MESA IMT Progression Study: Progress Report

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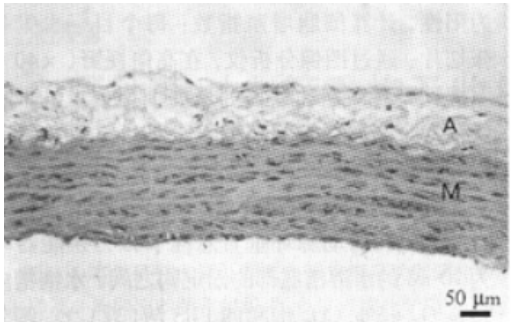
The issues

- How big is carotid IMT?
- How much should it change?
- What else changes with IMT?

The artery wall

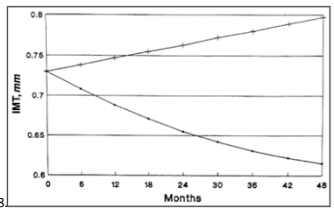


How big is carotid IMT?

- How thick is a nail?
  - Nail thickness in normals: 0.397 to 0.481 mm
    - Skin Research and Technology 2001; 7:60-64
- IMT average (common carotid artery) in MESA is:
  - 0.67 mm ± 0.19 mm
  - Far wall right common carotid artery

Why far wall common carotid artery?

- Emulates a recognized progression protocol
- Hodis / UCLA protocol
- Focuses on the far wall of the right common carotid artery
- Lovastatin



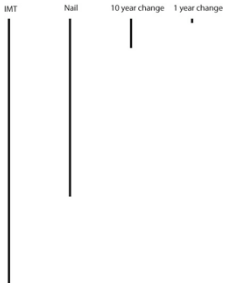
Hodis et al
Ann Internal Medicine 1996; 124: 548

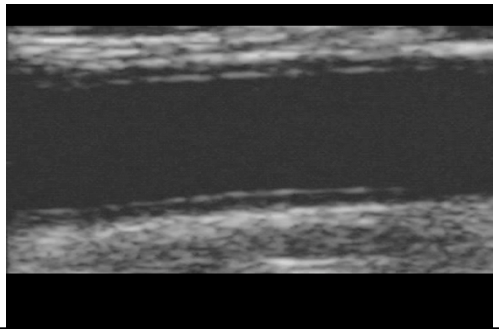
How much should it change?

- Look at slope of cross-sectional association between IMT and age
  - In CHS / ARIC:
    - 0.005 – 0.008 mm/year : Epidemiology, cross-sectional,
    - 0.0147 mm/year : Symptomatic, CHD trials

What to do in MESA?

- Precision in IMT measurement
- Magnitude of change in IMT
- Measure diameters
  - Specifically inter-adventitial diameters
- Not previously done in MESA





Change in IMT with cardiac cycle

Baseline demographics, risk factors, and subclinical disease measures	All (N=5636)	Gender	
		Female 2934 (52%)	Male 2702 (48%)
Age	61.91 (10.14)	61.80 (10.13)	62.04 (10.16)
Far wall mean IMT, at Diastole	0.67 (0.19)	0.66 (0.18)	0.69 (0.19)
Far wall mean IMT, at Systole	0.63 (0.18)	0.62 (0.17)	0.65 (0.19)
Far wall mean IMT difference (Dias – Sys)	0.04 (0.04)	0.04 (0.04)	0.04 (0.05)

Change in IMT with cardiac cycle

- Research Hypothesis: The carotid artery wall does not thicken during diastole.

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Baseline far wall mean IMT, at Diastole - Baseline far wall mean IMT, at Systole	0.04064	0.04445	0.00059	0.03948	0.04180	68.646	5635	<0.001

Hypothesis rejected

Change in IMT with cardiac cycle: association with gender

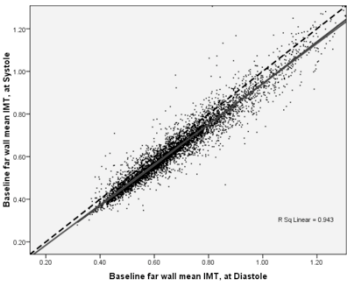
- Research Hypothesis: The carotid artery wall IMT change is similar for men / women.

Exploration of cardiac cycle related IMT changes by gender

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
0: FEMALE	2934	0.0421	0.04322	0.00080	0.0406	0.0437	-0.28	0.39
1: MALE	2702	0.0390	0.04570	0.00088	0.0373	0.0407	-0.49	0.29
Total	5636	0.0406	0.04445	0.00059	0.0395	0.0418	-0.49	0.39

NO : 0.0031 mm difference

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	0.014	1	0.014	7.003	0.008
Within Groups	11.118	5634	0.002		
Total	11.132	5635			



Scatterplot: IMT at Diastole versus IMT at Systole (reduced range 0.2 - 1.25 mm)

Change in IMT with cardiac cycle: association with risk factors

	Minimally adjustedmodel (IMT-Diastole)	Minimally adjusted model (IMT-Systole)	P for differences in predictor coefficient from the two models
Age	0.0070 [0.0065, 0.0074]	0.0067 [0.0062, 0.0071]	< 0.001
Race (reference Caucasian) Chinese African-American Hispanic	 -0.0068 [-0.0214, 0.0078] 0.0544 [0.0432, 0.0656] 0.0048 [-0.0071, 0.0168]	 -0.0011 [-0.0153, 0.0132] 0.0553 [0.0443, 0.0663] 0.0078 [-0.0039, 0.0195]	 0.015
Male gender	0.0255 [0.0166, 0.0344]	0.0287 [0.0200, 0.0374]	0.007

Change in IMT with cardiac cycle: association with risk factors

	Minimally adjustedmodel (IMT-Diastole)	Minimally adjusted model (IMT-Systole)	P for differences in predictor coefficient from the two models
Age	0.0070 [0.0065, 0.0074]	0.0067 [0.0062, 0.0071]	< 0.001
HDL Cholesterol (mg/dl) **LDL Cholesterol** (mg/dl) Adjusted for lipid lowering med use	-0.0008 [-0.0011, -0.0004] 0.0003 [0.0001, 0.0004]	-0.0008 [-0.0011, -0.0004] 0.0003 [0.0001, 0.0004]	0.740 0.857
Diabetes mellitus by 2003 ADA fasting criteria algorithm (reference Normal) IFG Untreated diabetes Treated Diabetes	 0.0129 [-0.0005, 0.0263] 0.0353 [0.0070, 0.0636] 0.0360 [0.0201, 0.0518]	 0.0121 [-0.0010, 0.0251] 0.0301 [0.0025, 0.0578] 0.0326 [0.0172, 0.0481]	0.247
Cigarette smoking status (reference Never) Former Current **Adjusted for pack-years**	0.0054 [-0.0058, 0.0166] 0.0171 [0.0012, 0.0331] 0.0002 [-0.0001, 0.0004]	0.0062 [-0.0047, 0.0171] 0.0168 [0.0012, 0.0324] 0.0002 [-0.0000, 0.0004]	0.788
Hypertension by JNC VI (1997)	0.0333 [0.0237, 0.0429]	0.0307 [0.0214, 0.0401]	0.045
Systolic Blood Pressure(mmHg) adjusted for anti-hypertension meds	0.0009 [0.0004, 0.0014]	0.0008 [0.0003, 0.0012]	< 0.001
Diastolic Blood Pressure(mmHg) adjusted for anti-hypertension meds	0.0014 [0.0012, 0.0016]	0.0013 [0.0010, 0.0015]	0.227
Pulse Pressure(mmHg) adjusted for anti-hypertension meds	0.0022 [0.0018, 0.0025]	0.0019 [0.0016, 0.0022]	< 0.001

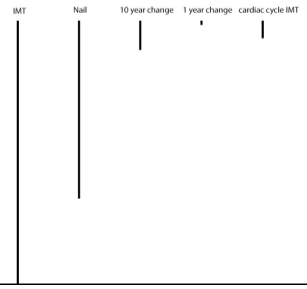
Change in IMT with cardiac cycle: association with risk factors

- Coefficient estimates (direction, magnitude, and significance) suggest similar results from either IMT-Diastole or IMT-Systole.
- A comparison of model R-square suggests that IMT-Diastole should be preferred over IMT-Systole when both measures are available.
- Using regression methodology known as Seemingly Unrelated Regression for these analyses, test results suggest statistically significant differences in between the two models for age, race, gender, hypertension (systolic blood pressure), and pulse pressure coefficients. While some differences are statistically significant, the magnitude of the coefficient estimate difference is typically small and perhaps not meaningful. The one exception to this appears to be pulse pressure which exhibits a somewhat stronger association with IMT and was noted earlier to be associated with the IMT differences at different points in the cardiac cycle (physiologically associated with the IMT thickness issue of interest in these analyses).

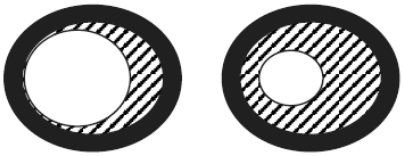
Difference in IMT during cardiac cycle

	Minimally adjusted model	Fully adjusted model
Age	0.0003 [0.0002, 0.0004]*	0.0001 [-0.0000, 0.0003]
Race (reference Caucasian) Chinese African-American Hispanic	 -0.0057 [-0.0089, -0.0026]* -0.0009 [-0.0040, 0.0023] -0.0030 [-0.0060, 0.0000]	 -0.0057 [-0.0088, -0.0025]* -0.0019 [-0.0051, 0.0013] -0.0039 [-0.0066, -0.0006] *
Male gender	-0.0032 [-0.0055, -0.0009] *	-0.0018 [-0.0041, 0.0005]
Body Mass Index	0.0000 [-0.0002, 0.0003]	
HDL Cholesterol (mg/dl) **LDL Cholesterol** (mg/dl) Adjusted for lipid lowering med use	0.0000 [-0.0001, 0.0001] 0.0000 [-0.0000, 0.0000]	
Diabetes mellitus by 2003 ADA fasting criteria algorithm (reference Normal) IFG Untreated diabetes Treated Diabetes	 0.0008 [-0.0029, 0.0046] 0.0052 [-0.0057, 0.0161] 0.0033 [-0.0010, 0.0076]	
Cigarette smoking status (reference Never) Former Current **Adjusted for pack-years**	 -0.0008 [-0.0035, 0.0019] 0.0003 [-0.0039, 0.0046] -0.0000 [-0.0001, 0.0000]	
Hypertension by JNC VI (1997)	0.0026 [-0.0000, 0.0051]	
Systolic Blood Pressure (mmHg) adjusted for anti-hypertension meds	0.0001 [0.0001, 0.0002]*	
Diastolic Blood Pressure (mmHg) adjusted for anti-hypertension meds	0.0001 [-0.0001, 0.0002]	
Pulse Pressure (mmHg) adjusted for anti-hypertension meds	0.0002 [0.0001, 0.0003]*	0.0002 [0.0001, 0.0003]

Change in IMT



Glagov phenomenon



	<40% Stenosis	>40% Stenosis
Lumen	NoΔ	↓
Vessel wall	↑	↑
Vessel r_{ext}	↑	↑

Glagov phenomenon: implications for IMT progression

	No Restenosis	Restenosis
Lumen	NoΔ	↓
Vessel wall	↑	↑
Vessel r_{ext}	↑	↓

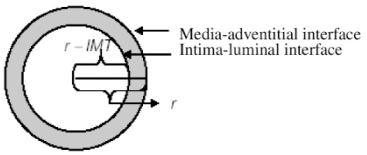
Remodeling and IMT

Q J Med 2004; **97**:729–737
doi:10.1093/qjmed/hch120

Mathematical estimation of the potential effect of vascular remodelling/dilatation on B-mode ultrasound intima-medial thickness

M.L. EIGENBRODT[1], Z. BURSAC[2], E.P. EIGENBRODT[3], D.J. COUPER[4], R.E. TRACY[5] and J.L. MEHTA[6]

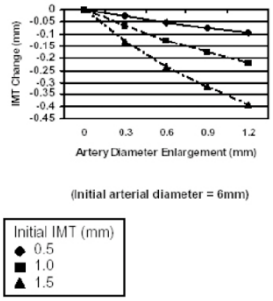
Some math !



$$IMT_N = (r + \Delta_r) - \sqrt{(r + \Delta r)^2 - \frac{A}{\pi}} \qquad \Delta_{IMT} = IMT_N - IMT$$

The hypothesis

- Change in IMT depends on change in diameters



Inter-adventitial diameters

	Unadjusted model	Minimally adjusted model	Fully adjusted model
Age	0.032 [0.030, 0.034]	0.036 [0.034, 0.038]	0.031 [0.029, 0.034]
Gender Male	0.603 [0.558, 0.647]	0.422 [0.363, 0.482]	0.377 [0.316, 0.438]
Race (reference Caucasian)			
Chinese	0.080 [0.004, 0.155]	0.336 [0.267, 0.405]	0.313 [0.243, 0.382]
African-American	0.196 [0.135, 0.258]	0.167 [0.113, 0.221]	0.095 [0.041, 0.150]
Hispanic	0.018 [-0.041, 0.078]	0.119 [0.064, 0.175]	0.095 [0.039, 0.151]
Height (cm)	0.013 [0.010, 0.016]	0.003 [-0.001, 0.006]	0.006 [0.002, 0.009]
Weight (lbs)	0.004 [0.003, 0.005]	0.006 [0.005, 0.006]	0.004 [0.004, 0.005]
HDL Cholesterol (mg/dl)	-0.012 [-0.013, -0.010]	-0.004 [-0.005, -0.002]	-0.003 [-0.004, -0.001]
LDL Cholesterol (mg/dl)	0.000 [-0.001, 0.000]	0.000 [-0.001, 0.001]	0.000 [0.000, 0.001]
Lipid-lowering medications	0.129 [0.064, 0.195]	-0.031 [-0.088, 0.026]	-0.078 [-0.136, -0.021]
Diabetes mellitus by 2003 ADA fasting criteria algorithm (reference Normal)			
IFG	0.320 [0.246, 0.393]	0.059 [-0.008, 0.126]	0.021 [-0.047, 0.088]
Untreated diabetes	0.308 [0.173, 0.443]	0.064 [-0.058, 0.186]	0.037 [-0.086, 0.159]
Treated Diabetes	0.464 [0.383, 0.545]	0.196 [0.120, 0.272]	0.115 [0.037, 0.193]
Hypertension by JNC VI (1997) criteria	0.557 [0.511, 0.603]	0.335 [0.291, 0.379]	0.331 [0.286, 0.376]
Cigarette smoking status (reference Never)			
Former	0.067 [0.003, 0.131]	-0.049 [-0.098, 0.001]	-0.045 [-0.093, 0.004]
Current	-0.009 [-0.097, 0.079]	0.126 [0.053, 0.199]	0.123 [0.050, 0.196]
Pack-years of cigarette smoking	0.005 [0.003, 0.007]	0.002 [0.001, 0.003]	0.002 [0.001, 0.003]
LV end-diastolic mass (g)	0.009 [0.009, 0.010]	0.008 [0.007, 0.009]	0.007 [0.006, 0.008]
Far wall mean IMT, at Diastole	2.830 [2.571, 3.090]	2.064 [1.807, 2.321]	1.906 [1.656, 2.156]

Current status

- Cross-sectional associations of IMT and IAD
- Combine both measurements
- Look at change over time