Endothelial Dysfunction in Patients with Insulin Resistance

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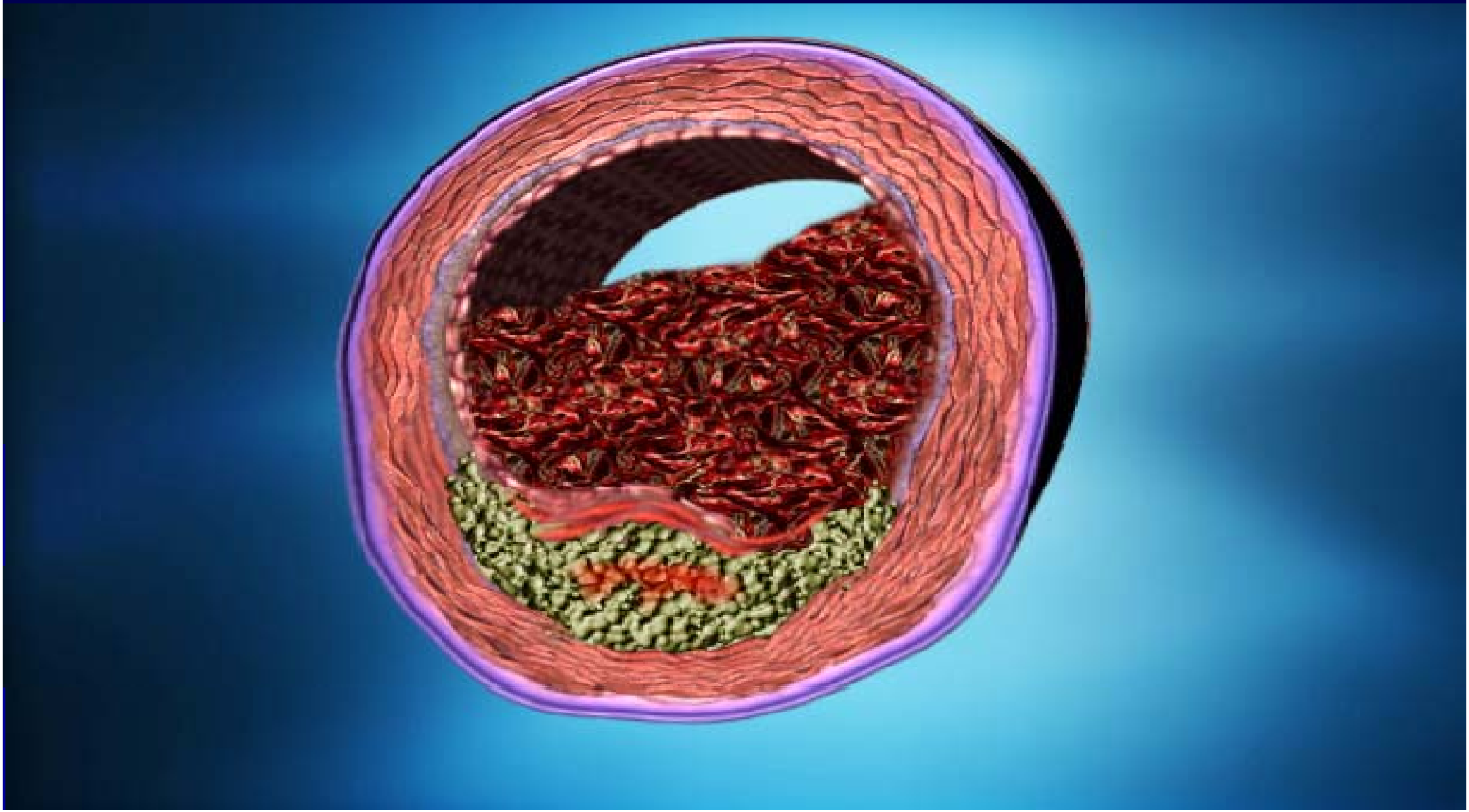
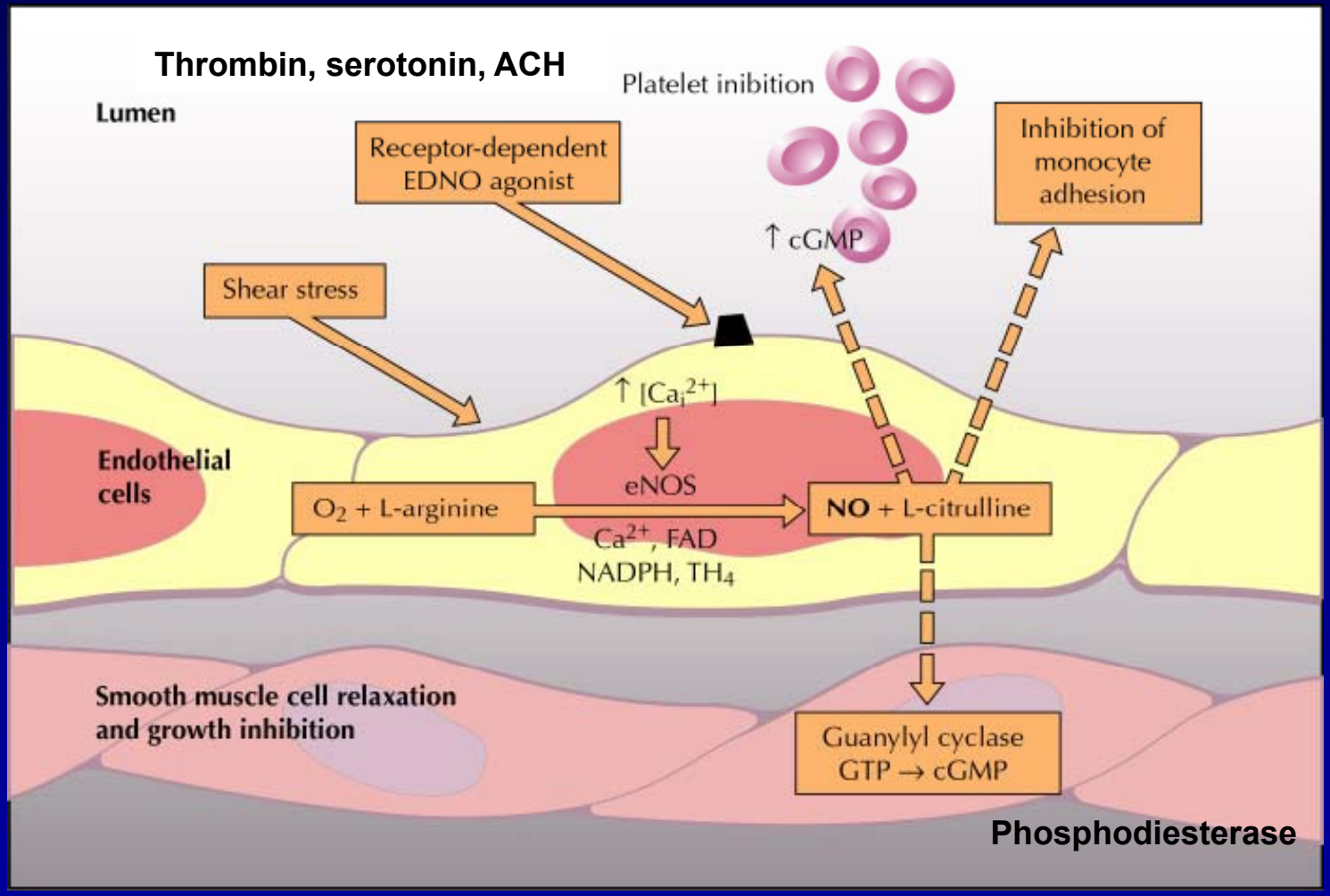
Professor of Medicine
Boston University School of Medicine

Memorial Lecture to Honor
Dr. Suh Soon Kyu

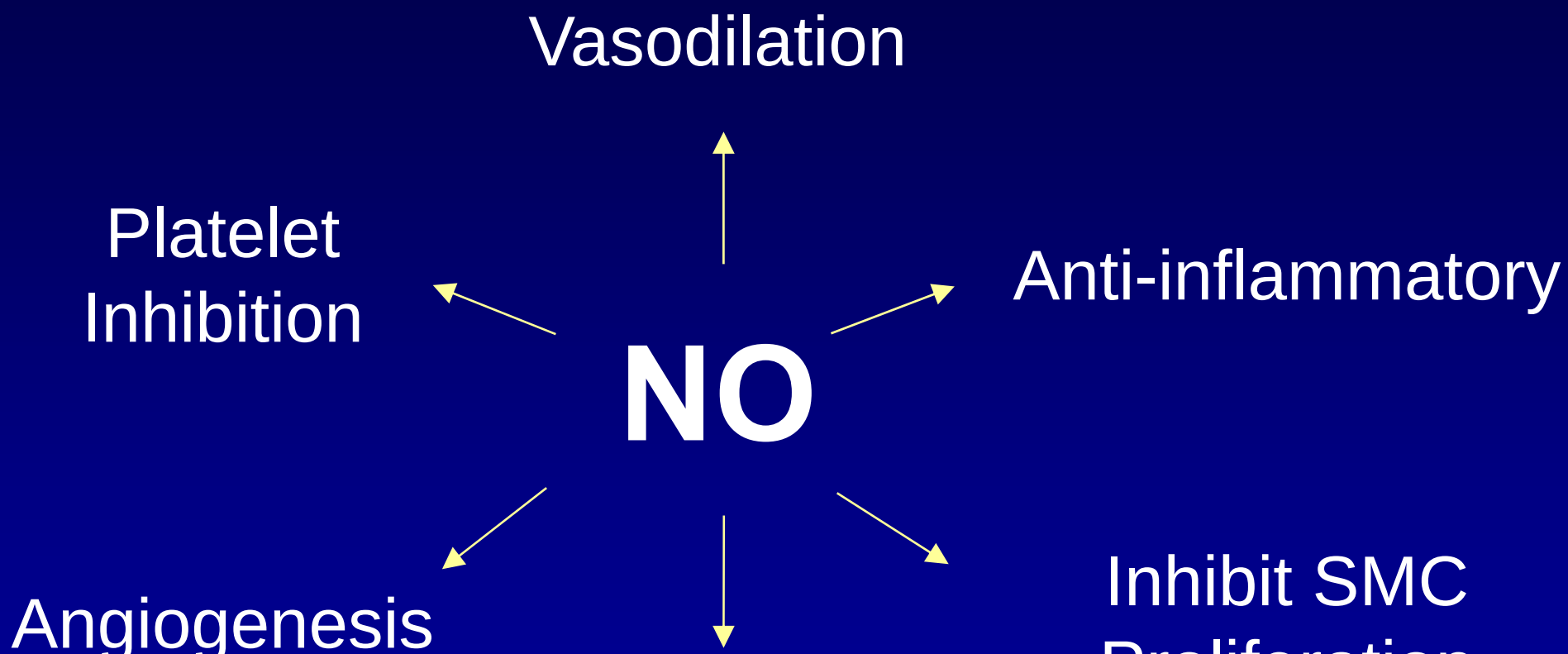
Pathogenesis of Acute Coronary Syndromes



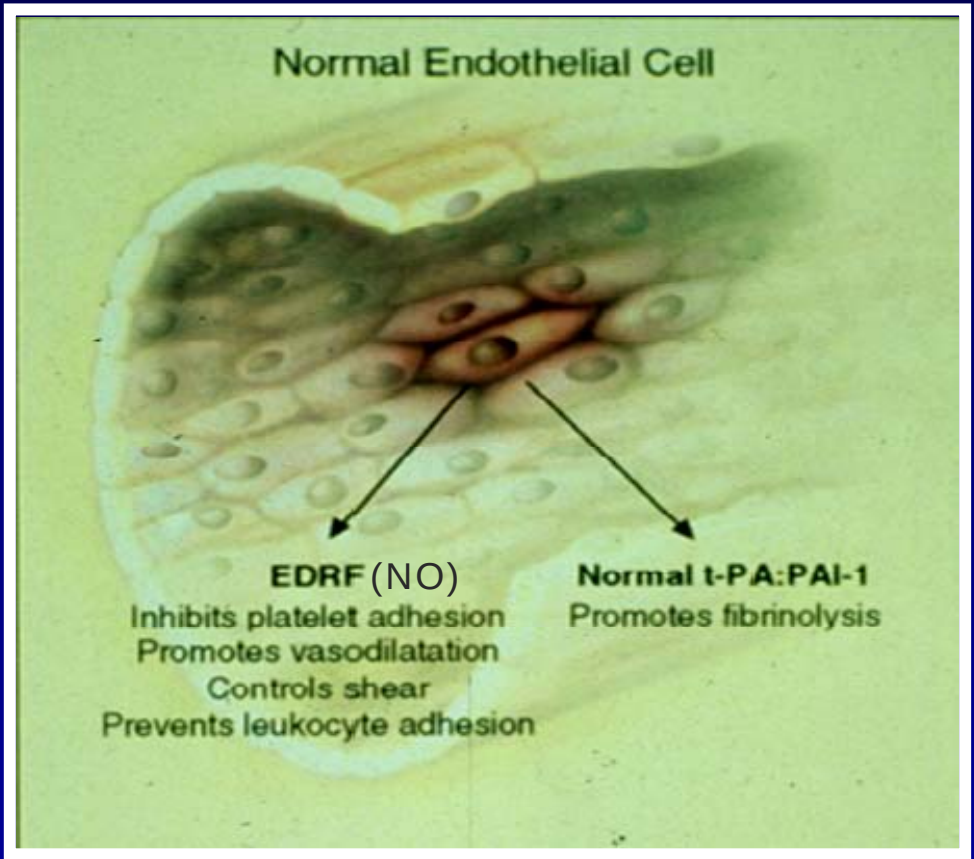
EDNO Synthesis and Action

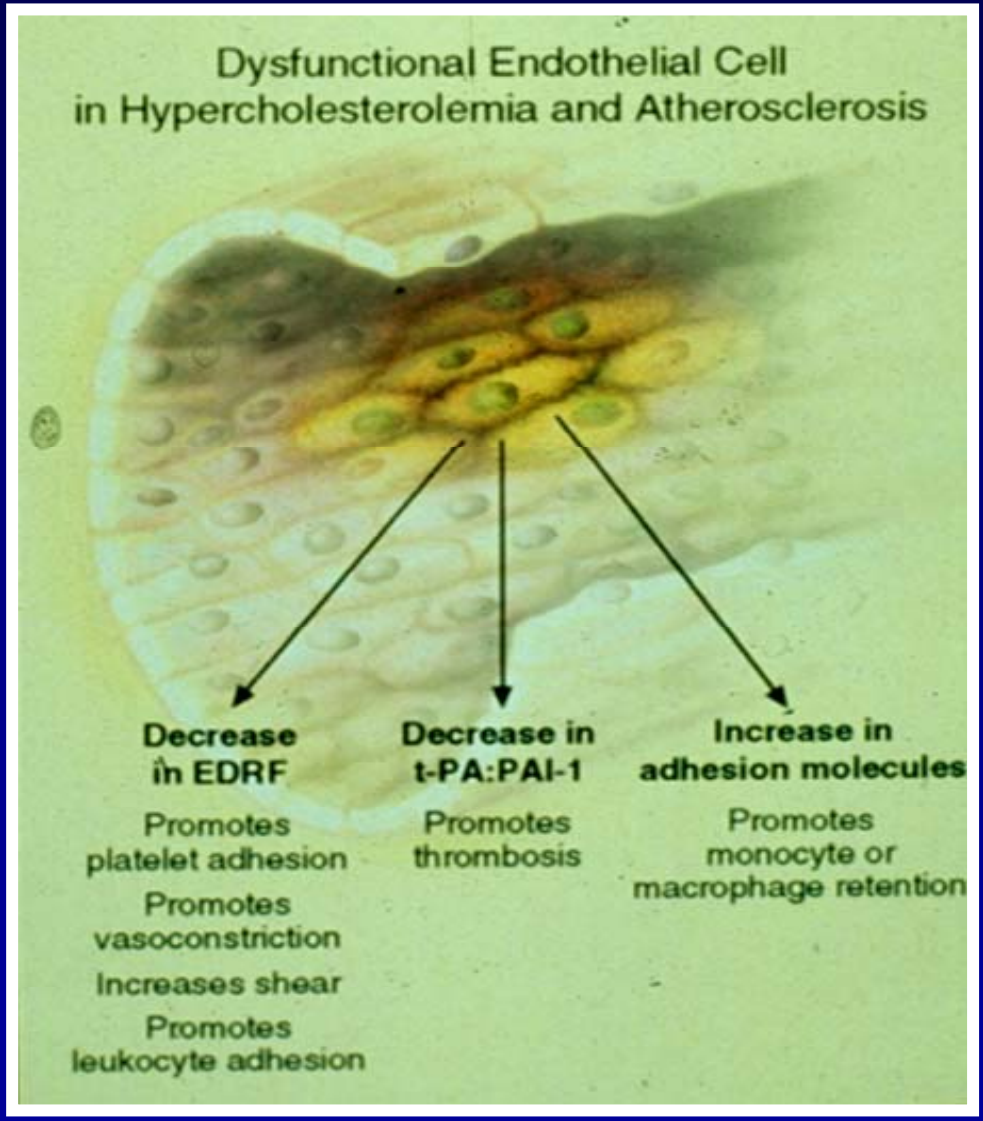


Vascular Effects of Nitric Oxide



Pathological Endothelial Phenotype





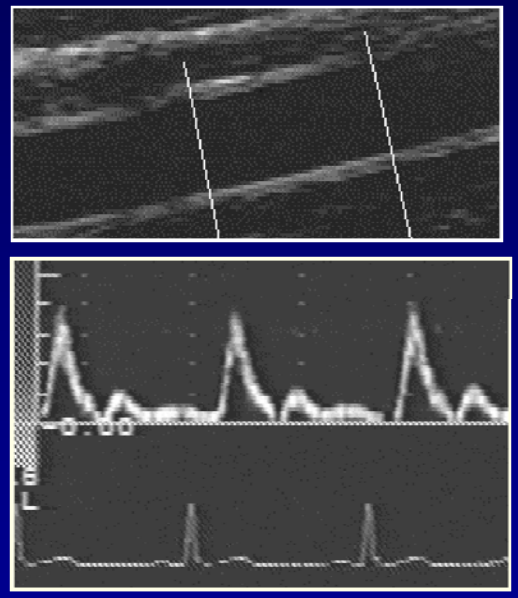
Levine NEJM 1995

Interventions Shown to Improve Endothelial Function

- **Lipid lowering therapy/statins**
- **ACE inhibitors/Ang II receptor blockers**
- **Insulin sensitizing agents**
- **Exercise**
- **Weight loss**
- **Smoking cessation**
- **Flavonoid containing foods and beverages**
  - Black tea
  - Grape juice/Wine
  - Chocolate
  - Cranberry juice

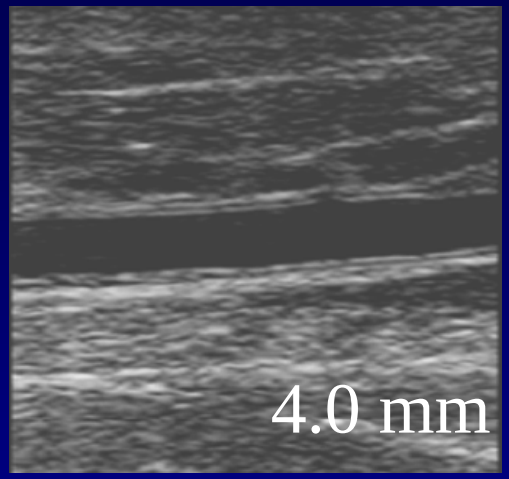
Non-invasive assessment of vascular function

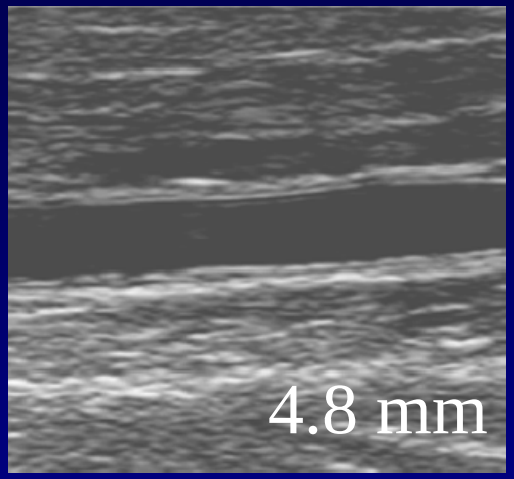
Non-Invasive Measurement of NO-Mediated Vascular Function

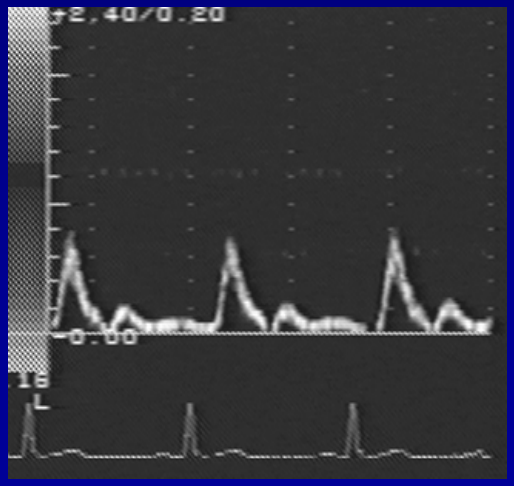


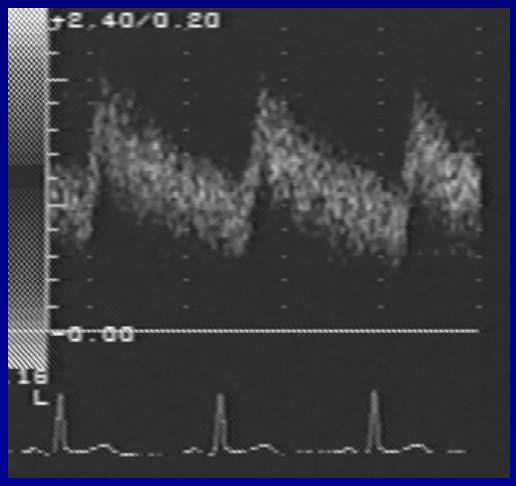
Real-time display of flow velocity and vessel diameter

Ultrasound Evaluation of Brachial Artery Endothelial Function





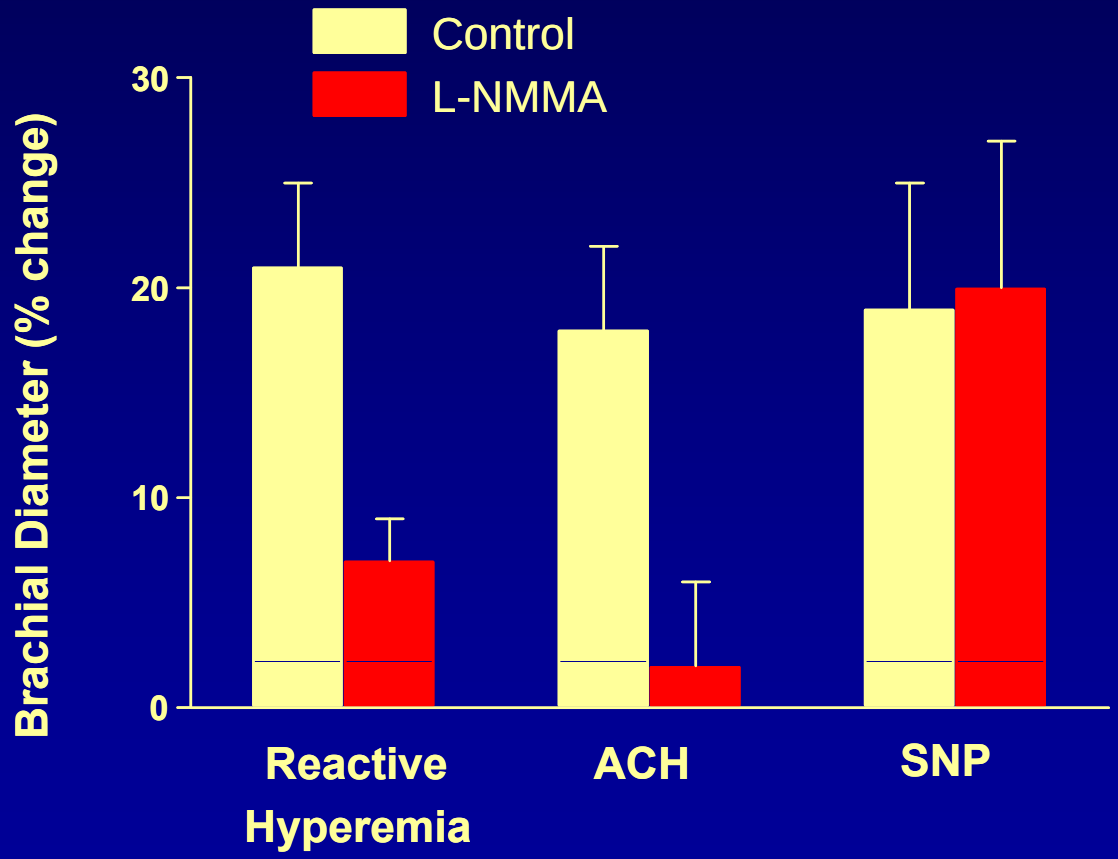




Baseline

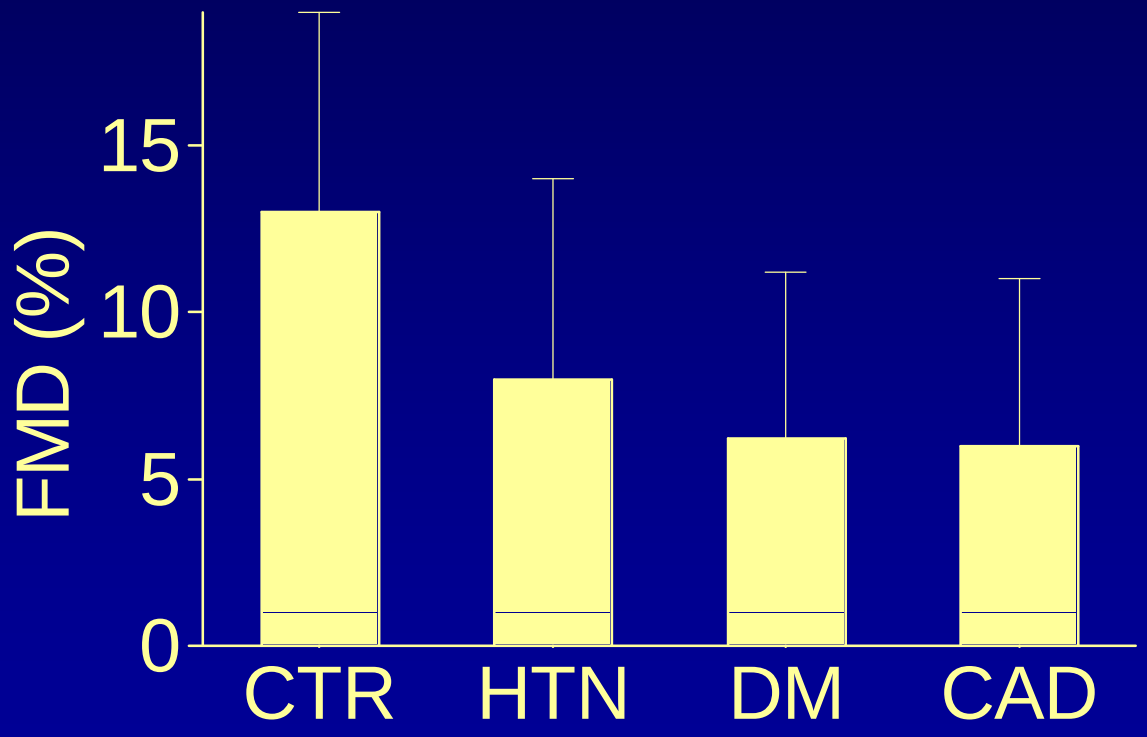
Hyperemia

Brachial Artery Flow-Mediated Dilation is NO Dependent

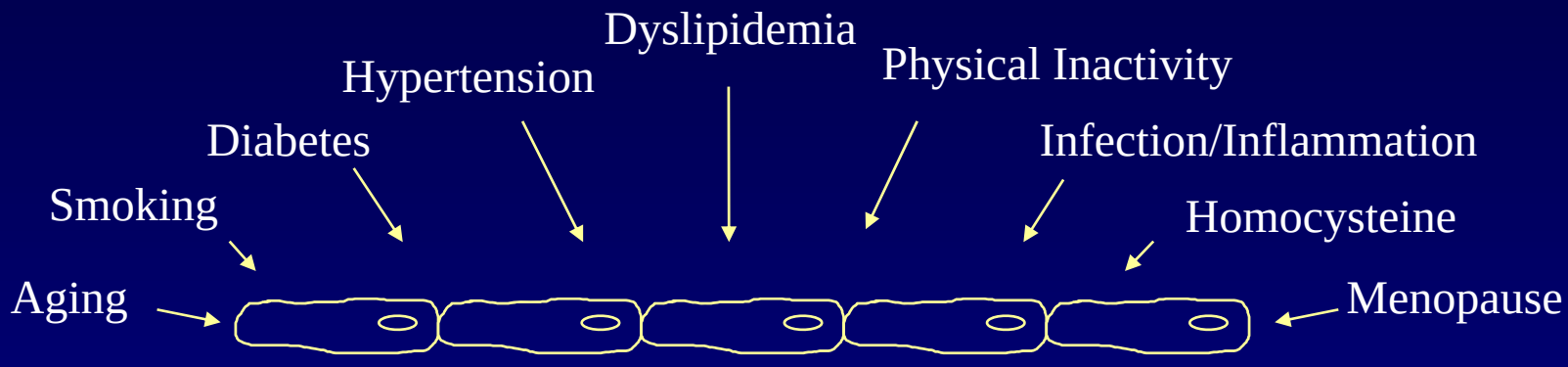


Lieberman et al. Am J Cardiol

Brachial Artery Flow-Mediated Dilation and Coronary Risk Factors



A Barometer for Vascular Health



Intrinsic and Extrinsic Defense Mechanisms

Endothelial Dysfunction

Decreased NO and Increased Vasoconstriction

Prothrombotic

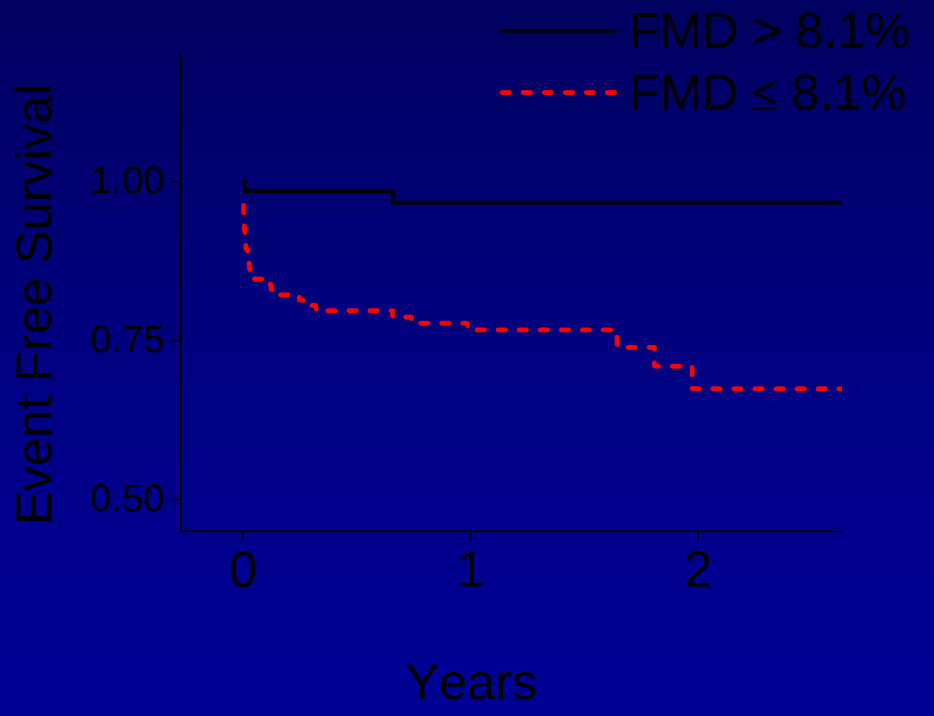
Increased Inflammation

Atherogenesis
Plaque Activation/Rupture
Worsened Thrombosis and Vasospasm

Coronary Events and Stroke

Brachial Endothelial Dysfunction Predicts Long-Term CVD Events in High Risk Patients

- 199 patients undergoing vascular surgery.
- 34 (death, MI, stroke, unstable angina).
- Endothelial function by USG
- Odds Ratio 9.3 (2.2 – 39) P<0.001, adjusting for other risk factors



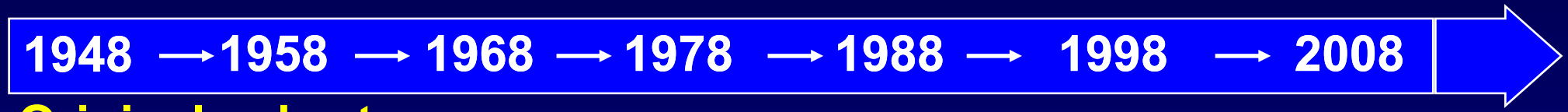
Gokce et al. JACC 2003

Prognostic Value of Endothelial Dysfunction

Author	Vascular Bed	N	F/U (yrs)	# events	Predictive
Suwaidi 2000	Coronary	157	2.4	6	+
Schachinger 2000	Coronary	147	7.7	16	+
Halcox 2002	Coronary	308	4	35	+
Heitzer 2001	FBF	281	4.5	91	+
Perticone 2001	FBF	225	2.5	29	+
Gokce 2002	FMD	199	30 d/1.2 y	45	+
Werner 2005	EPC count	519	1	219	+
Yeboah 2007	FMD	2792	5	674	+

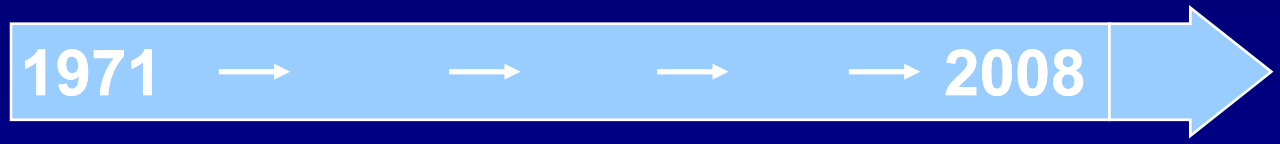
Endothelial Dysfunction and Insulin Resistance

Design of the Framingham Heart Study



Original cohort

N = 5209 men & women (ages 28-62)



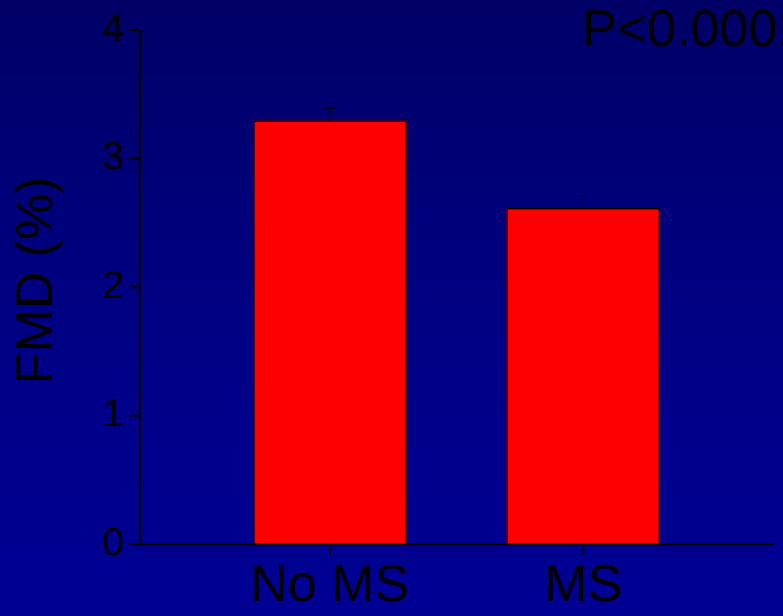
Offspring study

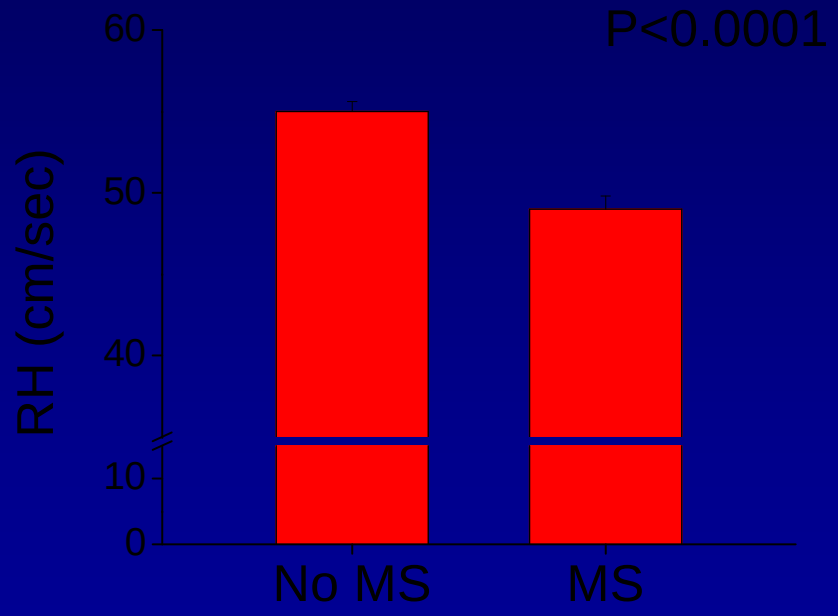
N = 5124 men and women (ages 5-70)

Third Generation study

EJ Benjamin AHA 2001

Framingham Heart Study – Metabolic Syndrome

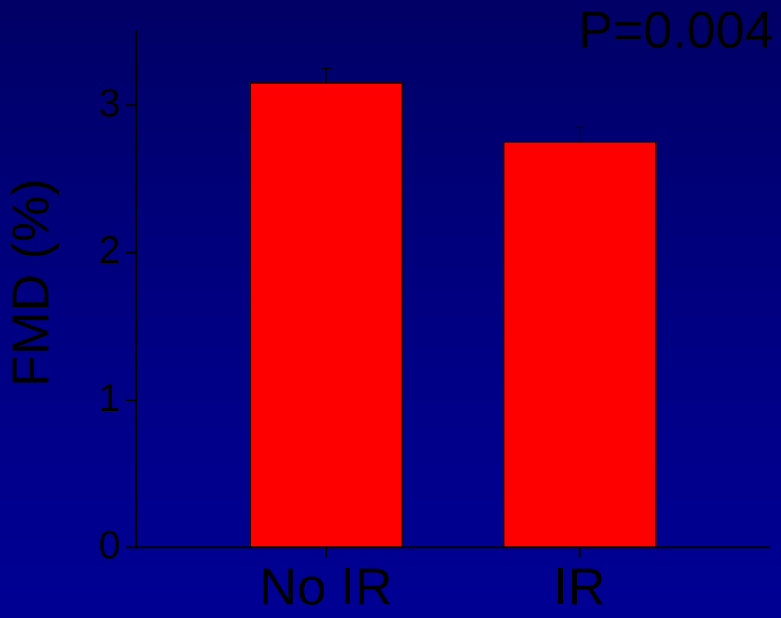


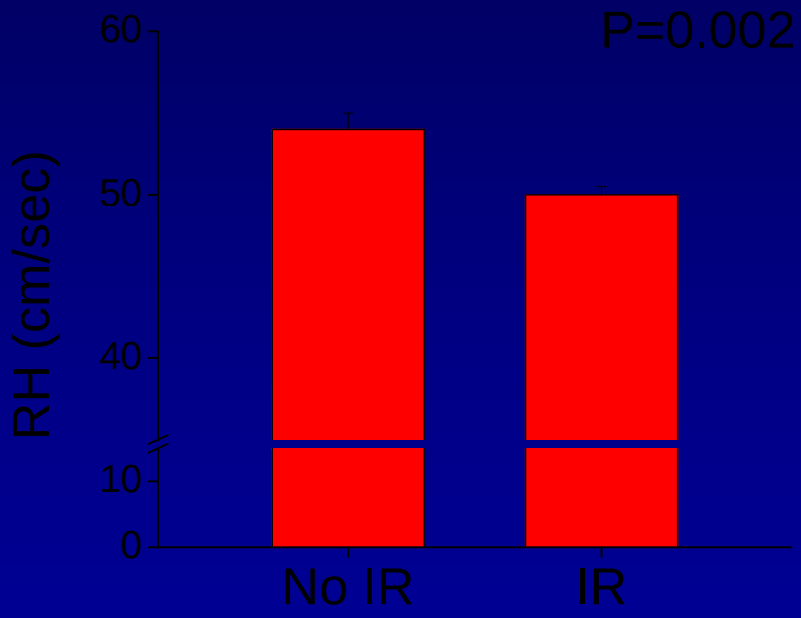


N=2,123 Offspring Cohort, no DM

Hamburg et al. Am J Cardiol 2008

Framingham Heart Study – Insulin Resistance





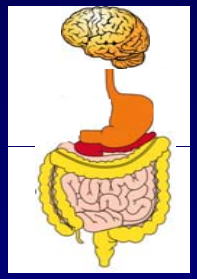
HOMA-IR
N=2,123 Offspring Cohort, no DM

Hamburg et al. Am J Cardiol 2008

Can we distinguish the direct effects of insulin resistance from the effects of concomitant risk factors?

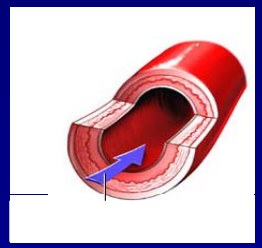
Obesity, Insulin Resistance, and CVD

↑Calorie Intake - ↓Activity



Systemic Responses

Neuroendocrine Gut-derived hormones
Cytokines
Free Fatty Acids



Inflammation

Cellular Responses

Insulin Resistance
Mitochondrial dysfunction
Innate Immunity

Vascular Dysfunction

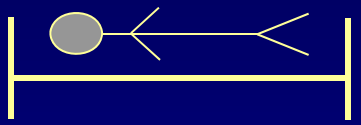
Endothelial dysfunction - Increased stiffness
Hypertension

Cardiovascular Disease

Background - Sedentary Lifestyle

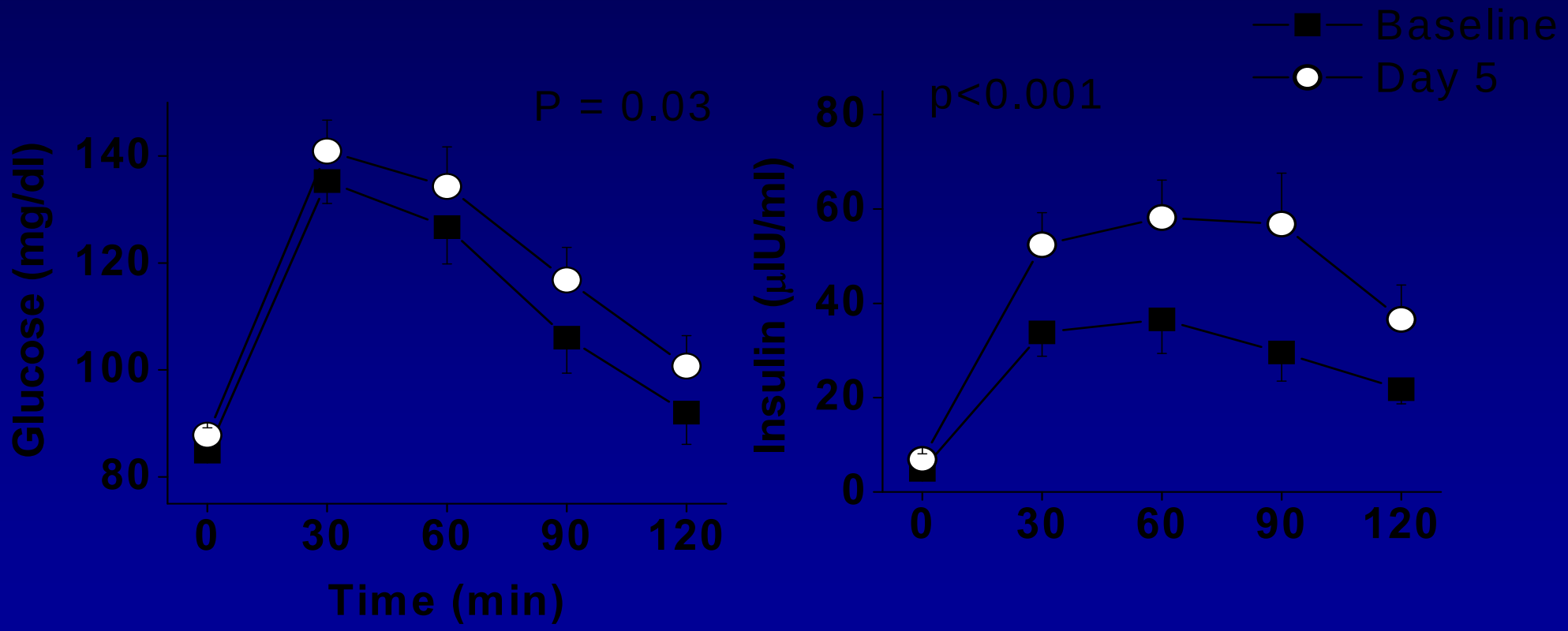
- Sedentary lifestyle associated with increased cardiovascular risk
- Physical inactivity rapidly induces insulin resistance – NASA studies with microgravity
- Insulin resistance in endothelial cells: loss of NO bioactivity, activation of NFκB, mitochondrial dysfunction

Study Design

Study Days				
1	2	3	4	5
				
	BEDREST			
Oral Glucose Tolerance Test		Vascular Function Study		Oral Glucose Tolerance Test
Vascular Function Study				Vascular Function Study

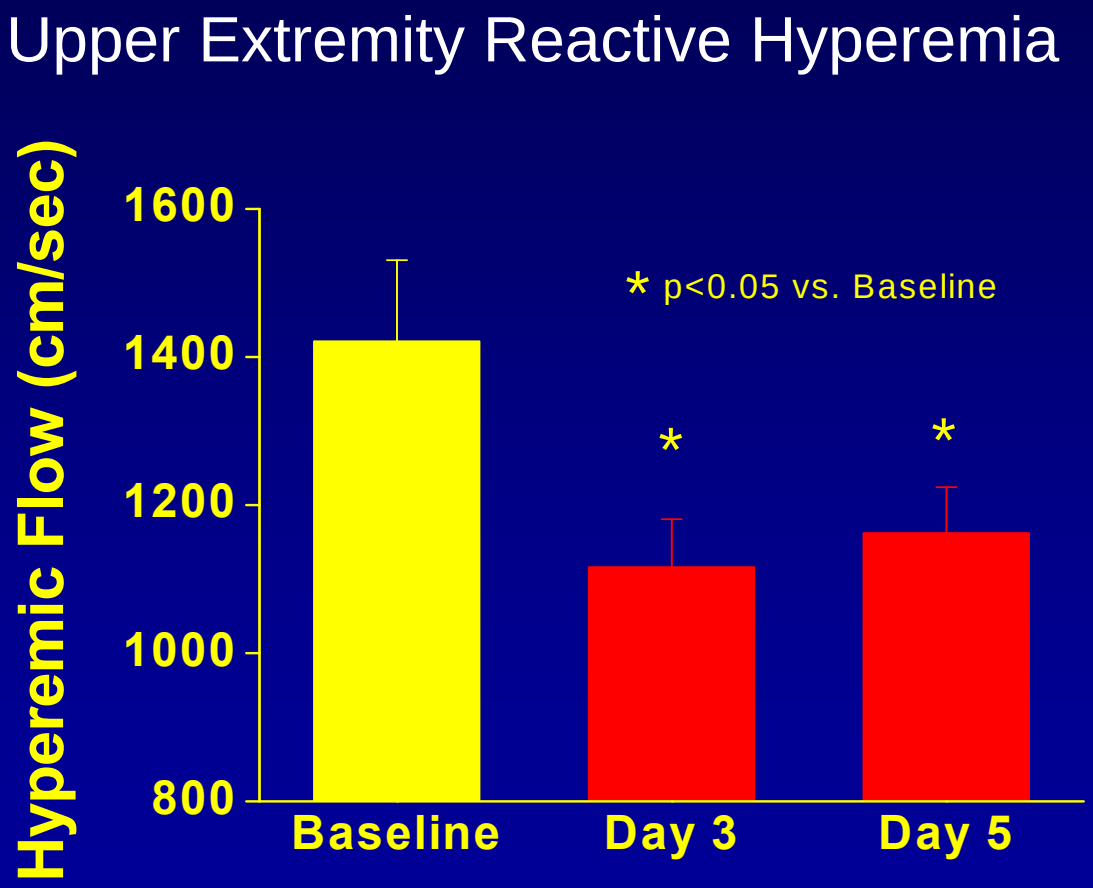
N = 20 Healthy subjects, age 31±8 years, background diet maintained

Physical Inactivity Induces Insulin Resistance



Hamburg et al. *ATVB* 2008

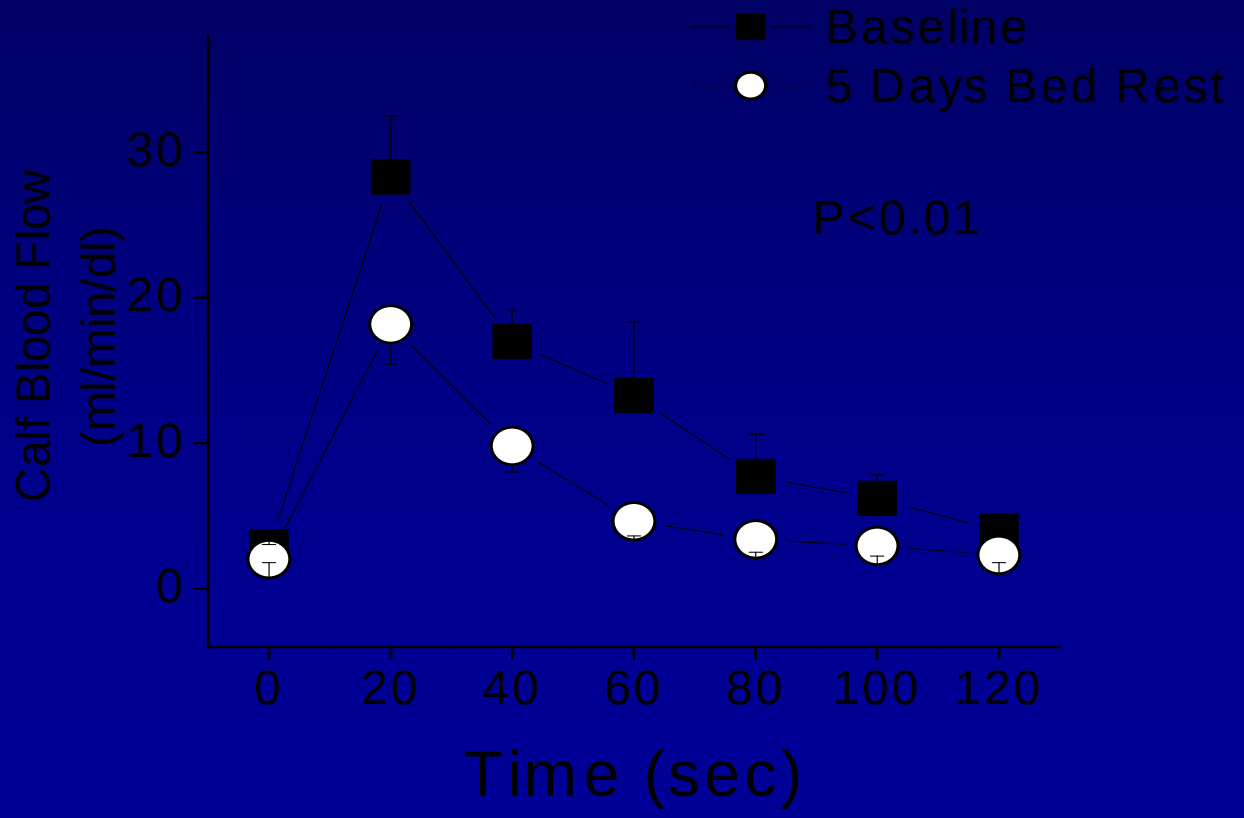
Physical Inactivity Impairs Microvascular Function



Hamburg et al. *ATVB* 2008

Physical Inactivity Impairs Microvascular Function

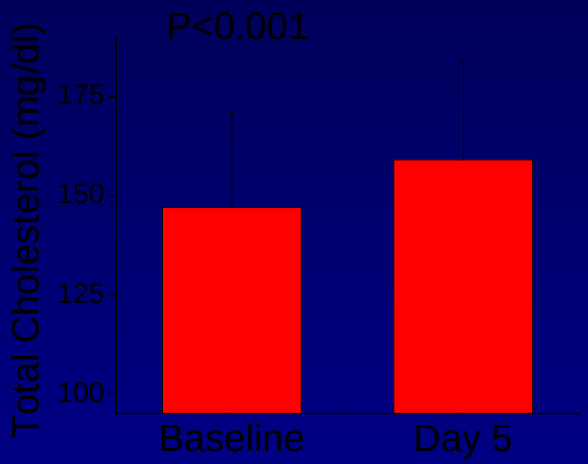
Lower Extremity Reactive Hyperemia

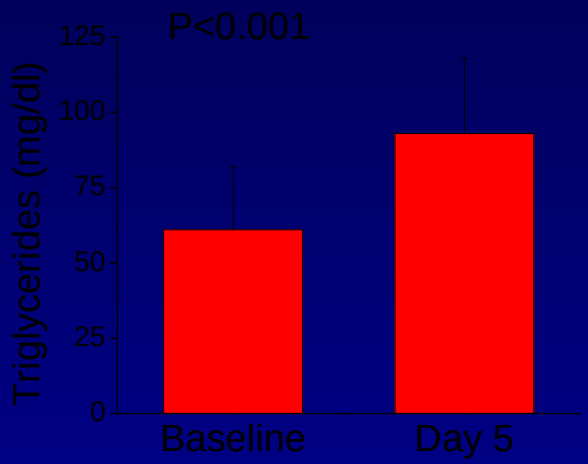


Hamburg et al. *ATVB* 2008

Bed Rest Induces Early Metabolic Abnormalities

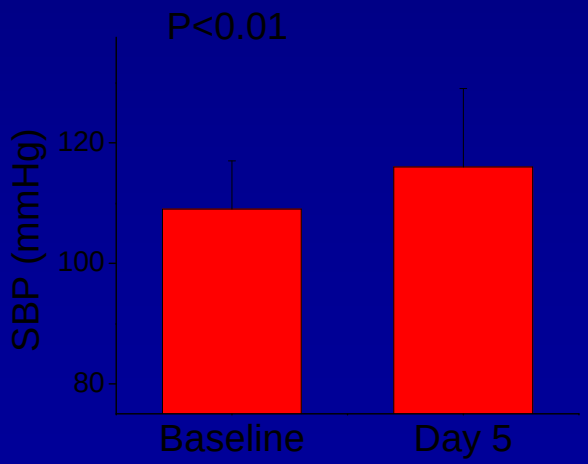
Total Cholesterol

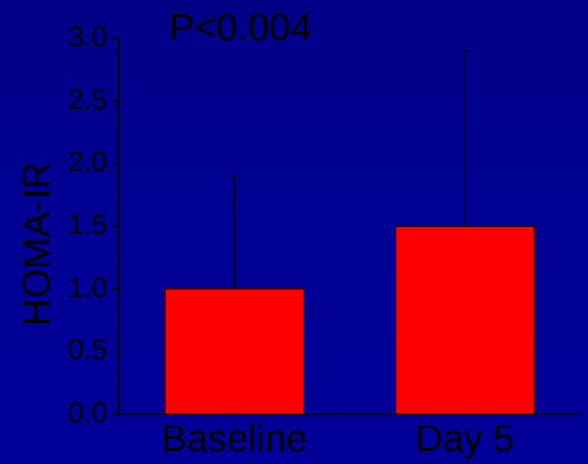




Triglycerides

Systolic Blood Pressure



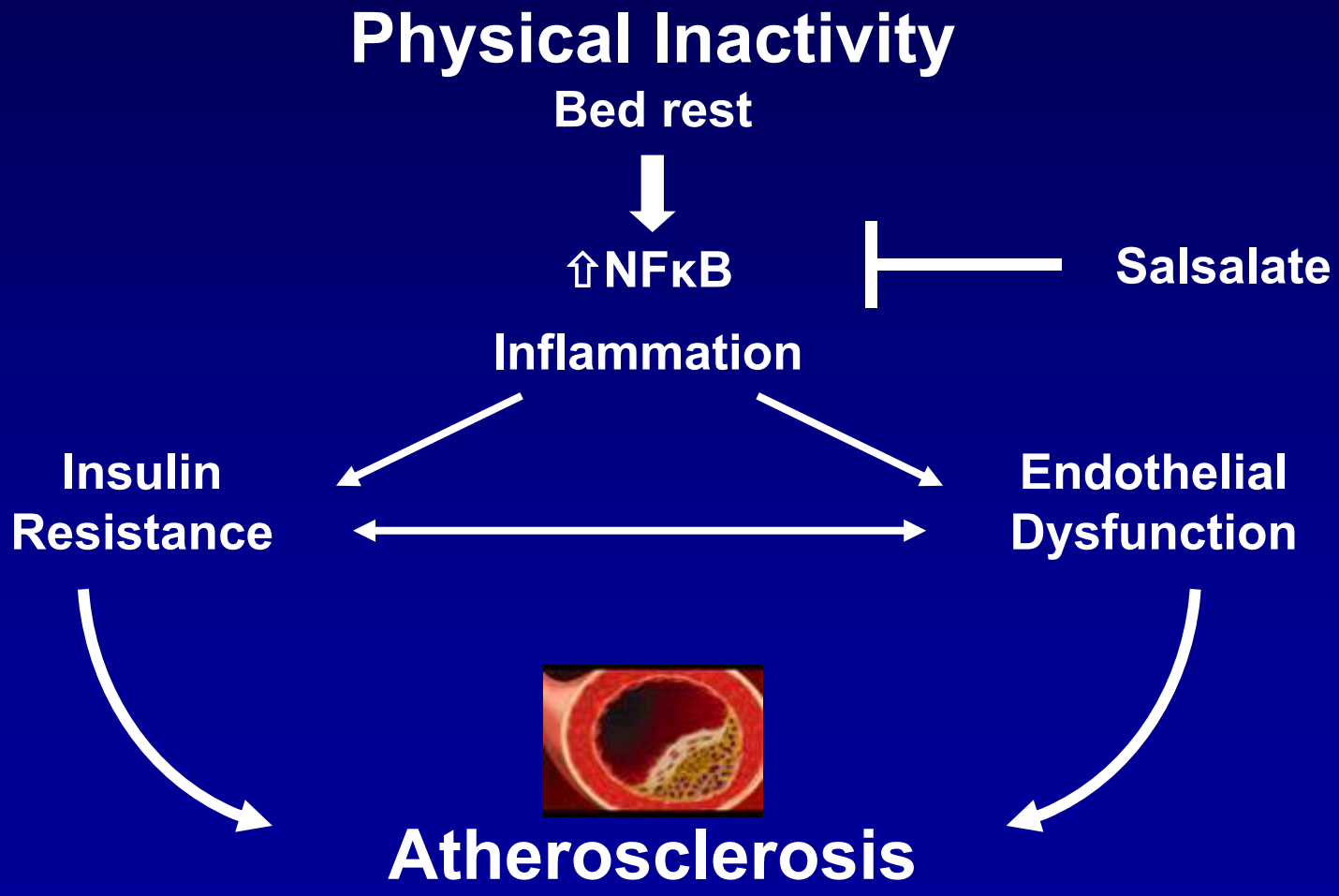


HOMA-IR

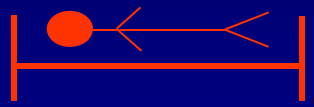
Other Consequences of Bed Rest

- Trend for increased serum ICAM-1
- No change in serum CRP, adiponectin, IL-6
- Decreased resting flow and arterial diameter
- No change in conduit artery FMD
- Vascular effects resolve after 3-4 days of normal activity

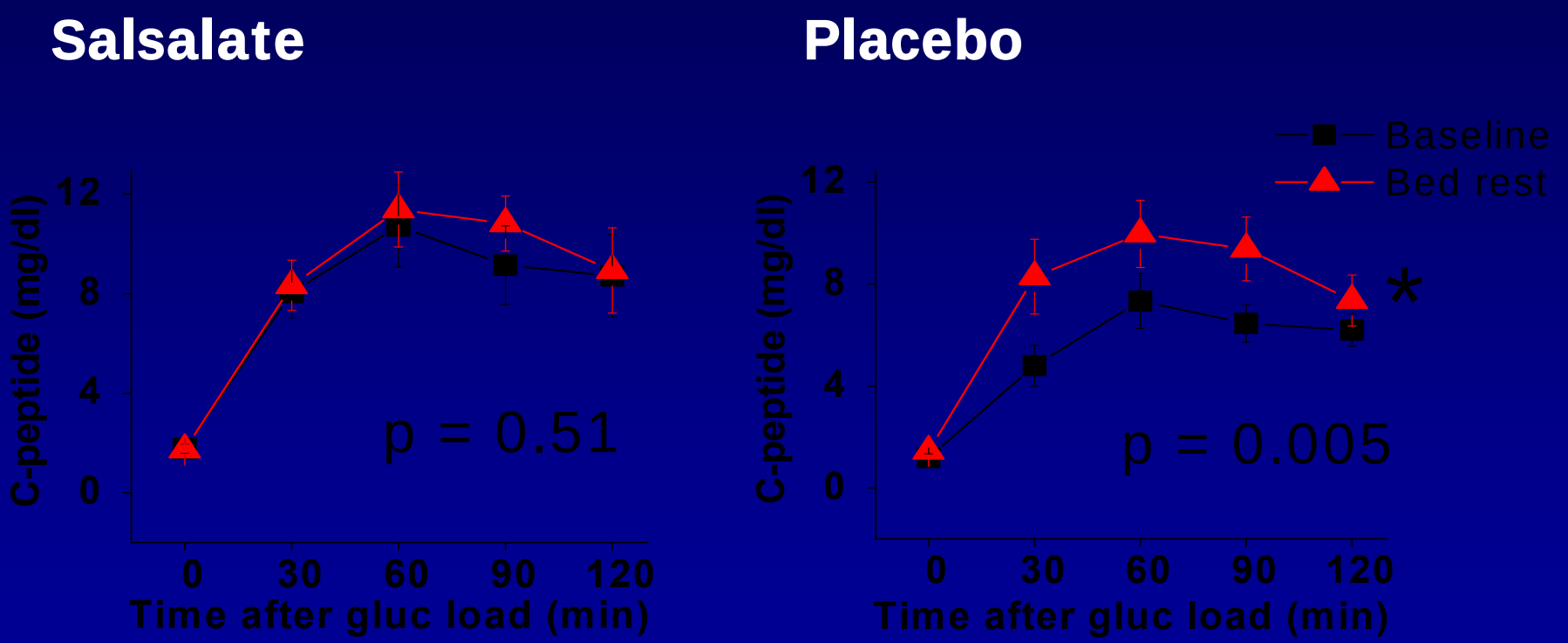
Study Hypothesis



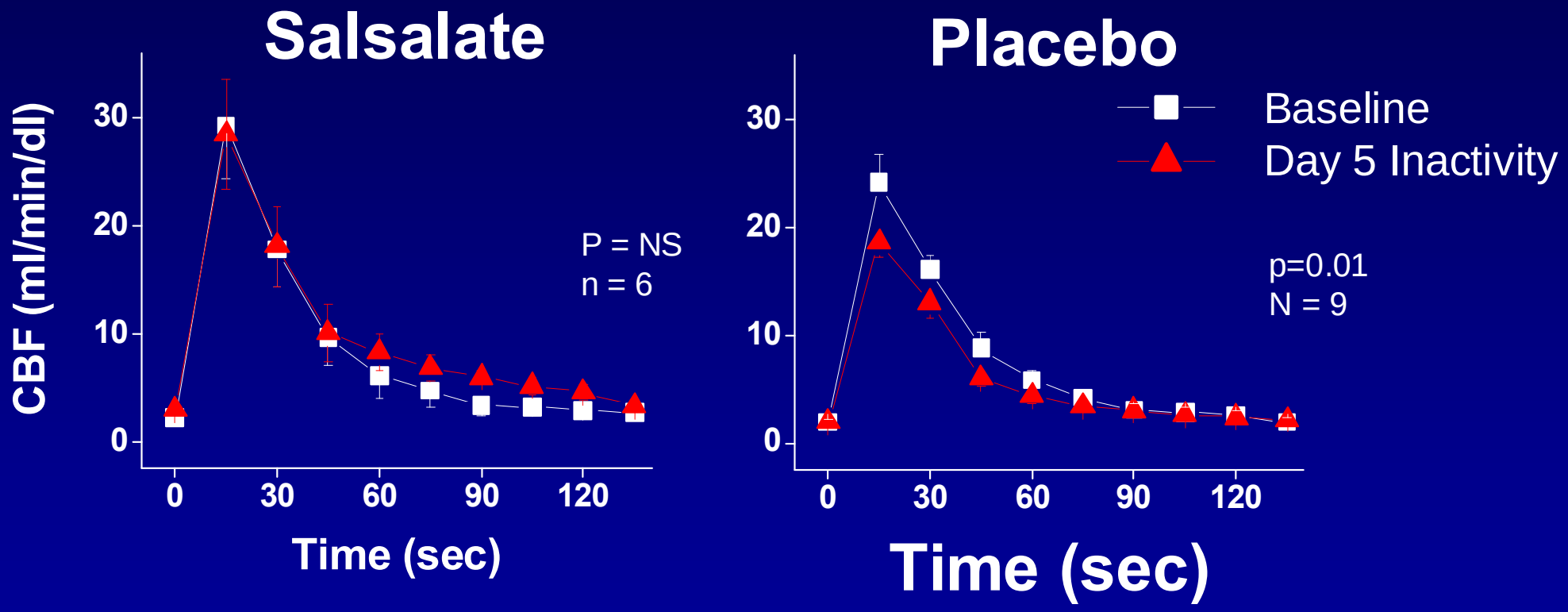
Study Design

STUDY DAY						
-7-14	-4	1	2	3	4	5
	SALSALATE or PLACEBO					
			 BED REST PERIOD			
Glucose Tolerance Test		Glucose Tolerance Test				Glucose Tolerance Test
Vascular Function Studies		Vascular Function Studies		Vascular Function Studies		Vascular Function Studies

Salsalate blocks Physical Inactivity-Induced Insulin Resistance



Salsalate Prevents Physical Inactivity Induced Vascular Dysfunction



Summary

- Early insulin resistance produced by bed rest rapidly induces clinical relevant vascular dysfunction
- Salsalate blocked physical inactivity induced insulin resistance and vascular dysfunction
- Pharmacologic NFκB inhibitors may protect the vasculature from the adverse consequences of sedentary behavior

Potential Clinical Utility of Endothelial Function

- Identification of novel risk factors
- Investigation of potential mechanisms of vascular dysfunction
- Surrogate to assess potential new therapies for CVD
- Evaluating CVD risk in individuals
- Monitoring response to interventions

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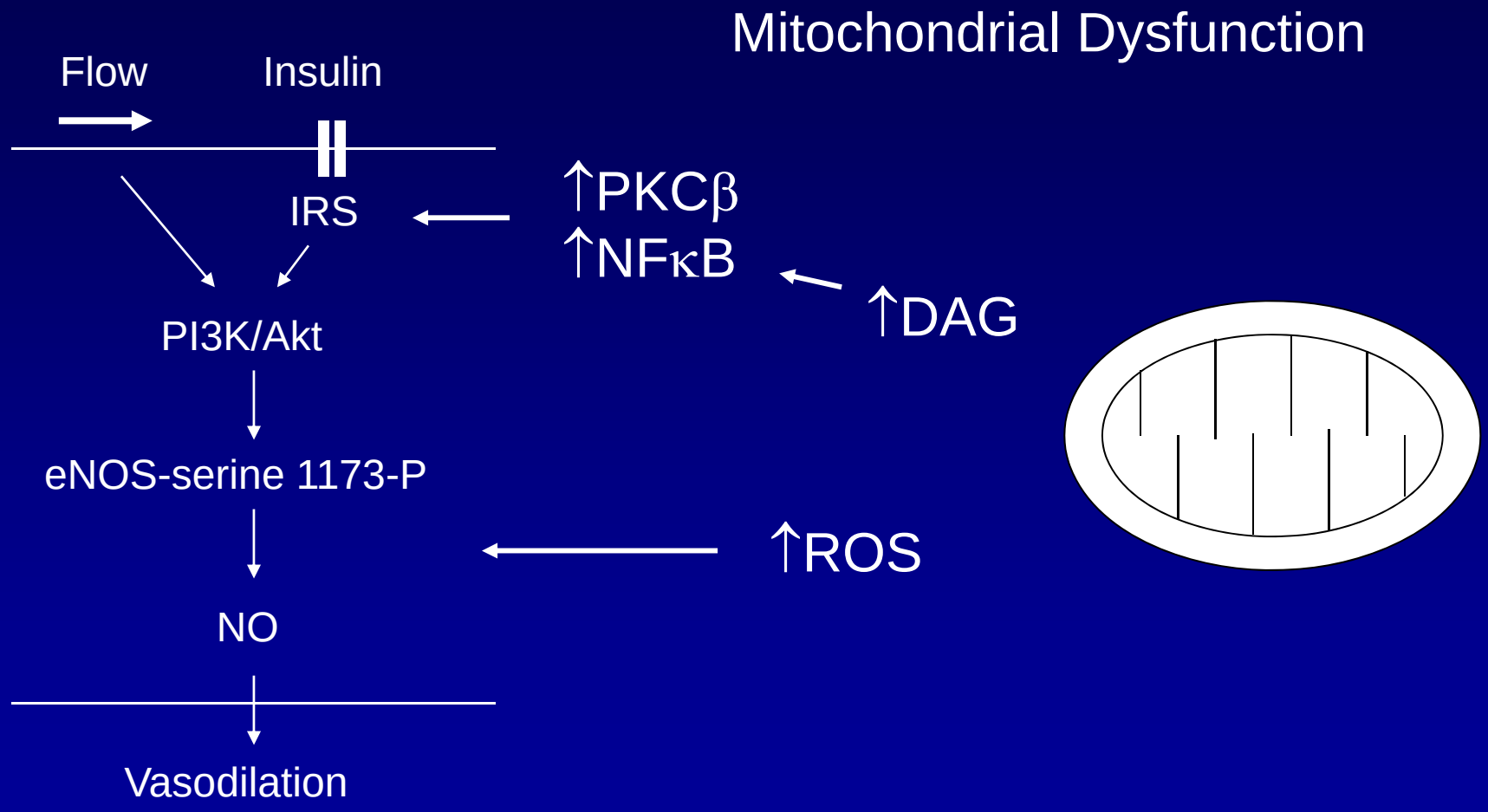
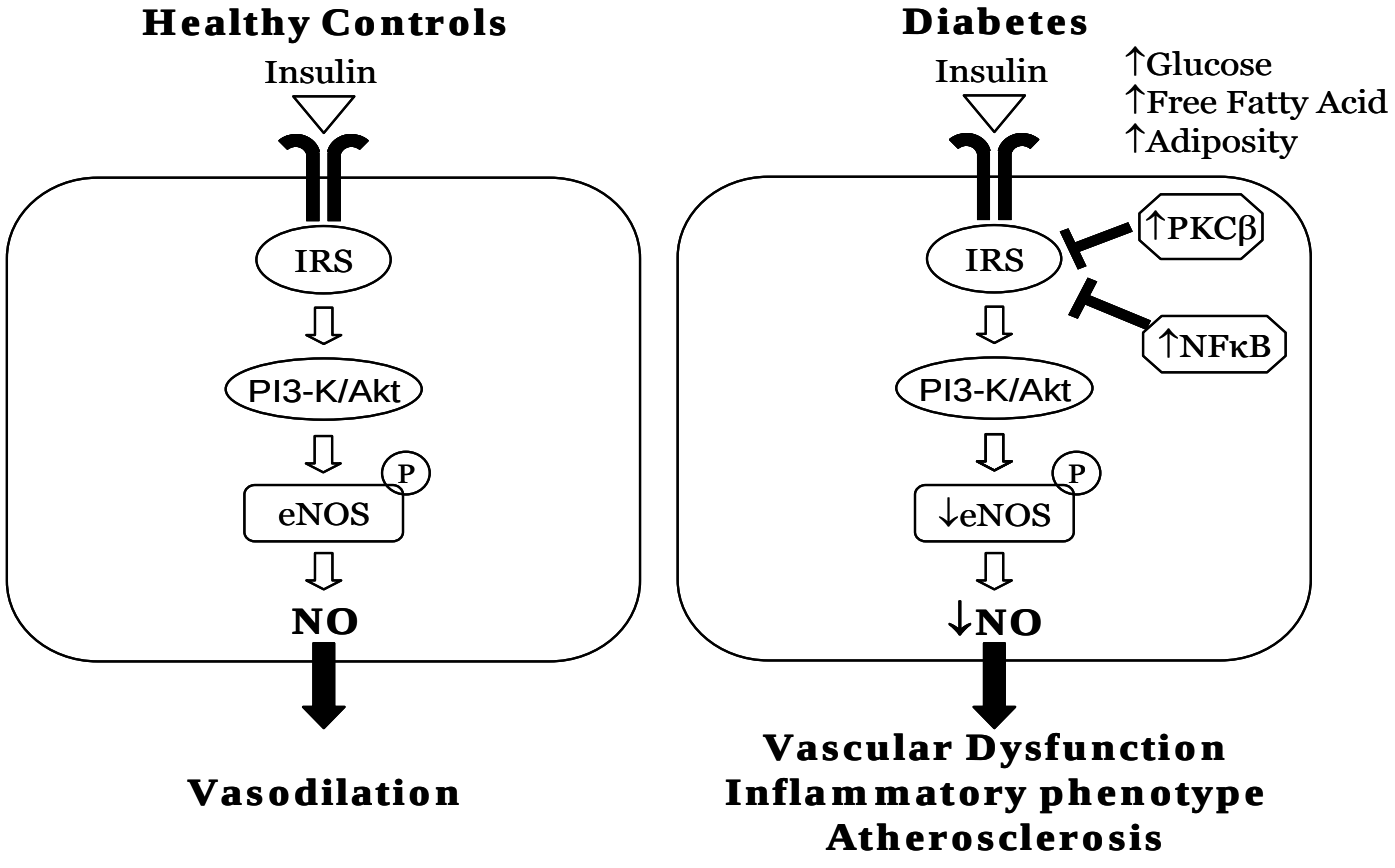
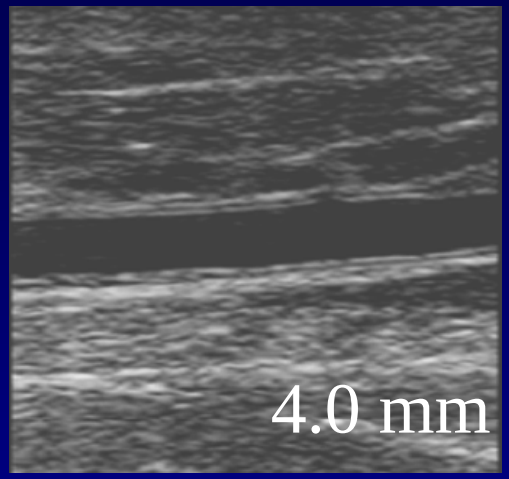
Working Hypothesis

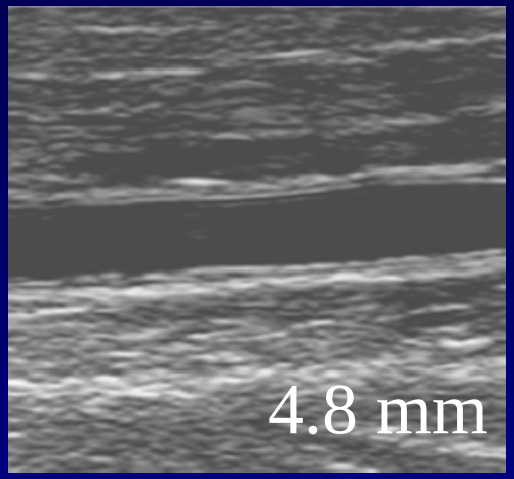


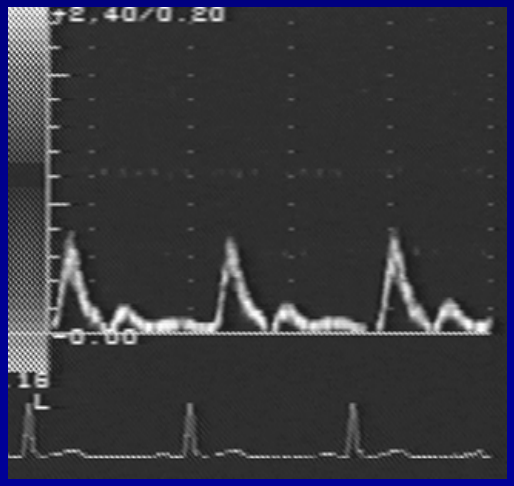
Endothelial Insulin Resistance

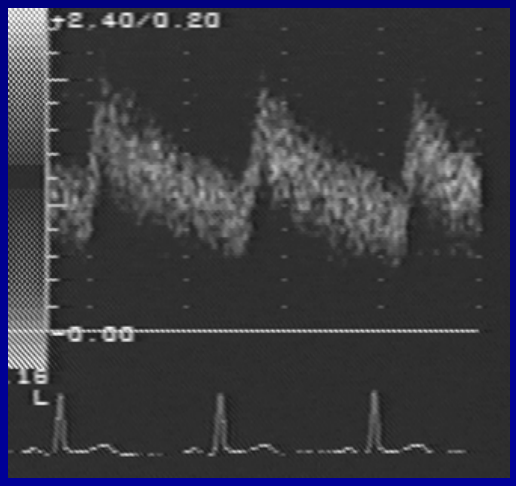


Ultrasound Evaluation of Brachial Artery Endothelial Function









Baseline

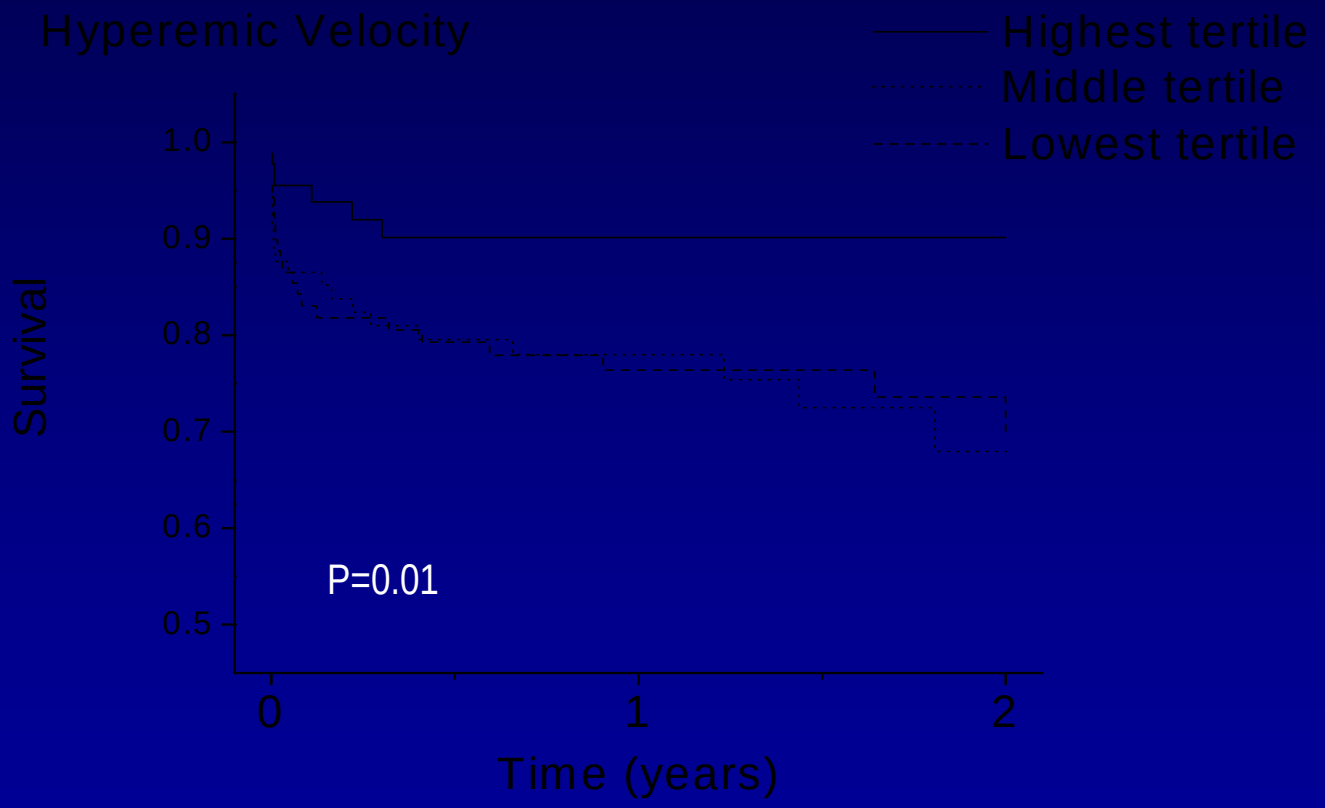
Hyperemia

Reactive Hyperemia Predicts CVD Events

N=267 patients undergoing vascular surgery

Adjusted hazard ratio 2.7 (1.2-5.9)

Risk factors and FMD



Huang et al. ATVB 2008