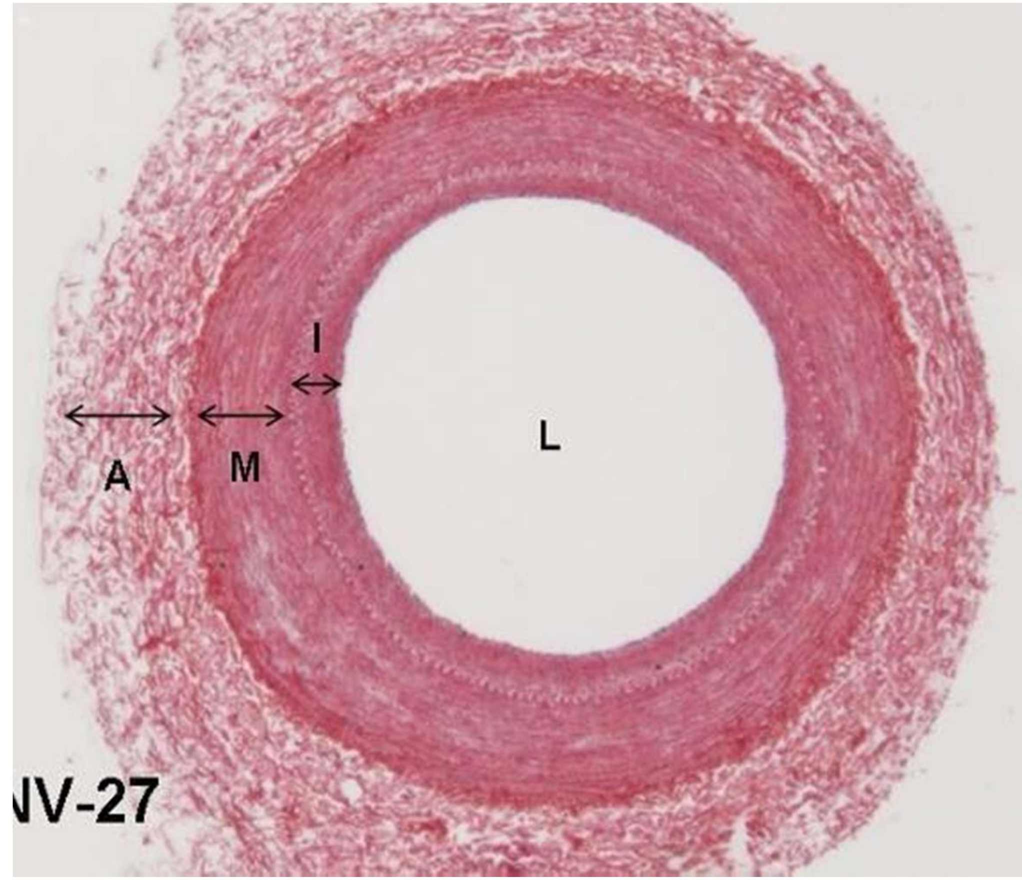
Echo for Early Detection of Atherosclerosis

Sung-Ai Kim, MD

Division of Cardiology
Hallym University Sacred Heart Hospital

Arterial wall



Arterial wall

- **Intima :** a source of substances and signal transduction mechanisms that influence mechanical properties
  - endothelial cell
  - internal elastic laminar
- **Media :** mechanical properties of elastic arteries
  - collagen and smooth muscle cells
- **Adventitia :** outermost layer
  - fibroblast and collagen

Hemodynamic forces on vessel

Endothelial cells experience 3 hemodynamic forces

① Hydrostatic pressure

② Circumferential stretch or tension

③ Shear stress

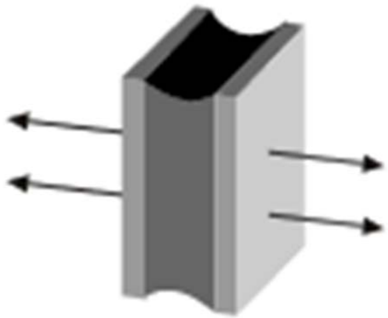
Shear stress (SS)

- A strong correlation between endothelial cell dysfunction and areas of low mean SS and oscillatory flow with flow reversal

- Low mean SS promotes <u>secretion of growth factors, regulation of coagulation, transmigration of leukocytes and increase proliferation of smooth muscle</u>

>> Low shear stress is related to atherosclerosis

Tensile stress

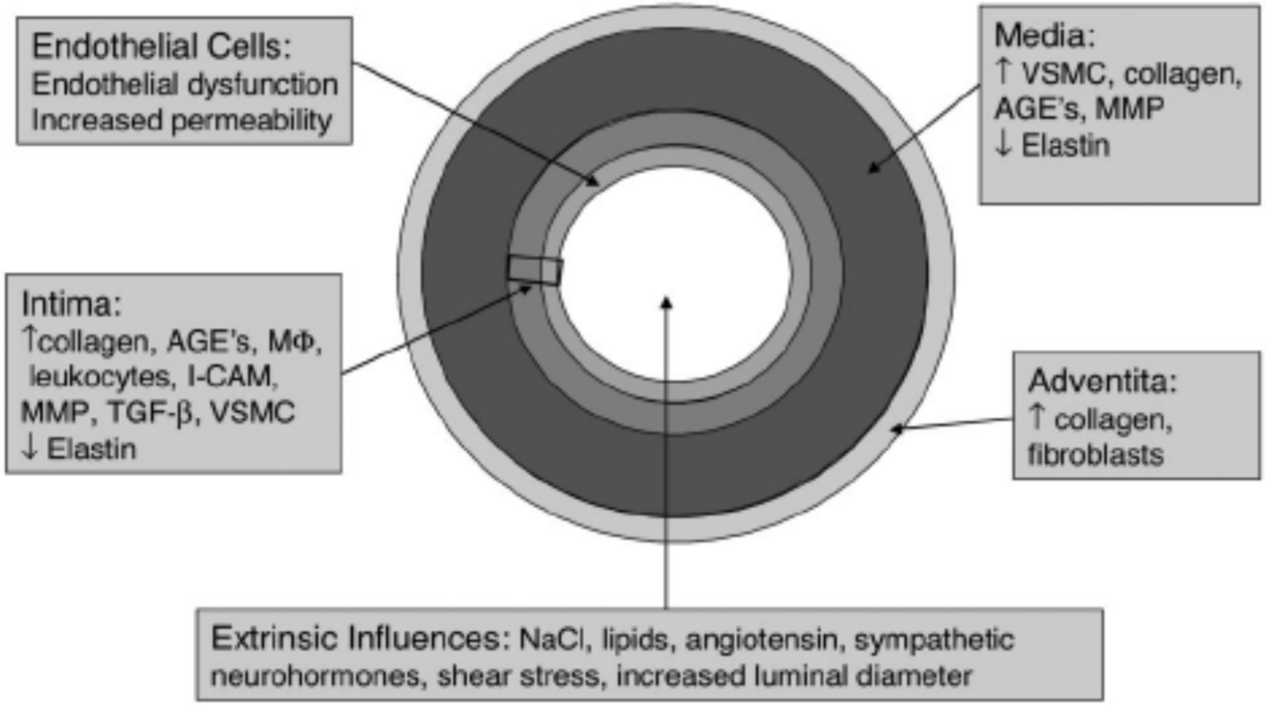


- To maintain basal levels of tensile stress (Laplace's law), progressive thickening of the vessel wall occurs as result of the proliferation and migration of vascular smooth muscle cells

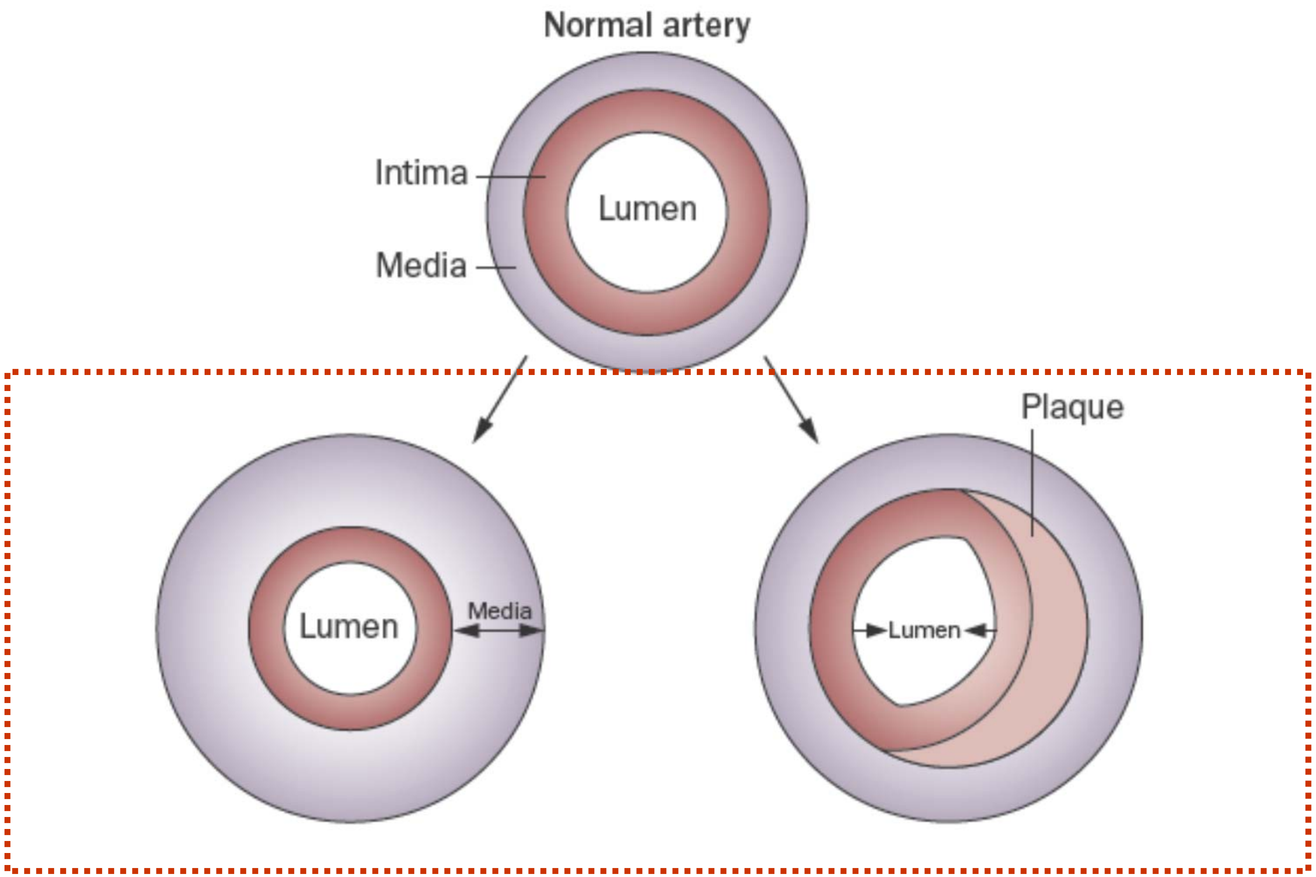
$$T = (P \times R) / M$$

(T = tension, P = pressure, R = radius, M = thickness)

Arterial remodeling



Arterioscler Thromb Vasc Biol. 2005;25:932-943



Arteriosclerosis **Atherosclerosis**

Nat.Rev.Cardiol. 2010;7:442-49

Pathophysiology of arterial remodeling

- **Structural Thickening**

  - less vascularized wall layer

  - receive less oxygen and other nutrient

  - early ischemia damage > atherosclerosis

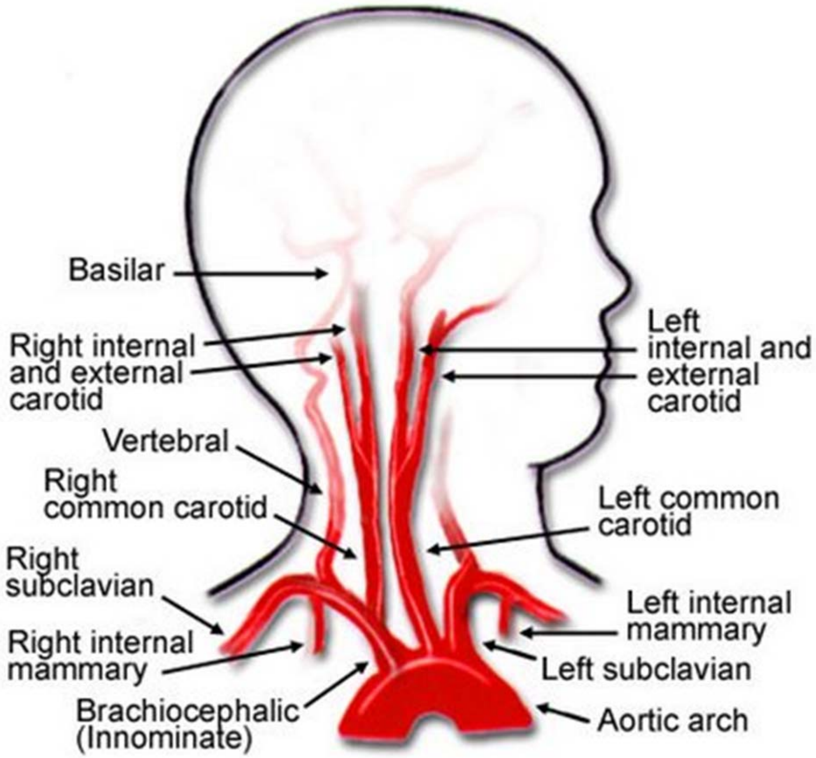
- **Functional Stiffening**

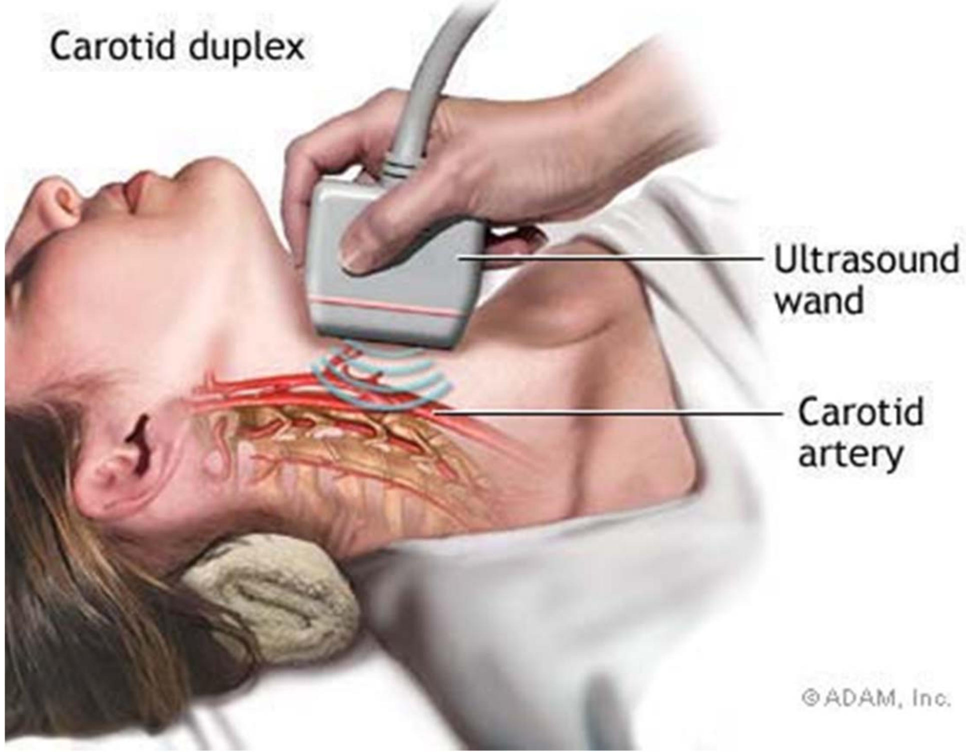
  - traumatic effect of blood pressure on vascular wall

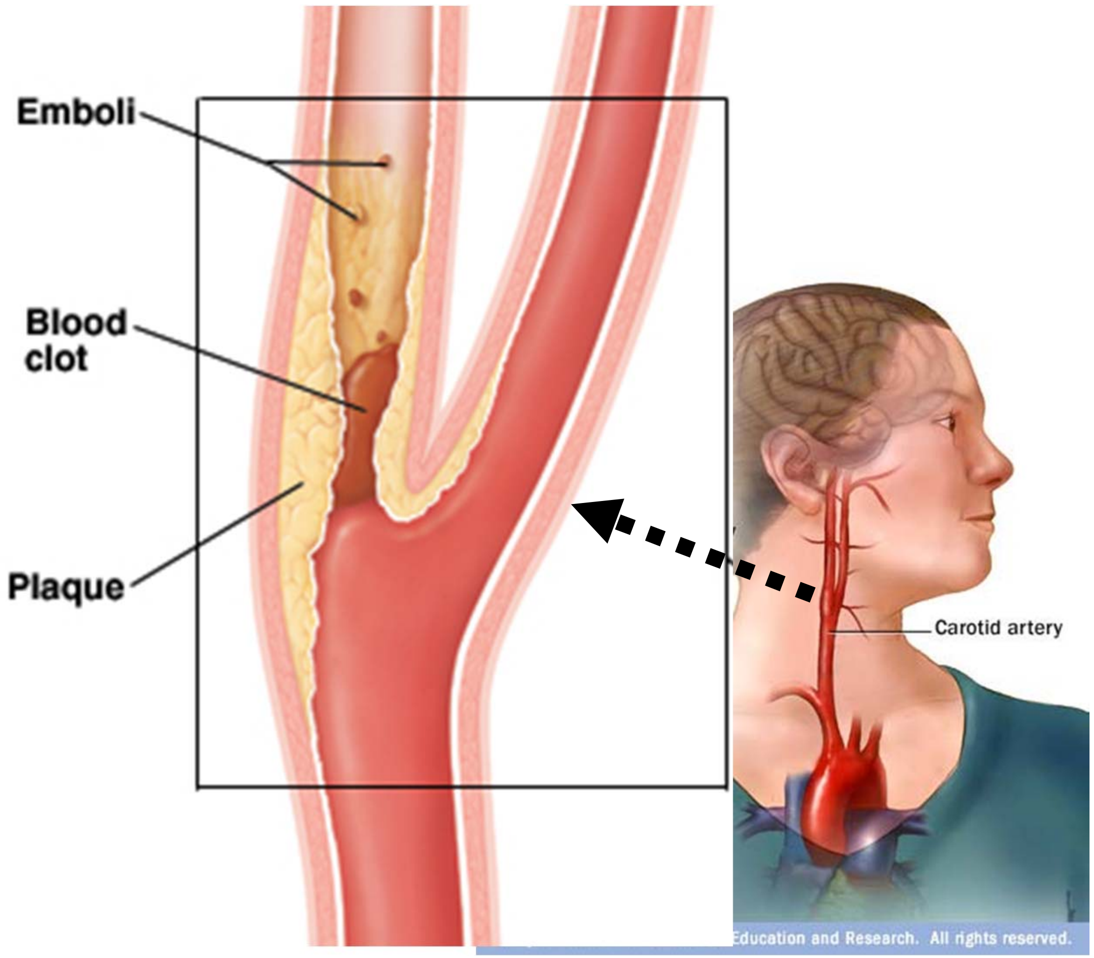
  > acts as proatherogenic factor

Diabetologia 1999;42:987-994

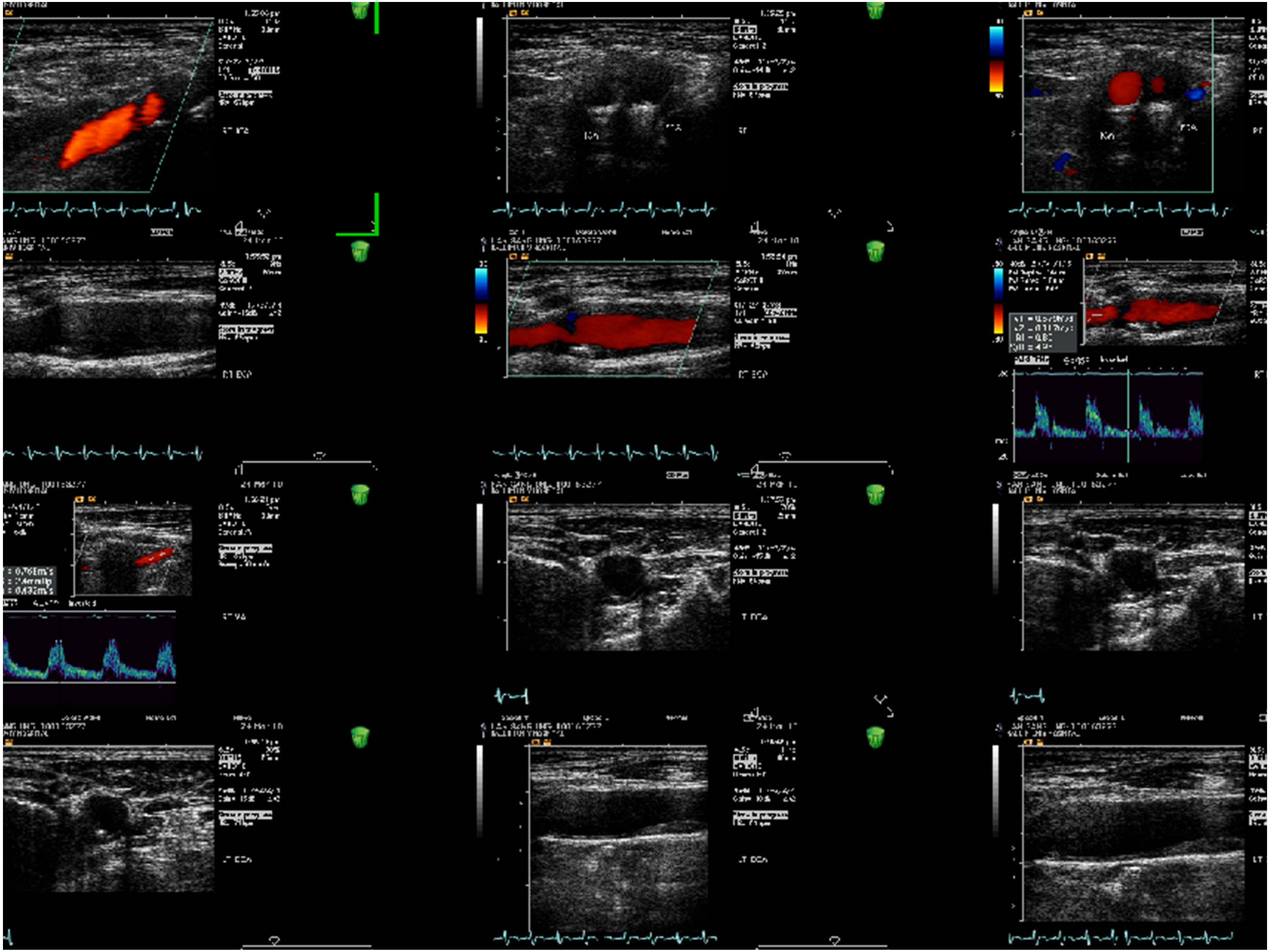
Carotid Ultrasound





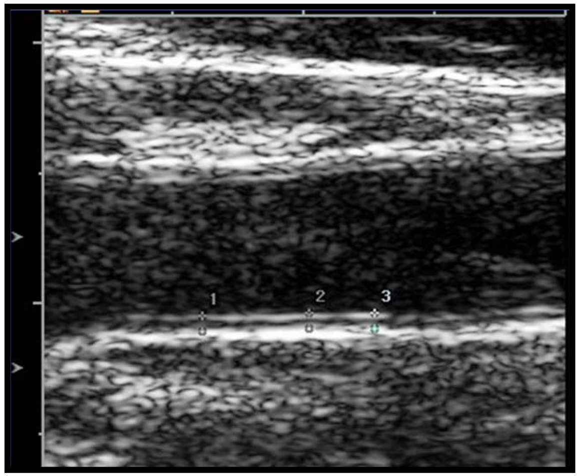


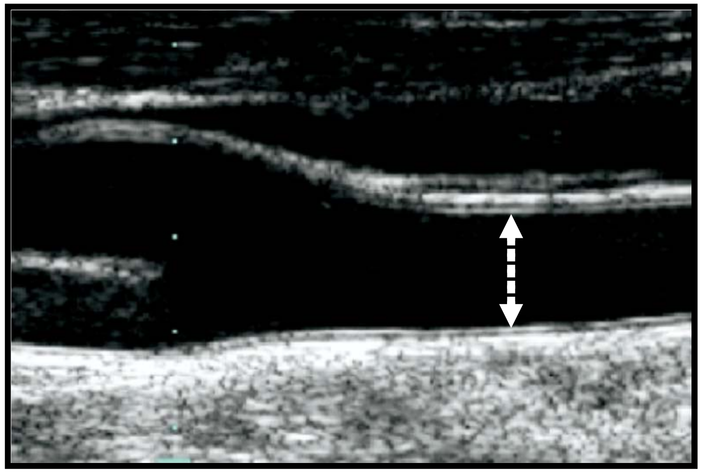
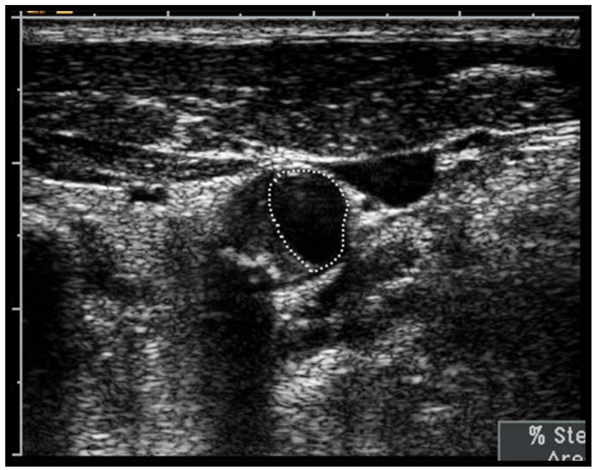
- ✓ ***Non-invasive***
- ✓ ***No Radiation hazard***
- ✓ ***Easily reproducible***
- ✓ ***Less expensive***



Measures in carotid US

- Structural property - IMT, vessel diameter
- Mechanical property – stiffness
- Atheromatous plaque



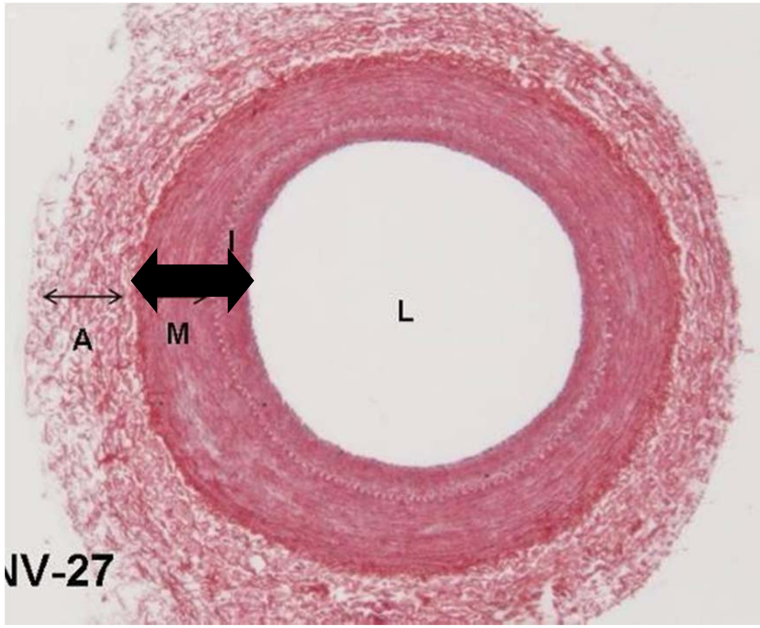



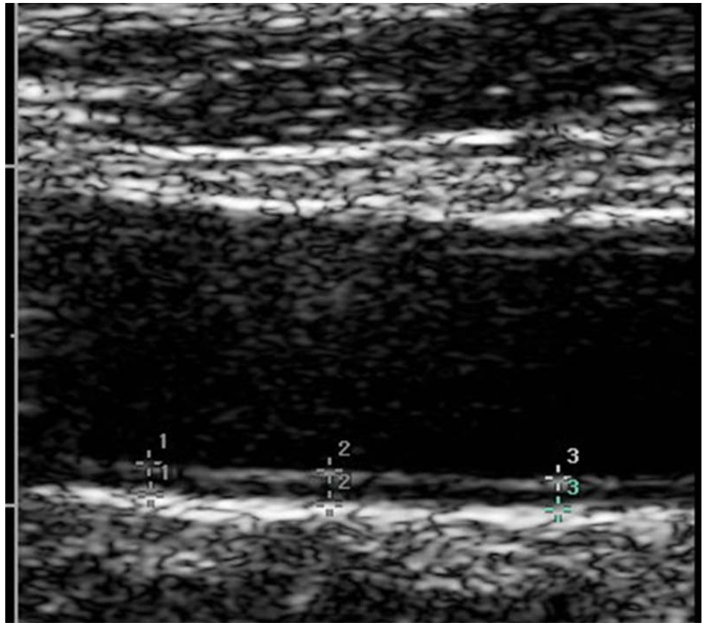
Vascular properties

(1) Structural property ; IMT, vessel diameter

(2) Mechanical property ; arterial stiffness

(1) Structural property

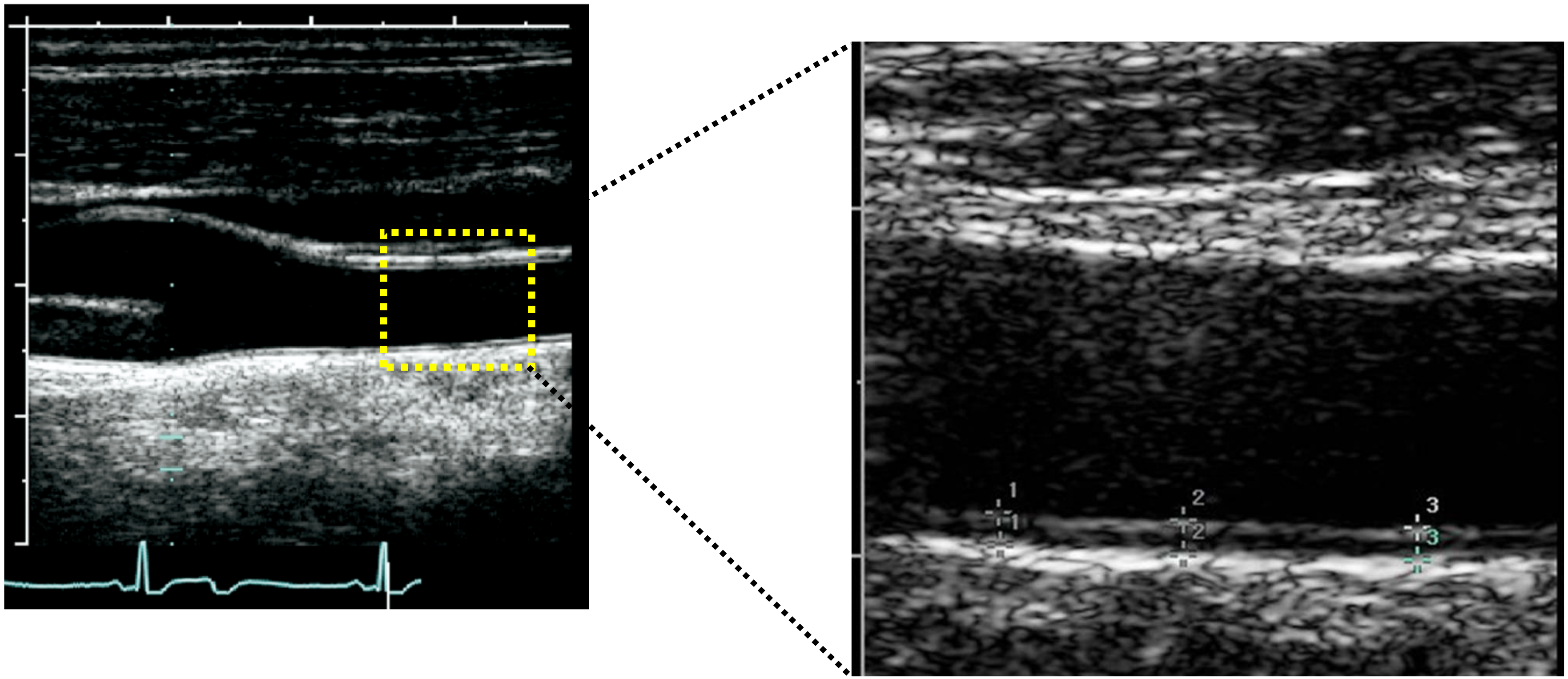




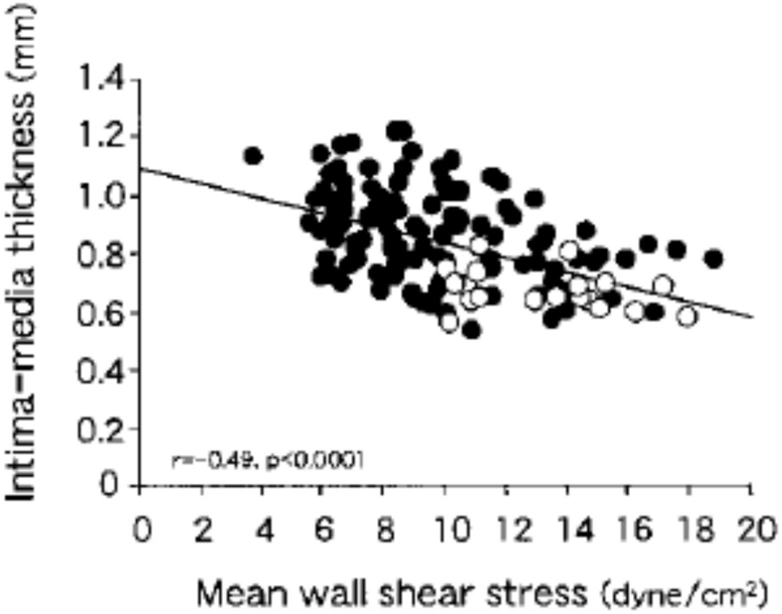
IMT (intima-media thickness)

① IMT

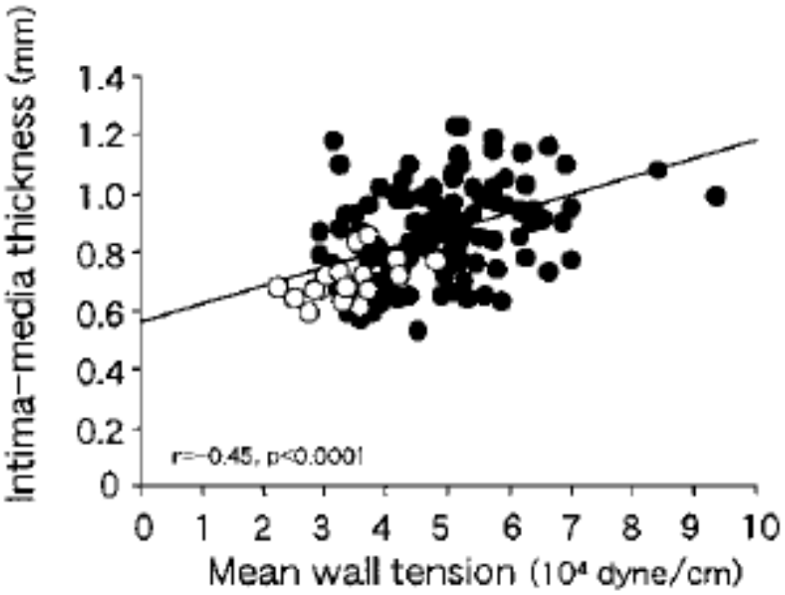
;Surrogate marker of subclinical atherosclerosis



IMT vs. hemodynamic force



Shear stress



Tensile stress

Stroke. 2000;31:2319-2324

Adaptive intimal thickening

In response

- to reduced wall shear, reducing lumen diameter to elevate flow velocity and thereby restore wall shear to baseline values

- to increased tensile stress, strengthening the arterial wall to maintain normal values of tensile stress

Increased IMT; Adaptive response or a reflection of atherosclerosis ?

- At lower degrees of IMT, the thickening may reflect an adaptive response to changes in shear stress, lumen diameter, tensile stress, and pressure instead of an atherosclerotic thickening
- Beyond a certain level, the IMT more likely represents atherosclerosis and is a graded marker for CV risk

Stroke. 1997;28:2442-2447

Structural properties in CV risk factor

1. HTN

- Positive association with increased IMT and LD

- High blood pressure

  => exert a fatiguing effect on the load-bearing elements of the arterial wall (elastin, collagen)

  => degenerative change and increase in LD

2. Diabetes mellitus

- Preservation of LD
- Positive association with increased IMT

- Altered glucose metabolism

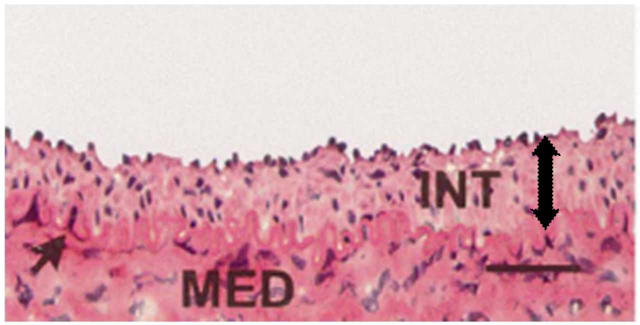
  1) Endothelial dysfunction (decrease NO secretion)

  2) Hemodynamic pressure load

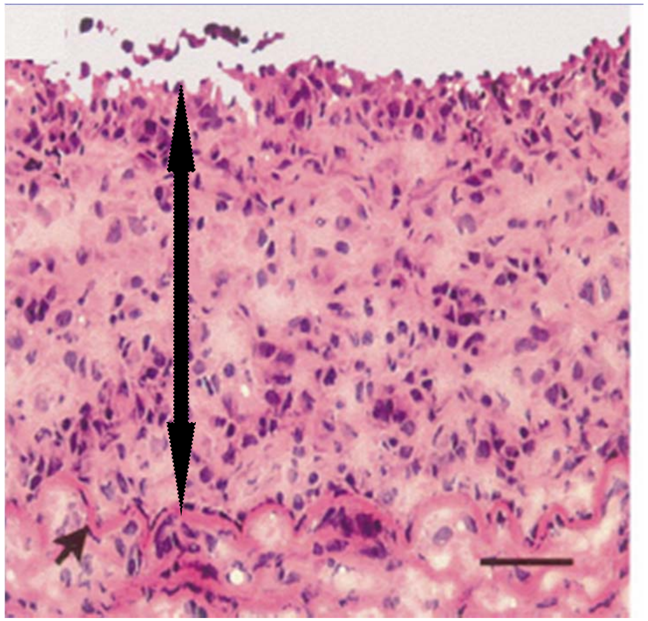
  3) Enhanced endothelial permeability due to harmful effects of chronic hyperglycemia and AGEs

  => Promote LDL accumulation in arterial walls

Intimal hyperplasia in DM



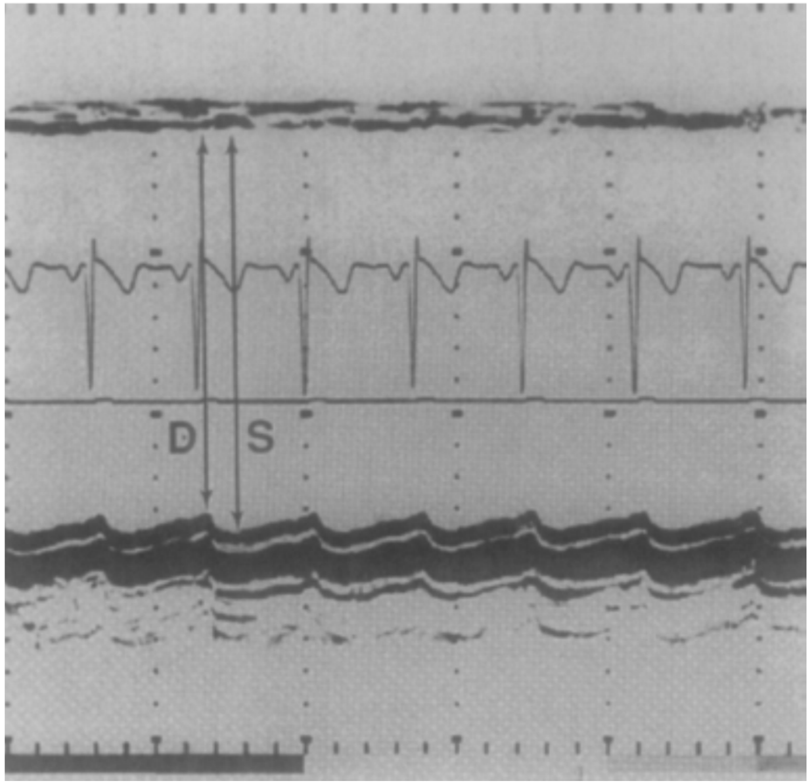
Control

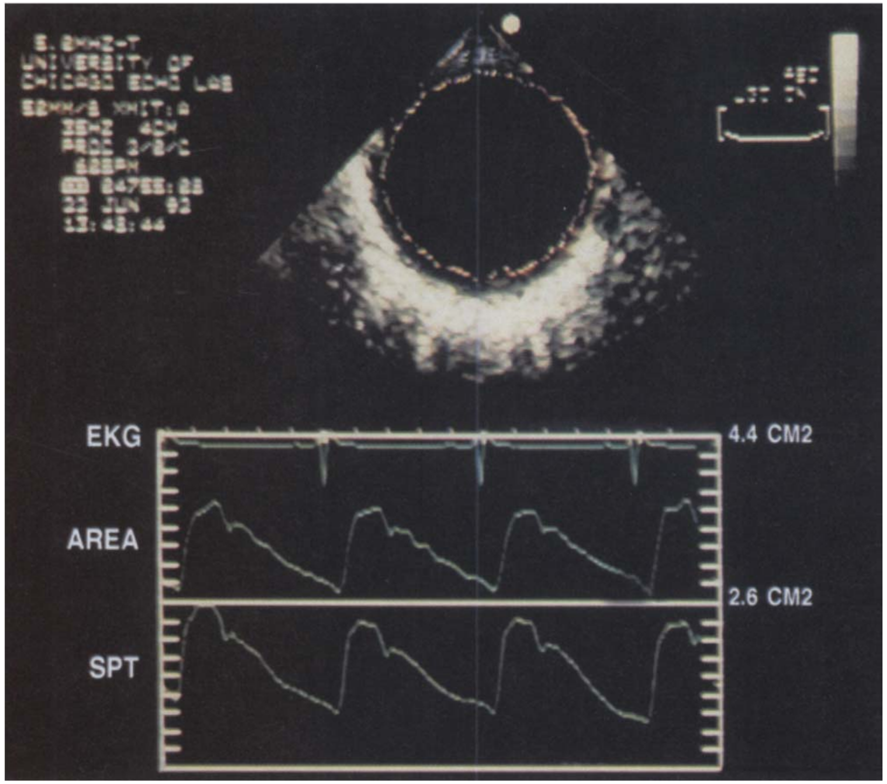


+ AGE-BSA

Cardiovascular Research 2000;47: 173–182

(2) Mechanical properties





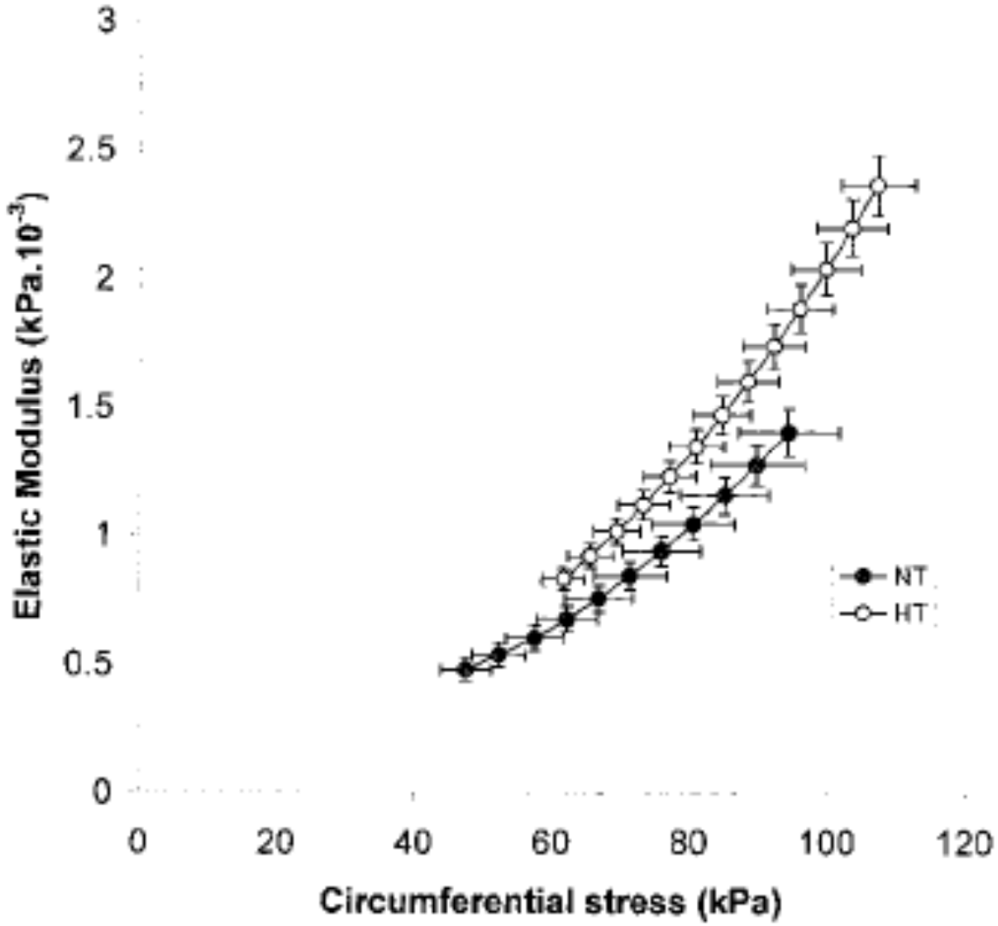
Tomasz J. et al. AHJ 1992
Lang RM. et al. Circulation 1994

Stiffness Indexes

- **Beta-stiffness (b)** = ln(Ps/Pd) / [(Dd-Ds) / (Dd)]
- **Cross-sectional compliance (CSC)** = (Dd-Ds) / (Ps-Pd)
- **Distensibility coefficient (DC)** = (Ad-As) / [Ad(Ps-Pd)]
- **Peterson's elastic modulus (EM)** = [(Ps-Pd)Dd] / (Dd-Ds)
- **Young's modulus** = [(Ps-Pd)Dd2] / [2(Dd-Ds)CIMT]

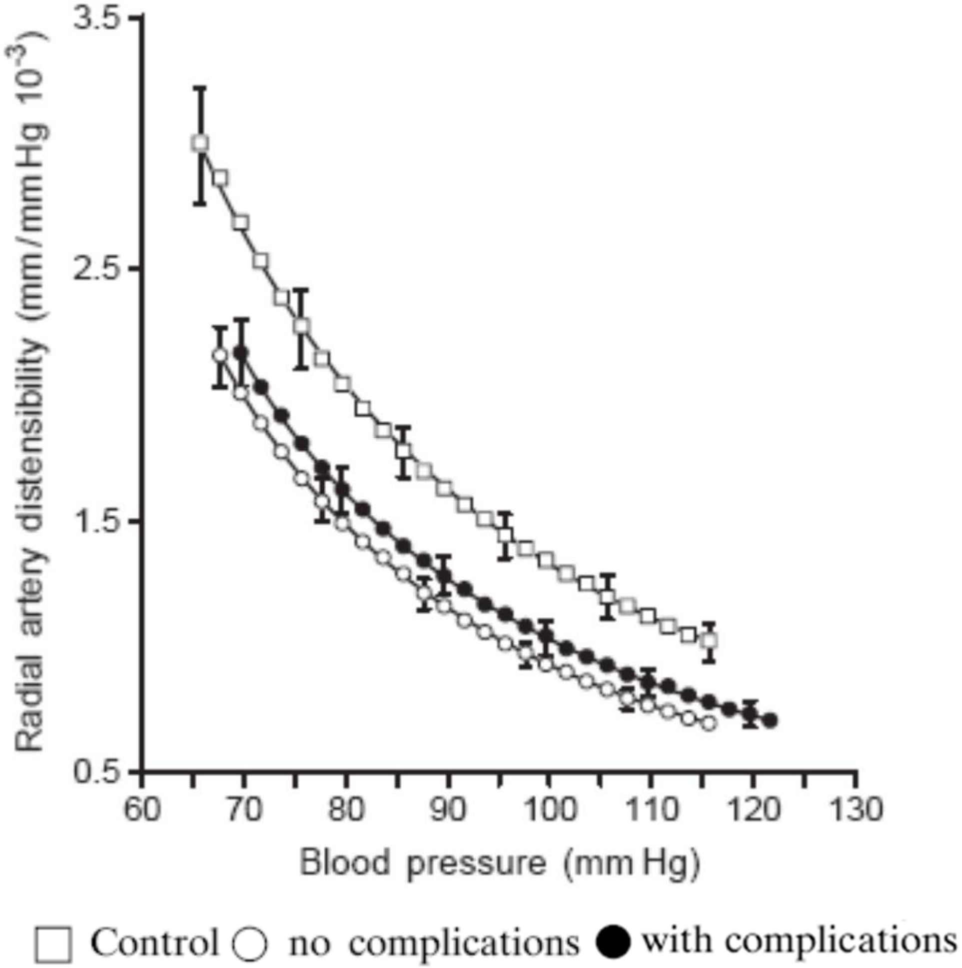
Mechanical properties in CV risk factor

1. HTN



Hypertension. 2000;35:1049-1054

2. DM



Diabetologia 1999;42:987-94

Vascular properties and CV risk

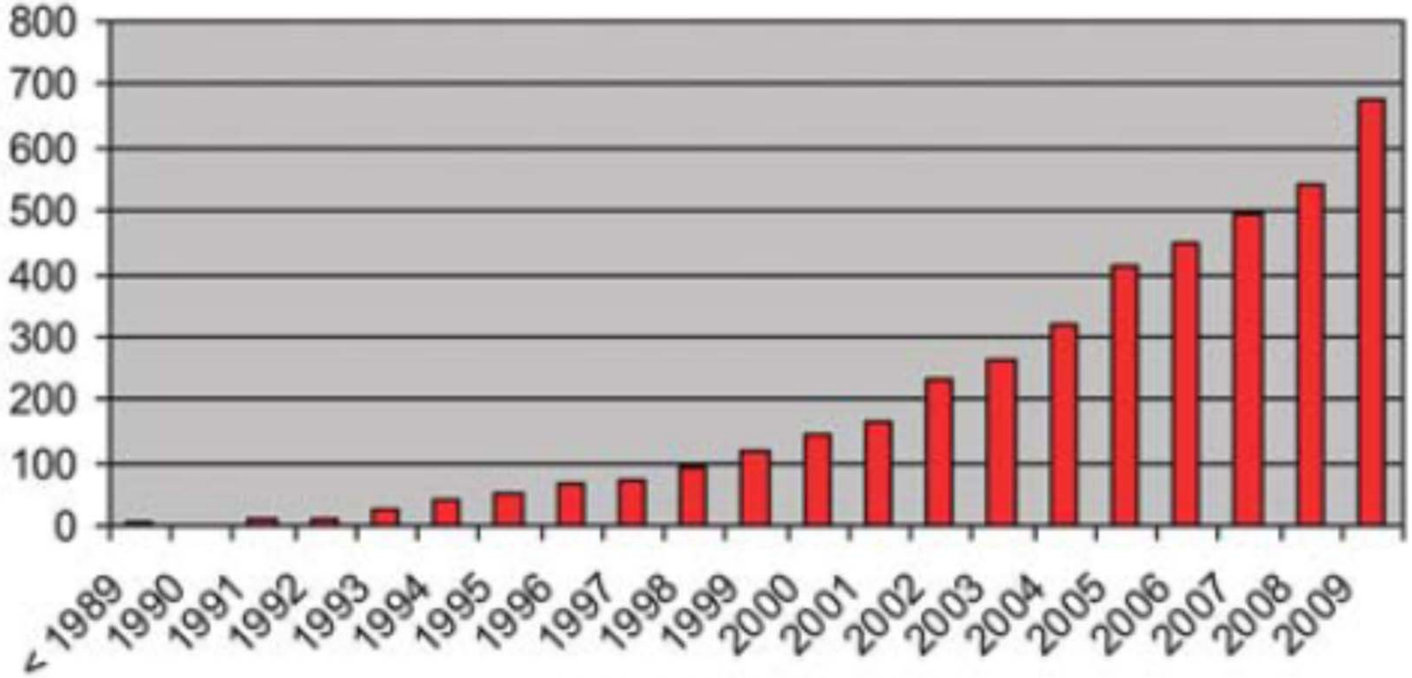
(1) Carotid IMT as a predictor of CV risk

- Strong predictor of myocardial ischemia
  peripheral vascular disease
  ischemic stroke
  cardiac dysfunction

The number of publication using "Intima media thickness"

No.

Article



Prevention Conference V : Beyond Secondary Prevention : Identifying the High-Risk Patient for Primary Prevention : Executive Summary

Carotid artery B-mode ultrasound imaging is a safe, noninvasive, and relatively inexpensive means of assessing subclinical atherosclerosis. The technique can measure IMT, an operational measure of atherosclerosis, in a valid and reliable manner. The severity of carotid IMT is an independent predictor of transient cerebral ischemia, stroke, and coronary events such as myocardial infarction. The writing group concluded that in asymptomatic individuals older than 45 years of age, carefully performed carotid ultrasound examination with IMT measurement can add incremental information to traditional risk factor assessment. In experienced laboratories, this test can now be considered for further clarification of CHD risk assessment at the request of a physician.

Circulation 2000;101:111-116

Carotid IMT to incident CV events in asymptomatic patients

Study	N	Sex/age, y	FU, y	Change in CIMT	Risk of event
KIHD (Finland)	1257	M / 42-60	3	Per 0.1-mm increase	111% MI
ARIC (United States)	12,841	M / 45-64	4-7	< 1 vs > 1mm	185% CHD
		F / 45-64			507% CHD
Rotterdam (Holland)	1567	M and F/ > 55	2.7	Per 0.163-mm increase	143% MI
					141% CVA
CHS (United State)	4476	M and F/ > 64	6	< 1.18 vs > 1.18 mm	203% MI and CVA
ARIC (United States)	14,214	M / 45-64	6-9	< 0.6 vs > 1 mm	360% CVA
		F / 45-64			850% CVA

JASE 2007;20:1-3

Associations between CIMT and risk of MI, Stroke and CVD

Study	Event Follow-Up, y	Sex/Age, y	Absolute Risk, %/y (Positive Test Result for CIMT)	Relative Risk (95% CI) [Hazard Ratio for CIMT]
KIHD[2]	1.0 (MI)	M/42–60	2.2 (>1mm)	2.2 (0.7–6.7) [CIMT ≥1 vs <1 mm]*
ROT[3]	2.7 (MI)	M/F/≥55	0.7 (>0.91 mm and 80th percentile)	1.4 (1.2–1.8) [per 0.16-mm CIMT, 1 SD]†
CHS[4]	6.2 (MI)	M/F/≥65	1.6 (>1.18 mm and 5th quintile)	3.2 (2.0–5.1) [5th vs 1st CIMT quintile]†
MDCS[5]	7.0 (MI)	M/F/46–68	NA	2.1 (1.2–3.4) [3rd vs 1st CIMT tertile]†
CAPS[6]	4.2 (MI)	M/F/19–90	2.1 (>0.79 mm and 4th quartile)	2.2 (1.9–4.0) [4th vs 1st CIMT quartile]†
ROT[3]	2.7 (stroke)	M/F/≥55	0.8 (>0.91 mm and 80th percentile)	1.4 (1.3–1.8) [per 0.16-mm CIMT, 1 SD]
CHS[4]	6.2 (stroke)	M/F/≥65	1.8 (>1.18 mm and 5th quintile)	2.8 (1.8–4.2) [5th vs 1st CIMT quintile]†
CAPS[6]	4.2 (stroke)	M/F/19–90	1.1 (>0.79 mm and 4th quartile)	2.3 (0.9–6.3) [4th vs 1st CIMT quartile]†
MDCS[7]	7.0 (stroke)	M/F/46–68	0.4 (>0.81mm)	3.0 (1.6–5.7) [3rd vs 1st CIMT tertile]†
Kitamura et al[8]	4.5 (stroke)	M/60–74	1.3 (>1.07mm and 4th quartile)	3.5 (1.3–9.5) [4th vs.1st CIMT quartile]
MESA[9]	5.3 (CVD)	M/F/45–84	1.8 (>0.97mm and 4th quartile)	2.3 (1.4–3.8) [4th vs 1st CIMT quartile]‡
CAPS[6]	4.2 (CVD)	M/F/19–90	3.2 (>0.79 mm and 4th quartile)	2.3 (1.4–3.8) [4th vs 1st CIMT quartile]†

Arterioscler Thromb Vasc Biol. 2010;30:182-185

Therapeutic interventions and IMT

Intervention	Risk factors involved	Finding
Amlodipine	Hypertension	Decreases CIMT
Lisinopril	Hypertension	Decreases CIMT
Pravastatin	Familial hypercholesterolemia	Decreases CIMT
Diet and exercise		Decreases CIMT
Intensive diabetes therapy vs conventional therapy	Diabetes mellitus	Intensive diabetes therapy results in less CIMT progression
Atorvastatin, pravastatin	LDL	Atorvastatin induced regression of CIMT
Pancreas transplantation	Diabetes mellitus	Regression of CIMT
Verapamil	Hypertension	Regression of CIMT with lower cardiovascular event rate
Fosinopril	Hypertension	Stops progression of CIMT
Pioglitazones	Inflammation, atherosclerosis	Reduction in CIMT, independent from glucose control
Rosiglitazones	Nondiabetic CAD	Reduction in CIMT progression

J Am Soc Echocardiogr 2007;20:907-914

(2) Arterial stiffness as a predictor CV risk

First author	Arterial stiffness measurement	Clinical events associated with CIMT	Patient details			Relative risk (confidence interval)
			Follow-up (years)	Age at entry (years)	Type of patient and (/	
Blacher [52]	CCA distensibility Young modulus	Non fatal and fatal CV events	2.1	58	ESRD (79)	CCA Dist: 6.4 (1.8–23.3) Youngs: 9.2 (2.4–35.0)
Blacher [42]	Aortic PWV	Non fatal and fatal CV events	6.0	51	ESRD (241)	5.9 (2.3–15.5)
Laurent [64]	Aortic PWV	Non fatal and fatal CV events	9.3	50	Hypertensives (1980	2.35 (1.76–3.14)
Boutouyrie [65]	Aortic PWV	Non fatal and fatal CV events	5.7	51	Hypertensives (1045	1.34 (1.01–1.79)
Meaume [66]	Aortic PWV	Non fatal and fatal CV events	2.5	87	70 years (141)	1.19 (1.03–1.37)
Barenbrock [67]	CCA distensibility	Non fatal and fatal CV events	7.9	40	Renal transplant (68)	*0.79 (not given)*
Van Dijk [68]	CCA distensibility	All cause mortality	6.6	65.5	IGT (140)	0.8 (0.4–1.3)

Journal of Hypertension 2002;20:2317–2325

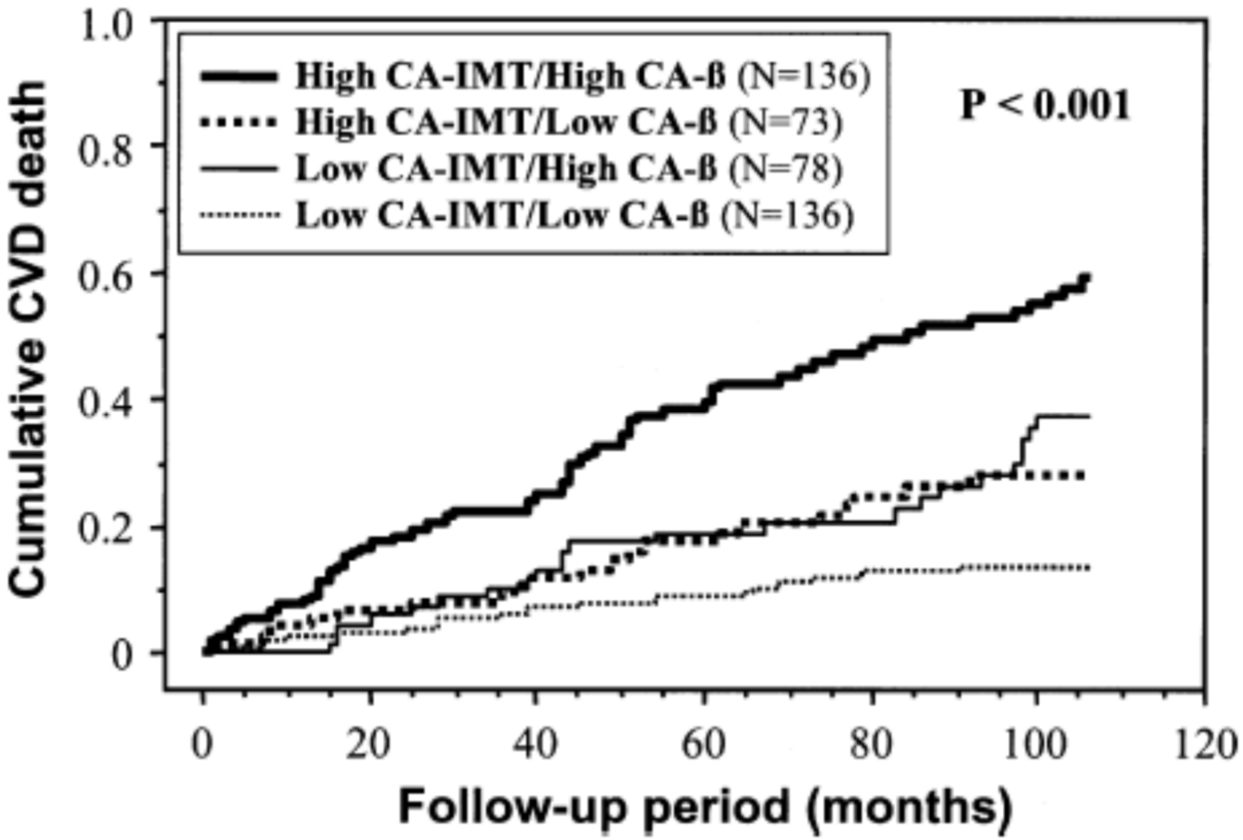
Aortic Stiffness is an Independent Predictor of Progression to Hypertension in Nonhypertensive Subjects

Variable	Odds Ratio (95% CI)	R^2
Systolic blood pressure	8.76 (8.47-9.05)	0.03
Diastolic blood pressure	6.69 (6.38-7.01)	0.02
Age^2	8.82 (9.920-9.927)	0.15
Strain	0.90 (0.80-0.93)	0.06
Distensibility	0.30 (0.18-0.48)	0.05
Aortic stiffness index (β)	1.21 (1.10-1.35)	0.07

Hypertension. 2005;45:426-431

(3) IMT, arterial stiffness as predictors of CV risk

Arterial stiffness predicts cardiovascular death independent of arterial thickness in a cohort of hemodialysis patients



Atherosclerosis. 2010;210:145–149

	Model 1		Model 2	
Log β stiffness	1,64 (1.34-2.01)	$p < 0.001$	1.38 (1.23-1.55)	$p = 0.006$
Log IMT	1.76 (1.50-2.07)	$p < 0.001$	1.39 (1.23-1.55)	$p < 0.001$
Age	-		1.02 (1.01-1.03)	$p = 0.042$
Male	-		1.87 (1.51-2.30)	$p = 0.003$
DM	-		2.14 (1.76-2.59)	$p = < 0.001$
Log CRP	-		2.28 (1.88-2.78)	$p < 0.001$
Serum creatinine	-		0.88 (0.84-0.92)	$p = 0.003$

Atherosclerosis. 2010;210:145–149

Common Carotid Intima-Media Thickness and Arterial Stiffness

Indicators of Cardiovascular Risk in High-Risk Patients

The SMART Study (Second Manifestations of ARTerial disease)

	SMART (CV risk)		Framingham (Coronary risk)		EPOZ (Total Mortality Risk)	
	ß	95% CI	ß	95% CI	ß	95% CI
IMT, mm	1.37	1.15-1.60	1.25	1.02-1.50	1.60	1.37-1.85
Distensibility, mm	-0.23	-0.27- -0.17	-0.25	-0.30- -0.19	-0.29	-0.35- -0.21

Circulation. 1999;100:951-957

Summary (1)

- Carotid ultrasound allows for characterization of both structure and functional vascular properties

- Measurement of IMT and arterial stiffness in carotid ultrasound provides directly identification of subclinical burden of atherosclerosis and can be used to identify individuals at increased risk of future CV event

Summary (2)

- **As a safe, reproducible, and relatively inexpensive technique, carotid ultrasound should be further explored as a primary tool for early detection of atherosclerosis**

Thank you for attention