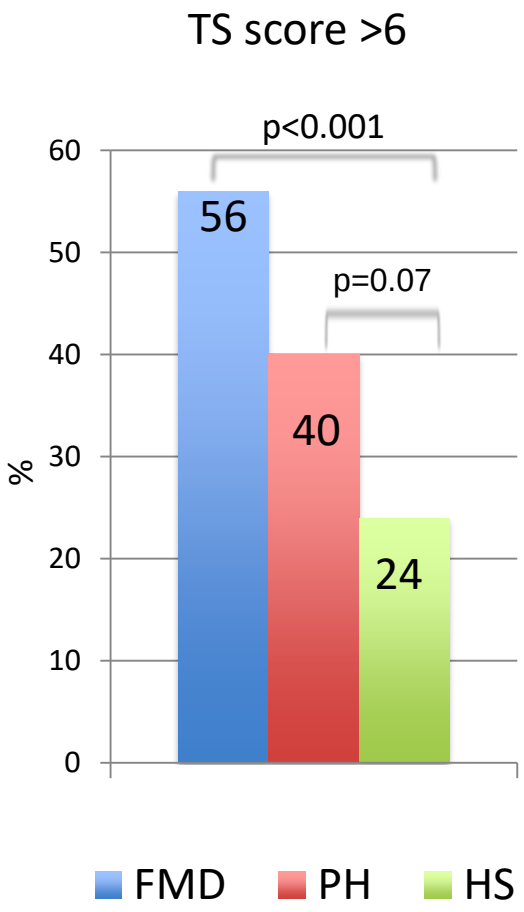
Results: carotid distensibility and intrinsic stiffness



	FMD (n=50)	PH (n=50)	HS (n=50)	p value
Diameter (µm)	6909±521	7061±627	6858±593	0.196
IMT (µm)	635±110	677±134*	619±112	0.044
Distensibility coefficient (kPa^{-1})	20.0±7.7	22.3±11.5	23.8±10.3	0.188
Einc (kPa)	539±251	513±260	451±143	0.217
Circumferential wall stress (kPa)	59.0±16.5	54.8±18.9	55.3±10.9	0.420
Carotid Stiffness (m/s)	7.51±1.51	7.36±1.84	6.88±1.22	0.196

*: p<0.05 vs HS; #: p<0.05 vs PH

Results: triple signal is a feature of FMD

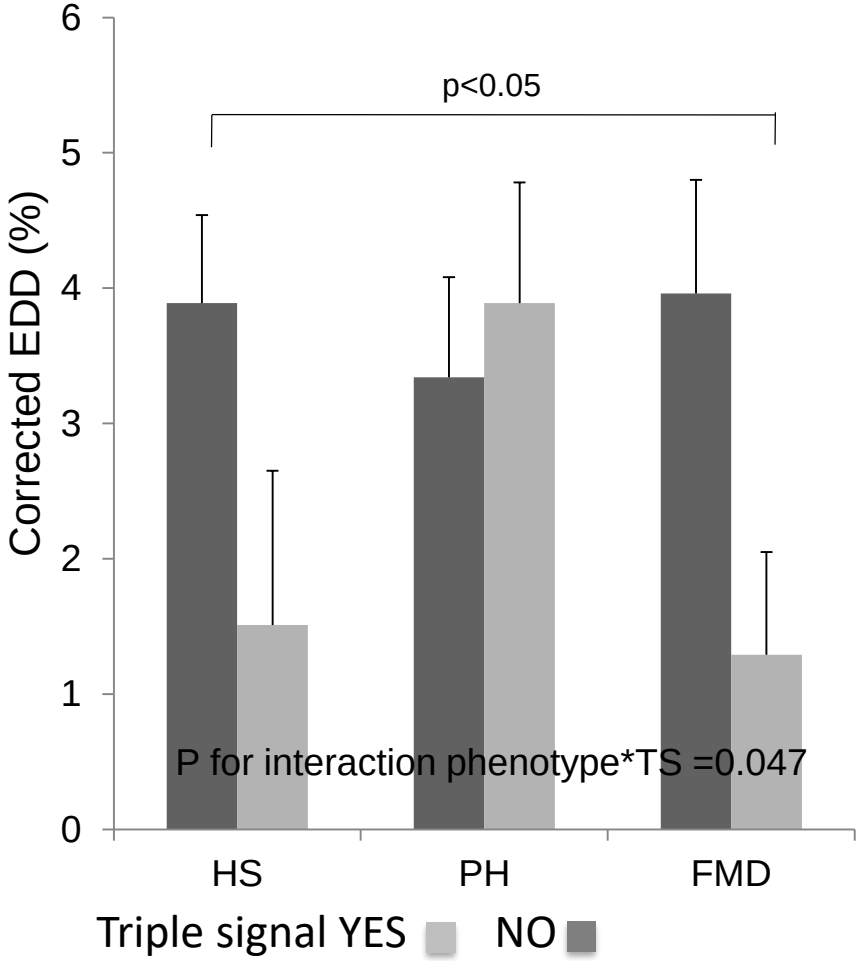


Linear regression model (TS score as dependent variable)

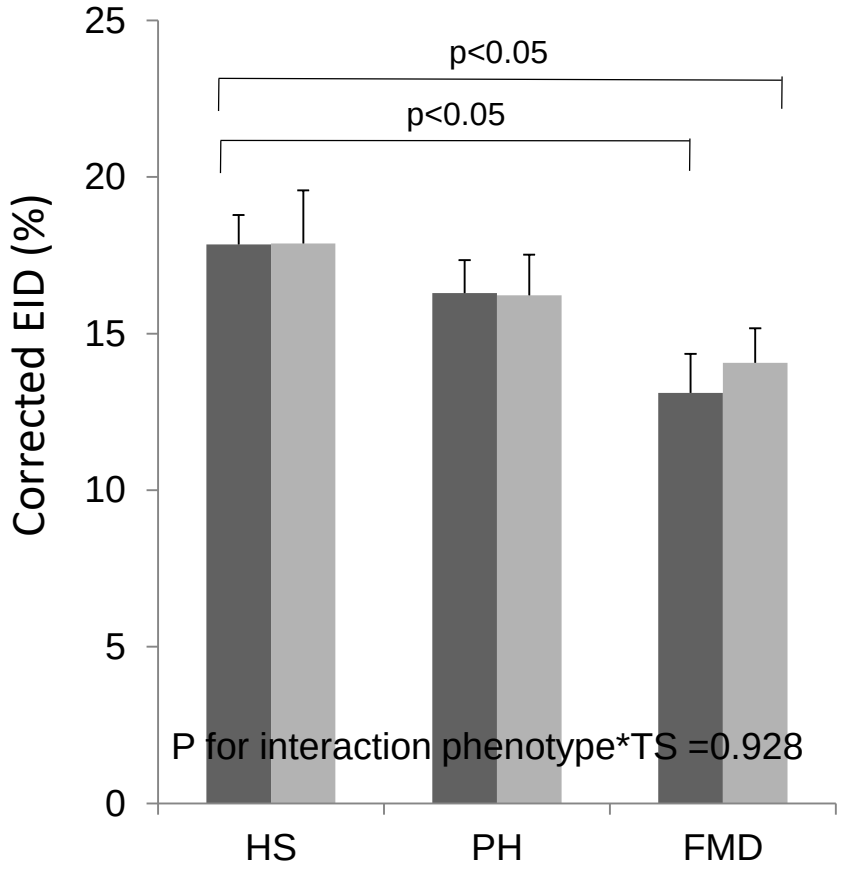
Multiple r2 full model 0.55	**beta**	**r2**	**p value**
Age	0.004 (-0.001;0.010)	0.009	0.106
Group=HS	0.00		-
Group=PH	-0.06 (-0.19;0.09)	0.058	0.486
Group=FMD	**0.14 (0.02;0.27)**		**0.022**
Hypercholesterolemia	0.13 (-0.01;0.27)	0.012	0.061
BP-lowering drugs	0.09 (-0.03;0.21)	0.007	0.310
cIMT	**0.002 (0.001;0.002)**	**0.188**	**<0.001**

FMD is associated with smooth muscle cell dysfunction in the brachial artery regardless of TS

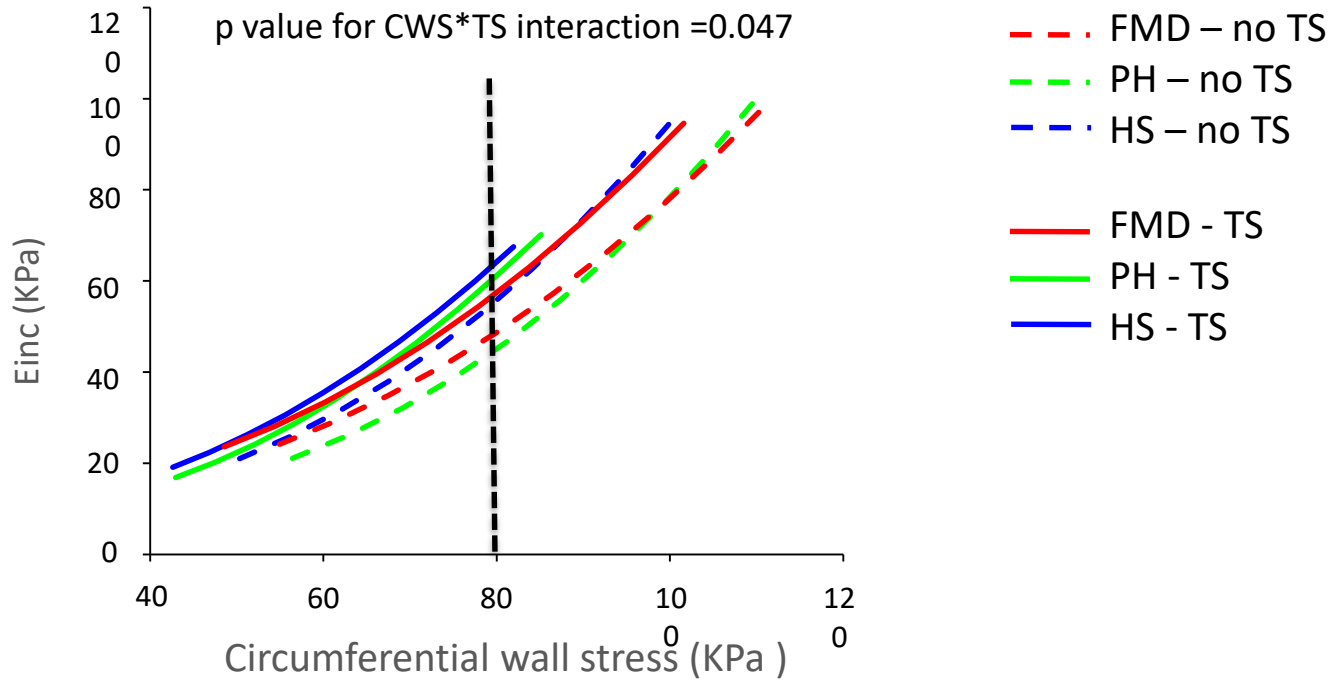
Flow-mediated dilation brachial artery



Nitrate-induced dilation brachial artery



Results: triple signal alters carotid mechanics, especially in FMD



The presence of a TS>6 changed the stress-strain relationship, with an upward shift of the Einc / CWS curves, indicating a stiffer material at a similar level of wall stress.

When analyzed at the CWS of 80 kPa, Einc was higher when TS>6 compared to TS≤6 (adjusted p=0.030), especially in FMD patients (adjusted p=0.033).

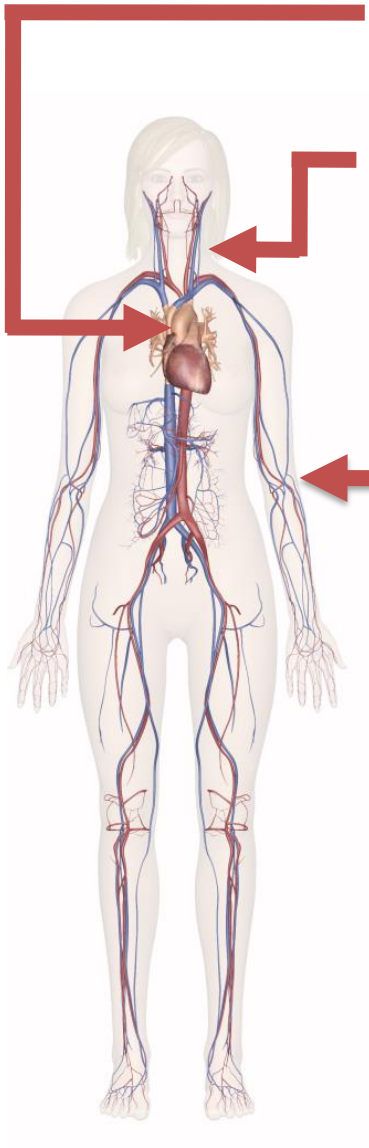
Fibromuscular dysplasia

pathophysiology

clinical practice

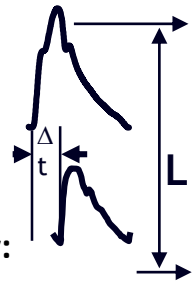
"muscular-to-elastic" gradient

Improve diagnosis / risk stratification



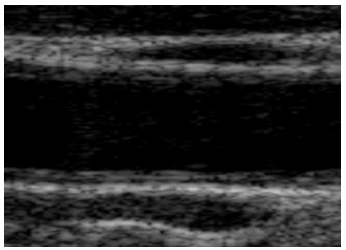
Aorta:

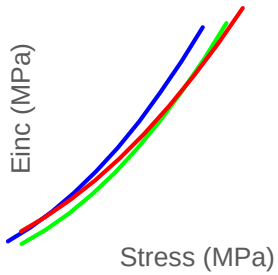
- Unchanged stiffness



Common carotid artery:

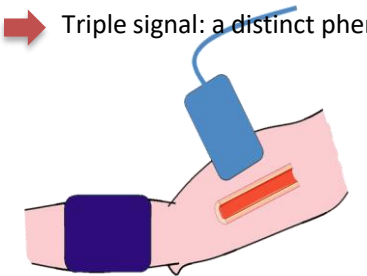
- ↑ triple signal → Medial fibrosis?
- ↑ intrinsic stiffness of wall material, especially in the presence of triple signal → Triple signal: a distinct phenotype?





Brachial artery:

- ↓ diameter → Inward remodeling
- ↓ dilation to nitrates → Smooth muscle cell dysfunction
- ↓ endothelial dysfunction only in the presence of triple signal → Triple signal: a distinct phenotype?



Thank you for the attention !