Coronary Heart Disease
Advanced Laboratory Testing
Module V Cardiology 2020

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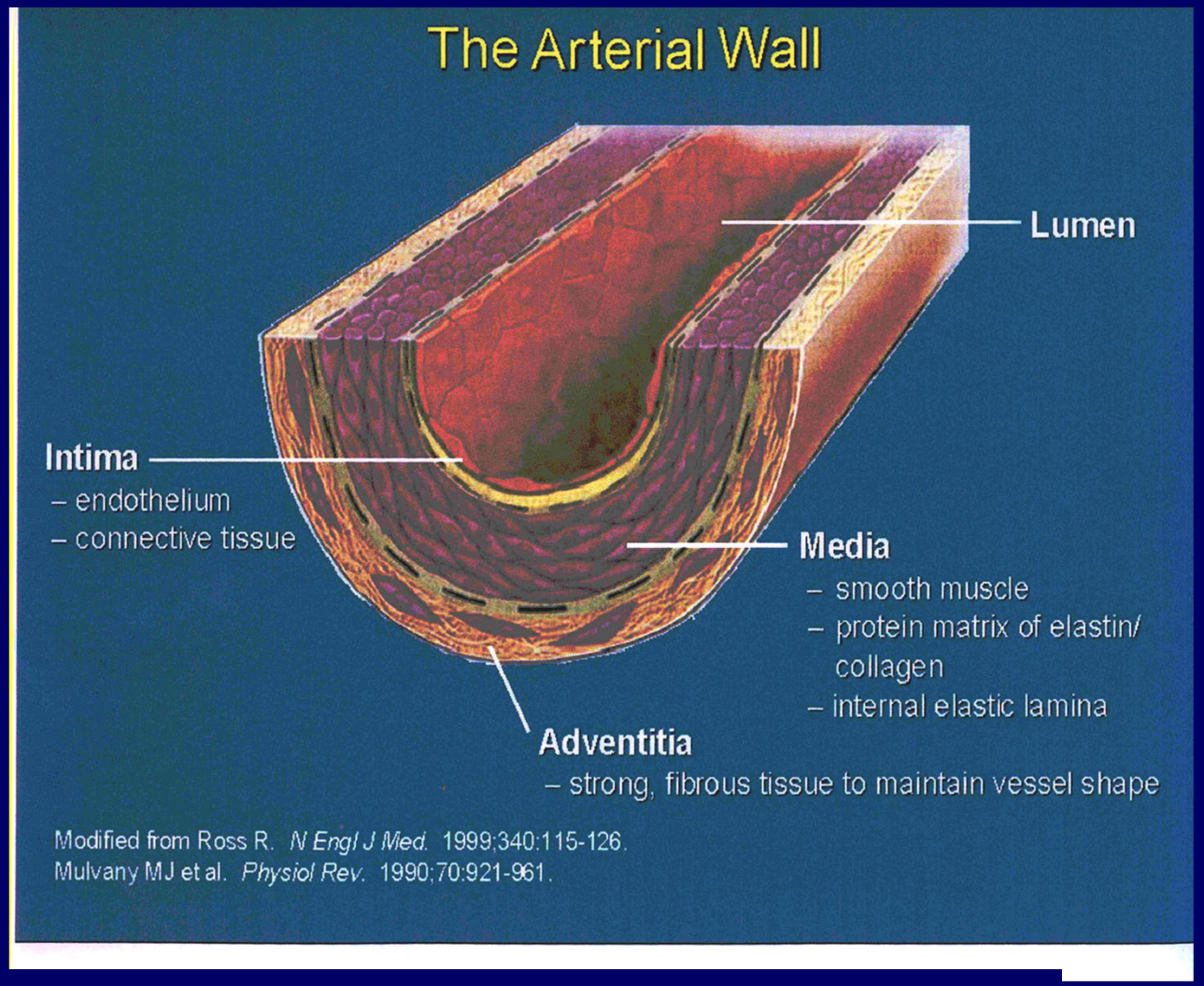
Objectives

Review the infinite insults and finite cardiovascular response theory of inflammation, oxidative stress and vascular immune dysfunction.

Review Cardiovascular Genomics and SNP's, the top 5 CHD risk factors, the details of the correct analysis of each, the top 25 modifiable key CHD risk factors, how to test and the interpretation.

Prioritize which laboratory and noninvasive laboratory and cardiovascular tests should be evaluated in patients in the primary care setting.

Discuss how to interpret and apply to the clinical evaluation and treatment of patients at risk for CHD.



Vascular Biology in Clinical Practice, Oct. 2000; Mark C. Houston,MD

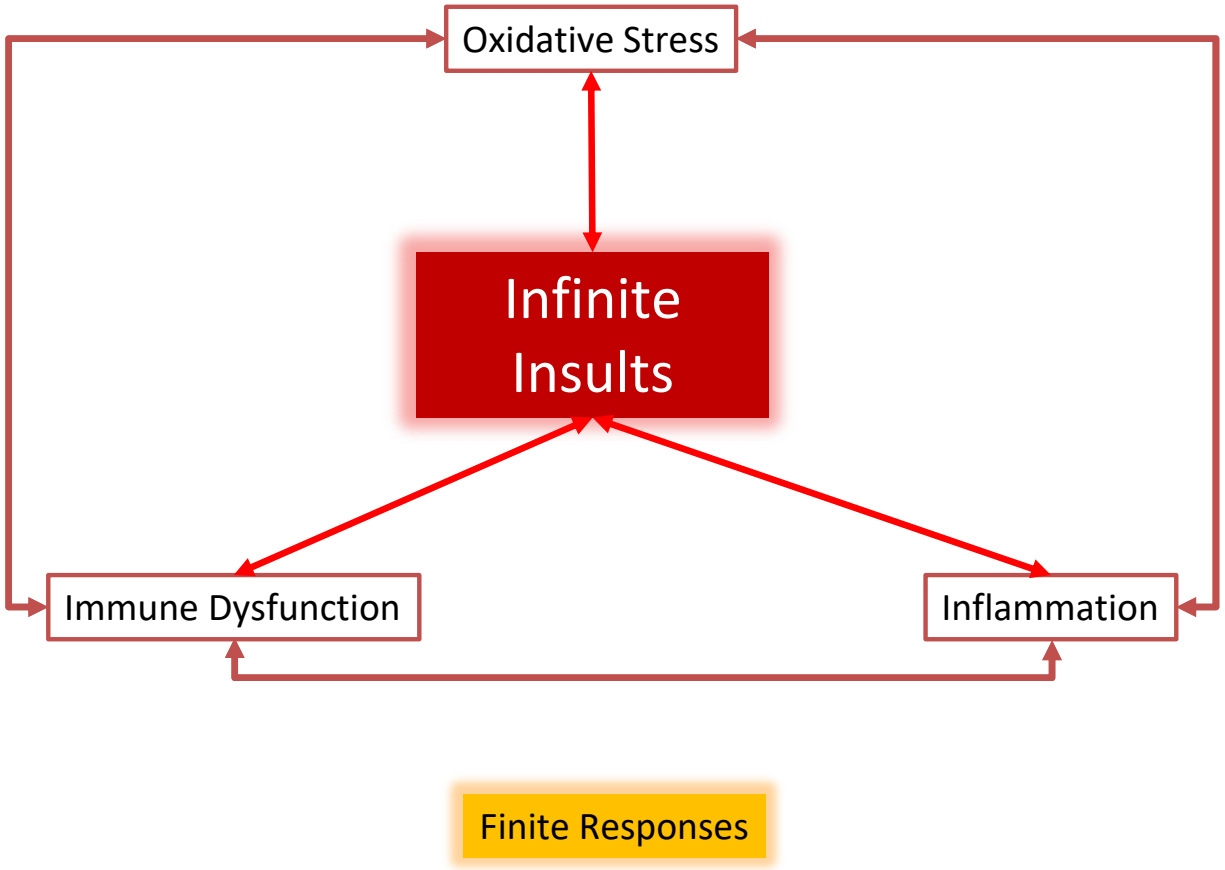
The blood vessel has only 3 finite responses to an infinite number of insults:

- Inflammation
- Oxidative stress
- Immune vascular dysfunction and imbalance

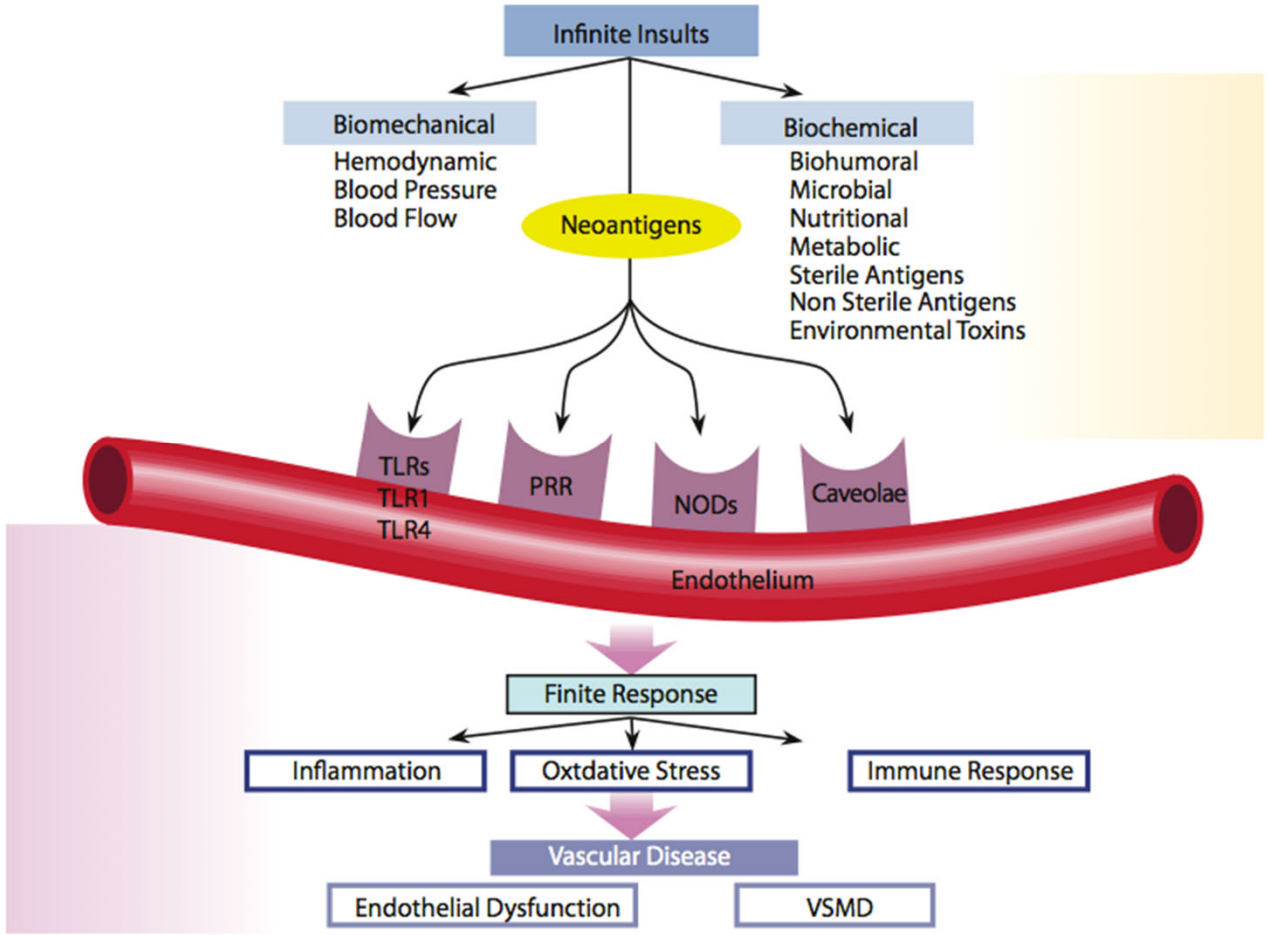
Houston 2011

He, Feng. Int J Mol Sci 2015;16:1-12

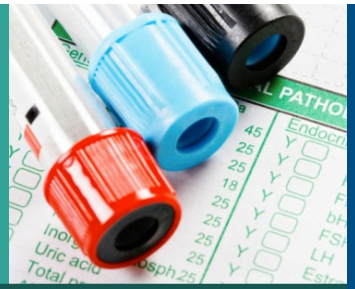
Mechanism Of Model



Infinite Insults



Coronary Heart Disease Risk Factors:General Classes



1. Genomics, SNP's and epigenetics
2. Gender and age
3. Inflammation
4. Oxidative stress
5. Vascular immune dysfunction
6. Infections
7. Metabolic and nutritional
8. Toxins
9. Psychological and neurological
10. Sleep disturbances
11. Lack of exercise
12. Structural and hemodynamic
13. Hormonal

Top 25 Modifiable CHD Risk Factors

Houston MC. What Your Doctor May Not Tell You About Heart Disease 2012

- Hypertension (24 hour ABM)
- Dyslipidemia (advanced lipid analysis)
- Hyperglycemia, metabolic syndrome, insulin resistance and diabetes mellitus
- Obesity
- Smoking
- Hyperuricemia
- Renal disease
- Elevated fibrinogen
- Elevated serum iron
- Trans fatty acids and refined carbohydrates
- Low dietary omega 3 fatty acids
- Low dietary potassium and magnesium with high sodium intake
- Inflammation: increased HSCRP, MPO, interleukins
- Increased oxidative stress and decreased defense
- Increased immune dysfunction
- Lack of sleep
- Lack of exercise
- Stress, anxiety and depression
- Homocysteinemia
- Subclinical hypothyroidism
- Hormonal imbalances in both genders
- Chronic clinical or subclinical infections
- Micronutrient deficiencies: numerous ones such as low vitamin D , K,E, CoQ10 etc .
- Heavy metals
- Environmental pollutants

Lab Testing

- CBC with diff, Urinalysis, CMP 12
- Advanced lipid profile with oxLDL, Lp(a)
- APO B , APO AI and AII
- Free T4,T3, TSH, RT3, TBG, thyroid antibodies
- Magnesium RBC
- Iron, TIBC and Ferritin
- Fibrinogen
- HSCRP
- Interleukins and TNF alpha
- Homocysteine
- Uric acid
- GGTP
- Myeloperoxidase (MPO)
- TMAO
- CoQ 10 serum level
- ADMA and SDMA
- Cortisol salivary
- Beta 2 macroglobulin
- Cystatin C
- Microalbumin/Cr ratio
- Coagulation profile
- LpPLA 2
- NT-BNP
- Troponin T
- Galectin 3
- Plasma viscosity
- Oxidative stress profile blood and urine F2 isoprostanes, 80H DG
- Oxidative defense profile
- Cardiovascular Genomics
- Toxicology and heavy metal screen 24hr urine and blood baseline and provoked
- Autonomic Function Testing
- Body composition BIA; total and regional body fat and epicardial fat

Lab Testing

- Vitamin D 3 and PTH levels
- C peptide, AIC, insulin, proinsulin, IGF- 1
- glycomark, adiponectin, leptin,2hr GTT
- Plasma renin activity and aldosterone
- Free testosterone, SHBG, estradiol, estriol. Progesterone, DHEA and DHEAS
- EKG and TMT or CPET
- Chest X Ray
- CAPWA: computerized arterial pulse wave analysis for arterial compliance C1/C2
- ENDOPAT for ED with augmentation index and heart rate variability
- Heart rate recovery time: HRRT
- ABI at rest and with exercise
- MNT- Micronutrient test
- Omega 3 index
- Telomere test
- ECHO
- Carotid duplex and IMT
- CT angiogram (CTA)
- CAC -Coronary artery calcium score
- Retinal scan and ocular pulse wave analysis
- Rest and exercise BP
- 24 hour ABM-ambulatory blood pressure monitoring
- CORUS gene expression testing
- PULS cardiac risk profile testing
- Magnetocardiography
- Exercise ECHO
- Nuclear Medicine Scans
- PET scans

HYPERTENSION: 24 hour ABM

- Dippers vs non dippers. Excessive dipping and reverse dipping
- Nocturnal BP
- AM BP surges
- Labile BP
- Mean BP
- BP load
- Central BP better than brachial BP measurements
- White coat hypertension
- Masked hypertension

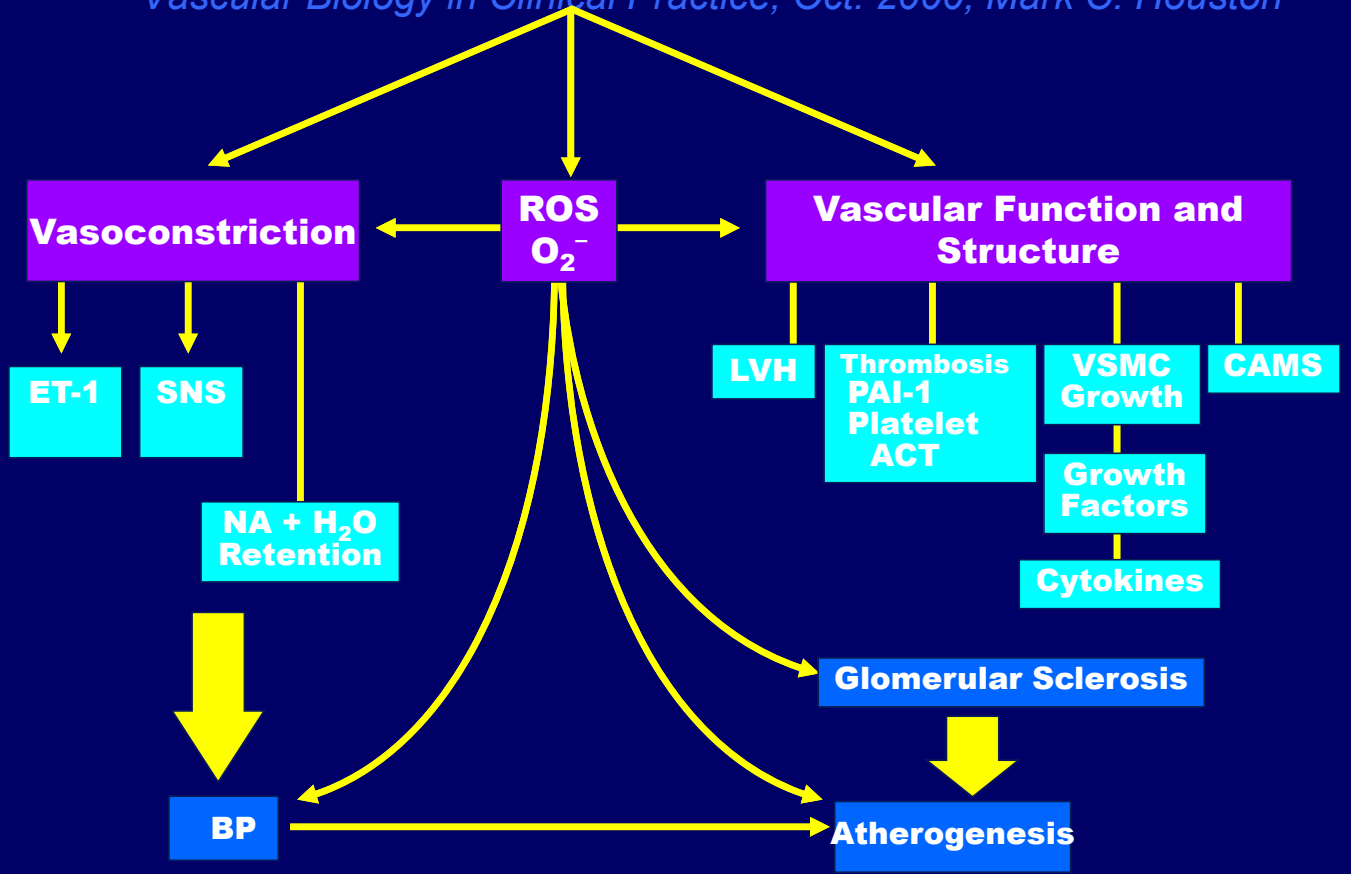
Plasma Renin Activity (PRA)

J of Hypertension 2011;29:2226
NEJM 1993;329:616
Am Heart J 2011;162:585-96

- **High PRA is associated with greater risk of:**
  - **Myocardial infarction and ischemic heart disease**
  - **Stroke**
  - **Congestive heart failure**
  - **Chronic kidney disease**
  - **Total cardiovascular disease and mortality**
  - **Total mortality**

Angiotensin II (A-II)

Vascular Biology in Clinical Practice, Oct. 2000; Mark C. Houston



Selection of Anti-hypertensive Treatment Based on BP Stratification Using Renin Profiling with PRA and Aldosterone levels

N Engl J Med 1972;286:441-449
Am Heart J 2011;162:585

- **Low renin hypertension (LRH):** Increased intravascular volume (volume dependent) PRA < 0.65 ng/ml/hr 30% of patients
- **High renin hypertension (HRH):** Decreased intravascular volume: PRA > 0.65 ng/ml/hr
- 70% of patients
- **Very high renin**: Volume depleted: PRA> 6.5 ng/ml/hr

PRA and Aldosterone

J of Hypertension 2011;29:2226
NEJM 1993;329:616
Am Heart J 2011;162:585-96

ARR: Aldosterone renin ratio

- ARR over 80 is LRH
- ARR over 40 is probably LRH

- ARR less than 10 is HRH
- ARR between 10 and 40 : not sure

DYSLIPIDEMIA:LDL

Houston MC. J of Clinical Hypertens 2012;14:121-32

LDL –C total

LDL-P Particle number

LDL size (dense type B vs Large type A)

Modified LDL (oxidized, glycated, acetylated)

Antibodies to LDL

APO B elevated

APO B immune complexes

Lp(a)

DYSLIPIDEMIA:HDL

Houston Journal of Clinical Hypertension 2012 EPUB

- HDL-C total
- HDL-P particle number
- HDL size (large 2b vs small type 3)
- Dysfunctional HDL
- Proinflammatory/proatherogenic HDL
- Low APO A
- Low PON 1 and PON 2

DYSLIPIDEMIA :VLDL and TG

Houston MC. J of Clinical Hypertens 2012;14:121-32

- Increased APO-CIII
- Serum free fatty acids
- VLDL and TG total
- Large VLDL
- VLDL –P particle number
- Remnant particles

Insulin Resistance, Metabolic Syndrome and Diabetes Mellitus

- Adiponectin
- Leptin
- Insulin
- Proinsulin and C peptide
- HgbAIc
- PPBG (post prandial blood glucose)
- 2 hour GTT
- FBS
- AGE
- HOMA index: FBS x insulin/ 400

FASTING BLOOD GLUCOSE AND CV RISK

(Diabetes Care 1999; 22:233-240)
(Diabetes Care 1998; 21:360-367)
Am J Cardiol 2010;106:1602

- Thus for each 1 mg% increase in FBG starting at 75 mg%, there is a 1% increase in CV events
- For 2 hr OGGT, there is a 2% increase in CV events per 1 mg% increase in glucose starting at 110 mg %.

HbAIC is an independent predictor of non fatal cardiovascular disease in patients without diabetes: Hoorn Study

European J of Preventive Cardiology 2012;19:23-31

- In men and women without DM between 50-75 years of age, HbAIC is an independent risk for CHD as a continuous variable starting with HbAIC as low as 5.1%.
- For each increase of HbAIC of 1% the risk for CHD increases by 40 % in men and 240% in women.

5. OBESITY

- Total body fat and visceral fat correlate with CVD, CHD, MI, arrhythmias CHF, CVA, Carotid artery stenosis, PVD generalized atherosclerosis and Cancer
- Normal body fat: 22 % for women and 16 % for men.
- Visceral or abdominal fat has highest correlation. Produces over 45 adipokines.
- Hyperinsulinemia, hyperglycemia, hypertension, dyslipidemia with high TG and low HDL, thrombosis
- Inflammation and oxidative stress.

ADIPOCYTE-ADIPOCYTOKINE BALANCE

(Arterioscler Thromb Vasc Biol 2004; 24:29-33)

Adiponectin and Others	VS	Adipocytokines
Anti-diabetic		Pro-diabetic
Anti-atherosclerotic		Pro-atherosclerotic
Anti-inflammatory		Pro-inflammatory
Anti-lipid		Pro-lipid
Anti-hypertensive		Pro-hypertensive
Anti-obesity		Pro-obesity

Epicardial Fat (EAT) and Severity of CHD in Asymptomatic Adults with or without DM

Am J Cardiol 2014;114:686-91

- EAT volume is an independent predictor of CHD
- Increasing volume of EAT predicts increasing severity of CHD even after adjustment for CAC score in both non DM and DM patients.
- Presence of over 120 cm to third power of EAT is highly correlated with the presence of significant CHD (OR 4.47)

8. SLEEP: Short Sleep Duration, Hypertension CHD, CVD, CVA

J of Am Soc of Hypertension. 2010;4:255 J of Hypertension 2012;30:13354 Clin. Cardiol 36: 11:671

- Short sleep duration is an independent risk factor for silent cerebral infarcts and of future stroke events (OR 2.01)in hypertensive patients. Less than 6 hrs
- Also increases risk for CVD, CHF (1.6), hypertension, diabetes, obesity, metabolic syndrome, CHD, MI (2.04)
- Prolonged sleep increases CVA risk also: over 10 hours
- 8 hours appears to be the perfect sleep duration to prevent CVA and CVD events etc.

Smoking

Homocysteinemia

Nutrition 2017;33:291

- Sulfur based amino acid derived from plant and animal based methionine.
- Metabolism is via methylation (50%) and transulfuration (50%)
- Continuum of risk for CVD starting at levels of 5 micromoles/L, but the greatest risk starts at 12mm/L or more
- Associated with oxidative stress, inflammation, inhibits GPx, arterial damage, ED, thrombosis, platelet aggregation, CVA, neurodegenerative disease , CHD, CVD and renal disease
- Quercetin reduces oxidative stress and increases catalase and GPx
- B vitamins: B6, B12, methylated folate, SAME, betaine, serine

Microalbuminuria (MAU)

Clin J Am Soc Nephrol 2010;5:1099
Am J Cardiol 2010;106:976
J of Hypertension 2011;29:1411
Crnt Opin in Nephr and HTN 2010;19:513
J of Hypertension 2010;28:1983
J Hypertension2010;28:2357

- Microalbuminuria is one of the earliest abnormalities in vascular system and kidney that reflects endothelial dysfunction and increased vascular permeability.
- High correlation with progression to proteinuria, renal disease, LVH and future CVD, CHD, MI, CHF, and CVA.
- Linear relationship of albumin /creatinine ratio: ACR starting below 5 mg/gm (previous cutoff for normal of 30 mg/gm is too high). Spot urine sample is required not 24 hour urine..
- MAU triggers tubular RAAS activation via megalin/cubilin receptors and inflammatory/oxidative stress reaction with NFkB/AP-1.
- Reduced best with excellent BP control with RAAS drugs and also with omega 3 fatty acids and lipoic acid.

Chronic Kidney Disease

Am Heart J 2013;166:373
Am Heart J 2013;167:86

- Chronic Kidney Disease (CKD) is associated with CHD risk that is equal to or greater than other established very high risk conditions.
- 2x the risk compared to DM, MS and smoking
- GFR, creatinine and cystatin C all correlates as independent risk factor for CVD

Elevated serum iron and Ferritin increases CHD

Clin Cardiol 2013;36:139
Am Heart J 2013;165:744

- Increased serum iron and Ferritin levels are associated with a stepwise increase in all cause mortality, CHD and MI.

Iron and Ferritin

Atherosclerosis 2001;154:739 (ARIC study)
Klin Med (Mosk) 2005;83:25
Diabetes Care 2007;30:101

- **Related to severity of perfusion and functional abnormalities of coronary arteries, but not always anatomic angiographic obstruction. Microvascular angina and endothelial dysfunction of the coronary arteries.**
- **Ferritin = Iron Stores (and CHD risk)**
  Ferritin > 200 ug/L = 2 x risk (Finnish)
  Ferritin x 10 = Iron Stores

Controlled Reduction of Body Iron Stores Reduces PAD, MI, and CVA

Am Heart J 2011;162:949

- Lower iron burden and controlled phlebotomy improved CV outcomes of PAD, MI and CVA and life expectancy.
- Ferritin levels of 76.5 ng/ml had lowest event rate for CVD.

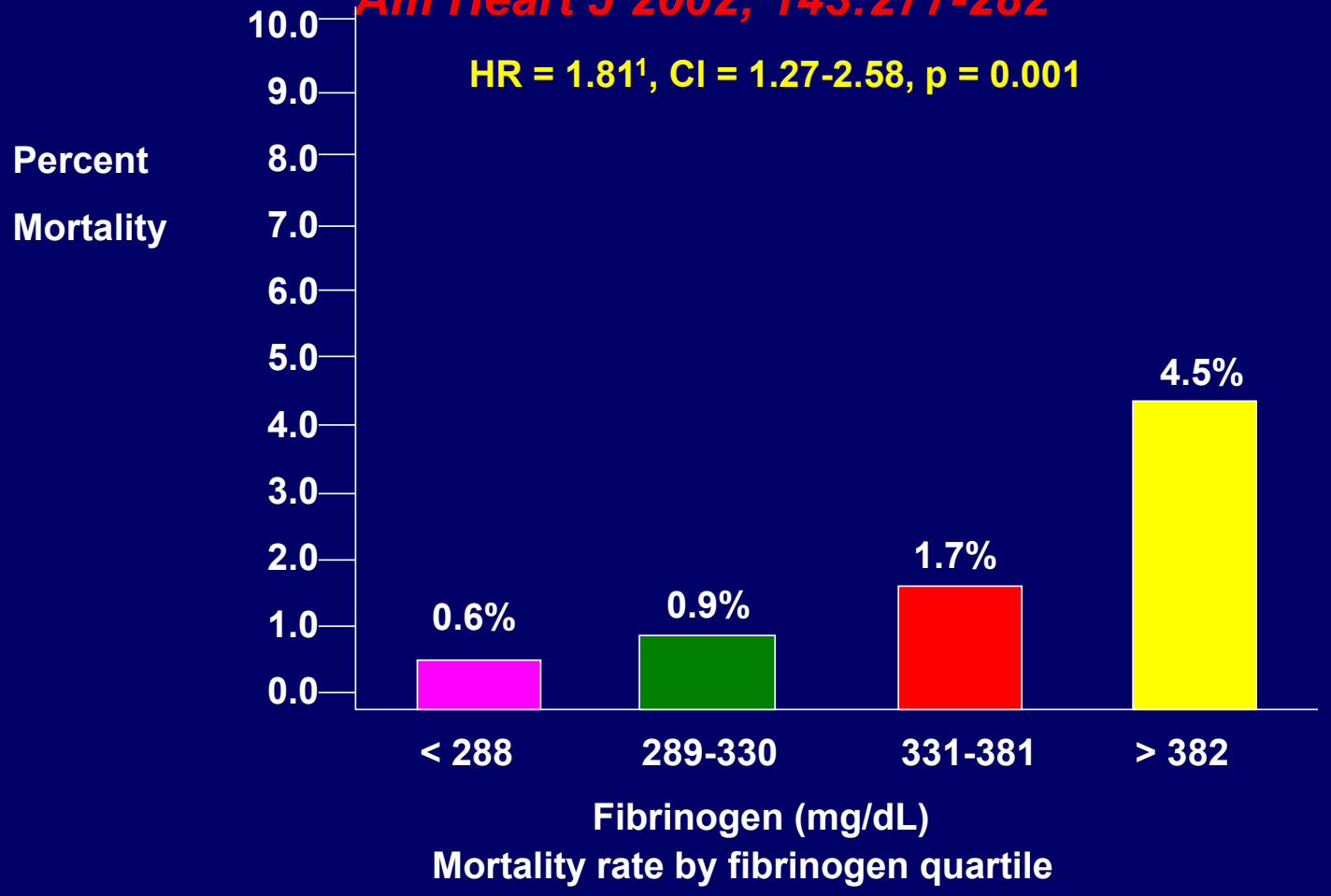
FIBRINOGEN

J Clinical Lipidology 2014;8:494-500 *Arterioscler Thromb Vasc Biol 1999; 19:368*)

- Meta-Analysis *Arterioscler Thromb Vasc Biol 1999; 19:368*) CV risk in highest tertile of fibrinogen was 2 x risk in lowest tertile (OR = 1.99) ($p < .05$)
- Each 50 mg/dL increase = 30% increase CHD
- Plasma viscosity correlates with fibrinogen and is independent risk factor. Compounds risk with fibrinogen.
- Acute and chronic phase reactant in liver
- Increases plaque growth, increases platelet adhesion, CAMs and WBC adhering to endothelium, increase cholesterol sysnthesis, increase lipid peroxidation and correlated with PCSK9 levels.

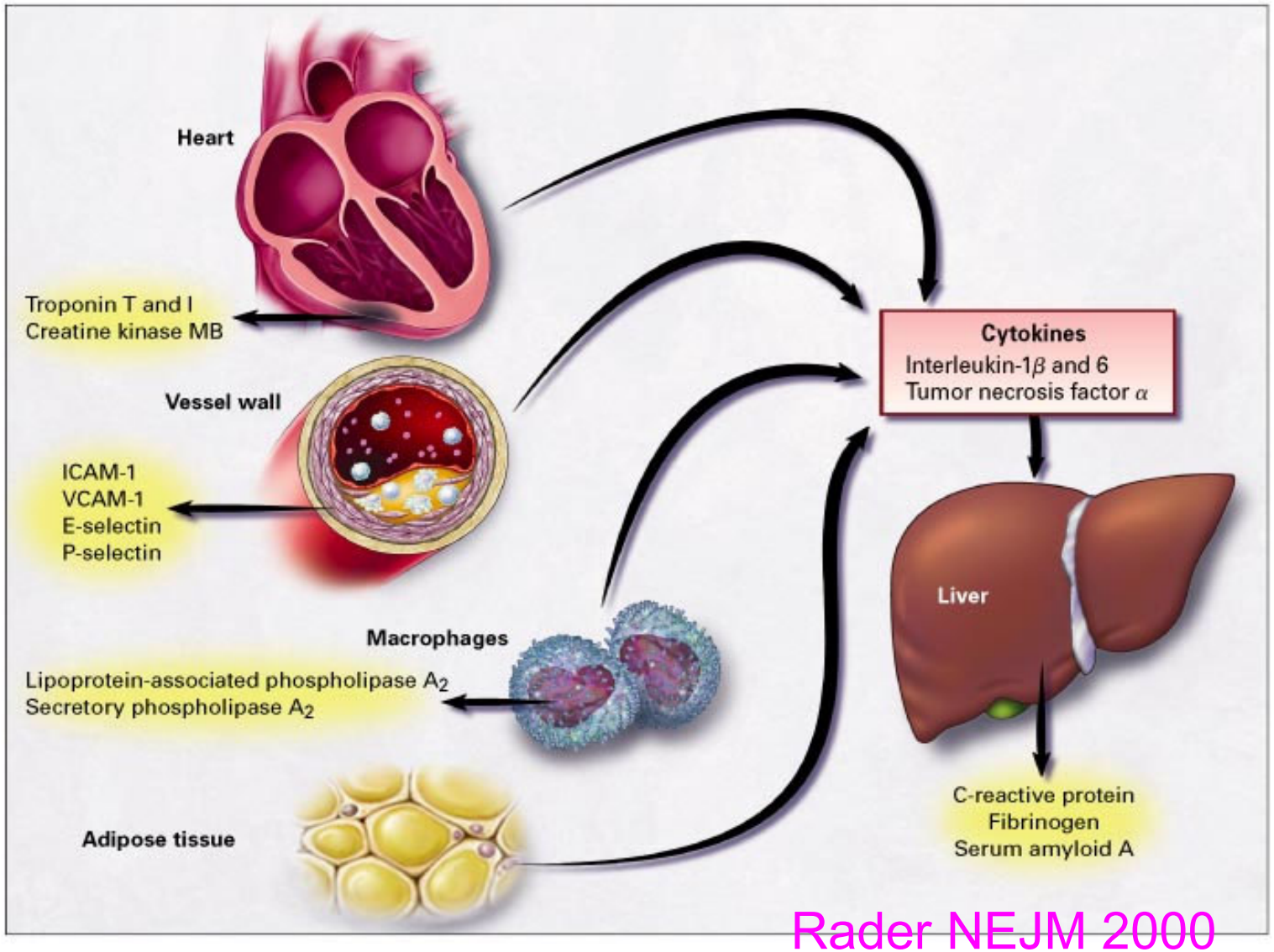
FIBRINOGEN

Am Heart J 2002; 143:277-282



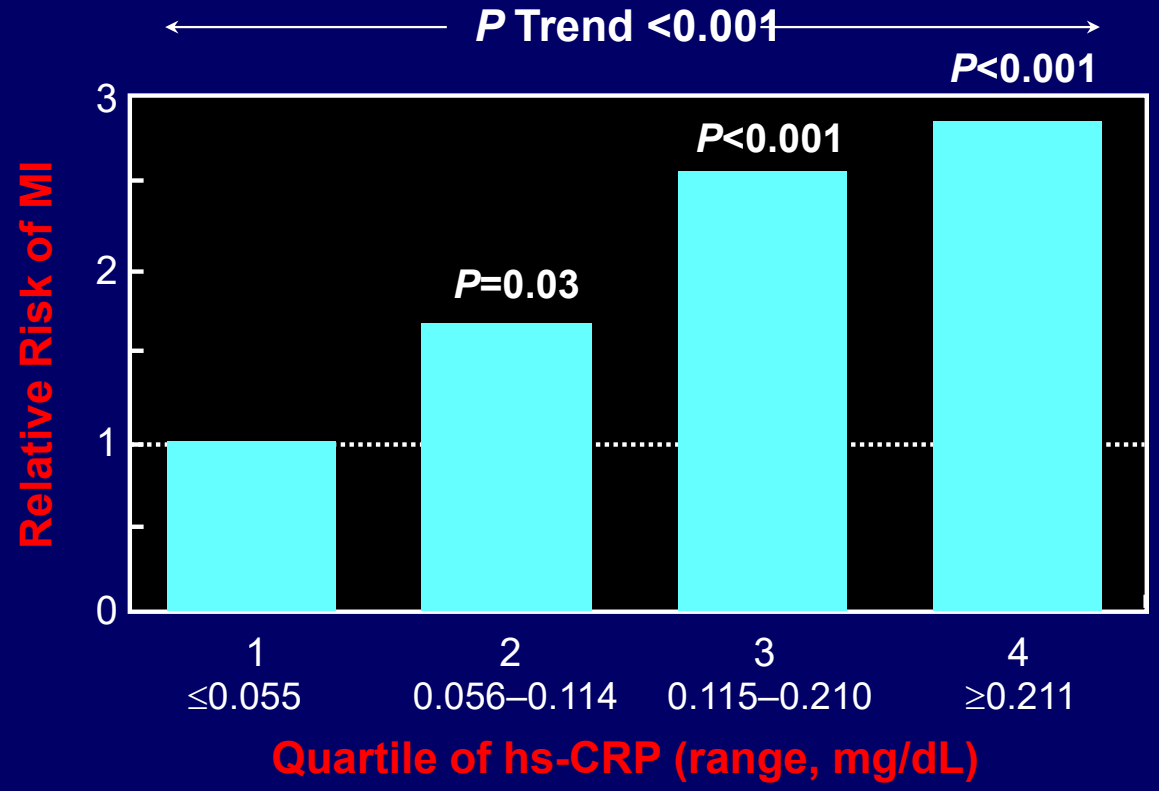
Mortality rate by fibrinogen quartile

[1] Adjusted for Framingham risk score



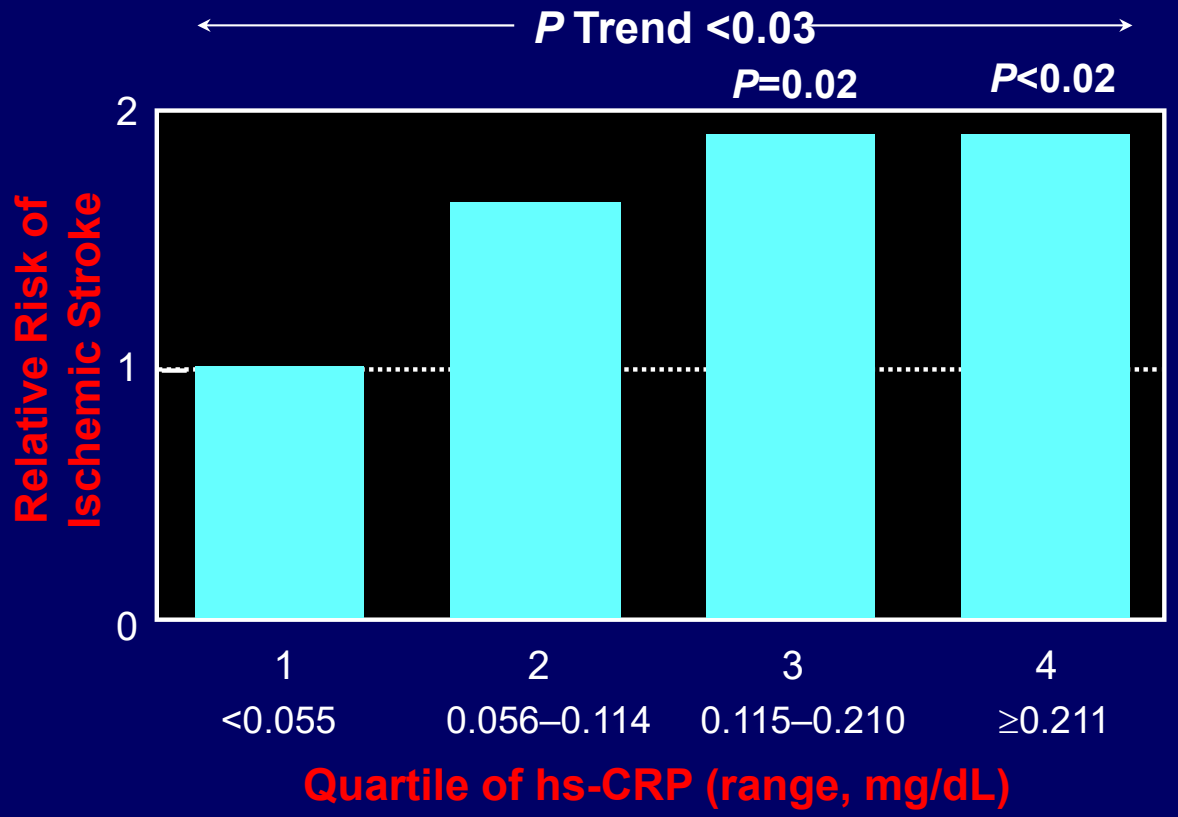
Rader NEJM 2000

hs-CRP and Risk of Future MI in Apparently Healthy Men



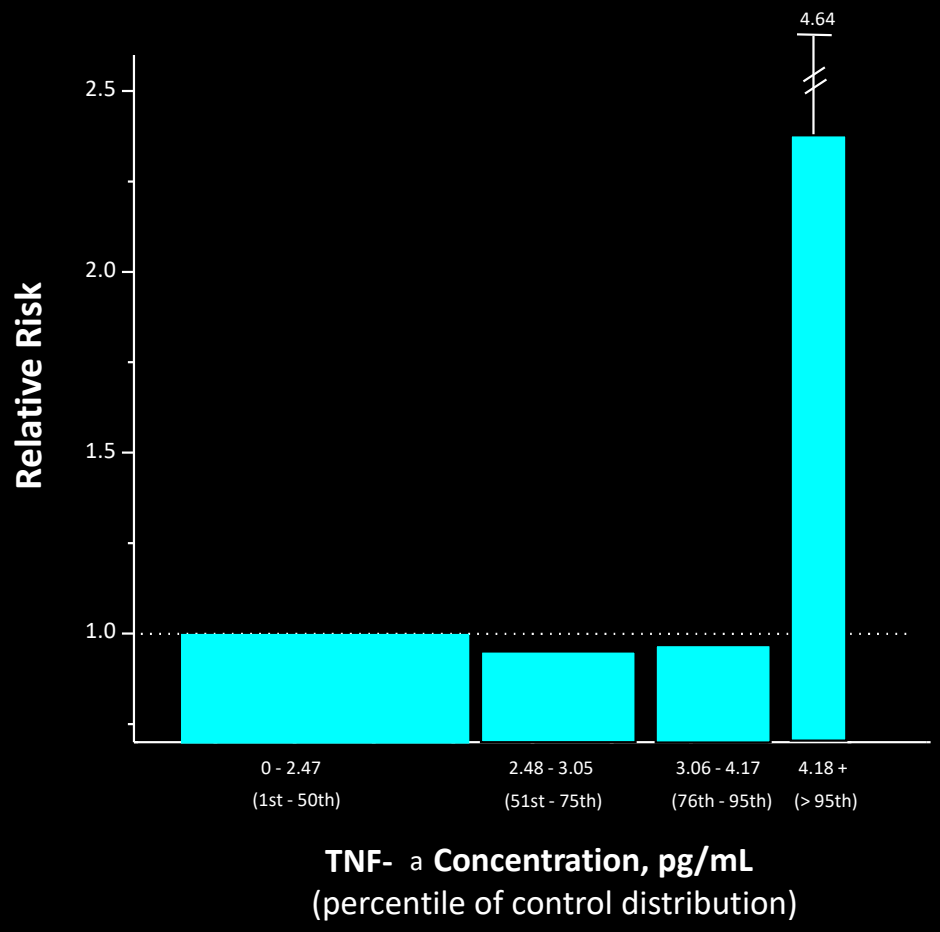
Ridker PM et al. *N Engl J Med.* 1997;336:973–979.

hs-CRP and Risk of Future Stroke in Apparently Healthy Men



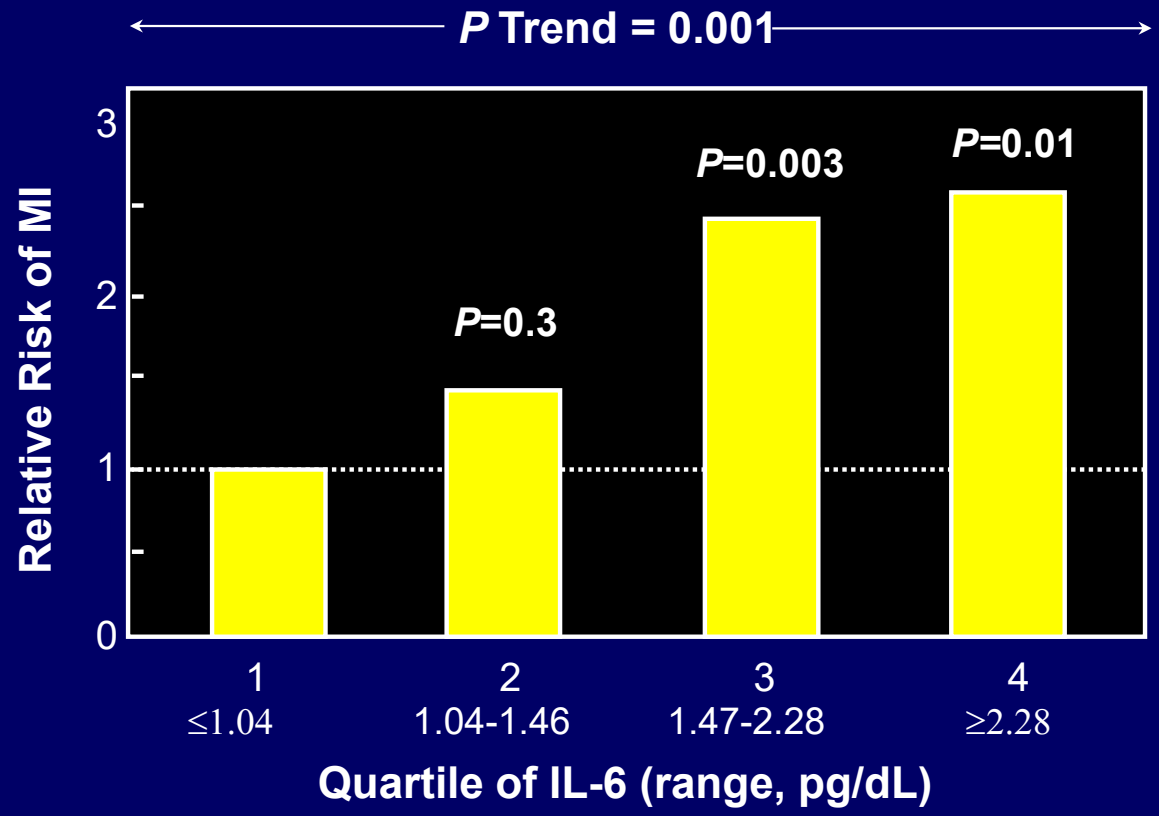
Ridker PM et al. *N Engl J Med.* 1997;336:973–979.

Plasma Concentration of TNF-alpha and Risk of Recurrent Coronary Events



Ridker et al, Circulation 2000;101:2149-53

IL-6 and Risk of Future MI in Apparently Healthy Men



Ridker et al, Circulation 2000;101:1767-1772

Lipoprotein-associated phospholipase A2 (Lp-PLA2)

J of Clinical Lipidology 2009;3:85
Curr Treatment Options CardiovascMed 2013;15:313
Nutr Metabl Cardiovasc Dis 2013; Nov 1 EPUB
J of Clinical Lipidology 2016;10:512

- Expressed in atherosclerotic plaques, foam cells and macrophages in fibrous cap
- Attached to LDL and is only enzyme responsible for hydrolysis of oxidized phospholipids to produce lysophosphatidylcholine and other lysophospholipids (proinflammatory and atherogenic) FA hydroperoxides and oxidized FA and stimulates IL-1B and IL-6
- Distribution between LDL and HDL determined by glycosylation.
- High levels mean unstable plaque and rupture vulnerability.
- Predicts MI and CVA and carotid IMT. Independent risk factor
- One gram Omega 3 FA in stable angina decrease LpPLA2 by 9.4% and oxLDL by 12.3%. No change in MPO or IL6. Expressed in atherosclerotic plaques, foam cells, and macrophages in fibrous cap
- Reduced by omega 3 FA (11%-20%), niacin (20-32%), fibrates (13%-30%) and statins (25%-41%)
- Rosuvastatin alone 41%, R +F=38% , R +O = 30%
- Also high protein, ETOH, MUFA, weight loss lowers LpPLA 2

GGTP and Hypertension

J of Hypertension 2015;33:704
J of Am Soc Hypertension 2016;9(12): 951
JASH 2016;10:772;J of Hypertension 2017;35:493

- GGTP increases predictive risk of hypertension, CHD, CVD, all cause mortality and DM
- Increased arterial stiffness and increased PWV
- Increase inflammation
- Increase ROS and oxidative stress
- Reduced GSH and oxidative defense
- Increase heavy metals
- Reduced hepatic detoxification and increased NAFLD
- Increased fibrinogen
- Increase MS, IR and NAFLD
- Increased hsCRP
- Alcohol
- Obesity
- NAFLD also increases risk of hypertension.

Plasma Viscosity

Therapeutic Advances in Cardiovascular Disease 2015;9:19-25

- Resistance to blood flow in a blood vessel
- Blood viscosity decreases as shear rate increases (non-Newtonian fluid due to RBC deformability and deaggregation).
- Worse at outer wall of vascular branches and inner wall of curves.
- Fibrinogen can bind RBC and induce aggregation.
- Seen in atherosclerosis, hypertension, dyslipidemia, DM, metabolic syndrome, tobacco use, obesity, aging, hyperfibrinogenemia, polycythemia, thrombocytosis, elevated globulins, cryoglobulinemia and male gender.
- LDL is large enough to bind RBC. HDL is smaller and cannot.
- Normal viscosity is 32.6 millipoise at shear rate of 100/s

Parathyroid Hormone elevation increases risk of CVD

Am Heart J 2013;165:655

- Increased PTH levels increase risk of CVD in a linear fashion based on quartiles.
- Increase BP
- Increase LVH
- Increase myocardial dysfunction
- PTH receptors on arteries and cardiomyocytes

Neurocardiology and HRV

Am J Cardiol 2012;109:685

- Underactive vagal tone , the PSNS and stressful emotions will increase IL 6, TNF alpha, HS-CRP, fibrinogen, resting HR and alter HRV.
- Resting HR of 62 is ideal. For each increase of 4 beats/ min the risk of CHD death increases 7-10 % At 76 bpm the risk is increased 68%

Thyroid and the Heart

Circulation 2003;107:708 J Cardiol 1993;23:205
Am J Med 2001;111:699 Eur J Cardiothorac Surg 2003;24:487
Ann Int Med 2000;132:270 Thyroid 1996;6:527, Am J Card 1998;81:443
J of Hypertension 2012;30:592;Arch Int Med 2012;172:811
Am J of Medicine 2014;127:691

- CVD,CHD/MI, PAD and general atherosclerosis
- V Tach and V fib
- A Fib post CABG
- Sudden death
- Predictor of death post MI in 12 months, especially in younger patients
- CHF, low EF, diastolic dysfunction
- Hypertension and dyslipidemia
- Homocysteinemia
- Endothelial dysfunction
- Obesity
- Metabolic syndrome, IR, DM
- Future risk for hypothyroidism
- Increased carotid IMT, PWV, AI and markers of ED and arterial stiffness
- Starts at TSH over 2.5 mIU /ml
- If TSH is below .10 mIU/ml in hyperthyroidism then CHD and AF increase.

BNP and CVD Risk

Am J Cardiol 2011;108:1564

Mayo Clinic Proc 2011;86:1154

- Elevated B-type natriuretic peptide (BNP) increase risk of CVD.
- Similar to Framingham risk score
- BNP over 37 pg/ml in men and 55 pg/ml in women increase CV risk
- Also NT-pro BNP increases CV risk

Blood Viscosity and CVD

Integrative Medicine 2013;12:24

- Stickiness and thickness of blood and resistance to flow.
- Primary determinants are hematocrit (most important) ,RBC deformability and plasma viscosity.
- As flow increases, viscosity decreases.
- LDL and fibrinogen increase aggregation of RBC at low flow
- Correlates with CVD, carotid IMT, PAD
- Treat with phlebotomy, hemodilution, apheresis, ozone, hydrotherapy,earthing, pentoxifylline, statins, anti-platelet agents,, hydration, omega 3 FA, chrysanthemum,dong quai, arginine, vinpocetine, CO Q 10, nattokinase, vitamin C, Selenium Vegetarian diet

Hyperuricemia

J of Hypertension 2015;33:1729-41

- Increases risk of hypertension, endothelial dysfunction, metabolic syndrome, CVD,CHD,MI,ACS,CVA,CHF and CKD.
- Humans lack uricase to convert UA to soluble allantoin.
- Keep UA level below 6 mg/dl
- Both anti-oxidant and pro-oxidant depending on level in localization.
- Increase oxidative stress, RAAS activation, inflammation, immune dysfunction of blood vessels, VSMH, lowers NO, sodium sensitivity and hypertension, arterial stiffness.
- Genetics, ETOH, drugs (diuretics, BB, ASA), obesity, diet increase UA..
- Allopurinol lowers BP 3.3/1.3 mm Hg, improves ED, PWV,CHD/ angina exercise time, LVH and perhaps CHF.

Relation of Lipid Content of Coronary Plaque to Level of Serum Uric Acid.

Am J Cardiol. 2015 .116(9):1346-50.

- Elevated serum uric acid (SUA) level is a prognostic factor in patients with acute coronary syndrome (ACS).
- A total of 81 patients with ACS underwent intravascular ultrasound (IVUS)
- Classified into 3 groups according to tertiles of SUA level.
- Tissue components were classified into 4 categories: calcium deposits, dense fibrosis, fibrosis, and lipid.
- Tertiles of SUA level : low tertile <5.0 mg/dl; intermediate tertile 5.0 to 6.4 mg/dl; and high tertile >6.4 mg/dl.
- There was a trend toward greater vessel volume in the high tertile group than in the low and intermediate tertile groups (p = 0.05).
- There was no significant difference in lumen volume between the 3 groups.
- Plaque volume was significantly greater in the high than in the low tertile group (, p = 0.01).
- IB-IVUS analysis demonstrated greater lipid (, p = 0.001) and less fibrous components (, p <0.001) in the high than in the low and intermediate tertile groups. Multivariate analysis shows high SUA as an independent predictor of increasing lipid volume.
- Elevated SUA level is associated with greater lipid content with less fibrous components of coronary plaque and plaque volume in patients with ACS than in patients with normal levels

ADMA (Asymmetric Di-methyl Arginine)

- Autocrine regulator of eNOS
- Inhibits eNOS and reduces NO (competitive substrate)
- Elevated in hypertensive children and young adults
- Elevated in DM, CRI, Smokers, HBP, HLP, homocysteine, Elderly, Atherosclerosis
- VCAM and VWF positively correlate with ↑ ADMA
- Levels of ADMA (Endothelial > Plasma levels)

Normal	1.0 ± 0.1 μmol/ L
HLP	2.2 ± 0.2 μmol/ L
HBP	2.2 ± 0.2 μmol/ L
Elderly *with* AS	2.5 ± 3.5 μmol/ L

- oxLDL → ↑ ADMA
  Citrullene →
- Methionine (Homocysteine) → DDAH

- eNOS + ADMA → O_2^- → NFκB activation → ↑ MCP-1

- **DDAH = Dimethyl Dihydroxy Arginine Hydrolase**
- **Inhibited by : oxLDL, PPAR, Cytokines (TNF-α) , homocysteine and insulin**

Vascular Biology in Clinical Practice, Oct. 2000; M C. Houston,

ADMA: Asymmetric Dimethlyarginine

Circulation 2004;109:1813-1818

- Most traditional risk factors mediate vascular and endothelial dysfunction by reductions in bioavailable nitric oxide(NO)
- The mechanism is by ADMA accumulation, in part, that is a competitive inhibitor of eNOS . This reduces the production of NO.
- activity of DDAH II (dimethylarginine dimethylhydrolase), the endothelial enzyme that breaks down ADMA.
- DDAH II is inhibited by oxidative stress, oxLDL, inflammation, cytokines, hyperglycemia, hyperlipidemia, homocysteinemia, infectious agents. (oxidize sulfhydryl group in the enzyme)
- If ADMA levels are high and eNOS is not working, then statins will only reduce LDL but will not increase NO or improve ED.

Clinical Interpretation

Test			Interpretation
ADMA		SDMA	
Low		Low	• Normal endothelial function
Med / High		Low	• Endothelial dysfunction and possible presence of pre-diabetes/diabetes or CVD
Low		High	• Reduced renal function
Med / High		High	• Endothelial dysfunction and possible presence of pre-diabetes/diabetes or CVD • Possible renal failure

TMAO, Hypertension and CVD

Nature Medicine 2013 April 7 Epub
NEJM 2013;368:1575;Cell Metabolism 2013;17:49
Mayo Clin Proc 2013;88(8):786; Am J Clin Nutr 2016;103:703
Atherosclerosis 2013;231:456; Cell 2015;16 3: 1585-95; Nutrition 2018;46:7-12

- Elevated TMAO is associated with CVD, MI,DM, hypertension,PAD and CRI. Seen also with low HDL and PL and hypomethylation.
- TMAO is produced by certain gut microbes in the cecum to make TMA (gas) then metabolized in liver by FMO3 . Various foods (meat, chicken, turkey , fish and eggs) have high concentrations of carnitine and choline that are used as food by the bacteria to form the TMAO.
- Antibiotic administration decreases TMAO
- DMB (3,3 dimethyl-1butanol inhibits TMA production and atherosclerosis in mice
- TMAO reduces RCT and increases modified LDL uptake into macrophages by SRA and CD 36.
- TMAO prolongs the effect of A-II and hypertension

Oxidative Stress Markers

F 2 isoprostanes

MDA- malondialdehyde

8 hydoxydeoxyguanosine- 8OH DG

MPO- myeloperoxidase

OxLDL-Oxidized low-density lipoprotein

Pathogenic Burden and CHD
The Microbial Connection

Pak J Pharm Sci 2012;25:89
In Vivo 2005;19:351
Circulation 2003;108:678
Circulation 2002;106:184

- **The pathogenic burden of various microorganisms has a significant correlation with endothelial dysfunction with impaired responses to nitric oxide and acetyl choline in coronary arteries and both the presence and severity of CHD defined by coronary calcification and coronary arteriograms (p =0.001).**
- **Individual micro-organisms also have significant correlations with CHD including HSV, CMV, *H. Pylori*, Chlamydia Pneumoniae, Hepatitis A, B, C, and EBV as defined by IgG, IgA and IgM antibodies.**
- **HSV DNA is detected in CHD arteries and plaque at autopsy.**

PULS(Protein Unstable Lesion Signature) Cardiac Test (CHL)

Curr Med Res Opin 2012;28:1819-30

Elevated score related to:

- CHD development
- Presence of unstable or vulnerable arterial plaque
- Increased near-term risk of myocardial infarction

Biomarkers:

- **MCP-3**: immune cell direction and activity
- **sFas**: prevents apoptosis
- **Fas Ligand**: initiates cell recycling and death
- **Eotaxin**: activates immune cells at areas of injury
- **CTACK**: Helps to clean up damaged cells
- **IL-16:** recruits and activates immune cells, inflammation
- **HGF**: stimulates tissue repair.

Normal less than 3.5. Borderline 3.5 -7.49. Elevated > 7.5

Carotid IMT

Cerbrovasc Dis 2007;23:75
Curr Cardiol Rep 2009;11:21.
J of Hypertension 2012;30:1690

- **Normal values without any plaque present but must be adjusted for age and gender:**

- **Less than 0.6 mm : Normal low risk**
- **0.6 to 0.7mm : Moderate risk**
- **0.7 to 0.95 mm : High risk**

- **The normal IMT accretion rate (CIMTAR) is less than 0.016 mm / year.**

Carotid IMT and Future Vascular Events: Meta-analysis

Circulation 2007;115:459

- Age adjusted and sex adjusted overall estimates of relative risk for future events: 37,197 subjects
- Nonlinear risk, but linear models fitted relatively well for moderate to high IMT values
- **Myocardial Infarction**
- 1.26 (95% CI 1.21-1.30) per one SD common carotid artery IMT difference and 1.15 (95% CI 1.12-1.17) per 0.10 mm common carotid artery IMT difference over 5 years

Ocular Pulse Amplitude (OPA)

J of Am Acad Opthalmology 2012

- Reliably detects carotid artery stenosis by measuring inside the eye during systole and diastole and calculating the difference as the OPA.
- Low OPA means little difference between SBP and DBP indicating carotid artery stenosis.

Coronary Artery Calcification and Carotid IMT (MESA)

Arch Intern Med 2008;168:1333.

- Coronary artery calcification was associated more strongly than carotid IMT with risk of incident CVD. (n=6698) over 5.3 years
- CAC: CVD risk increased 2.1 fold per one SD
- Carotid IMT: CVD risk increased 1.3 fold per one SD

Coronary Artery Calcification.(CAC)

JAMA 2010;303:1610;Am J Cardiology 2015;116:520
Am J Cardiol 2010;105:459
Arterioscler Thromb Vasc Biol 2004;24:1272
Clin Cardiol;2010;33:658;JAMA 2014;311:271

- CAC progression over 15 % annually provides increase CHD risk analysis with 17 fold increase in CVD.
- CAC is composite of volume and density of calcium
- Higher calcium density lowers CHD risk and is seen in statin treated patients due to reduction in lipid core and plaque stabilization.
- Baseline CAC score predicts CHD risk beyond traditional risk factors. CAC score of over 300 has hazard ratio of CHD of 10
- Positive CAC increases risk of major cardiac event by 6-35 fold
- CAC is tip of iceberg :90% of noncalcified plaque below
- CAC correlates with traditional risk factors but also with increased oxidative stress , autoantibodies to oxLDL and apoB-immune complexes.
- Correlates with glycemic load and index.
- Progression from zero calcium score to calcification does not occur until 5 years and this occurs in 25%
- Low radiation .5mSv (25 CXRs)

CT Angiogram (CTA) and CAC

Am J Cardiol 2010;106:1574; Am J Cardiology 2011;107:799;Am J Cardiol 2012;109:1449; Mayo Clinic Proc 2014;89(10): 1350-59
Am J Card 2104;114:1707; Am Heart J 2016;177:17
Am J of Cardiology 2017;120:2154

- The risk of major CV events or death increased in a graded manner with the degree of coronary atherosclerosis as defined by CTA even in the absence of high grade coronary artery stenosis
- Both the CAC score and the number of calcified plaques improve risk strategication
- In the absence of high grade stenosis there is not a superior prognostic value of CTA compared to EBT CAC
- CAC is superior to predict future CHD events compared to the Framingham risk score and other biomarkers for CHD. Predicts increase risk A. Fib.
- CAC imparts increased CHD risk in younger and elderly individuals, across all age groups.
- Sugar –sweetened beverages have the highest correlation with CAC of food groups.

Pulse Wave Velocity and Arterial Compliance and Elasticity CV Profiler

J Am Coll Cardiol 2002;39 abstract 3523
Blood Pressure Monitoring. 2002.7: 231
Am Heart J 2003;146:679;J Hypertens 2010;28:1935
J of Clinical Hypertension 2015;00:1-11

- C2 compliance identifies the presence of endothelial dysfunction in the microvascular circulation, the very small arterioles and arteries. (range 4-9)
- C1 compliance is a measure of the elastic behavior of the aorta and larger arteries (range 8-17)
- Lower numbers indicate diseased arteries and are age and gender adjusted
- Improves risk stratification beyond usual risk factors including MAU ,ECHO and Carotid IMT.
- Low C2 and increased PWV predict CVD/CHD

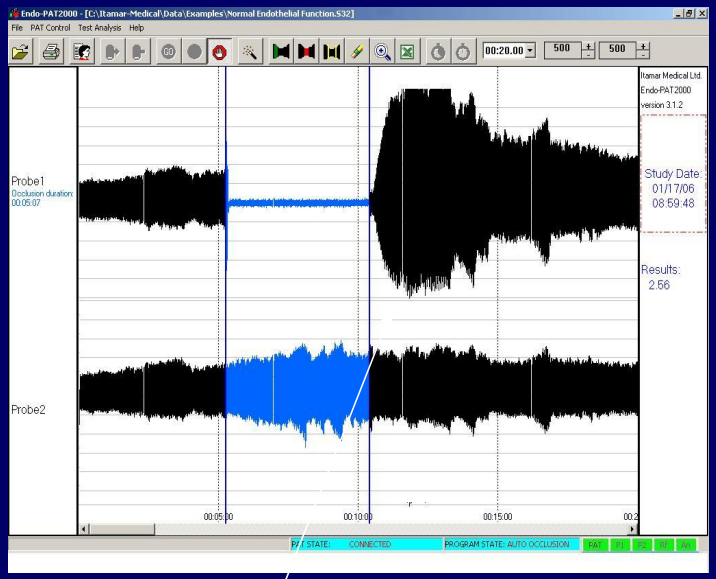
Endothelial Dysfunction predicts CVD and Hypertension

J of Hypertension 2014;32:2393

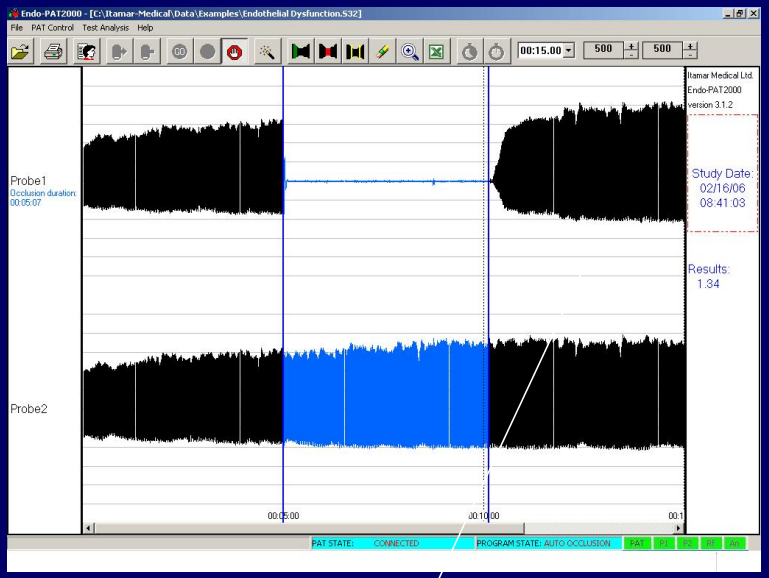
Journal of Hypertension 2016;34:1464-1472

- **Endothelial dysfunction is a very accurate predictor of future cardiovascular events (CVD) and target organ damage (TOD) such as CHD, MI, CVA, CRF and CHF**
- **For each 1% increase in endothelial function by FMD there was an 8 % decrease in CVD**
- **This is particularly true in low risk hypertensive patients and less so in the late stages of CV TOD.**

ENDOPAT Good and poor results



Normal EF



Poor EDF

St. Thomas Medical Group
4230 Harding Road
Nashville, TN 37205

Endo-PAT2000

Test Date: 06/03/13 07:41:07

Patient Information

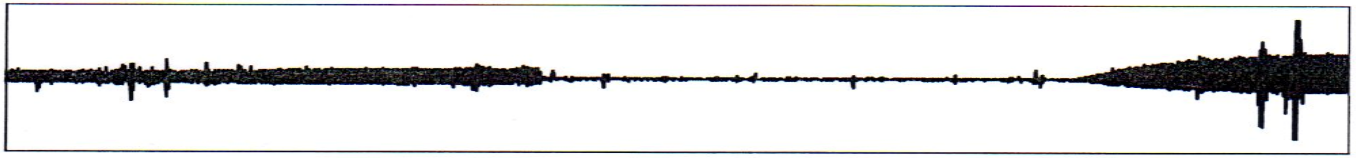
ID:	[redacted] mch 2	Name:	[redacted]	Systolic BP	130 mm Hg
Age:	75	Gender:	Female	Diastolic BP:	76 mm Hg
Height:	5' 3"	Weight:	140 lb	BMI:	24.8
User Field 1:		User Field 2:			
Comments:					

Study Information

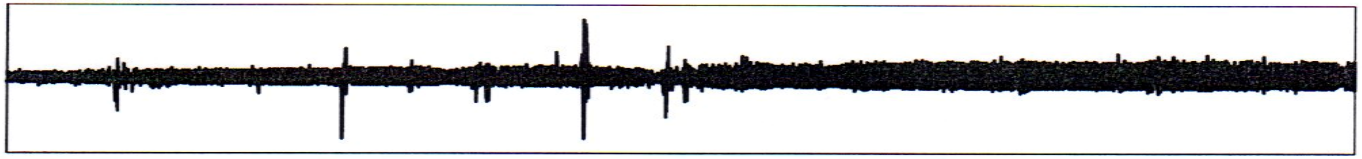
Test Duration:	00:14:20	PATographer:	NK		
Recording Ver:	3.4.4	Analysis Ver:	3.4.4	Occ. Borders:	Automated

PAT Signals

Occluded Arm



Control Arm



Baseline(05:43) Occlusion(05:35) Dilatation(03:02)

Study Results

RHI: 1.58 Endothelial Dysfunction

Heart Rate: 50 bpm

Recommendations

Physician's Name: _____ Signature: _____

St. Thomas Medical Group
4230 Harding Road
Nashville, TN 37205

Endo-PAT2000

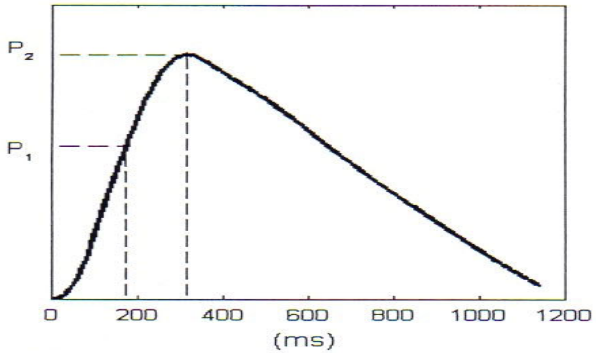
Test Date: 06/03/13 07:41:07

Augmentation Index (AI) - a measure of Arterial Stiffeness

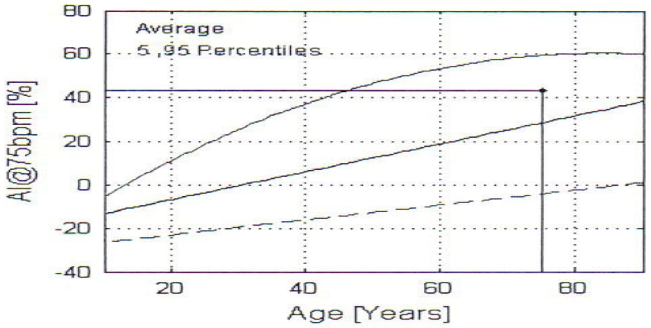
AI: 59%
AI@75bpm: 44%
AI = (P2-P1)/P1 x 100 [%]

Averaged - 123 pulses

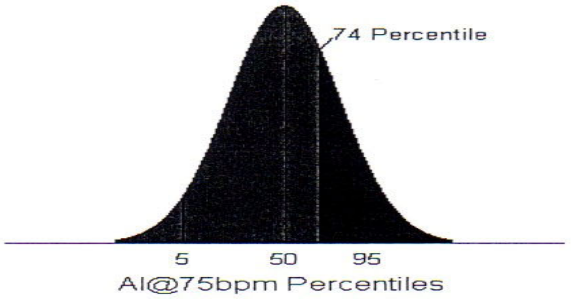
Average PAT Waveform (from baseline segment)



AI@75bpm in female population as function of age



Patient Relative to Age and Gender matched distribution



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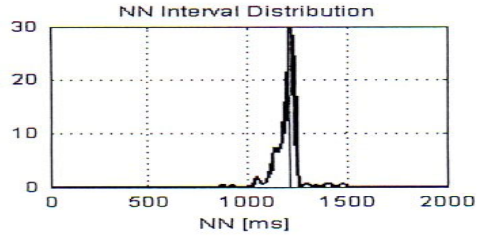
Endo-PAT2000

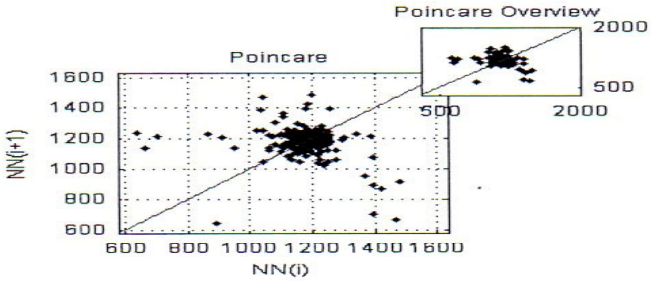
Test Date: 06/03/13 07:41:07

Heart Rate Variability (HRV)

Time Domain

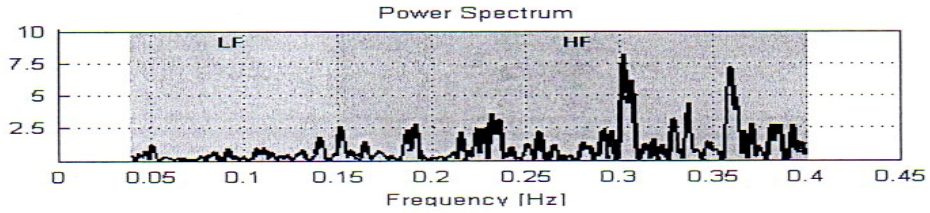
Mean NN:	1196	ms
SDNN:	63.59	ms
RMSSD:	95.00	ms
NN50:	35	
pNN50:	14.58	%
Triangular Index:	8.13	





Frequency Domain

LF (0.04-0.15 Hz):	36.83	ms^2
HF (0.15-0.4 Hz):	279.11	ms^2
LF/HF:	0.13	



Ankle Brachial Index

Diabetes Care. 2006;29:637-42
J Am Coll Cardiol 2008;52;1736
Ren Fail 2004;26: 433
Korean Circ J 2010;40:224
JAMA 2008;300:197

- Low ABI < 0.9 and PAD are associated with increased risk of CVD and CHD independent of the metabolic syndrome and other major CVD risk factors and predicts CKD
- 10 year CV mortality with ABI < 0.9 is 4 x greater than normal ABI.
- Improves CV risk prediction beyond Framingham Risk Score (FRS)

Ankle Brachial Index

Atherosclerosis, Thrombosis and Vascular Biology. 2005;25:1463

Blood Pressure 2010;19:308

- Meta-analysis of 22 studies 28,000 patients with low ABI outcomes
- CHD: 16.5 % sensitive, 92. 7% specific
- Stroke: 16% sensitive, 92.2 % specific
- Cardiovascular mortality: 41% sensitive and 87.9% specific
- Incidence of PAD in patients with previous CHD or CVA is 35%.

Post-exercise ABI predicts all-cause mortality

Am J Cardiol 2011;107:778

- Post exercise ABI is a powerful independent predictor for all-cause mortality and provides additional risk stratification beyond the ABI at rest.
- HR 1.67 with p <0.0001.
- Defined as ABI < 0.85.

Heart Rate Variability: HRV

J of Hypertension 2014;32:374
Global Advances in Health and Medicine;2015;4 (1):46-61.

- Underactive vagal tone and PSNS will increase IL 6, TNF alpha, HS-CRP, fibrinogen, resting HR and alter HRV.
- Heart varies with respiration. This respiratory sinus arrhythmia (RSA) is normal and if decreased will increase CV morbidity and mortality. Neurologic, biochemical, biophysical and EMF communications.
- Activation of PSNS reduces inflammation and improves HRV. Role of trained respiration
- Abnormal HRV occurs with aging, hypertension, DM and CHF
- Accupuncture increases PSNS activity
- Increased dietary sodium intake adversely effects HRV, especially during mental stress. Also increases RHR

COSEHC Global Cardiovascular Risk Calculation Definitions

Houston MC et al Am J Medical Sciences 2005;329:276-291 and 292-305

- **HIGH CARDIOVASCULAR RISK with expanded CHD risk factors beyond Framingham**
- **Relative Risk > 60th percentile**
- **Absolute Risk: Risk score > 40**
  > 2.3% risk of CV death / 5 years

CHD RISK SCORING: COSHEC
(*Merged Framingham, PROCAM and INDANA Data Tables)

Houston MC et al Am J Medical Sciences 2005;329:276-291 and 292-305

Risk Factors: Men = 17, Women = 12

- Being male
- Age (years)
  Extra for cigarette smoking
- Systolic blood pressure (mm Hg)
- Total cholesterol conc. (mg / dL)
- LDL cholesterol (mg / dL)
- HDL cholesterol (mg / dL)
- Triglyceride (mg / dL)
- Height (inches)
- Creatinine conc. (mg / dL)
- Homocysteine (µmol / L)
- Prior MI
- Family history of MI pre- 60
- Prior Stroke
- LVH
- Diabetes
- Non-Diabetic, FBS (mg / dL)

COSHEC ABSOLUTE RISK ANALYSIS FOR DEATH FROM CHD IN 5 YEARS

Risk Score	% dying from cardiovascular disease in 5 years
0	0.04
5	0.07
10	0.11
15	0.19
20	0.31
25	0.51
30	0.84
35	1.4
40	2.3
45	3.7
50	6.1
55	9.8
60	15.6
65	24.5
70	37.0

COSHEC ABSOLUTE RISK CALCULATION

Houston MC et al Am J Medical Sciences 2005;329:276-291 and 292-305

- VERY LOW RISK: SCORE 0-10
- LOW RISK: SCORE 10-20
- MODERATE RISK SCORE 20-30
- MODERATE/HIGH SCORE 30-40
- HIGH RISK SCORE 40-50
- VERY HIGH RISK SCORE > 50
- NOTE TRIPLE RISK WITHIN EACH 10 POINT RISK SCORE

COSHEC MEN

Risk factor	Addition to risk score											Risk Score
Being Male	Add 12 points											+12
Age (years)	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74				
	0	+4	+7	+11	+14	+18	+22	+25				
Extra for cigarette smoking	+9	+7	+7	+6	+6	+5	+4	+4				
Systolic Blood pressure (mm Hg)	110-119	120-129	130-139	140-149	150-159	160-169	170-179	180-189	190-199	200-209	≥210	
	0	+1	+2	+3	+4	+5	+6	+8	+9	+10	+11	
Total cholesterol conc. mg/dL	≤ 193	194-231	232-269	270-308	309-347	≥348						
	0	+2	+4	+5	+7	+9	Only if total ≤193 see below					
LDL cholesterol mg/dL	If total cholesterol ≤ 193; LDL:		<100	100-129	130-159	160-189						
			0	+1	+ 3	+ 4						
HDL cholesterol mg/dL	If total cholesterol ≤ 193; HDL:		<35	35-44	45-54	≥ 55						
			+ 4	+ 2	+ 1	0						
Triglyceride mg/dL	If total cholesterol ≤ 193; TG:		< 100	100-149	150-199	≥ 200						
			0	+0	+1	+ 1						
Height (inches)	<63	63 - <67	67- <71	71 - < 75	≥75							
	+6	+4	+3	+2	0							
Creatinine conc. (mg/dL)	≤ 0.8	0.9	1.0	1.1	1.2	1.3	1.4	>1.4				
	0	+1	+1	+2	+2	+3	+3	+4				
Homo-cysteine (µmol/L)	≤ 5	5 – 5.9	6 – 6.9	7 – 7.9	8 – 8.9	9 - 9.9	10 – 11.8	11.9-12.9	13-13.9	14-14.9	15-15.9	≥16
	-6	-5	-4	-3	-2	-1	0	+1	+2	+4	+5	+6
Prior MI	No 0	Yes +8										
Family History of MI pre-60	No 0	Yes +1										
Prior Stroke	No 0	Yes +8										
LVH	No 0	Yes +3										
Diabetes	No 0	Yes +2	If not diabetic, see below									
Non-diabetic, FBS (mg/dL)	≤ 75	76-81	82-88	89-99	100-105	106-111	112-117	118-125	≥ 126			
	-1.5	-1	-0.5	0	+0.5	+1	+1.5	+2	Diabetic (above)			
Total Risk Score =												

Rasmussen Center CV scoring

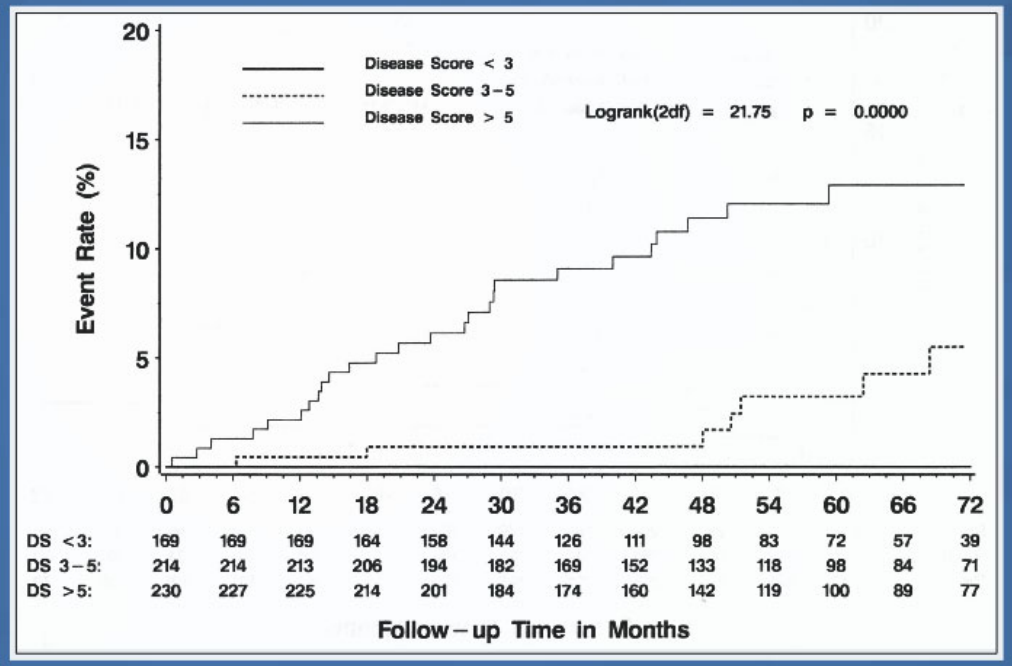
J Am Society of Hypertension 2011;5:2011

- Disease score 0-2: no CV events in 6 yrs
- Disease score 3-5: 5%CV events in 6 yrs
- Disease score over 6: 15 % CV events in 6 yrs
- Superior to Framingham risk score
- Variables measured: CAPWA, BP at rest and exercise, LV mass by ECHO, microalbuminuria, BNP, retinal score, Carotid IMT and US, EKG

Rasmussen Center CV Scoring

J Am Society of Hypertension 2011;5:401

Test	Normal	Borderline	Abnormal
Score for each test	0	1	2
Large artery elasticity		(age- and gender-dependent)	
Small artery elasticity		(age- and gender-dependent)	
Resting BP (mm Hg)	SBP <130 and DBP <85	SBP 130–139 or DBP 85–89	SBP ≥140 or DBP ≥90
Treadmill exercise BP (mm Hg)	SBP increase <30 and SBP ≤169	SBP increase 30–39 or SBP 170–179	SBP increase ≥40 or SBP ≥180
Optic fundus photography retinal vasculature	A/V ratio >3:5	A/V ratio ≤3:5 or mild A/V crossing changes	A/V ratio ≤1.2 or A/V nicking
Carotid IMT		(age- and gender-dependent)	
Microalbuminuria (mg/mmol)	≤0.6	0.61–0.99	≥1.00
Electrocardiogram	No abnormalities	Nonspecific abnormality	Diagnostic abnormality
LV ultrasound LVMI (g/m^2)	<120	120–129	≥130



Kaplan-Meier curves of time morbid events during 6 years of follow-up in the three Rasmussen Disease Score (DS) Groups.
The difference among the curves (P = .0000) is highly significant.
Two events after 72 months are not depicted.

Credit: D. A. Duprez et al. / Journal of the American Society of Hypertension 5(5) (2011) 401 - 409

Hypertension INSTITUTE

CHAN2T3 CHD Risk Score

Am Heart J 2017;193:95

Risk Factors

- HS-CRP > 3.4 mg/L
- Homocysteine >8.9 umol/L
- Albuminuria > 30 mg/g
- N terminal prohormone of BNP >117 picograms/mL
- Troponin-T detected

Ten year risk of CHD event per risk factor above

0 = 2.09 %

1 = 4.16 %

2 = 6.09 %

3 = 6.95 %

4= 10.22 %

5= 25 %

CASE

52 yo WM smoker 2 ppd for 20 years
BP 160/90 mm Hg
TC 240 LDL 166 HDL 34 TG 175
Height 6 ft
Cr 1.3
Homocysteine 10.5
Positive FH MI but patient has no history of previous MI or stroke
No DM but FBS 104
Abnormal CAPWA AC 1 and AC 2
Abnormal EKG diagnostic
Abnormal Fundoscopic exam
Positive MAU 120 high
SBP increase ≥180 with TMT(CPET)
LVH with LV mass index over 130 on ECHO
Abnormal carotid IMT
HS-CRP 3.6 mg/L high
N terminal prohormone of BNP 150 picograms/mL elevated
Troponin-T detected
Endopat 1.55 Low
Corus Score is 40 and PULS score is 7.5 both high

CASE CHD RISK SCORES

- COSHEC Score is 49. 5 = 6.1 % chance of dying of CHD in 5 years
- Rasmusen score is 18 = 13% CHD event in 6 years
- CHAN2T3 score is 5 = 25 % 10 year risk of CHD event
- CORUS Score is 40
- PULS score is 8

- All scoring systems indicate very high risk for CHD
- What do you want to know or do at this time

CASE DIAGNOSIS

- CPET: 3 mm ST depression in inferior lateral leads with chest pain and dyspnea
- Coronary Arteriogram LAD 94 %, LCX 78 %, RCA 90%

- CABG 3 vessels

Summary and Take Home Points

- Evaluate advanced CV biomarkers CHD risk factors for inflammation, oxidative stress and vascular immune dysfunction. (Advanced lipid testing, 24 hour ABM, new glycemic marker and body composition>
- Review the Top 25 Modifiable CHD risk factors
- Understand CV genetics and nutrigenomics combined with gene expression tests such as CORUS and PULS.
- Evaluate CHD risk scores to predict CHD and MI such as COSHEC, Rasmussen and CHAN2T3.
- Evaluate non invasive CV testing for endothelial dysfunction, arterial compliance and autonomic function testing