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OMICS Journal of Radiology

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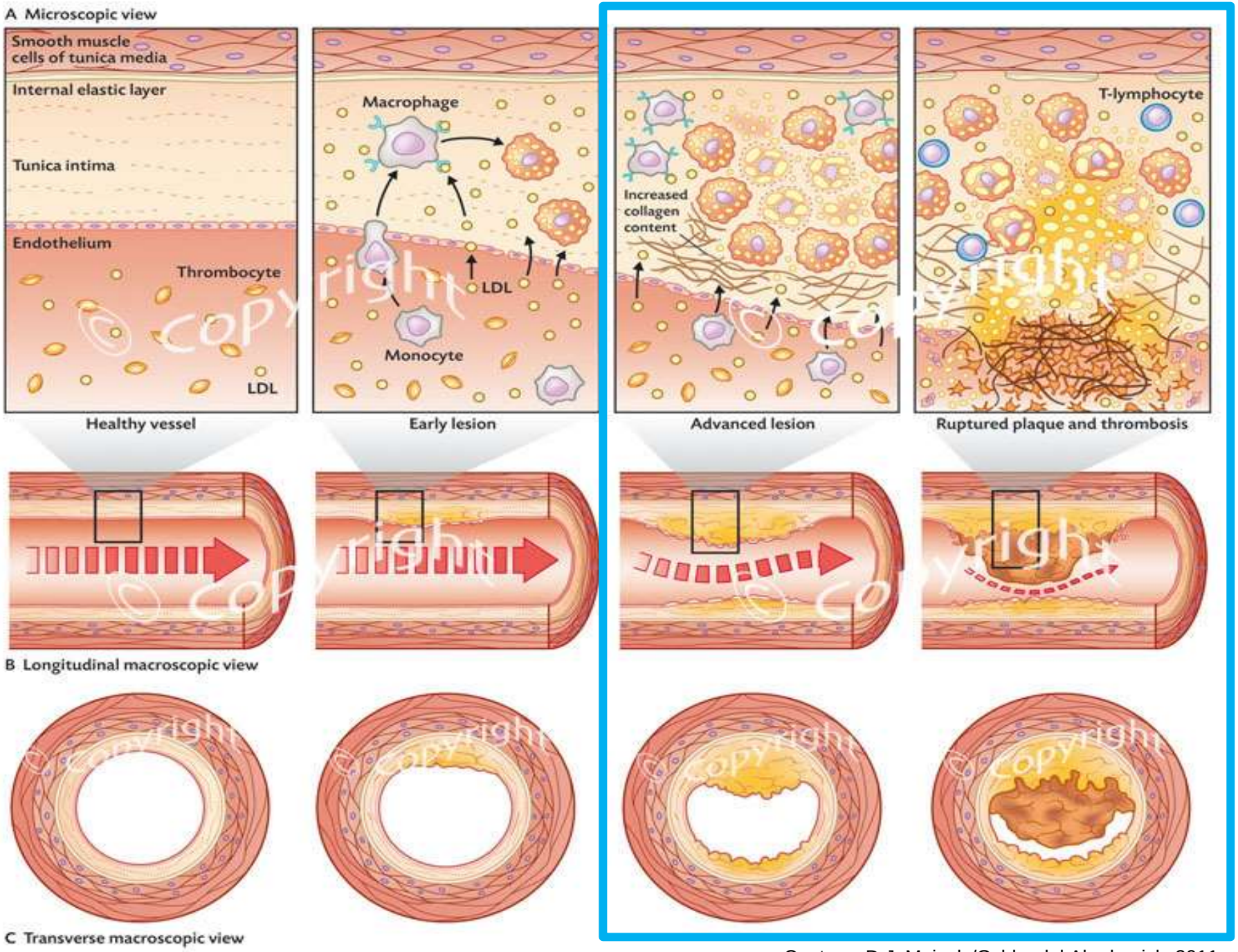
Imaging atherosclerosis

Dr. Christopher Lai

The Hong Kong Polytechnic University

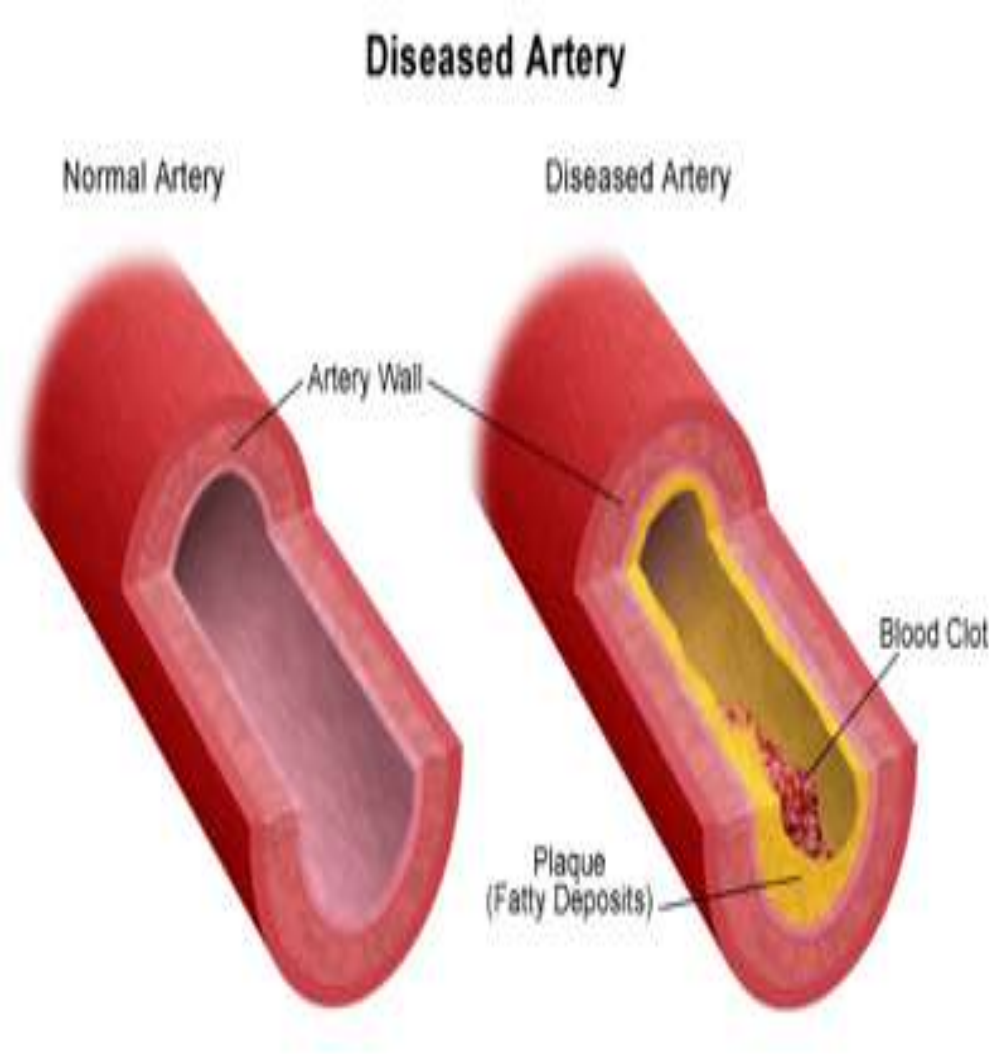
My research profile

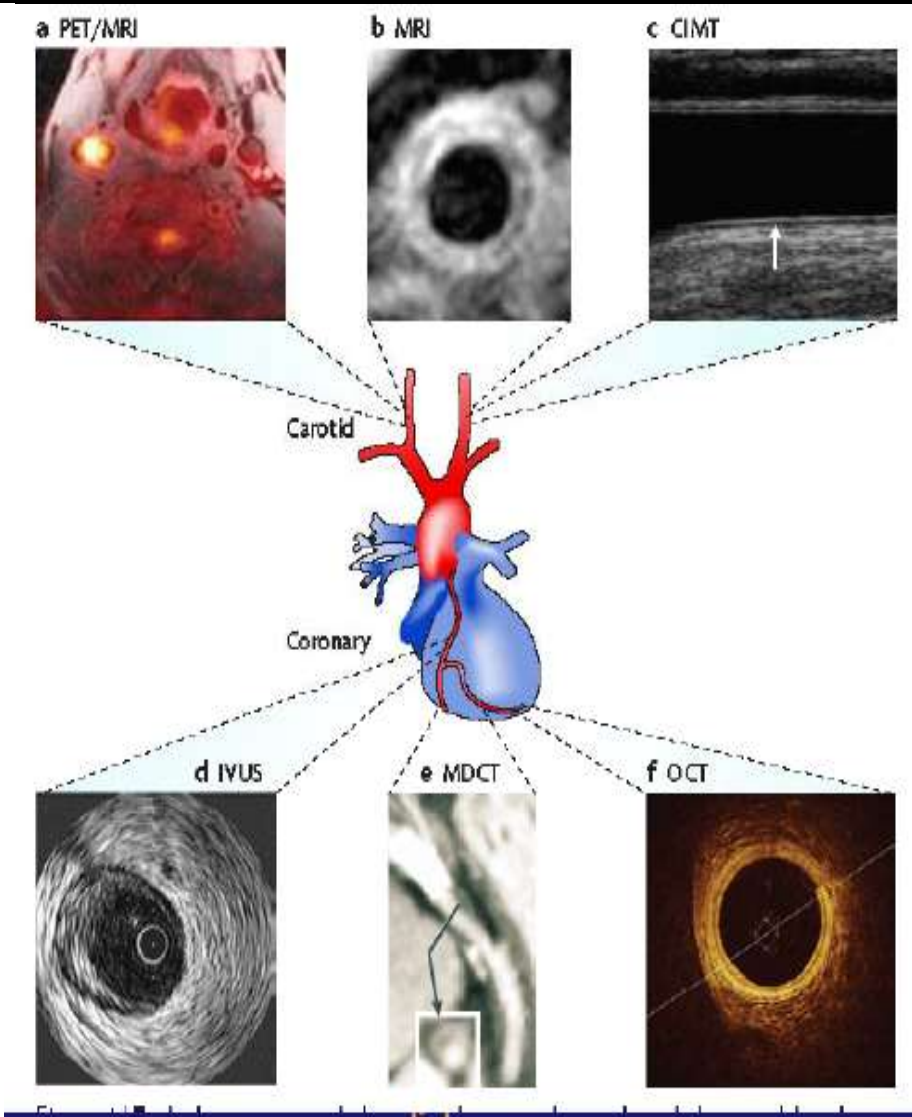
1. Imaging Atherosclerosis
2. Identification of new imaging probes
3. Radiation Protection
4. Upper limb functional imaging related to daily activities



Coutesy: D.J. Maizels/Gyldendal Akademisk, 2011

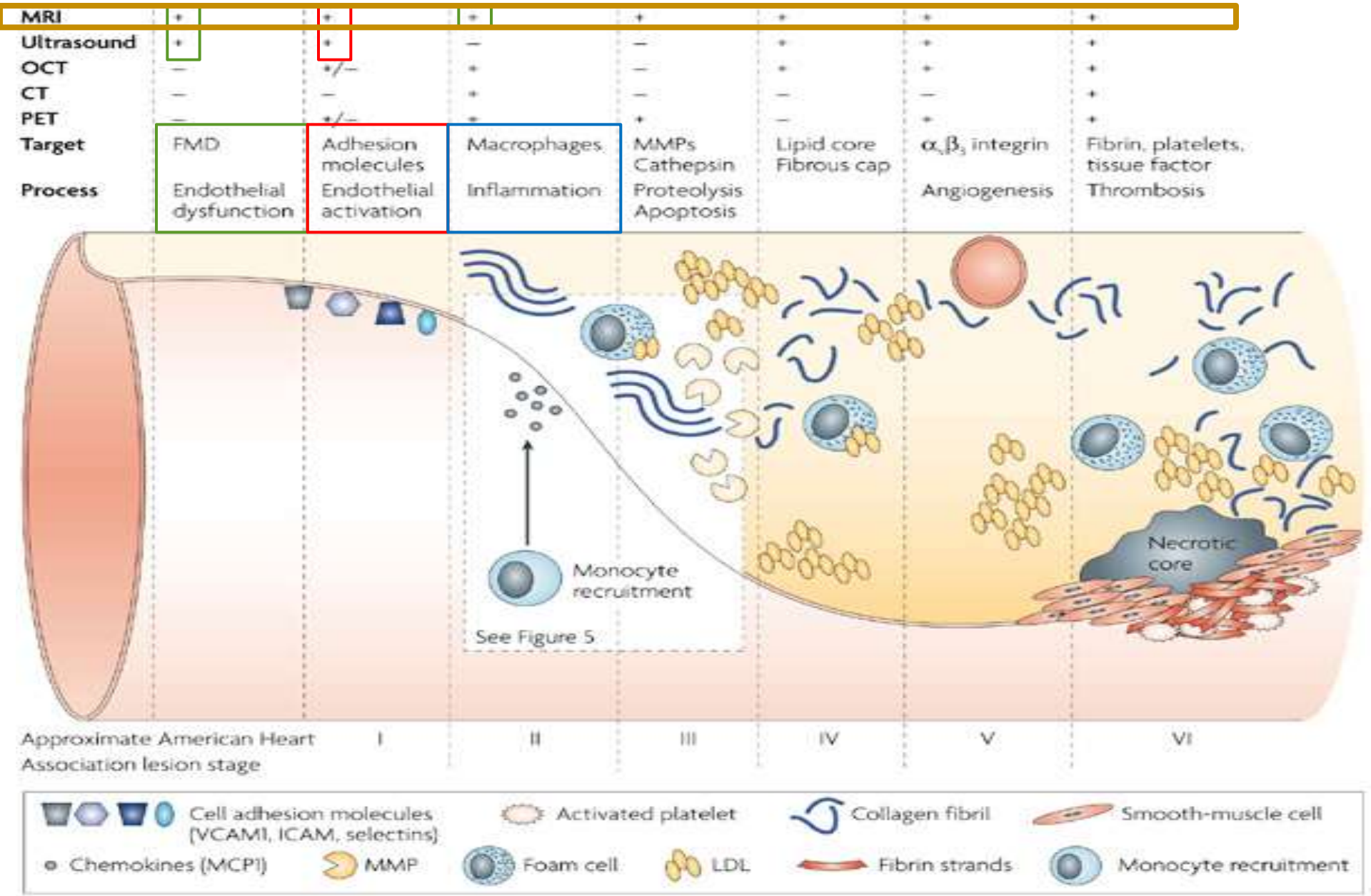
Clinical detection of plaque and stenosis





Lindsay and Choudhury, Nature Rev Drug: Disc 7: 517 2008

Pre-clinical and sub-clinical detection of atherosclerosis



Impaired Endothelial cells encourage the secretion of various molecules

A glycoprotein involved in haemostasis

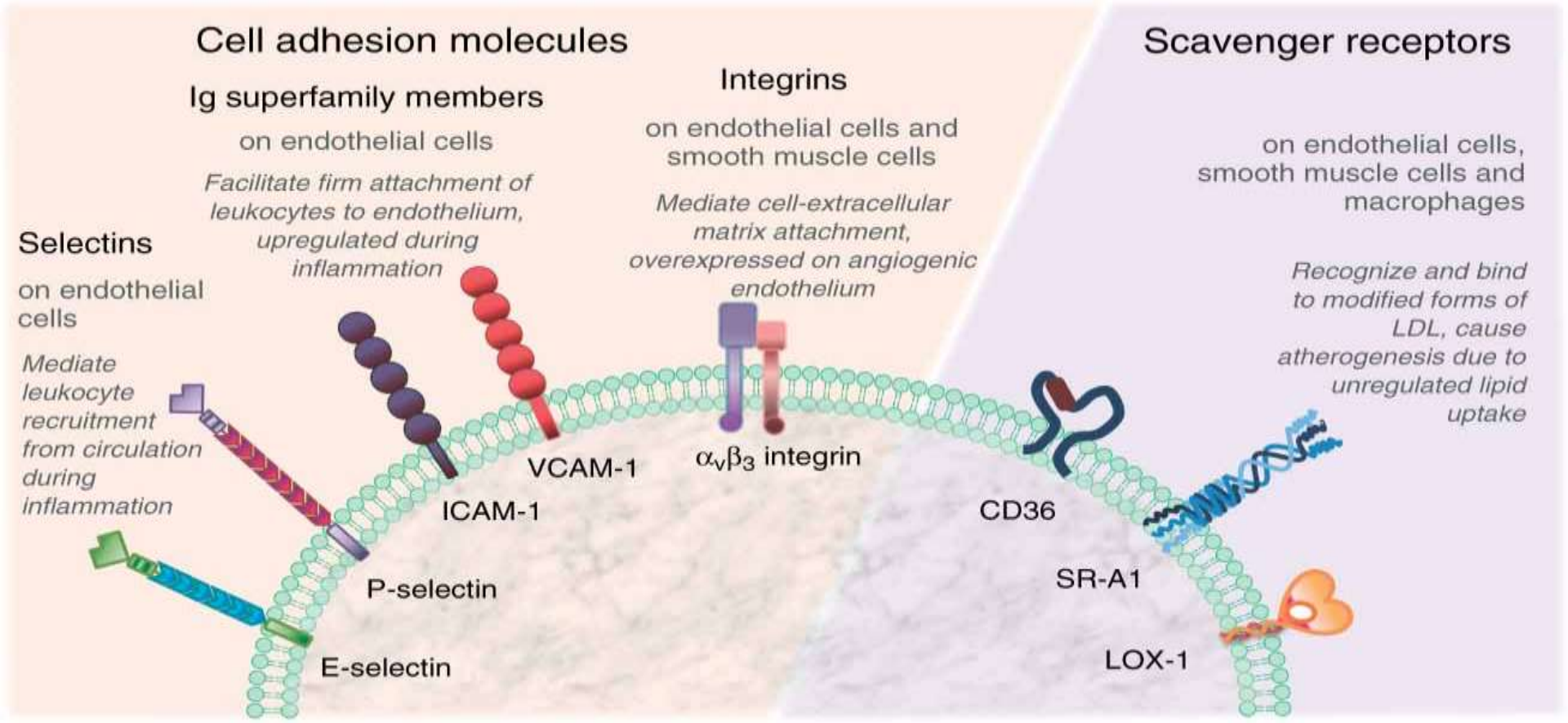
- Von willebrand factor (Mannucci PM et al, 1998)

Markers of Inflammations

- C-reactive protein
- Cytokines

Upregulated adhesion molecules and selectin

- Intracellular adhesion molecule-1 (ICAM-1)
- Vascular cell adhesion molecule-1 (VCAM-1)
- E- or P- Selectin



Vascular endothelium

In response to various
insults (oxidative stress)
promote endothelial dysfunction

- Vasomotor tone
- Thrombosis
- Haemostasis

Initiate step in atherosclerosis

- coronary arteries
- peripheral conduit arteries

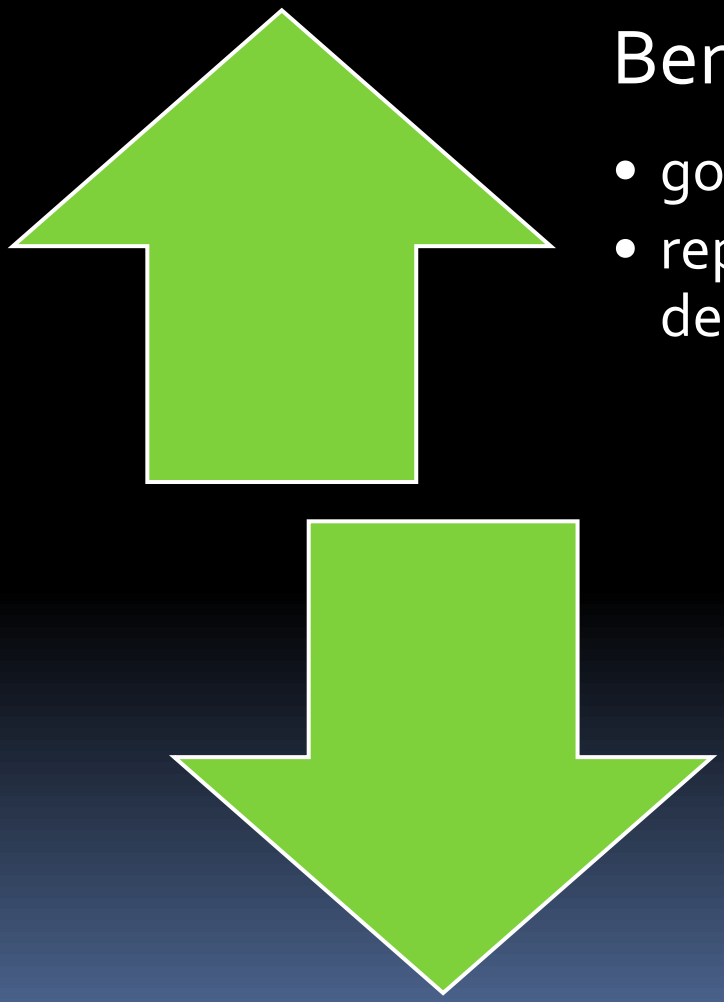
ED found important

- advanced atherosclerosis subjects
- asymptomatic subjects

Forearm blood flow (Strain-gauge plethysmography)

- 1990: Panza and co-workers
- Resistance vessel reactivity in response to pharmacological or physiological stimuli
- FBF is measured by temporarily occluding the venous return (by a cuff inflated to 40 mmHg) and measured the slight swelling of the distal portion of the limb due to pharmacological or physiological stimuli

Forearm blood flow (Strain-gauge plethysmography)



Benefits

- good sensitivity and specificity
- reproducible and less observer dependent

Drawback

- relatively invasive
- cannot examine large vessel physiology which is more relevant to vascular disease

Flow Mediated Dilation

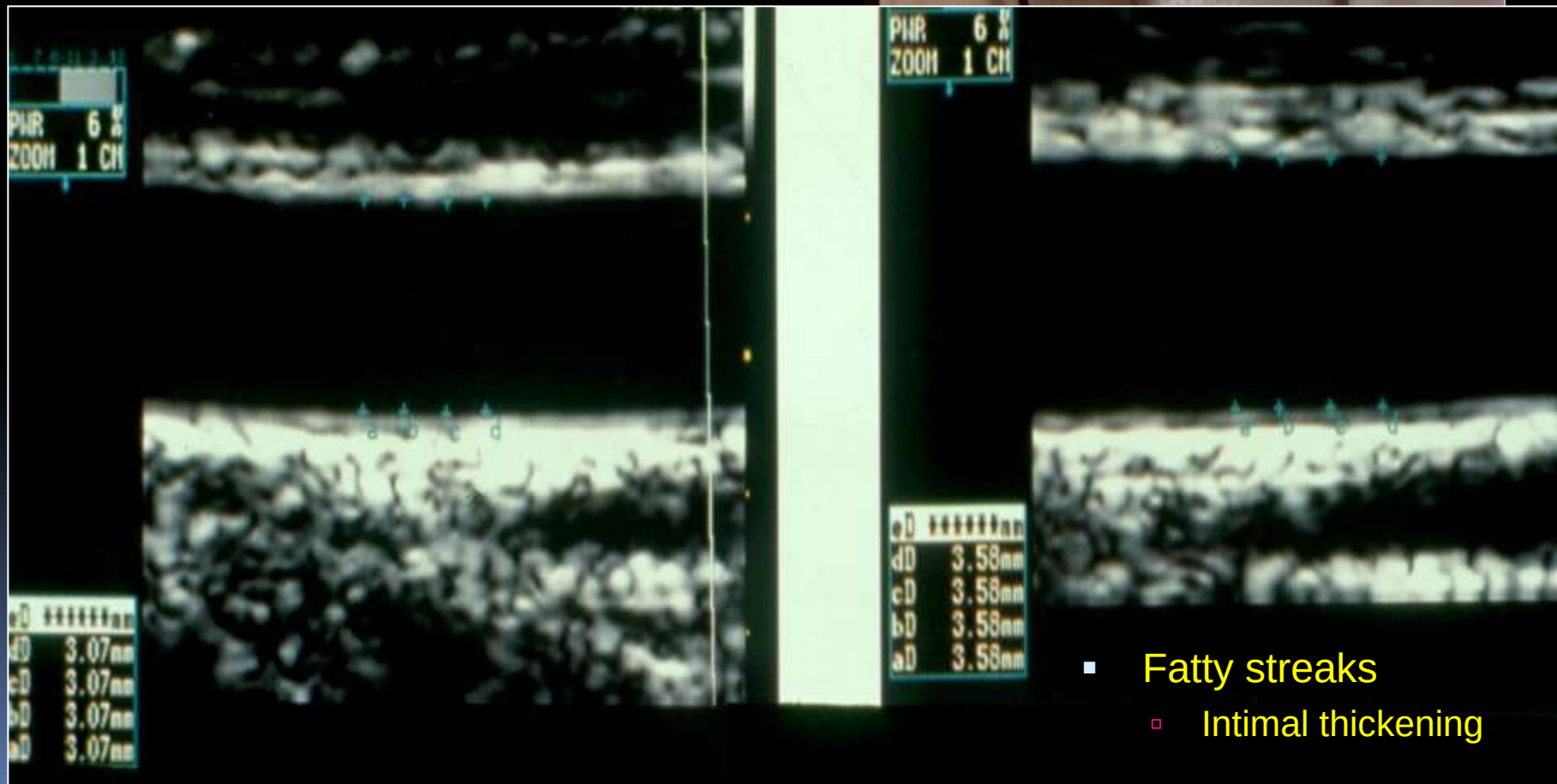
Brachial flow-mediated dilation(FMD)

- 1989: Anderson and co-workers
- a validated non-invasive measure of endothelial function
- Surrogate Marker for CHD
- measurement of changes up to 0.1mm in arterial diameter

Impaired FMD :

- subjects with overt vascular disease
- subjects with cardiovascular risk factors even in asymptomatic subjects
- diabetic patients

The Setup

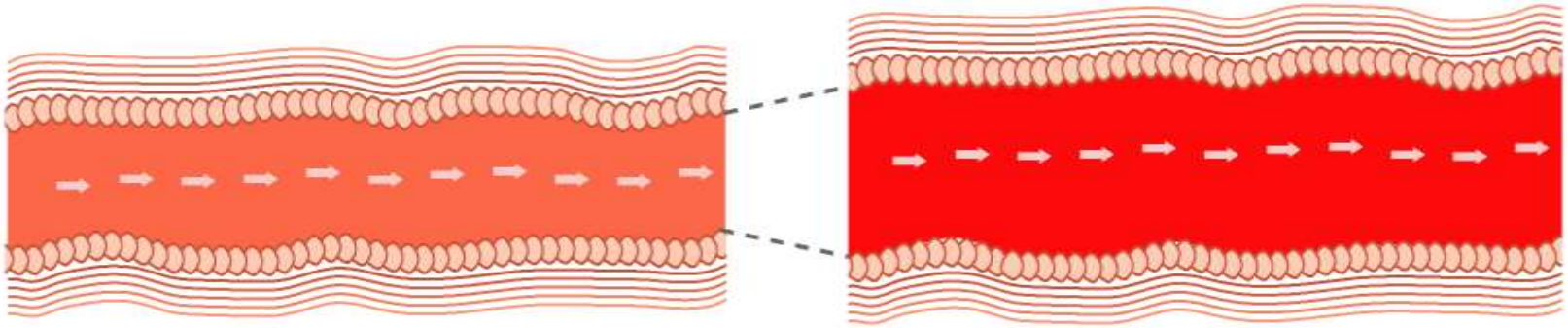


- Fatty streaks
  - Intimal thickening

Healthy endothelium mediated vasodilation

Normal flow conditions

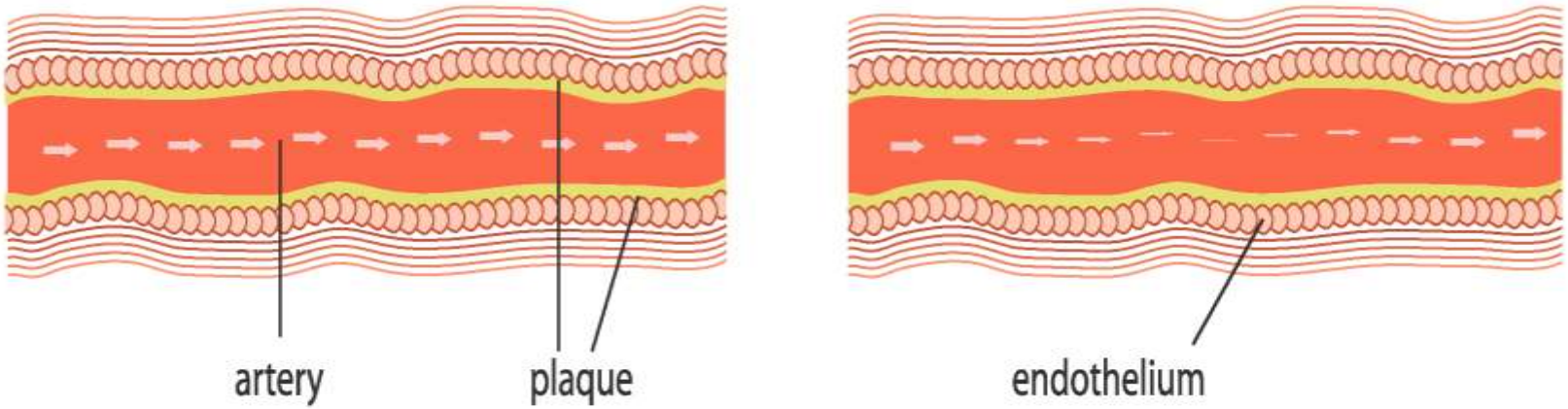
Increased flow conditions



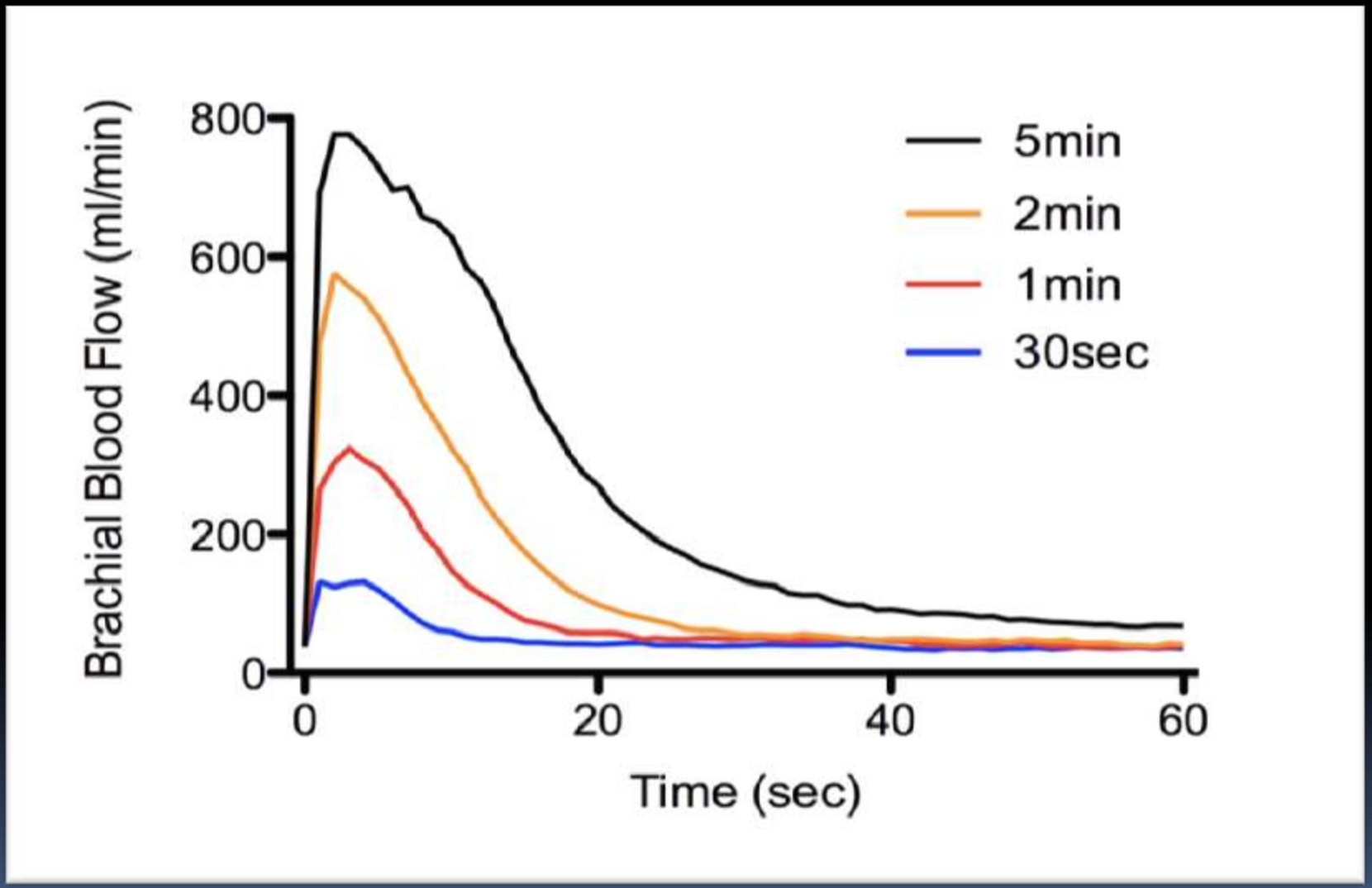
Impaired endothelium mediated vasodilation

Normal flow conditions

Increased flow conditions



Reactive Hyperemia

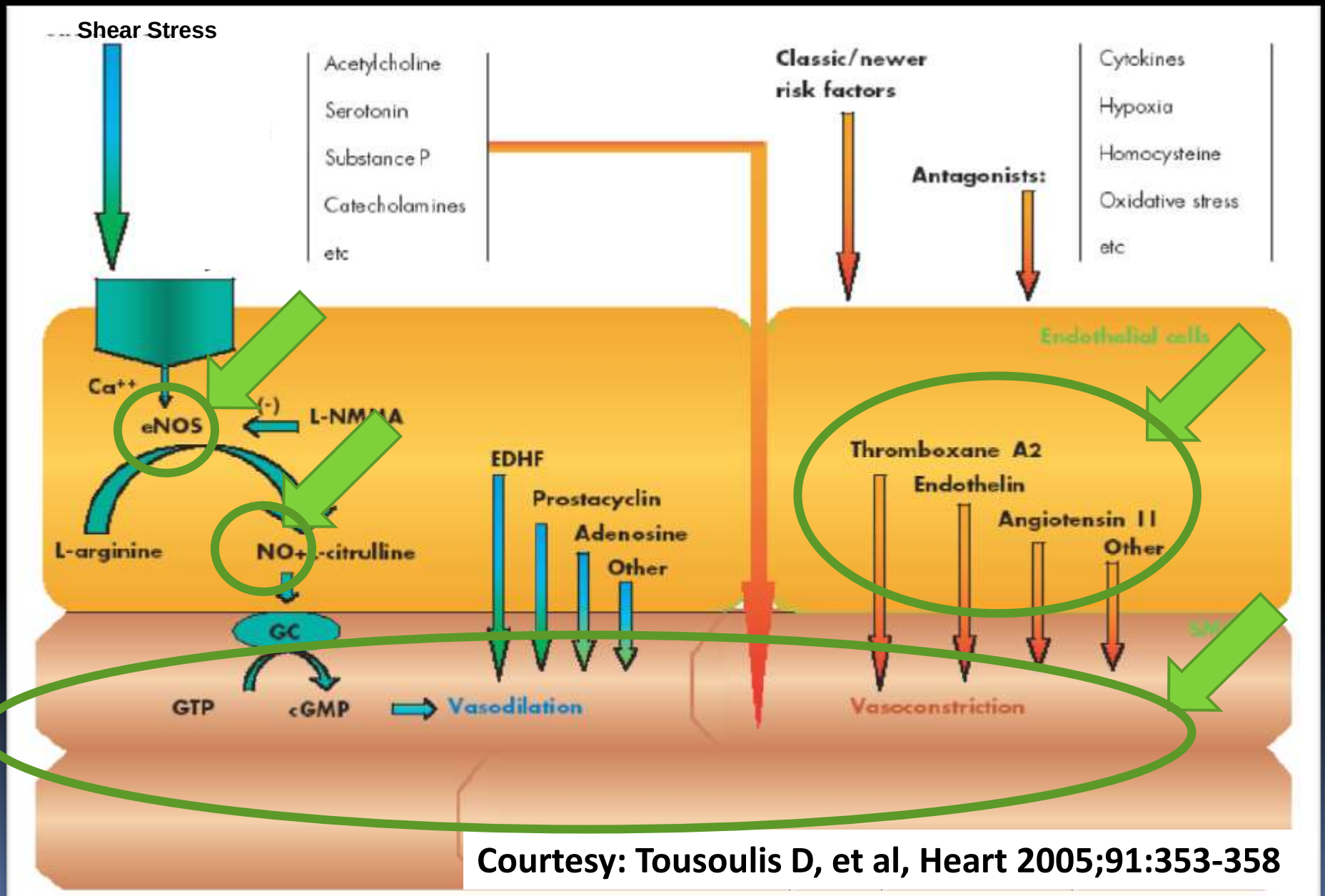


From Clifford et al. *FASEB J*. 24: 804.12, 2010.

The Examination

- Placement of Cuff at forearm
- Locate the brachial artery by color flow and pulsed Doppler
- Inflate and then deflate the cuff
- Hyperemic flow generated
- Monitor the lumen diameter continuously
- Offline measurement with computer aids

Factors influence the resultant vessel dilatation



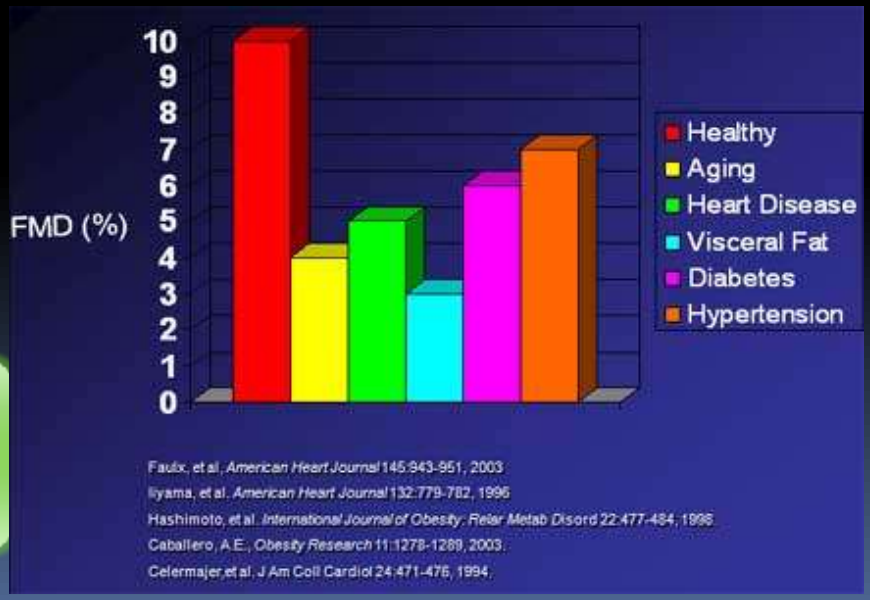
Courtesy: Tousoulis D, et al, Heart 2005;91:353-358

Factors induce vascular dilatation impairment

- Dysfunction in NO production in the endothelial cells (e.g. deficiency of NOS co-factor)
- Over production of endogenous inhibitors of NOS
- Reduced NO bioavailability
- VSMC insensitivity to NO
- Dysfunction of VSMC

FMD was proposed as a new tests for evaluating endothelial function

Cost-effective, reproducible and standardization	Ability to predict risk and relationship to established tests of risk.	Can identify individual patients •predict a reduction in the risk of clinical events.	Useful as a screen for drug development.



Research / clinical Application

FMD was proposed as a new tests for evaluating endothelial function (surrogate marker)

Cost-effective, reproducible and standardization	Ability to predict risk and relationship to established tests of risk.	Can identify individual patients • predict a reduction in the risk of clinical events.	Useful as a screen for drug development.

http://www.kidney-international.org

Vascular defect beyond the endothelium in type II diabetic patients with overt nephropathy and moderate renal insufficiency

WB Chan[1], NN Chan[1], CWK Lai[2], WY So[1], MKW Lo[1], KF Lee[1], CC Chow[1], C Metreweli[3] and JCN Chan[1]

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- In Chinese subjects with type 2 diabetes, hyperglycaemia, hypertriglyceridemia, smoking and albuminuria were independent predictors for endothelial dysfunction
- Type 2 diabetic subjects with overt nephropathy had impaired endothelium-dependent and endothelium-independent dilatation, suggesting vascular dysfunction beyond the endothelium.
- In agreement with studies from Caucasians, smoking was the most important determinant for vascular dysfunction in Chinese type 2 diabetic patients with overt nephropathy.
- Furthermore, FMD was predictive of new onset of cardiovascular events and related death in Chinese type 2 diabetic patients with overt nephropathy.

My study……

Recruitment

- Invite those relatives of diabetes patients whom follow up at the diabetic mellitus and endocrine clinic at the Prince of Wales Hospital
- at least 40 years old (middle-aged Chinese)
- No previous diagnosis for diabetes
- No previous diagnosis for any cardiovascular disease
- Not taking any kind of long-term medications except hypertensive drugs

Demographic N=52

Age (y)	Male Sex	Height M)	Weight (Kg)	BMI
55y±8	32(62%)	1.59±8.3	59.3±8.9	23.6±2.5

Waist Circumference (cm)	Hip Circumference (cm)	WHR	With regular exercise	Smoker
82.8±9.7	97.4±13.3	0.86±0.08	35 (67%)	19 (37%)

Systolic BP (mmHg)	Diastolic BP (mmHg)	Mean BP (mmHg)	Hypertension
126 ± 21	83±10	98±13	6 (12%)

Total Cholesterol (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	TG (mmol/L)	Glucose (mmol/L)
5.5±0.9	1.49±0.34	3.0±0.90	1.40±0.68	5.1±1.2

Measurement

Carotid Artery:

- Intima-media Thickness (IMT)

Brachial artery:

- Timed-averaged velocity (TAV)
  - % change in brahcial blood flow velocity
- % change in brachial blood flow volume (Q)
  - $Q=TAV(\pi r^2)$
- FMD
  - % change in Lumen diameter

Results

Carotid IMT (mm)	0.74±0.23
% change in Brachial blood flow Volume (%)	554±195
Flow Mediated Dilation (FMD%) (endothelium dependant)	4.54±2.26
Glycerin Tri-nitrate Induced Dilation (GTND%) (endothelium independent)	14.3±3.77
FMD/GTND ratio	0.32±0.15

Main findings

*=p<0.05, **=p<0.01

Spearman's Correlation coefficients with FMD	
Age	- 0.343*
Waist circumference	-0.363*
BMI	-0.313*
Carotid IMT	-0.349*
Systolic BP	-0.233
Diastolic BP	-0.143
Glucose	-0.290
TC	-0.290
HDL	0.206
LDL	-0.127
TG	-0.529**

Available online at www.sciencedirect.com
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Diabetes Research and Clinical Practice 64 (2004) 93–98
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Increased leptin concentrations and lack of gender difference in Type 2 diabetic patients with nephropathy

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Accepted 28 October 2003

- Leptin plays an important role in the regulation of body weight and energy balance
  - women have higher circulating leptin level than men.
- However, the present study demonstrate that:
  - Serum leptin concentrations were higher in Type 2 diabetic patients with nephropathy than normoalbuminuric diabetic patients and controls.
- Finding:
  - Diabetic men with nephropathy had proportionally higher serum leptin such that the gender difference in leptin observed in non-nephropathic individuals was abolished.

Further study using MRI

Table 15.1 Types of nanoparticles that have been used for MRI molecular imaging of atherosclerosis

Class of agent	Nanoparticle type	Diameter	Targeting moiety	Target
Iron oxide nanoparticle (superparamagnetic)	USPIO	~20 nm	None	Macrophage [5]
	CLIO	~40 nm	Peptide	VCAM (activated endothelium) [4]
	SPIO	~100 nm	None	Macrophage
	MPIO	~5 μm	Antibody	Platelets [6]
Lipid-based nanostructure (paramagnetic)	HDL mimic	~15 nm	None	Areas of HDL trafficking [7]
	Micelle	~20 nm	Peptide, antibody, hydrophobic tyrosine residues	Oxidation [8], macrophages [9] lipid-rich areas [10]
	Liposome	80–500 nm		
	PFC emulsion	~200 nm	Peptide, antibody	$\alpha_v\beta_3$ integrin [11] fibrin [12]

1

2

J.C. Carr and T.J. Carroll (eds.), *Magnetic Resonance Angiography: Principles and Applications, 199* DOI 10.1007/978-1-4419-1686-0_15

1. MR imaging of lipid-rich plaques
   - •Gadofluorine : Macrocyclic Gd chelate (diameter 5 nm)
   - •T1W MR imaging in atherosclerotic NZW rabbits at 1.5 T
   - •Successful targeting of lipid-rich plaques
   - •Successful differentiation between early and advanced plaques
2. MR imaging of fibrin
   - •EP-1873 : fibrin-binding peptide coupled to 4 Gd chelates
   - •T1W MR imaging of plaque rupture in atherosclerotic NZW rabbits
   - •Successful targeting of thrombus in ruptured atherosclerotic plaques

Further study using Ultrasound

Table 3. Molecular targets utilized in in vivo studies for stage-specific visualization of plaque progression.

AHA stage	Characteristic	Molecular target (location)	Ligand	NP	Imaging modality
I	Activated endothelium	VCAM-1 (luminal)	Peptide sequence (not specified)	^{123}I or ^{99m}Tc	Nuclear
	1	VCAM-1 (luminal)	Antibodies	- Magneto-optical nanoparticles	- Optical
				- Microbubbles	- Ultrasound
				- Iron oxide particles	- MRI
		VCAM-1 (luminal)	Peptide sequence VHSPNKK	Magnetofluorescent NPs	Optical and MRI
		VCAM-1 (luminal)	Peptide sequence VHPKQHR	Magnetofluorescent NP	Optical and MRI
		P-selectin (luminal)	Antibodies	- Iron oxide NPs	- MRI
				- Microbubbles	- Ultrasound
II/III	Macrophages/ Inflammation	MMPs (sub-endothelial)	Peptide sequence GGPRQITAG	Near infrared probe	Optical
		Cathepsin K (sub-endothelial)	Peptide sequence GHPGGPQKC	Near infrared probe	Optical
	2	Macrophage Scavenger Receptor (CD204) (sub-endothelial)	Antibodies	Immunomicelles	Optical and MRI Ultrasound
		P2 receptors or adenosine nucleotide receptors (sub-endothelial)	Adenosine nucleotides	^{18}F	Nuclear
		Glucose transporters (sub-endothelial)	FDG	^{18}F	Nuclear

Radiology

Radiology: Volume 260: Number 2—August 2011

Efficacy of Contrast-enhanced US and Magnetic Microbubbles Targeted to Vascular Cell Adhesion Molecule–1 for Molecular Imaging of Atherosclerosis[1]

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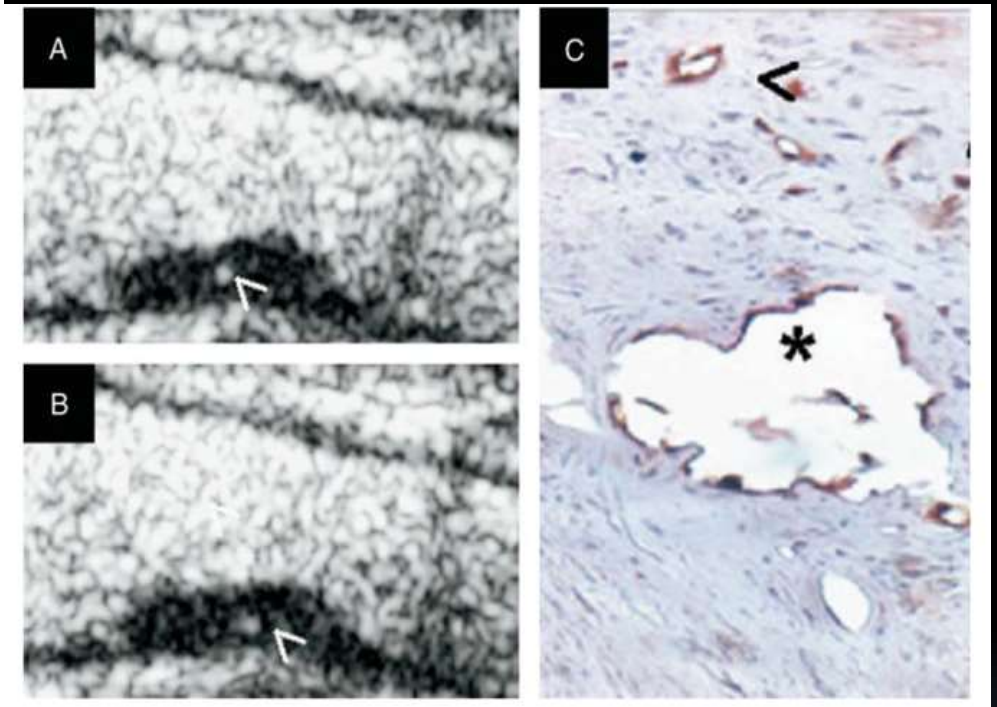
Purpose: To evaluate whether microbubbles targeted to vascular cell adhesion molecule-1 (VCAM-1) (CD106) coupled with a magnetic guidance system could improve the efficacy of contrast-enhanced molecular ultrasonography (US) of atherosclerosis in the aorta.

Materials and Methods: The animal research committee at Southern Medical University approved all experiments. Adherence of magnetic VCAM-1–targeted microbubbles, control inactive magnetic microbubbles, and nonmagnetic VCAM-1–targeted microbubbles to VCAM-1-Fc was determined in vitro by using a flow chamber at variable shear stress (1–24 dyne/cm^2) under magnetic field guidance. Attachment of microbubbles under magnetic field guidance was determined in vivo with fluorescent microscopy and contrast-enhanced US of the abdominal aorta in wild-type (C57BL/6) or apolipoprotein E (APOE)–deficient mice on a regular or hypercholesterolemic diet. General factorial analysis of variance was used to compare the targeted effect of the microbubbles among different animal groups to identify significant differences.

Conclusion:
Use of a magnetic targeted microbubble system results in greater attachment to endothelial VCAM-1 in atherosclerotic aorta in conditions of high shear stress and improved detection of early inflammatory changes of atherosclerosis.

Plaque neo-vascularisation detected by contrast-enhanced molecular ultrasound.



✓A and B : showing microbubles with the plaque
✓ C: immunohistological staining of the fibrous cap of the lesion imaged showing positive staining for CD31 corresponding to a large first-order neovessel (asterisk) and a smaller second-order neovessel (arrowhead)

Reproduced from Coli et al, Elsevier.

- Common ultrasound molecular imaging probes:
  - microbubbles
  - microparticles like echogenic liposomes
  - acoustically active nanoparticles
- Characteristic:
  - These particles are targeted to specific molecular structures present on the cell surface in the tissue of interest.
  - The concept of ultrasound molecular imaging is that, after intravenous injection,
    - these probes bind to disease-specific epitopes and can then be imaged noninvasively in real time.

1. Plaque composition
2. Arterial wall biomechanics
3. Plaque neo-vasuclarisation
4. Molecular imaging of vascular phenotype changes on a sub-cellular level

Ultrasound molecular imaging of atherosclerosis

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Time for primary review: 26 days

KEYWORDS
Atherosclerosis;
Ultrasound;
Contrast;
Molecular imaging

Recent advances in our understanding of the pathophysiological mechanisms of atherosclerosis have created the need for better non-invasive imaging of vascular phenotype. Ultrasound is widely available, inexpensive, and well suited for high-throughput screening in populations that are at risk for atherosclerosis. Novel ultrasonic approaches for the diagnosis of vascular changes in atherosclerosis include (1) assessment of plaque composition by evaluation of the backscattering properties of tissue, (2) assessment of the changes in arterial wall biomechanics, (3) assessment of plaque neovascularization, and (4) molecular imaging of vascular phenotype changes on a subcellular level. It is thought that such new imaging methodologies will lead to earlier detection of atherosclerosis, and better assessment of the risk for aggressive disease progression. Novel therapies for atherosclerosis will undoubtedly become available within the next decades, and non-invasive imaging techniques will be needed for cost-efficient application of existing and new drugs.

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