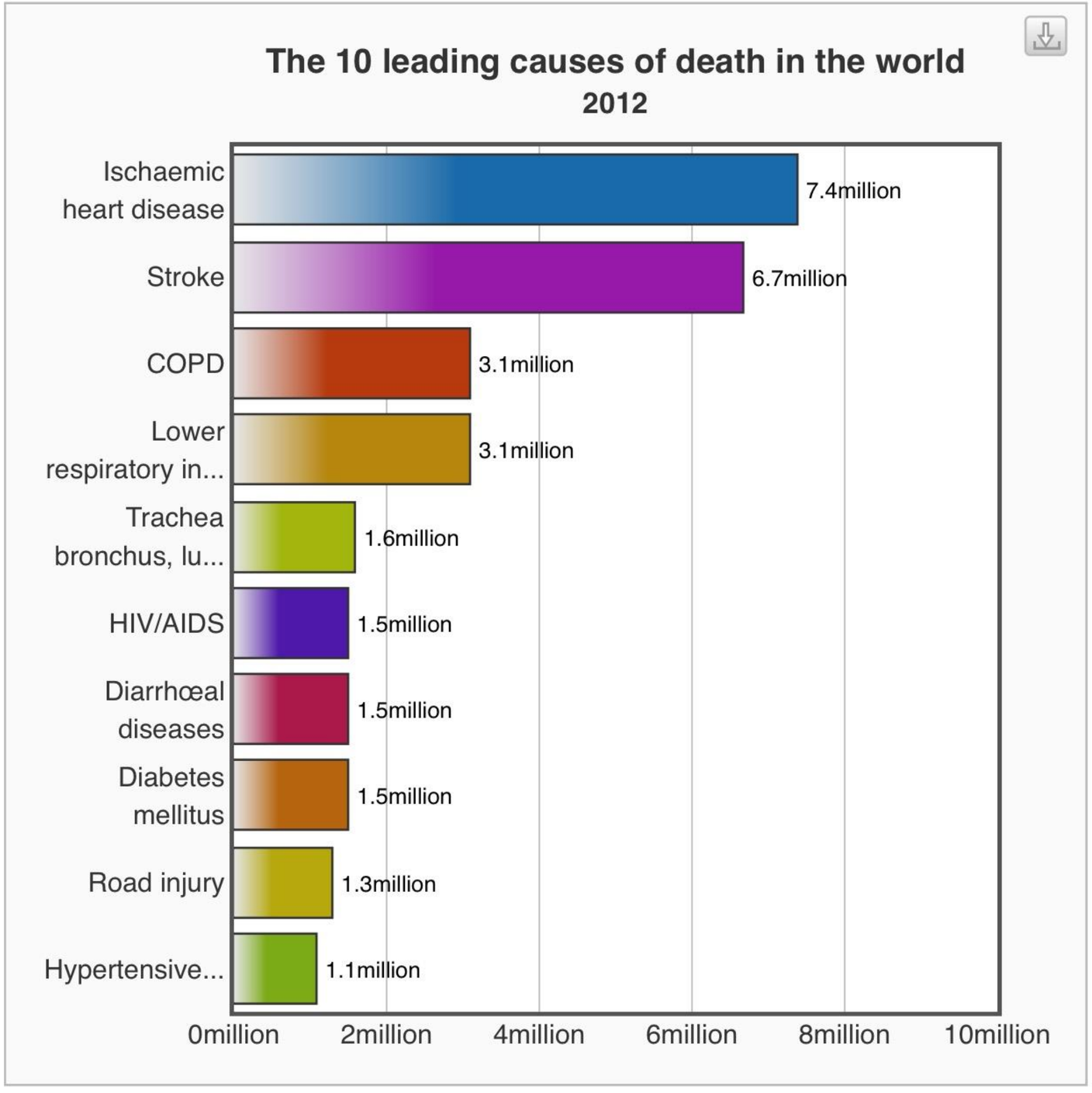
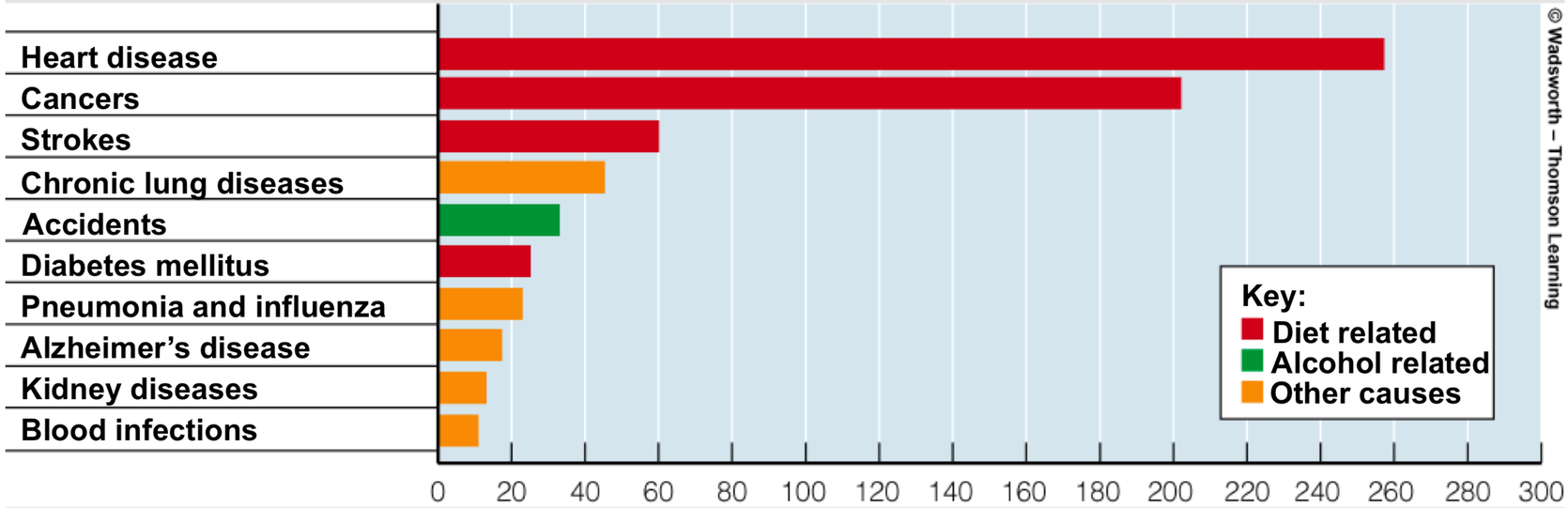

The 10 leading causes of death in the world
2012
Ischaemic heart disease
7.4million
Stroke
6.7million
COPD
3.1million
Lower respiratory in...
3.1million
Trachea bronchus, lu...
1.6million
HIV/AIDS
1.5million
Diarrhœal diseases
1.5million
Diabetes mellitus
1.5million
Road injury
1.3million
Hypertensive...
1.1million
0million
2million
4million
6million
8million
10million

Patho-biology of Atherosclerosis

The Ten Leading Causes of Death in the United States

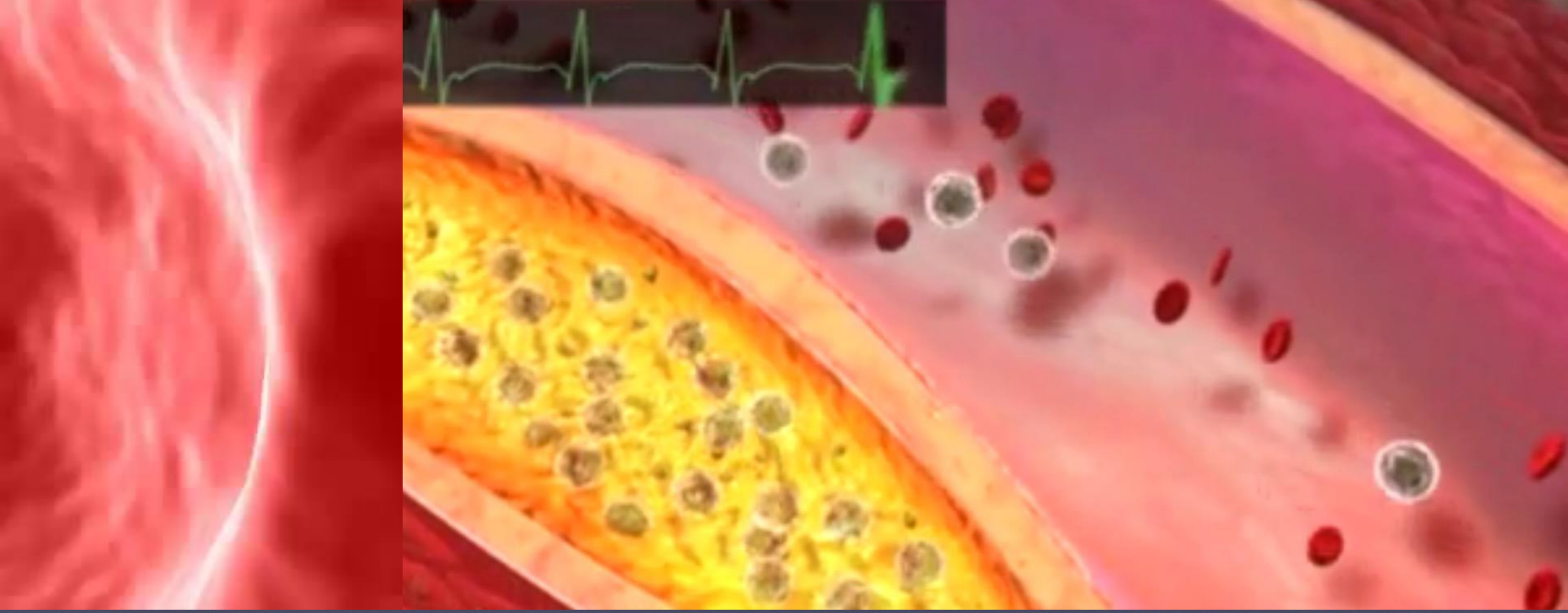


Cardiovascular Disease

- Coronary artery disease, stroke, and peripheral artery disease involve ***ATHEROSLEROSIS***
- Atherosclerosis - most common cause of CVD

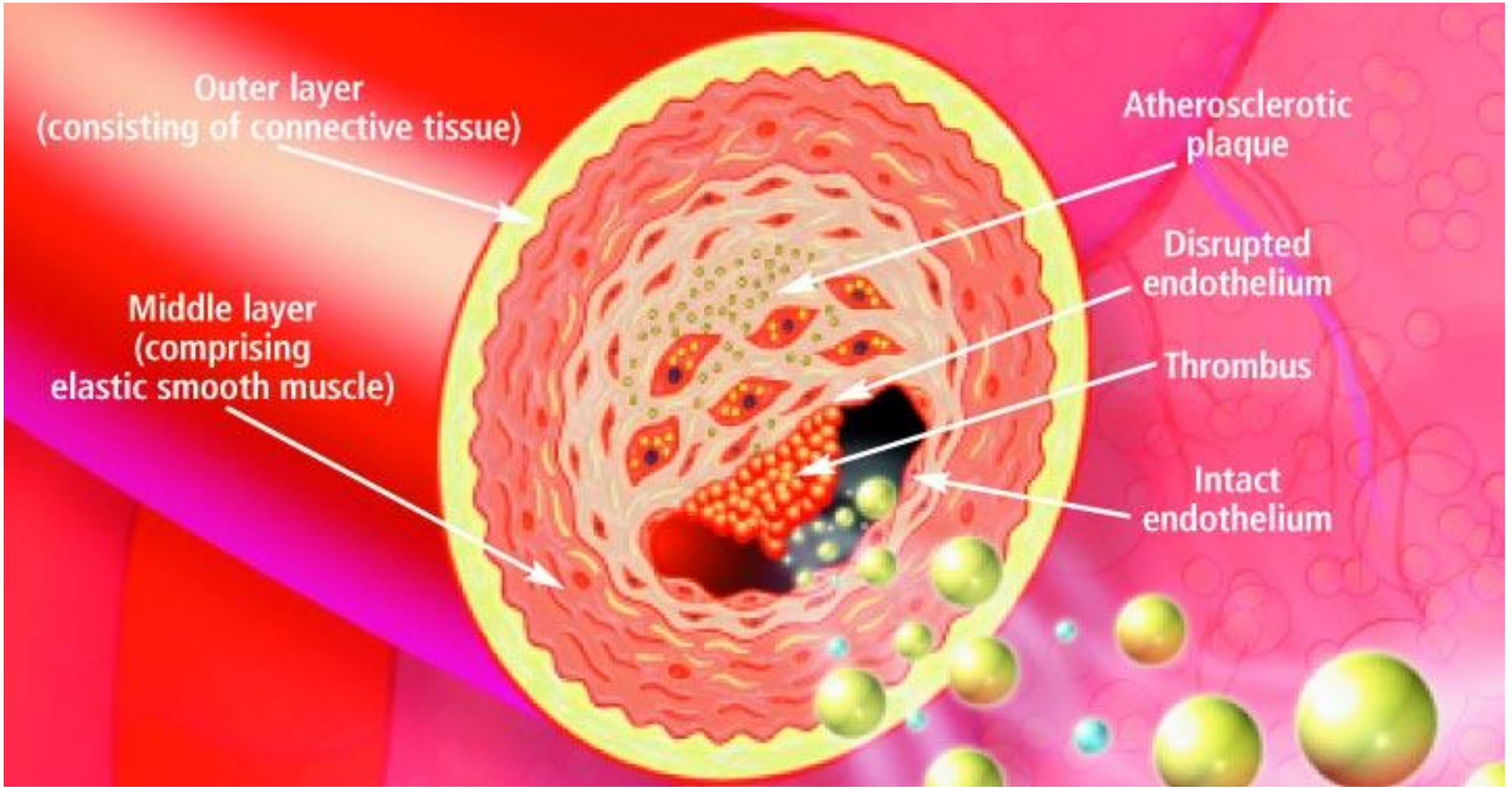
Cardiovascular Diseases

- **Arteriosclerosis** – loss of elasticity of the arteries; thickening and hardening of artery walls.
-
- **Atherosclerosis** – process where fatty material is deposited along walls of arteries. This material thickens, hardens, and can eventually block the artery. Atherosclerosis is just one type of Arteriosclerosis.



Pathobiology of Atheroslerosis

Pathobiology of Atheroslerosis

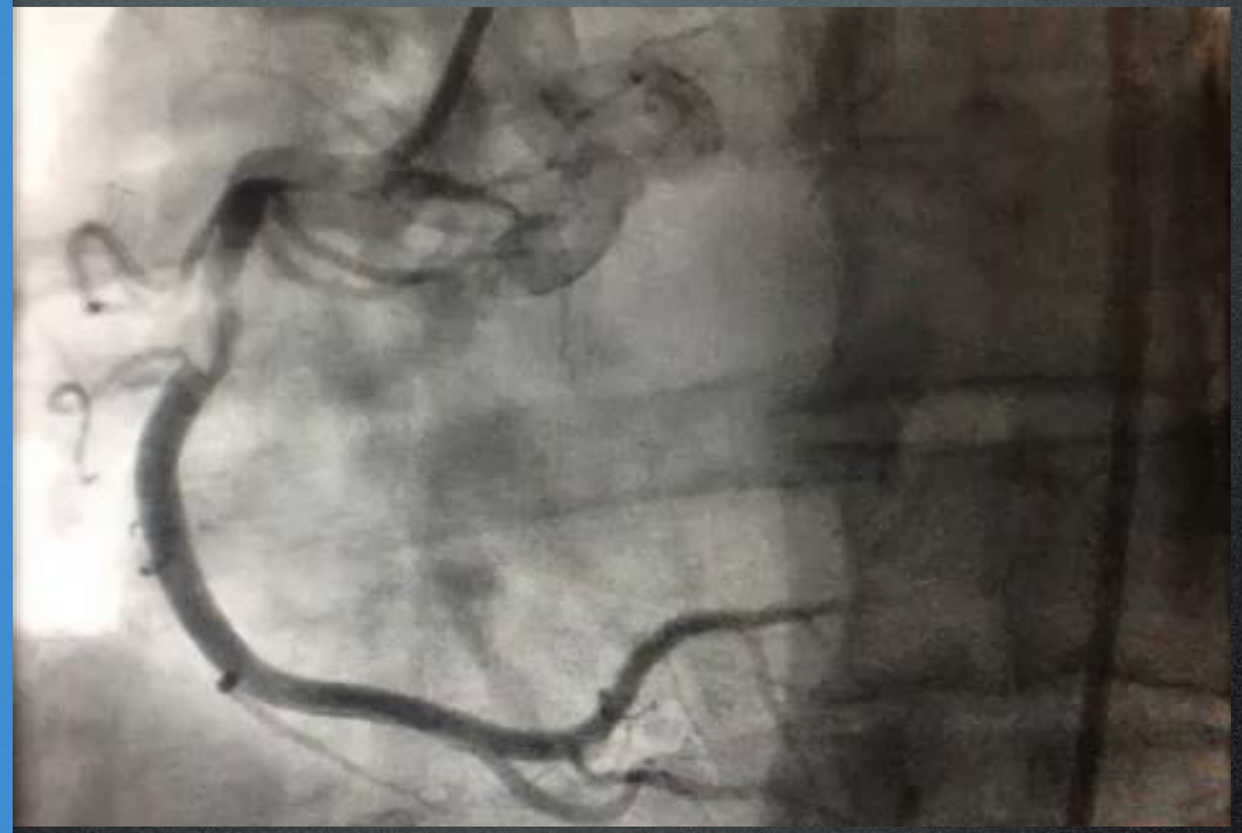


Atherosclerosis

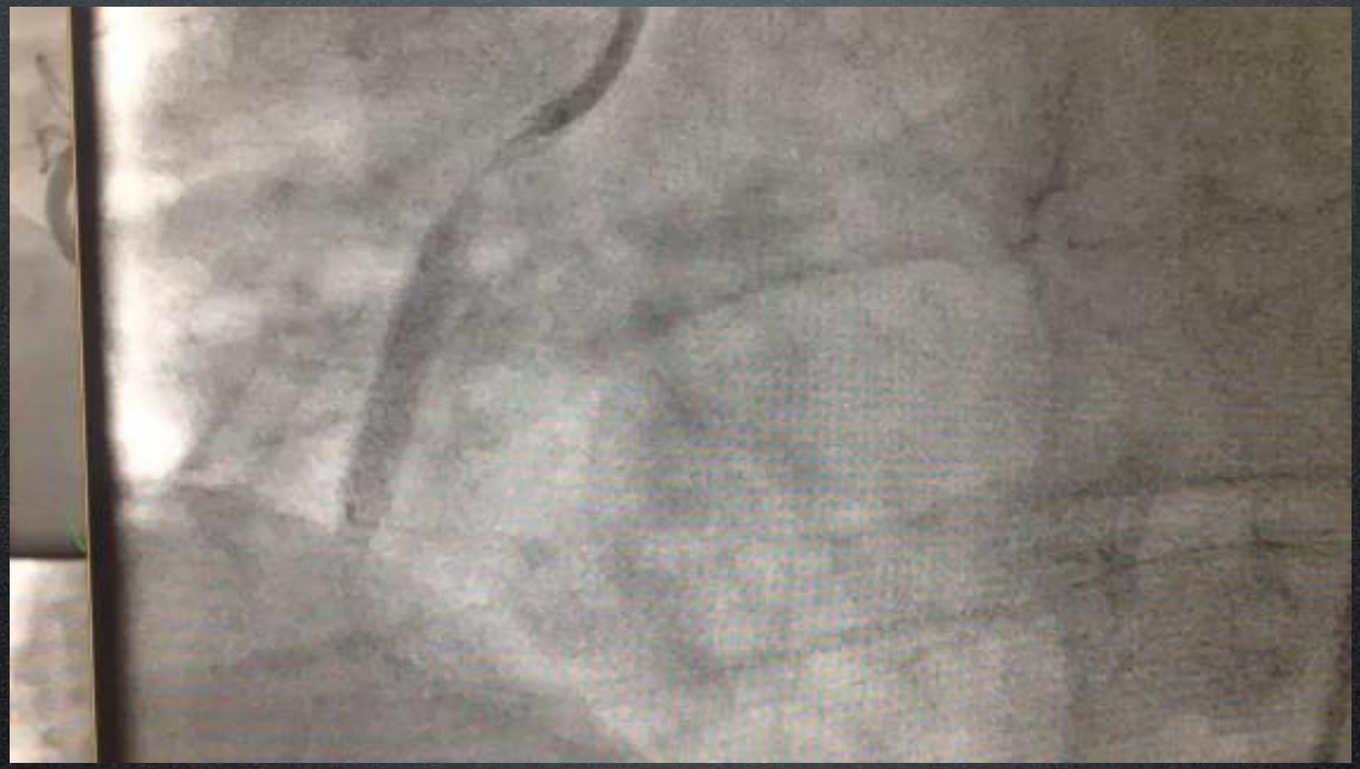
a disease of the arteries characterized by the deposition of plaques of fatty material on their inner walls.

Plaque - consists of cholesterol, lipids, calcium, white blood cells and clumps of platelets)

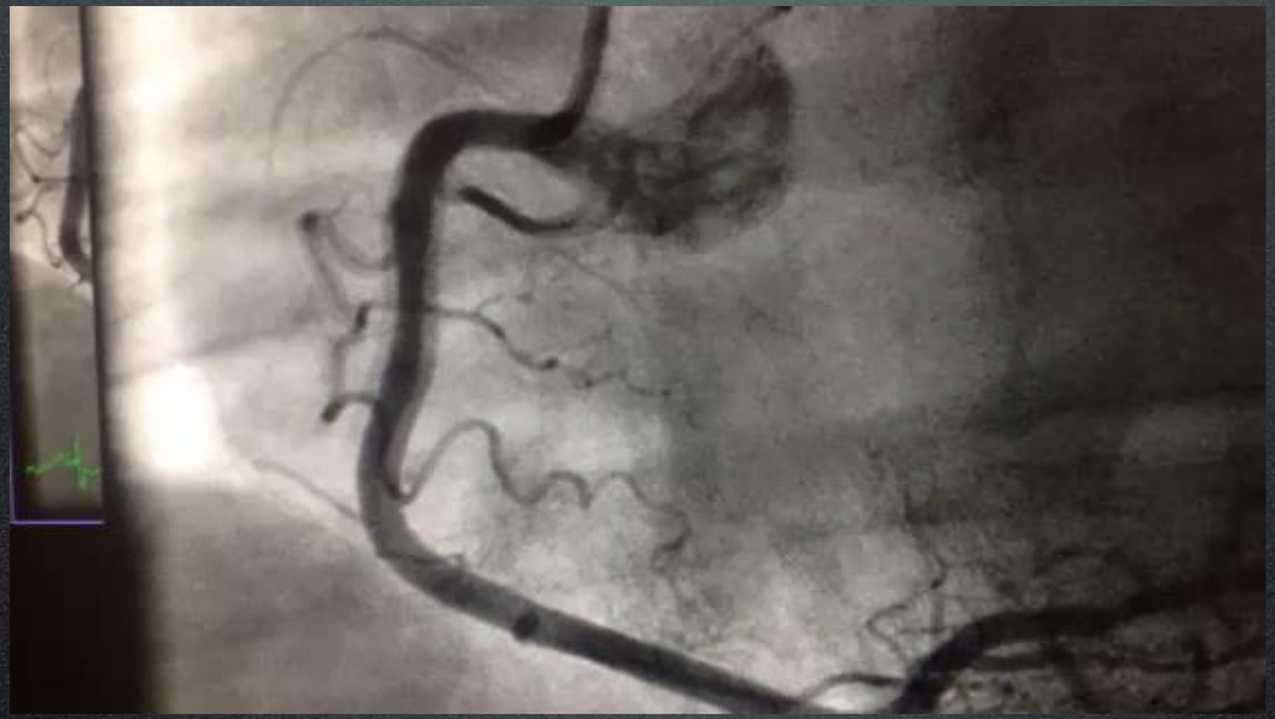
Health Span
40y/o Female



40y/o F



40y/o F



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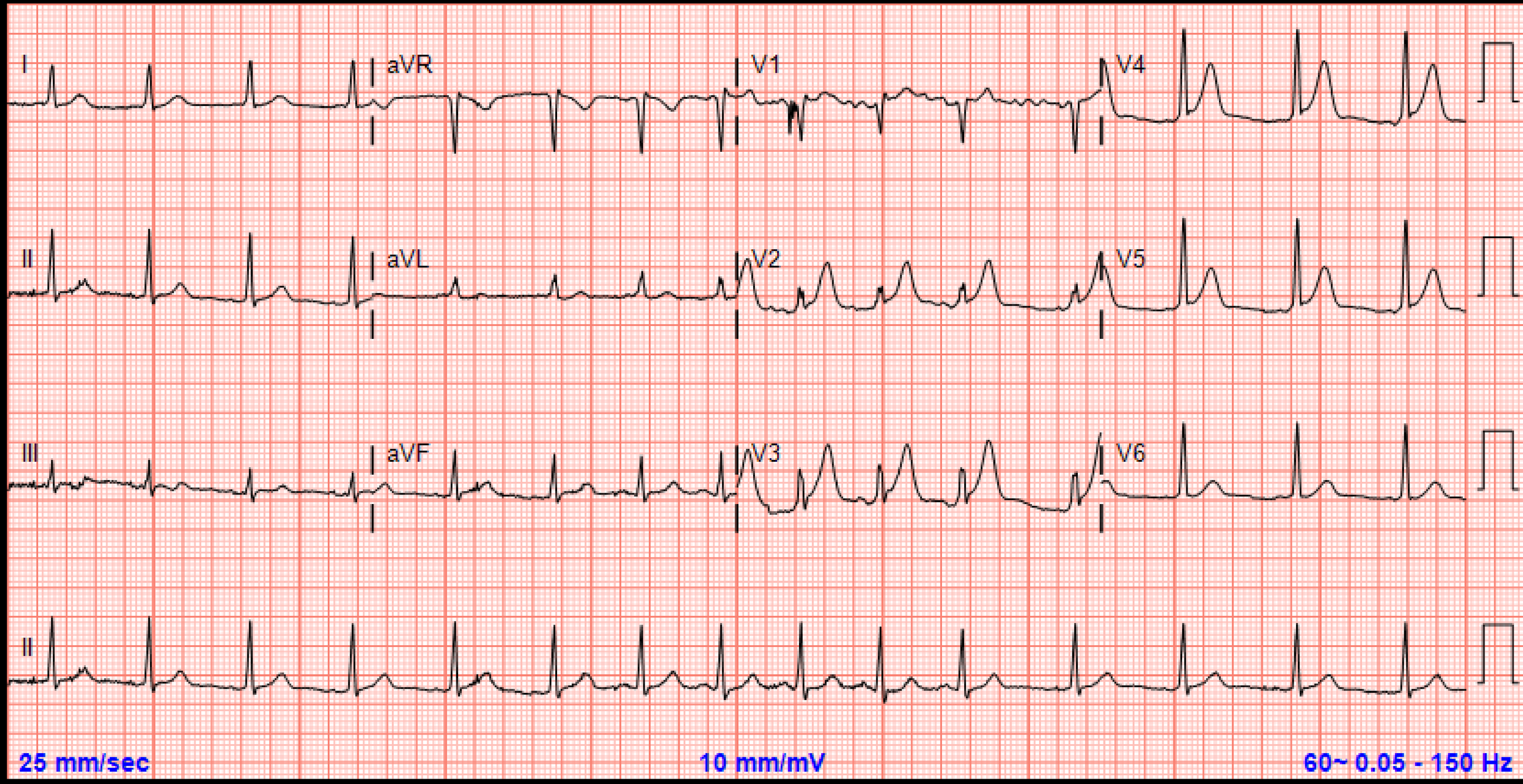
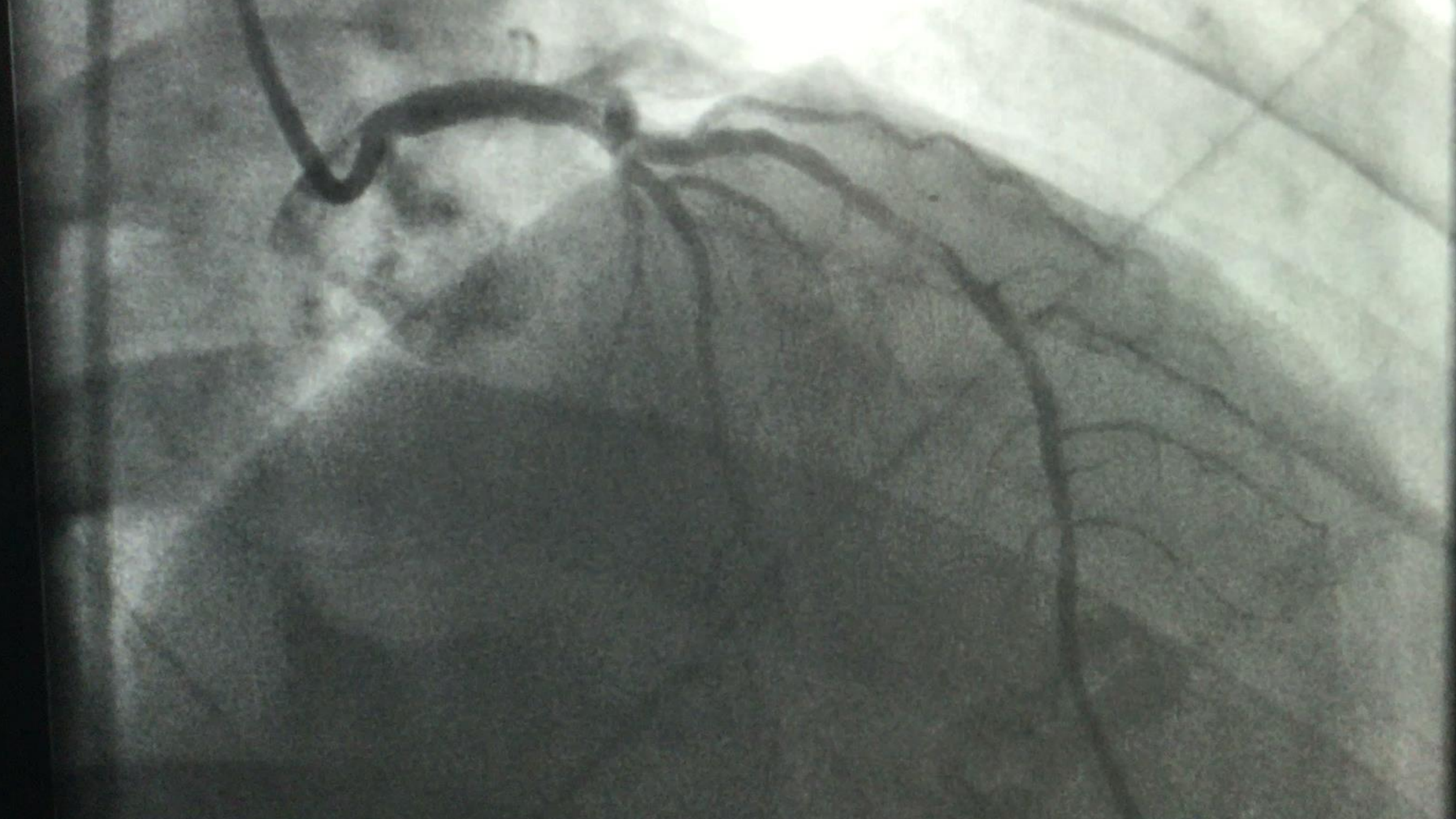
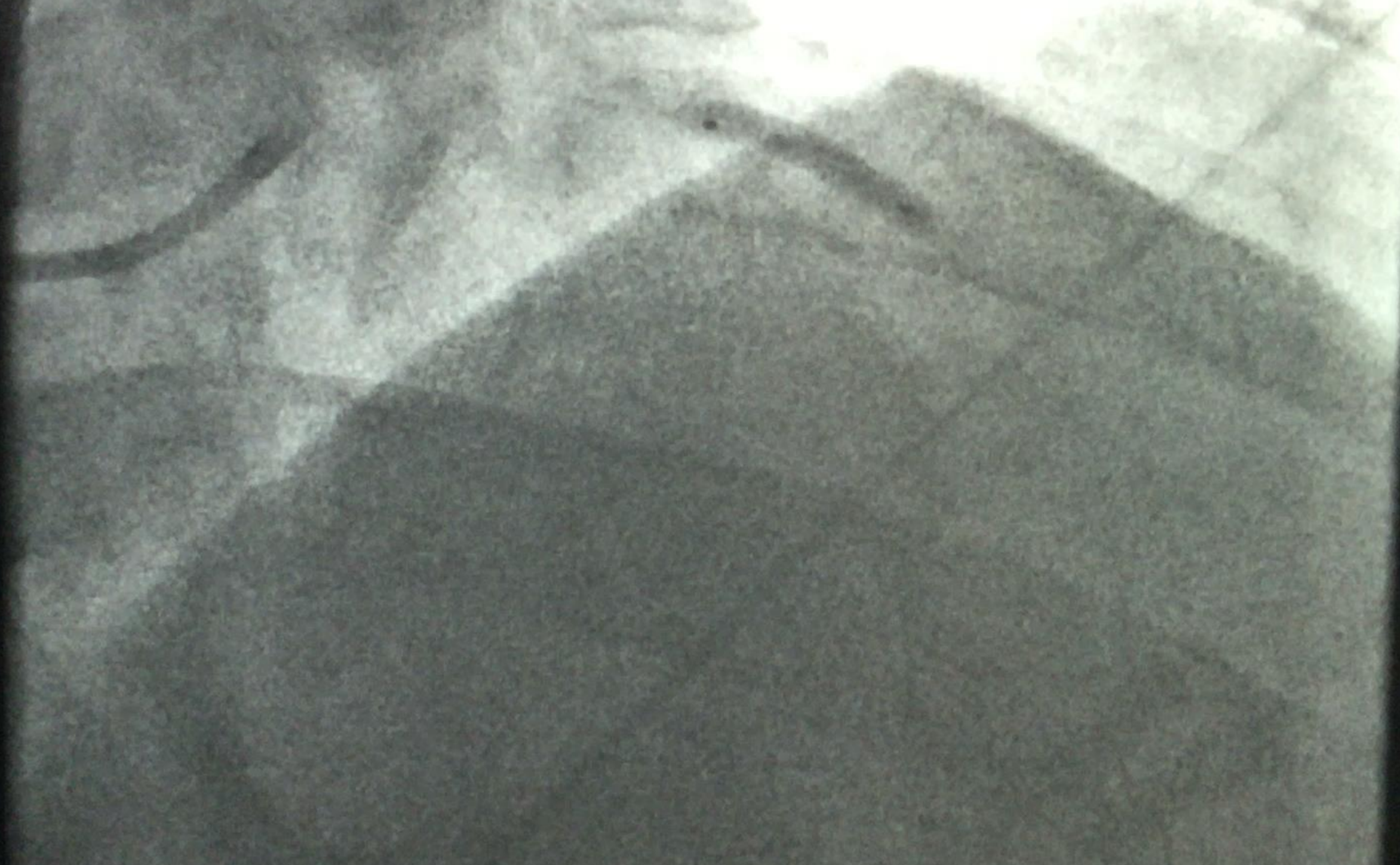
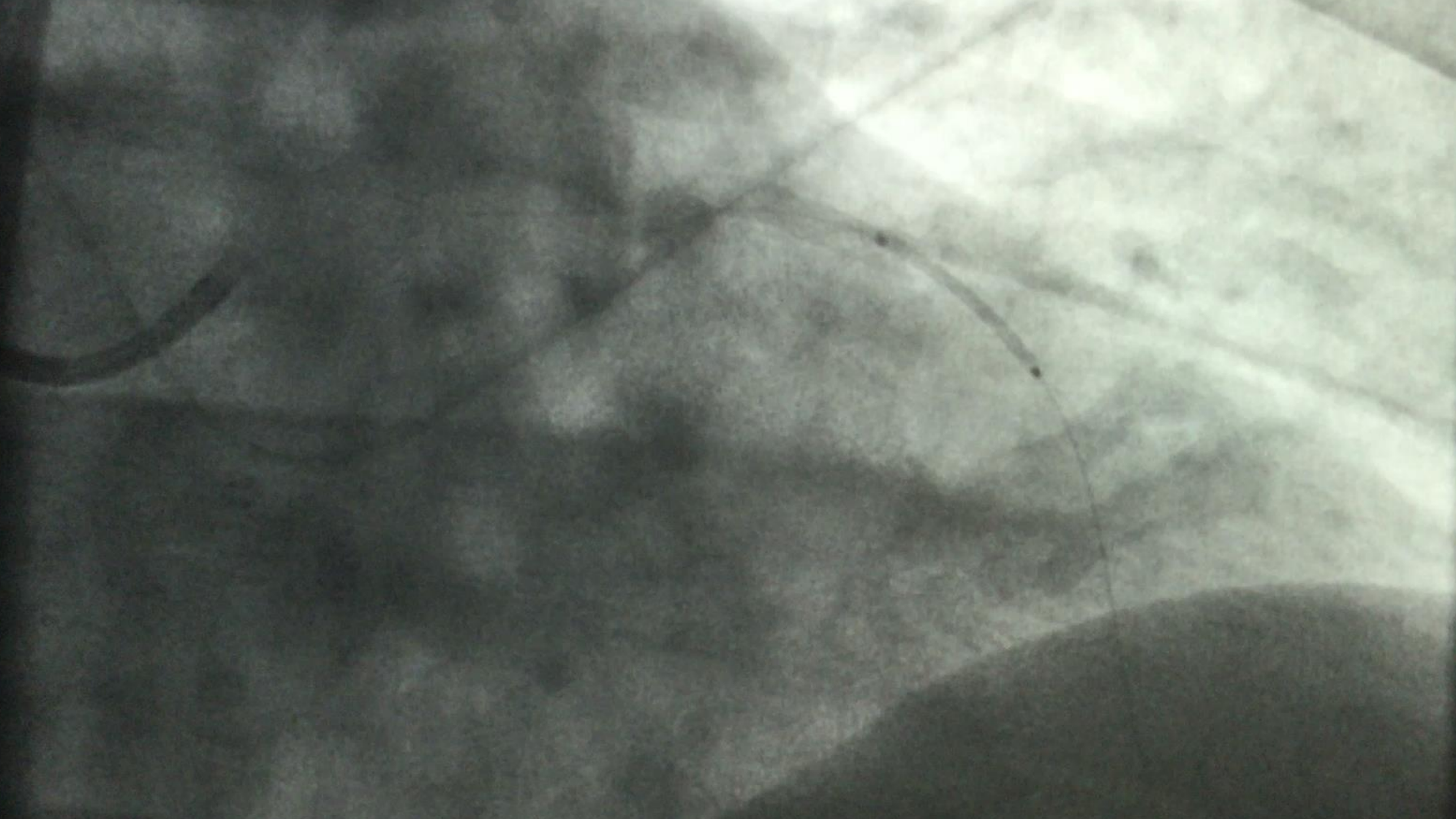
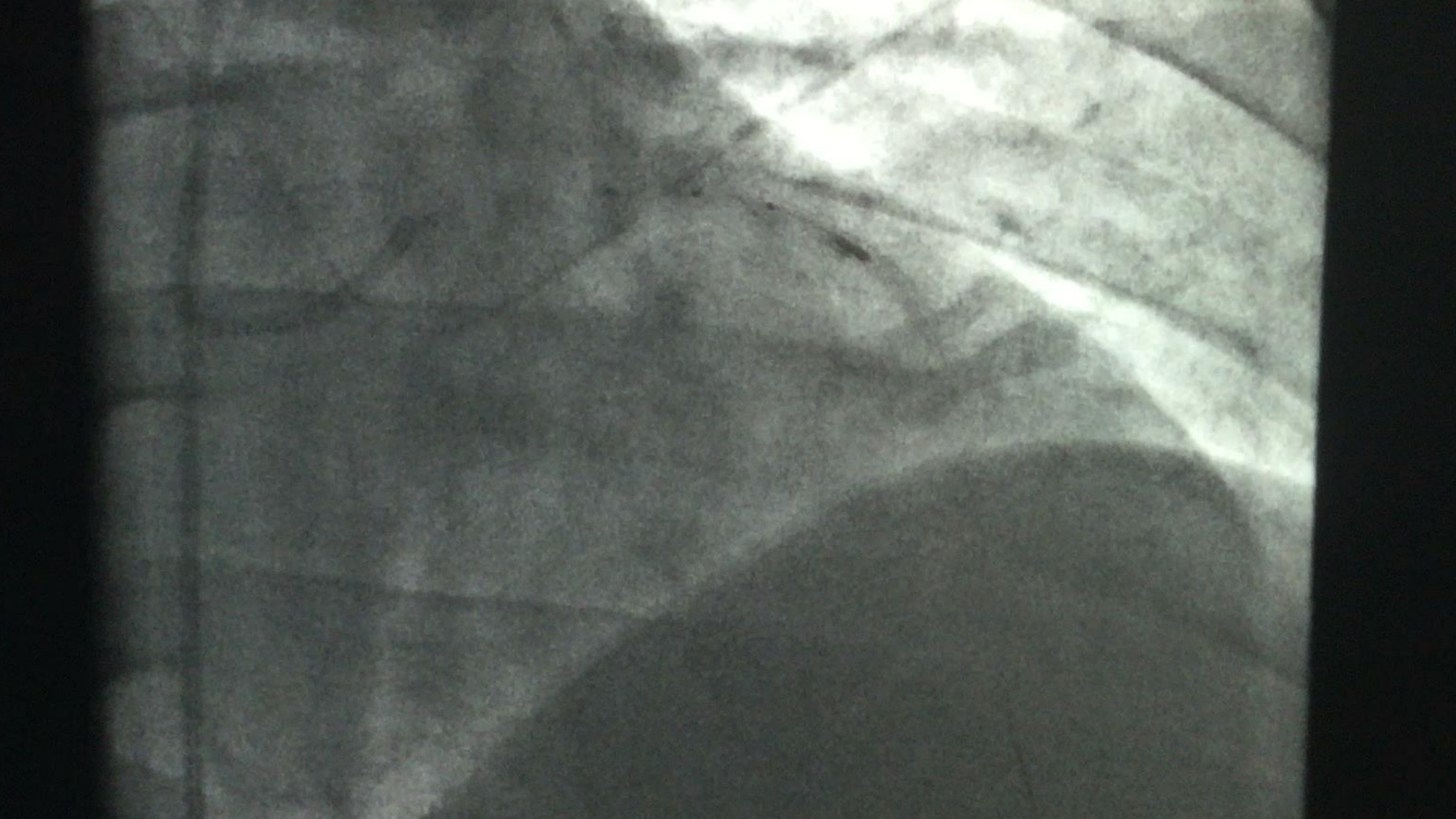
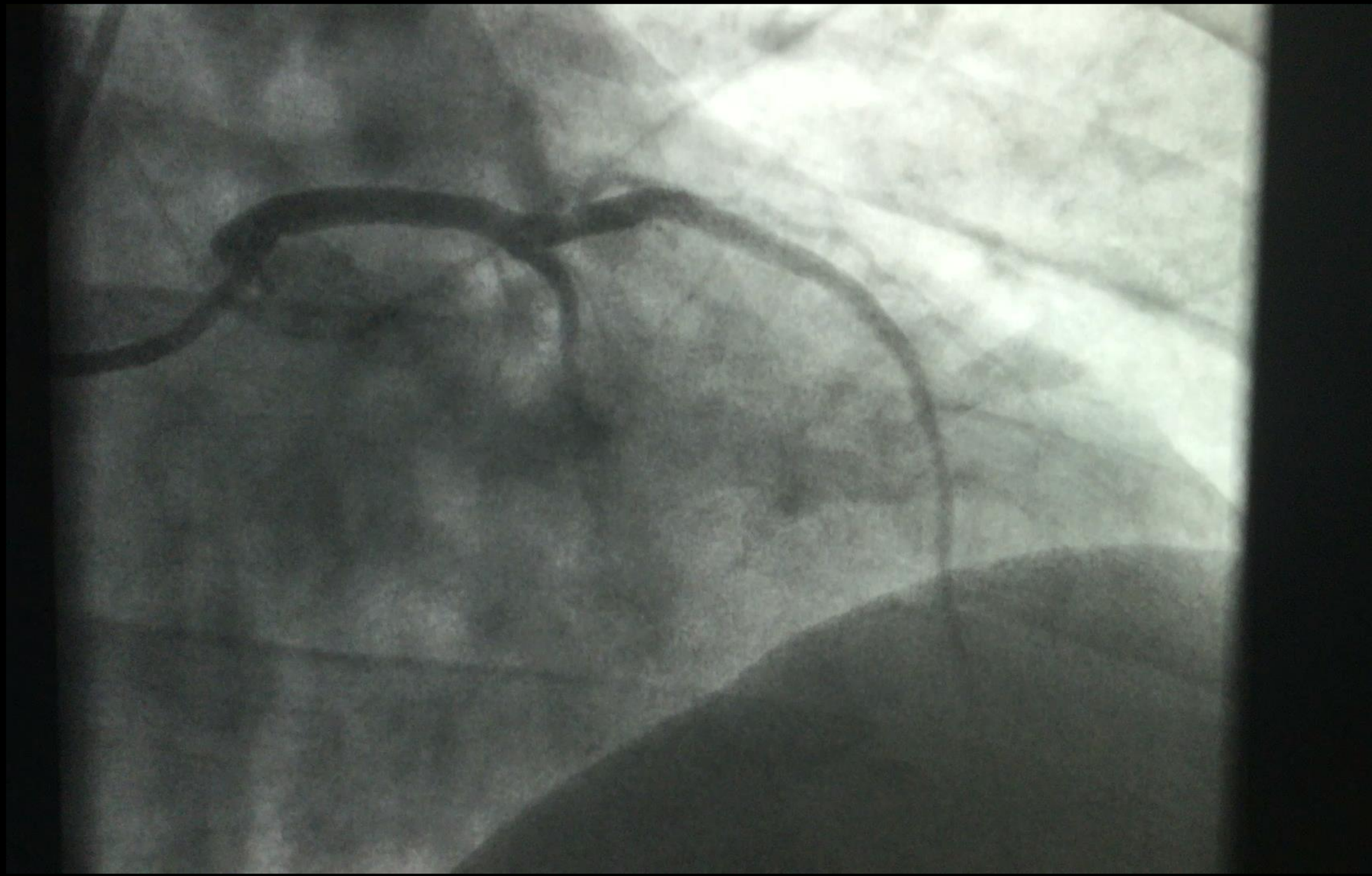

I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
25 mm/sec
10 mm/mV
60~ 0.05 - 150 Hz





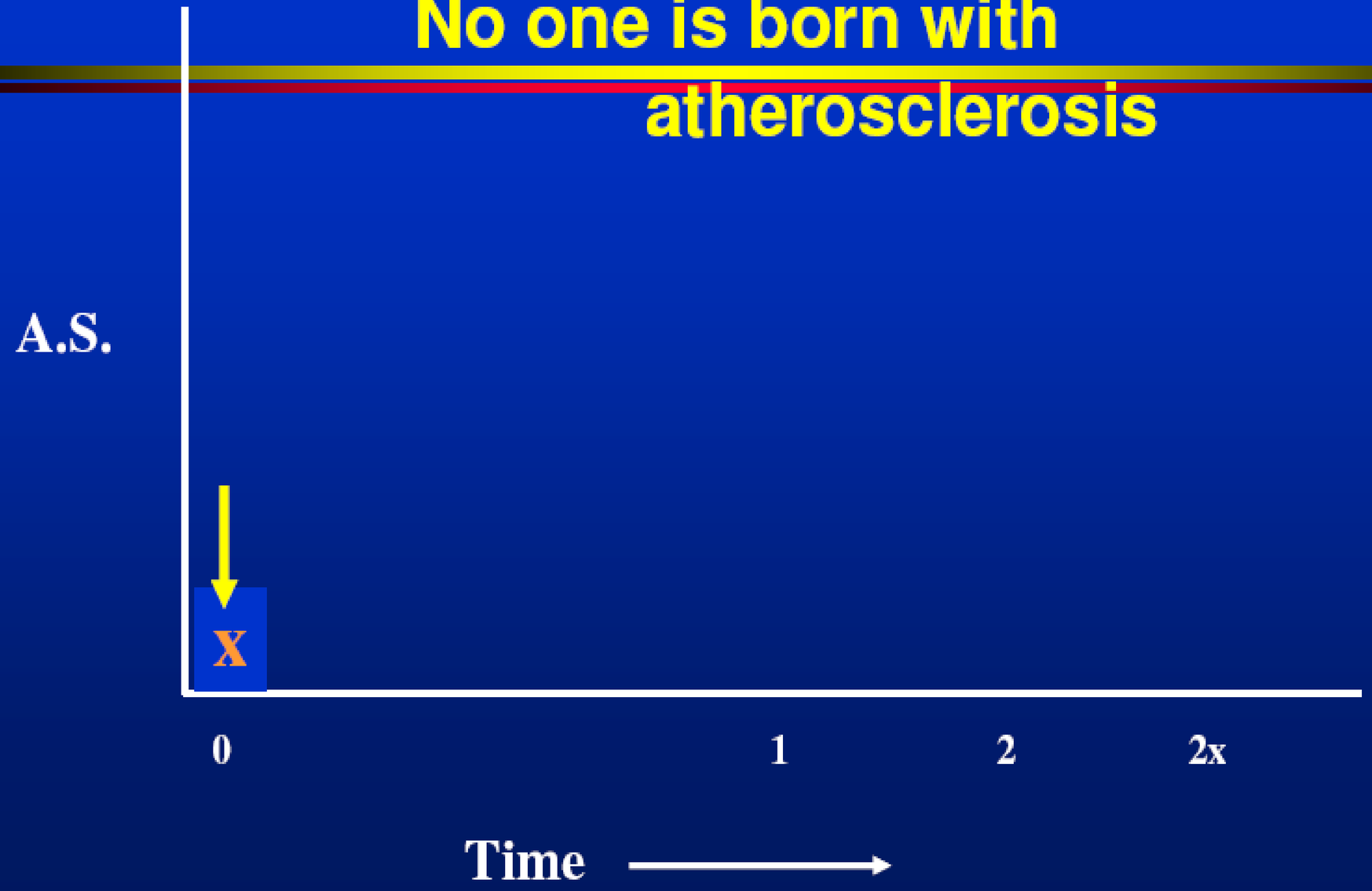






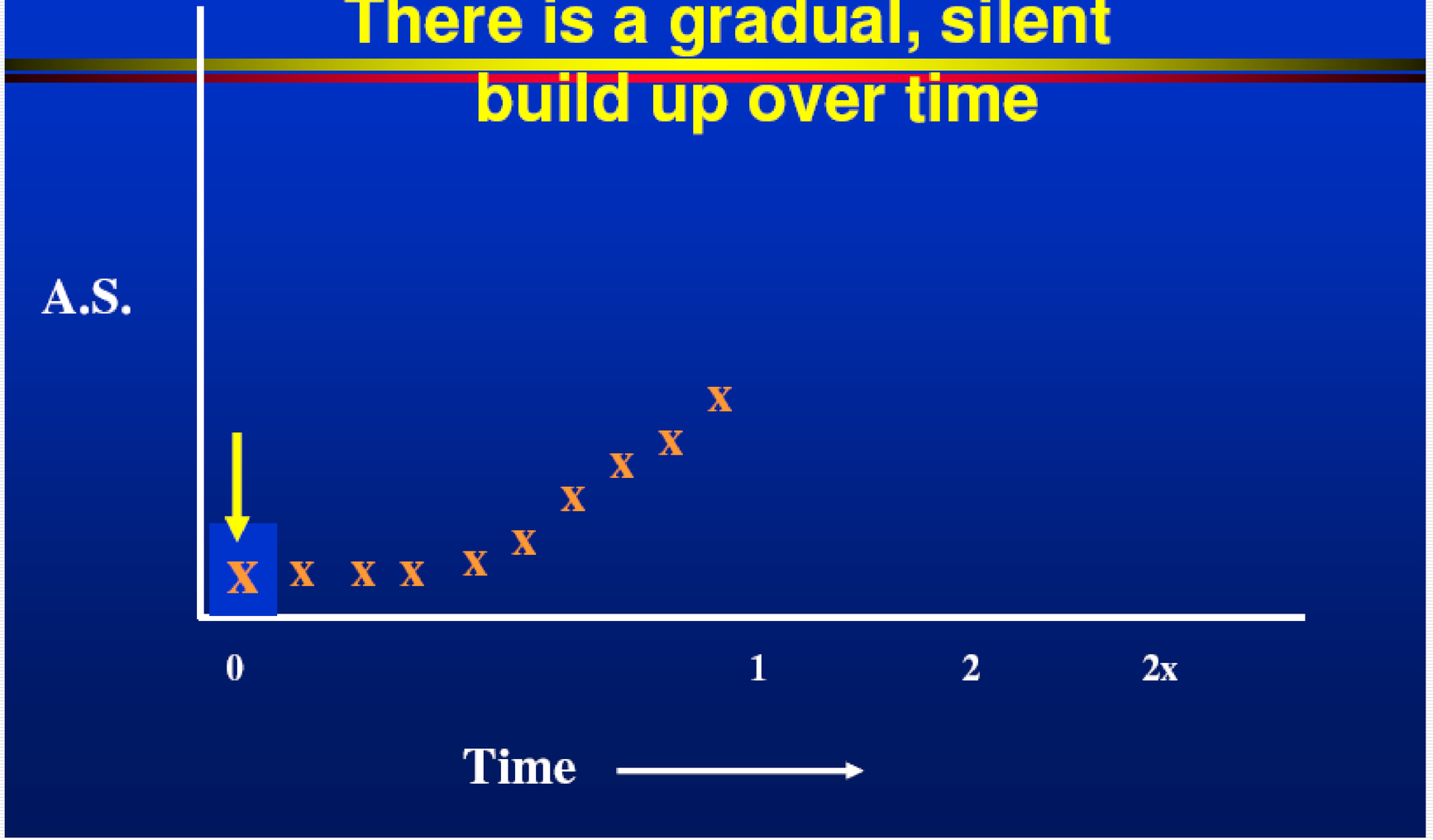
Coronary atherosclerotic burden –

No one is born with atherosclerosis



Coronary atherosclerotic burden –

There is a gradual, silent build up over time



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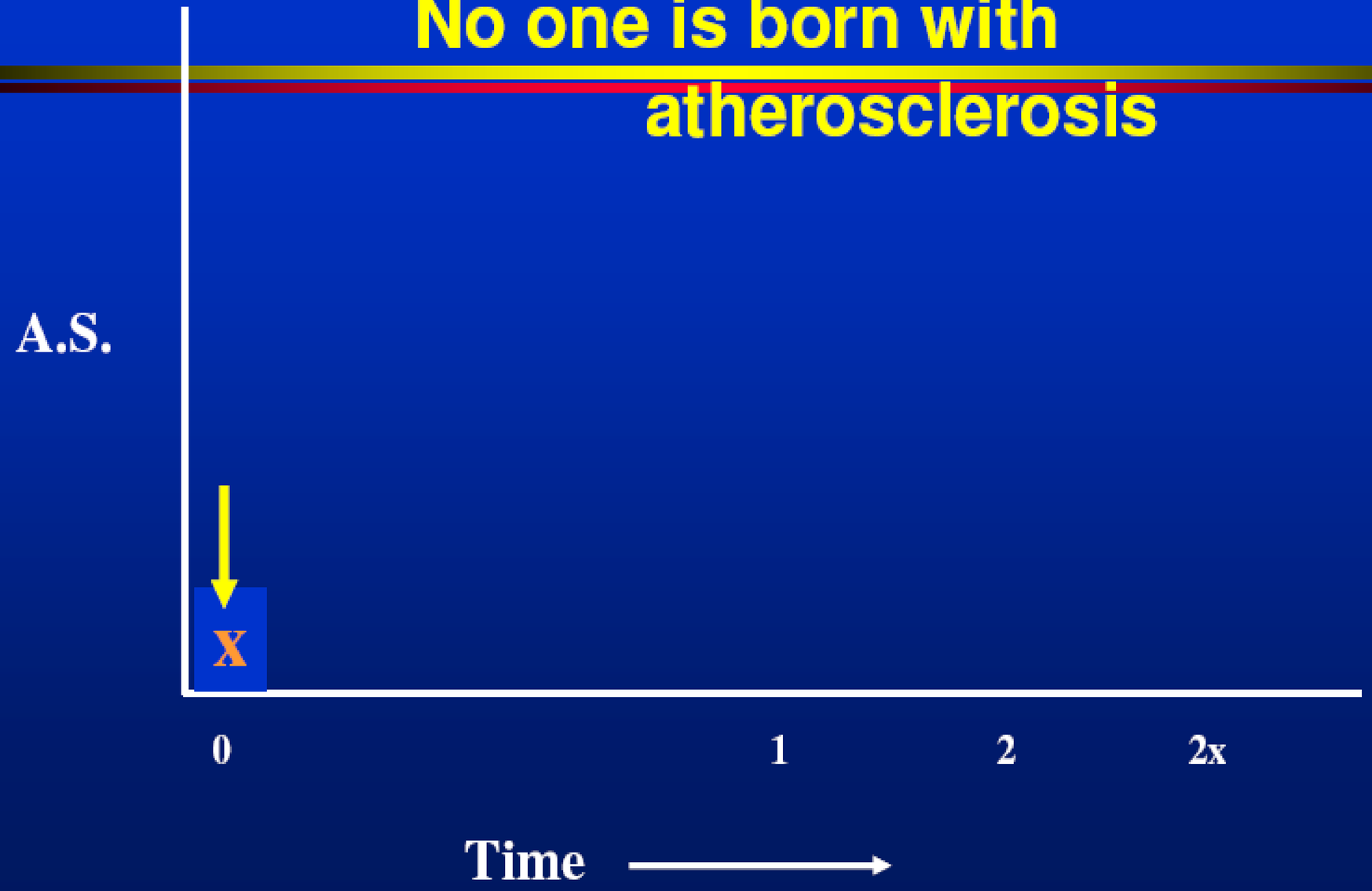

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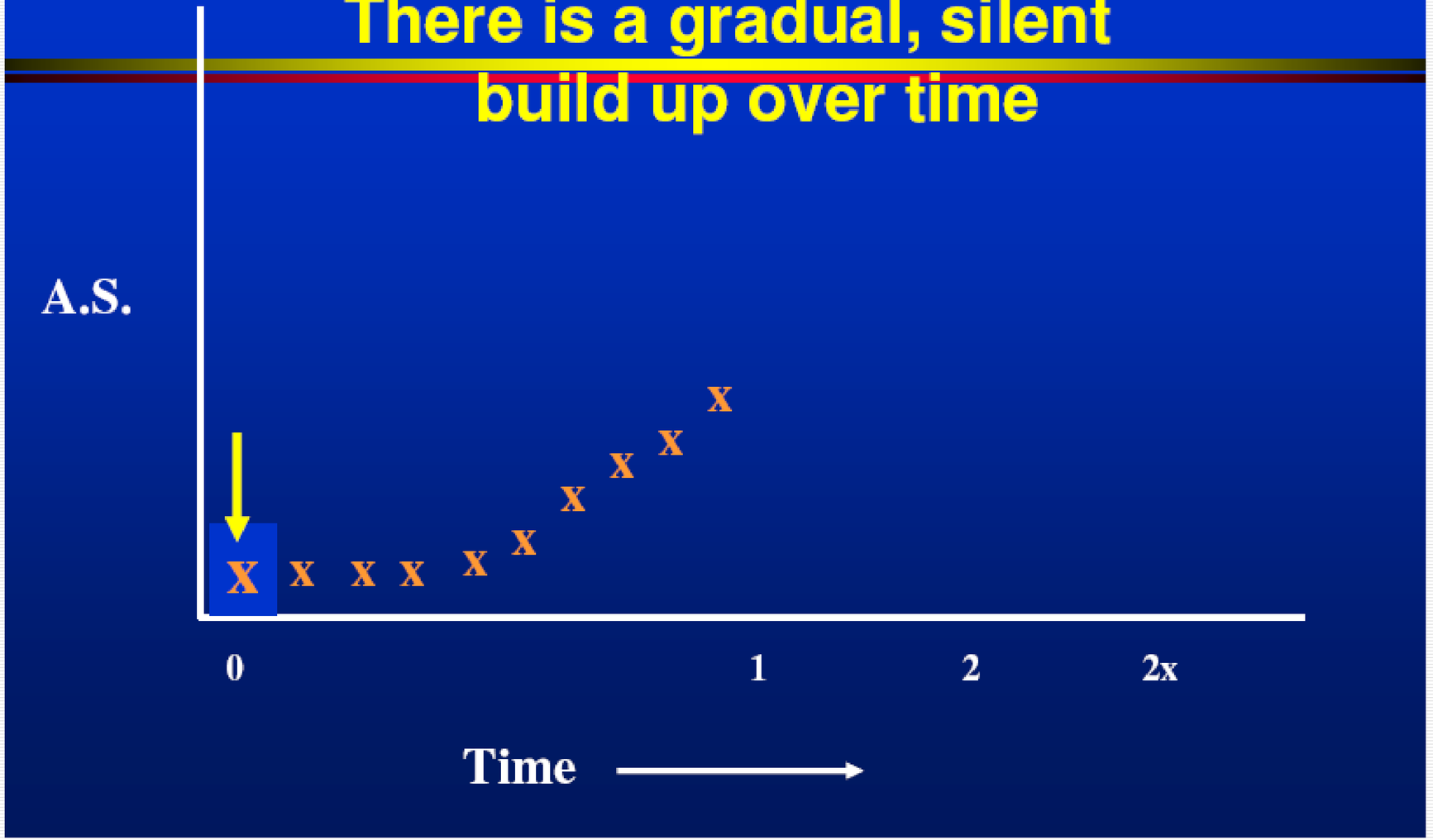
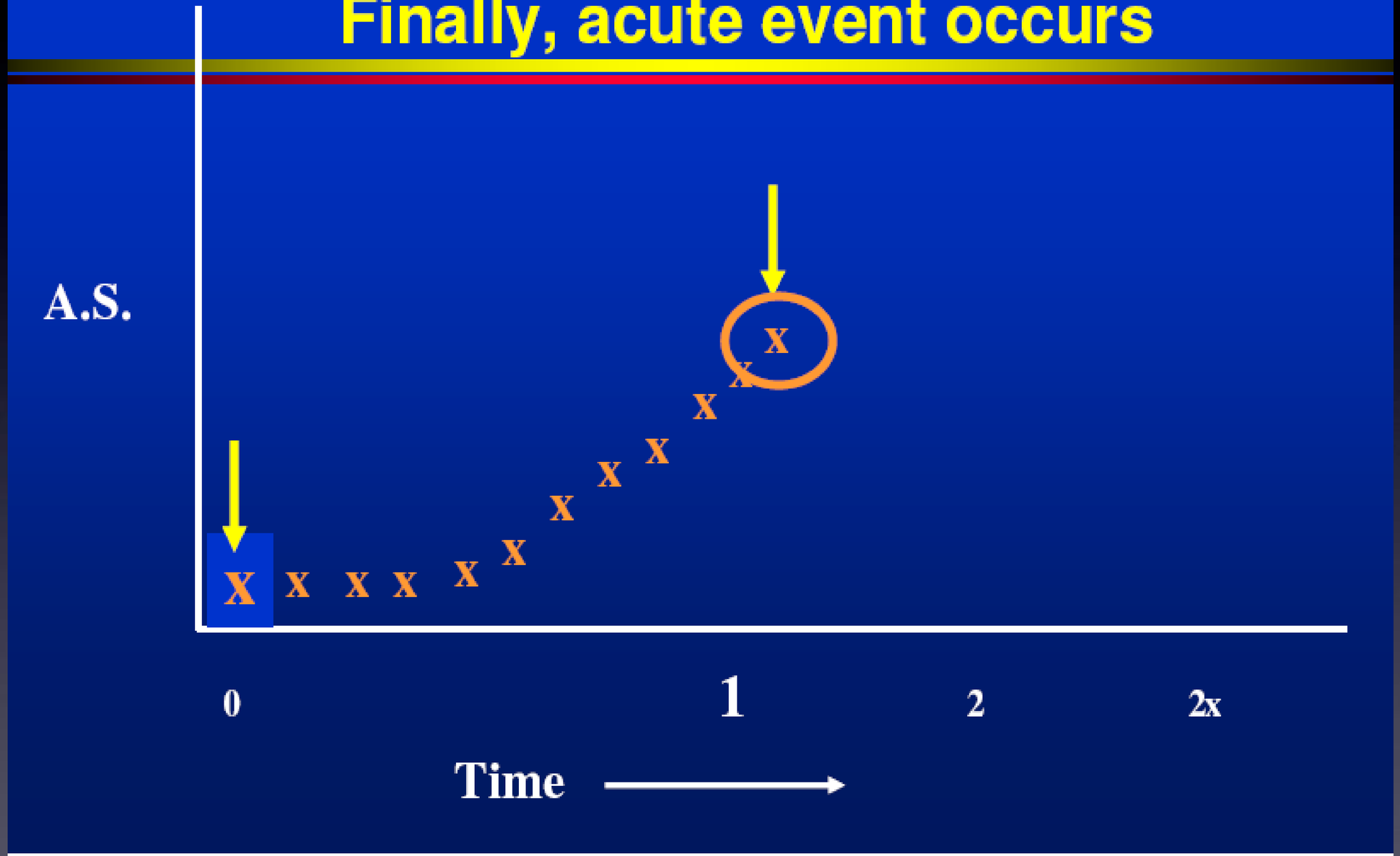


Coronary atherosclerotic burden –

Finally, acute event occurs



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Familial hypercholesterolemia

- **Genetic disorder**
- **Characterized by high cholesterol levels, specifically very high levels of low-density lipoprotein**
- **Early cardiovascular disease.**

Familial Hyperlipemia

- ***Homozygous*** FH: Severely elevated cholesterol levels (total cholesterol and LDLc levels >600 mg/dL); triglyceride levels within the reference range

- ***Heterozygous*** FH: Elevated LDLc levels commonly greater than 250 mg/dL; in patients younger than 20 years, an LDLc level higher than 200 mg/dL is highly suggestive of heterozygous FH or, possibly, familial ligand defective apoB-100; in adults, LDLc levels higher than 290-300 mg/dL suggest heterozygous FH

Familial Hyperlipemia

- **Homozygous FH**

- **The following are used in the management of homozygous FH:**

- **Lifestyle changes: Recommended for cardiovascular benefits [9, 10]**
- **High doses of HMG-CoA reductase inhibitors (statins) combined with bile acid sequestrants, ezetimibe, and niacin [11]**
- **Anti–proprotein convertase subtilisin/kexin type 9 (anti-PCSK9) monoclonal antibodies (specifically, evolocumab and alirocumab) can be used as an adjunct to diet and maximally tolerated statin therapy, [12] or**
- **Mipomersen, or**
- **Lomitapide**
- **Estrogen replacement therapy in postmenopausal women**
- **LDL apheresis for selective removal of lipoproteins that contain apo-B (when the LDL receptors are absent or nonfunctional)**

Heredity

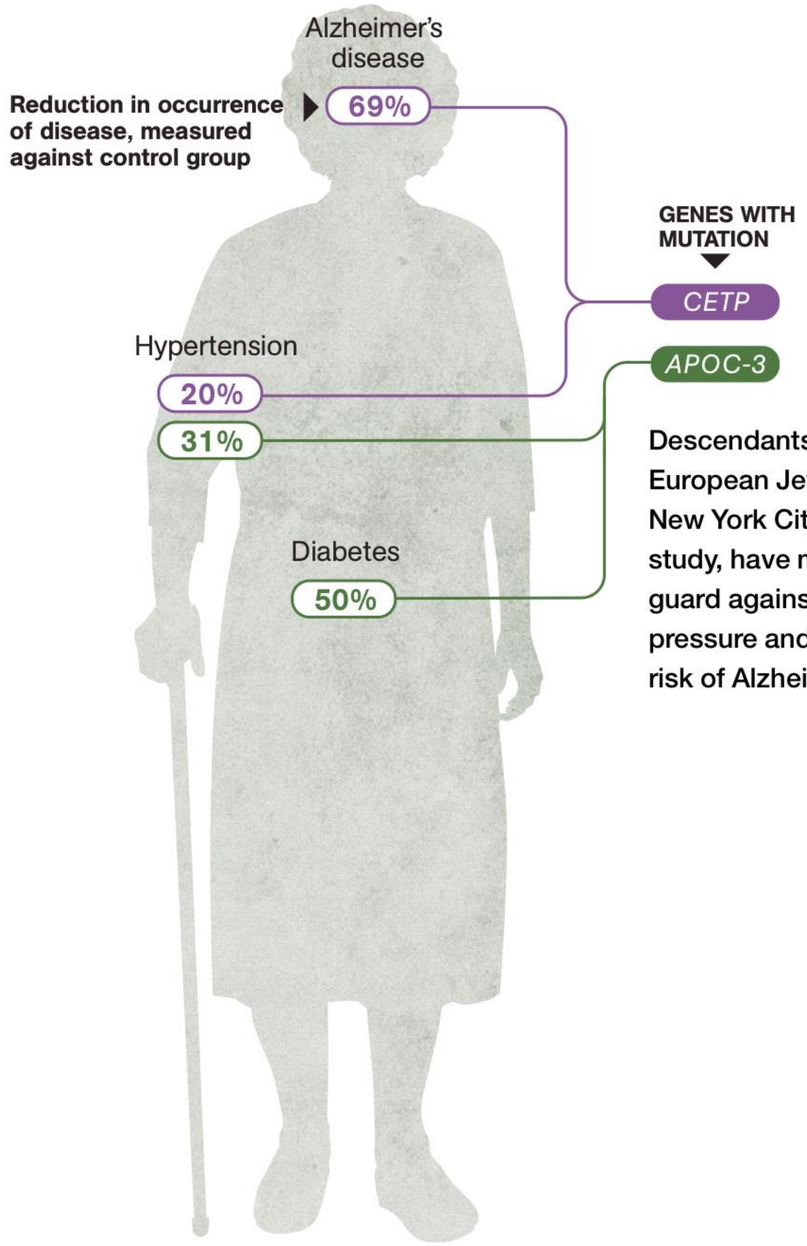
- **Research has shown that the risk of developing atherosclerosis can be influenced by heredity**
- **Researchers have been unable to identify the specific genes associated with this risk.**

Genetic clues to long life

Scientists studying groups of people genetically isolated by location or culture have found gene mutations that seem to prevent the diseases that most often shorten life. The mutations aren't limited to these groups, and not all group members have them. Learning how these genes work could help extend life for us all.

TAP on a study group to learn more

- **ASHKENAZI JEWS**
- OLD ORDER AMISH
- LARON SYNDROME ECUADORIANS
- JAPANESE AMERICANS



Descendants of central European Jews, most in New York City in this study, have mutations that guard against high blood pressure and also lower risk of Alzheimer's.

CREDITS

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GENE WITH MUTATION

APOC-3

Members of this tight-knit faith, studied in Lancaster, Pennsylvania, carry a mutation* that dramatically lowers fat in the blood.

*A DIFFERENT *APOC-3* MUTATION APPEARS IN ASHKENAZI JEWS.

CREDITS

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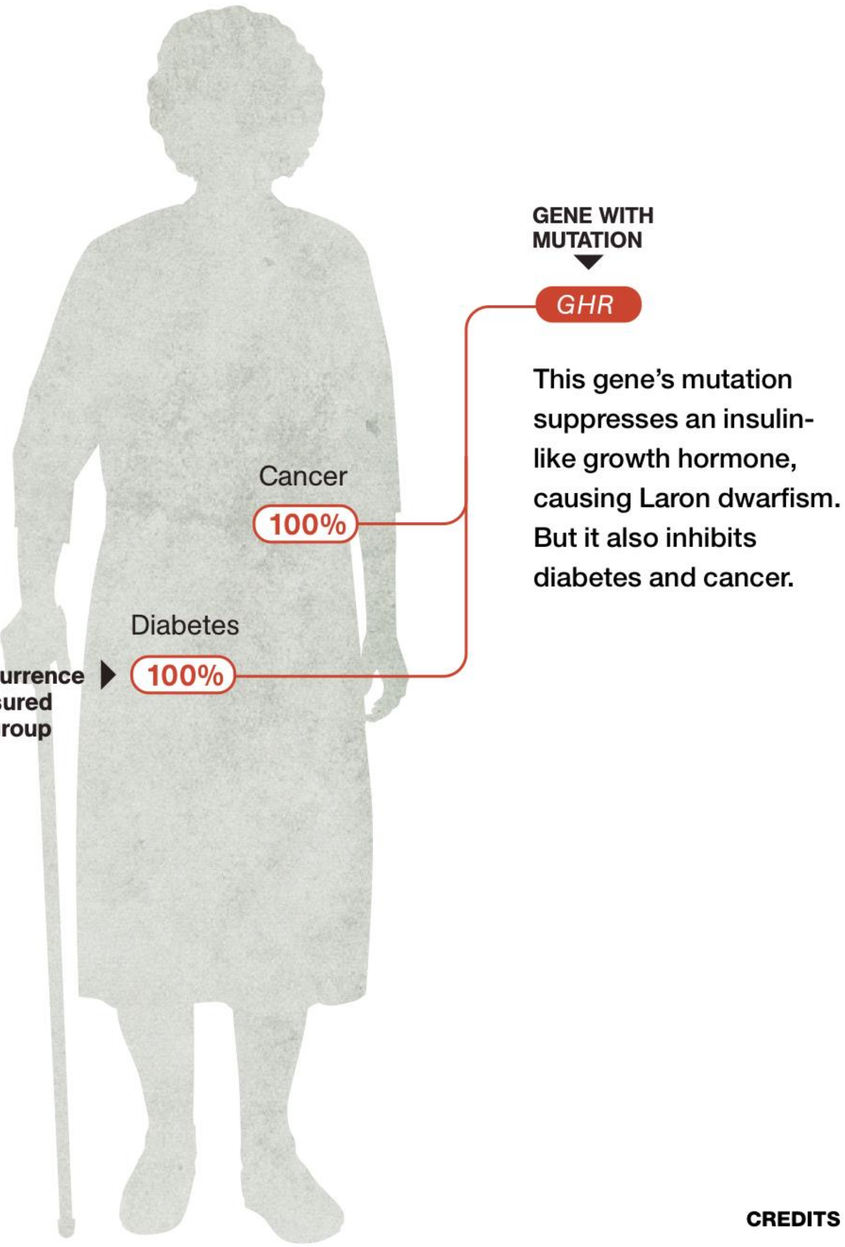

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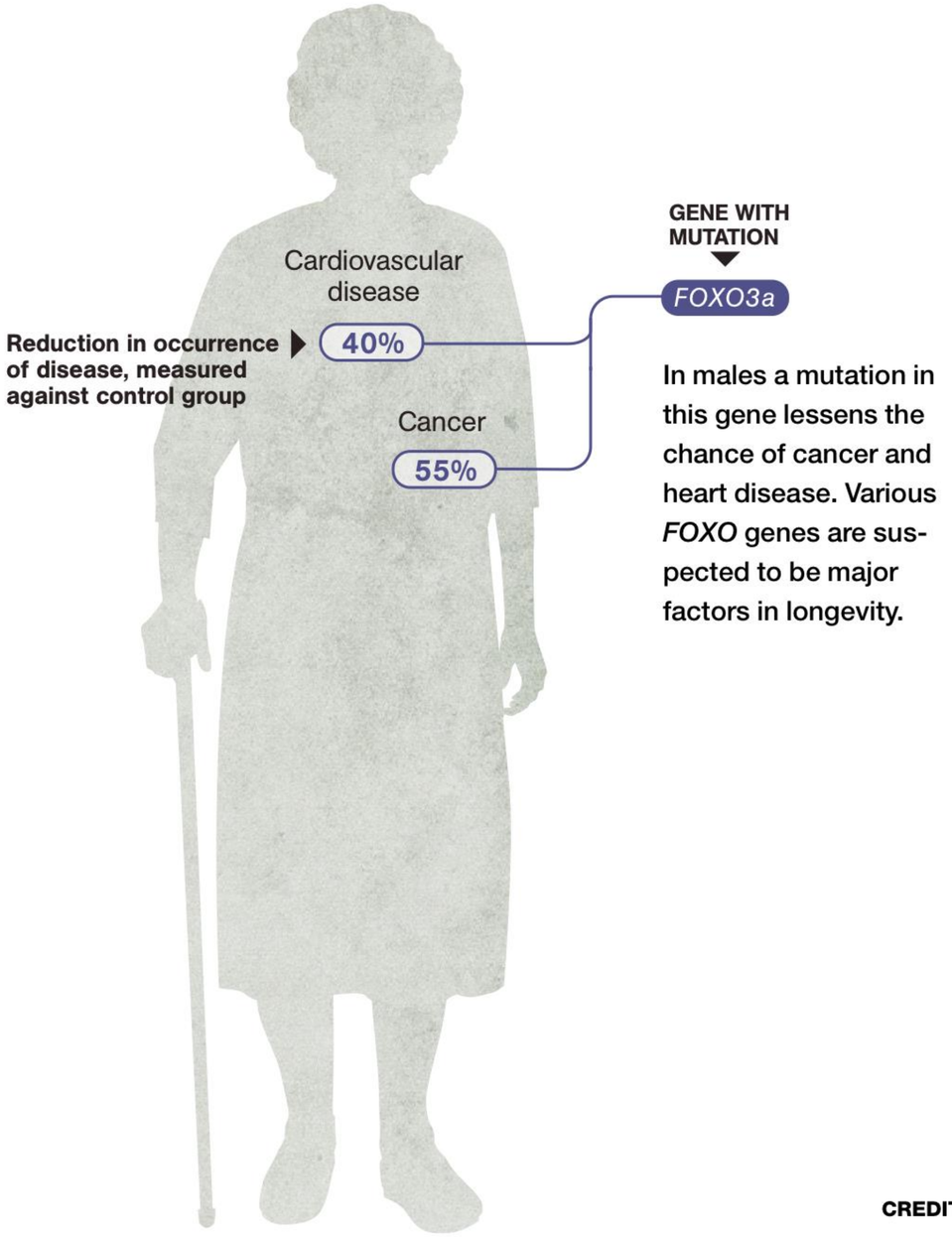

In males a mutation in this gene lessens the chance of cancer and heart disease. Various *FOXO* genes are suspected to be major factors in longevity.

CREDITS

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Cigarette Smoke

- **Cigarette smoke is a complex mixture containing a range of individual components**
- **Only a small number of these have been examined in isolation.**
- **Nicotine and carbon monoxide have been the subject of a number of investigations**
- **Their damaging effects in model systems are less than those seen with whole smoke.**
- **Free radicals are an important component of cigarette smoke**
- **It seems likely that free radicals are critical to the link between cigarette smoking and cardiovascular disease.**

Free Radicals….???

- Free radicals are organic molecules. They are beneficial, but in excess they accelerate ageing, tissue damage, and some diseases.
- These molecules are very unstable, therefore they look to bond with other molecules, destroying their vigor and perpetuating the detrimental process.
- **Antioxidants**, present in many foods, are molecules that prevent free radicals from harming healthy tissue.

Free Radicals are produced in response to many different everyday things, such as:		
Cooked Food (especially animal products (chickens and other birds, cows, pigs, fishes, lambs, eggs, dairy products, animal fats and proteins, and metabolic waste products contained in animal tissues and organs) and refined foods such as white sugar, white flours, hydrogenated oils, etc.) Any foods other than raw foods from the plant kingdom Environmental pollution (from air, water, household chemicals, asbestos, pesticide residues, & other man-made pollutants including the out-gassing of plastic and other synthetics) Preservatives, Colorings, and other food additives Metabolism	Smoking and passive smoke Exposure to excess heat or cold Medical Treatment including medications Alcohol Bacteria Parasites Chemotherapy & Radiation Prescription & Over The Counter Drugs Exercise Lack of Truly Clean & Fresh Air Radiation (including electromagnetic radiation from anything electric such as outside power lines; wires in your home/work, TVs, computer monitors, etc.	Heart Disease & Strokes Computers/Monitors/TVs Use of Ovens **(microwaves are the worst!)** Refrigerators Nutrient deficiencies (major & minor) which can still occur even on the best of diets (even fresh, raw foods contain only as many nutrients as the soil in which they were grown) Sunburn Stress (any) Judgment or any other non-positive mental state Synthetic materials such as Polyester, Acetate, Satin, Plastics, etc. Tap Water, etc.

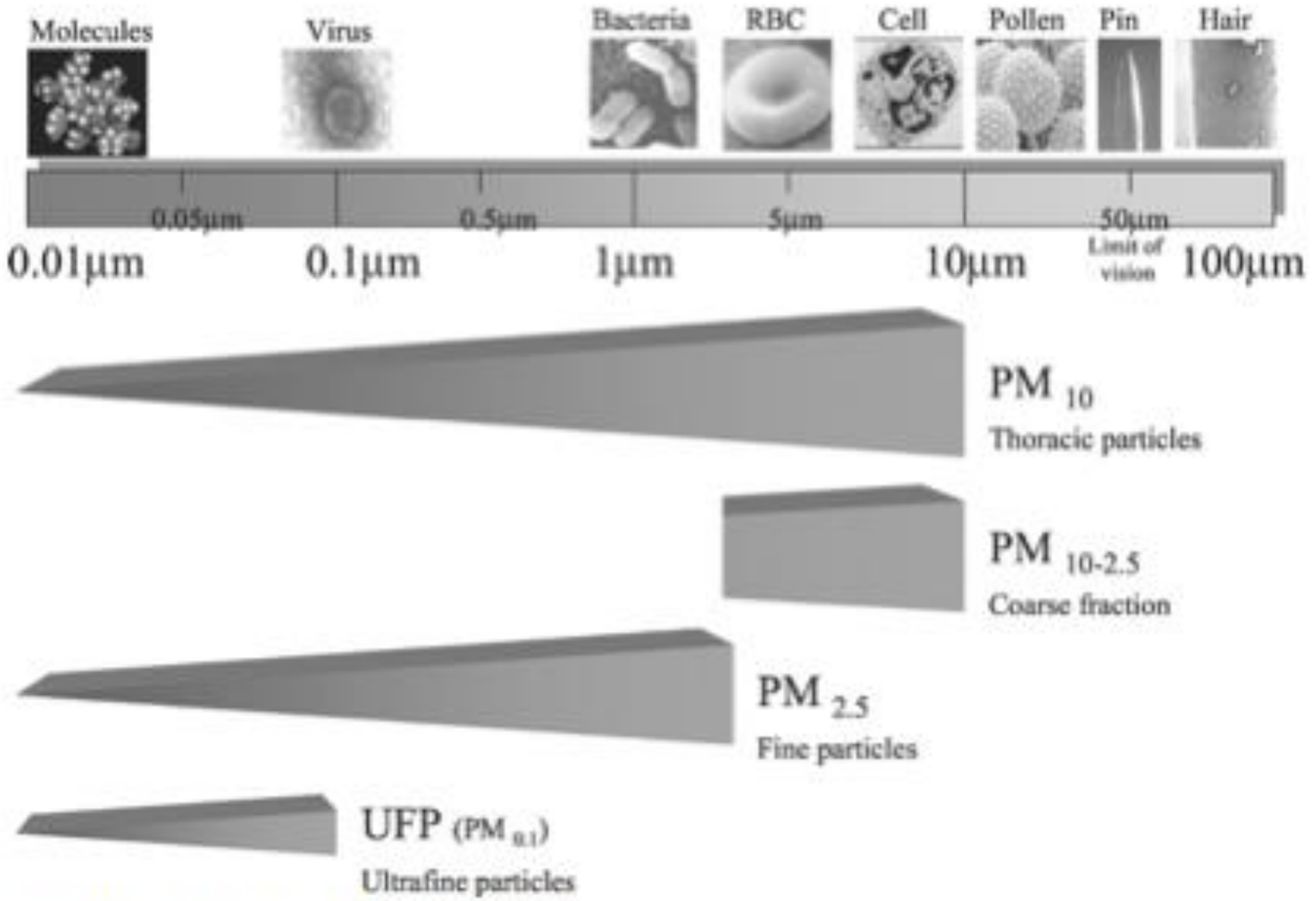
air pollution & cardiovascular disease (pollutants)

- Carbon Monoxide
- Oxides of Nitrogen
- Sulfur Dioxide
- Ozone
- Lead
- Particulate Matter (Thoracic Particles <10 micrometers in aerodynamic diameter)

PM

- Tiny Particles
- Coarse (10 - 2.5 micrometers)
- Fine (2.5 - 0.1micrometers)
- UltraFine (0.1 and Smaller)
- Human Hair (70 micrometers in Diameter)

Figure 1. Particulate matter air pollution size distribution.



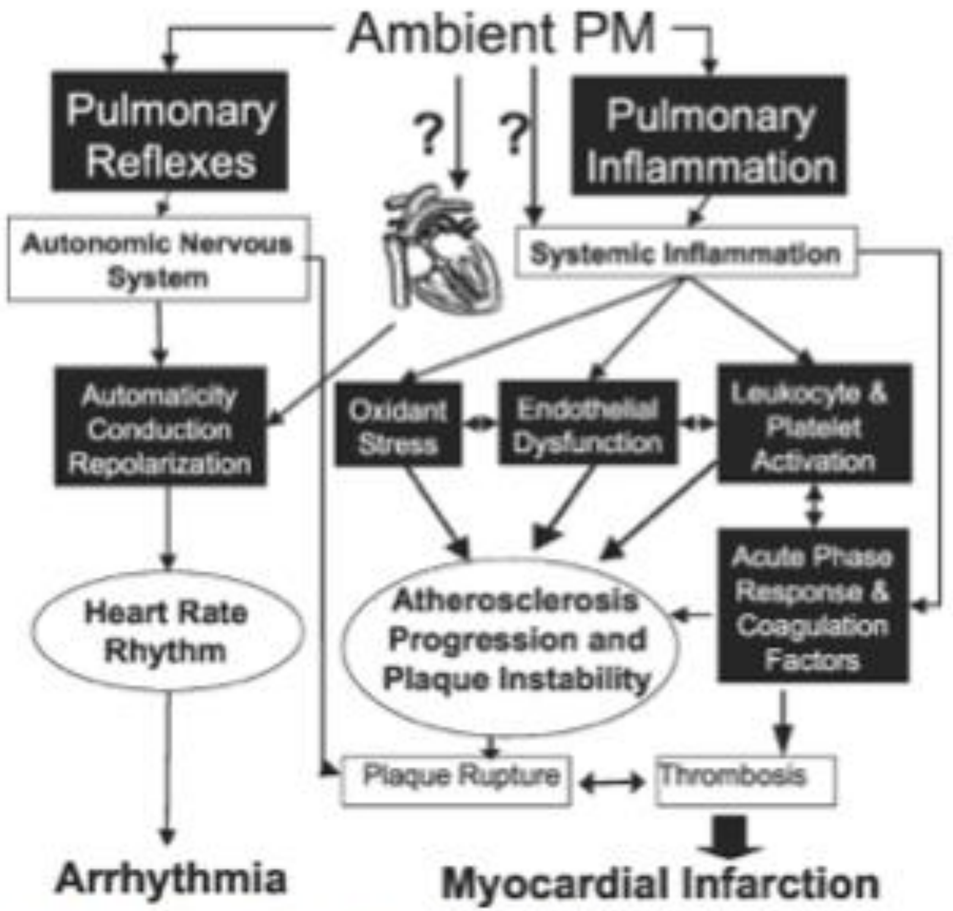
Brook R D et al. Circulation 2004;109:2655-2671

American Heart Association
Learn and Live

Formation of : Environmentally Persistent Free Radicals

- A Free Radical Forms a “Loose” Bond With the Surface of Particulate Matter
- Loosely Bonded Free Radical Forms a Chemical Bond with Metals Present in the Particle
- This Process Reduces the Metal & Creates EPFR
- Attached EPFR Can Now Have a Half-Life Up to Several Days Rather Than The Fractions of a Second of a Normal Free Radical.
- Inhaling EPFR’s exposes the average person up to 300 times more free radicals daily than from smoking one cigarette .

Figure 2. Possible biological mechanisms linking PM with cardiovascular disease.



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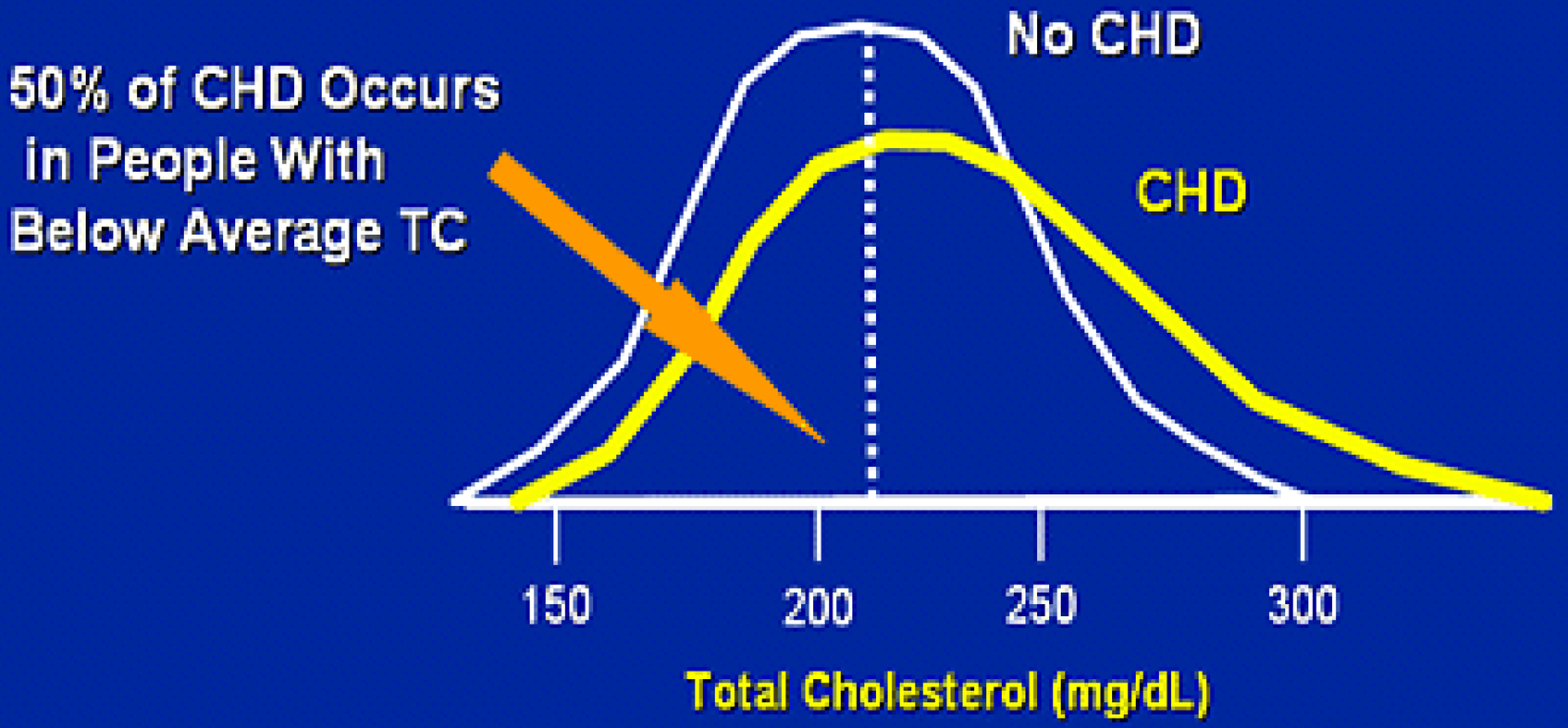
Total Cholesterol Distribution: CHD vs Non-CHD Population

Framingham Heart Study—26-Year Follow-up



Adapted from Castelli. *Atherosclerosis*. 1996;124(suppl):S1-S9.

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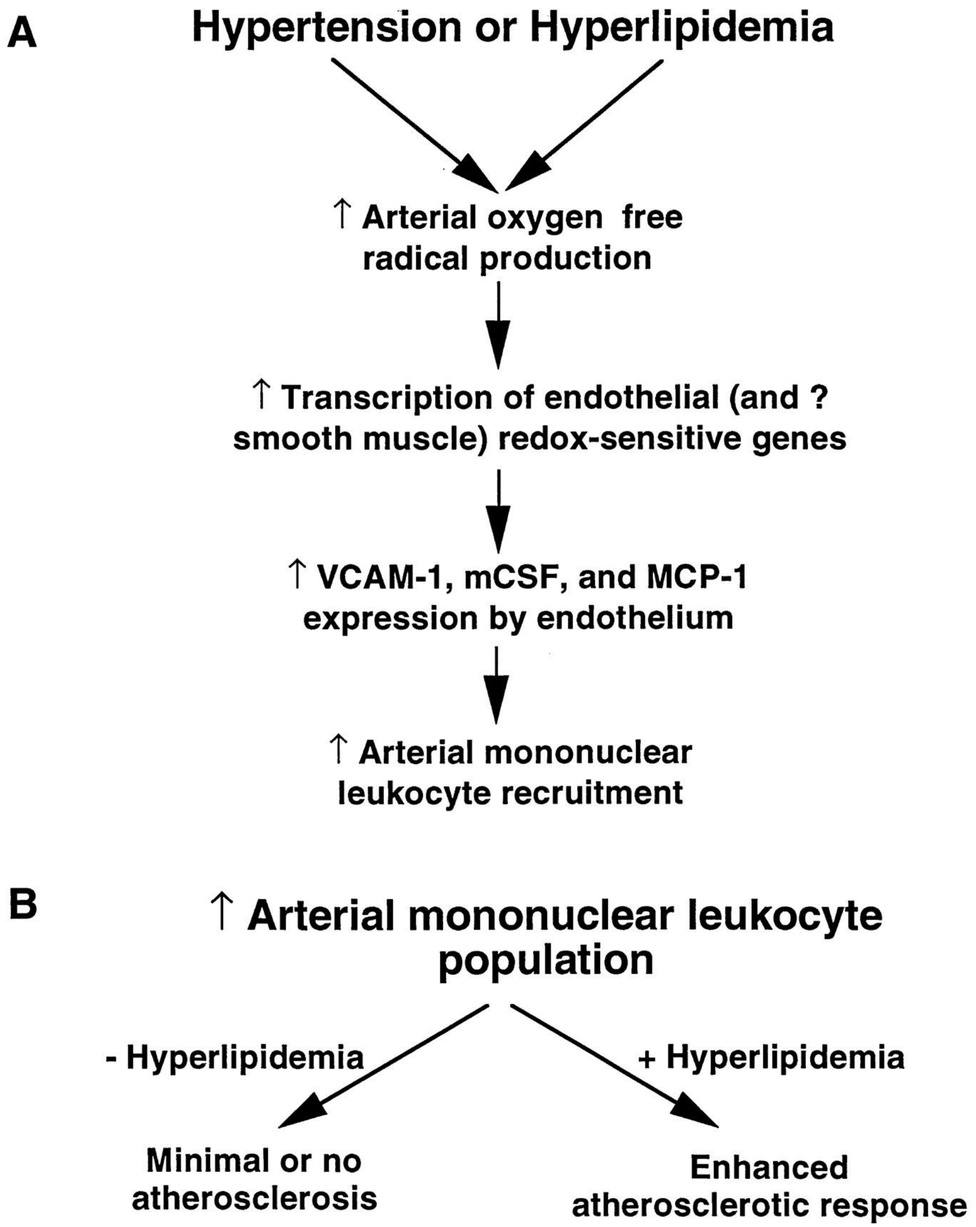
Flow chart shows mechanism of synergism of hypertension and hyperlipidemia in the pathogenesis of atherosclerosis.



Modified LDL shown to stimulate the chemokine, monocyte chemotactic protein-1 (MCP-1).29 Modified LDL shown to stimulate the production of monocyte colony stimulating factor (mCSF).

American Heart Association.

Hypertension and the Pathogenesis of Atherosclerosis
Oxidative Stress and the Mediation

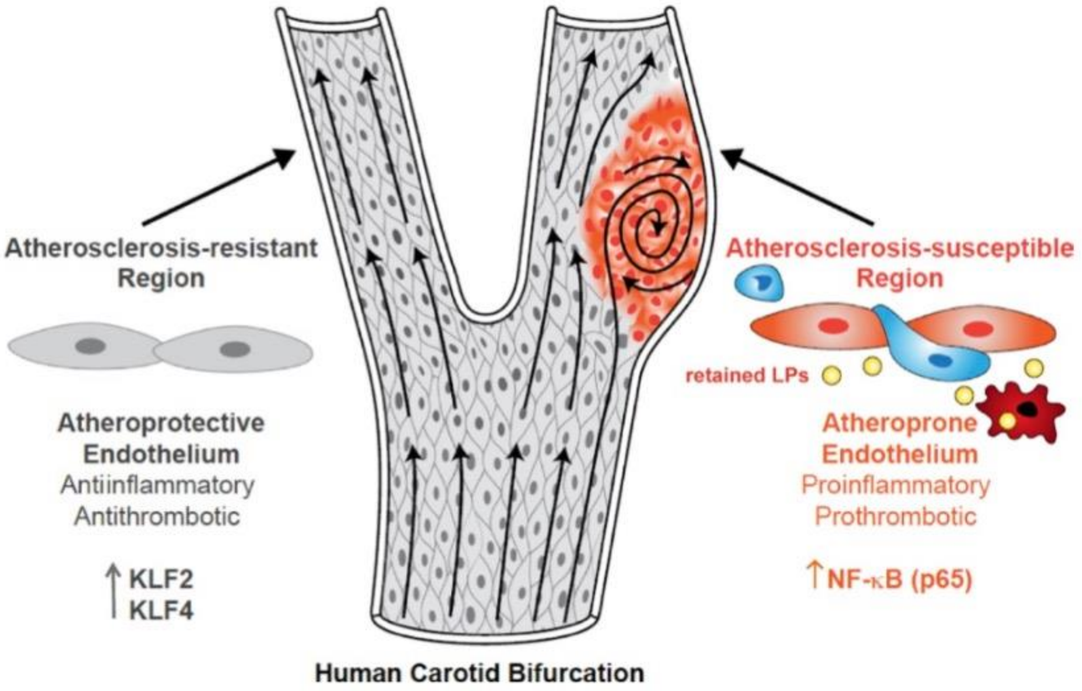
R. Wayne Alexander Hypertension. 1995;25:155-161

RHEOLOGY

RHEOLOGY

Rheology is the study of the flow of matter, primarily in a liquid state, but also as 'soft solids' or solids under conditions in which they respond with plastic flow rather than deforming elastically .

- **Arterial flow patterns** largely determine whether endothelial cells stand poised for facile inflammatory activation or will resist activating signals.
- **Atherosclerosis** develops almost exclusively in areas of slow flow or low shear stress, often with eddy currents
- **Turbulence** is not a feature of flow at these sites. Indeed, turbulence, defined as blood flow exceeding the critical Reynolds number, occurs almost nowhere in the normal human circulatory system.



KLF2

- Klf2 - potent inhibitor of cytokine-mediated induction of VCAM-1 and E-selectin expression in endothelial cells
- Several studies suggest a link between KLF2 and statins in atherosclerosis.
- Statins have been reported to induce expression of endothelial NO synthase and thrombomodulin in a KLF2 dependent manner
- Statins - induce KLF2 expression in endothelial cells as well as T cells
- In mice, Klf2 deficiency is lethal, because it is required for normal tunica media formation and blood vessel stabilization

Protective Role for Myeloid Specific KLF2 in Atherosclerosis, Iftach Shaked, Klaus Ley
May 11, 2012, Volume 110, Issue 10, ((Circ Res. 2012;110:1266.)

Krüppel-like Factor 2 (KLF2), also known as **lung Krüppel-like**

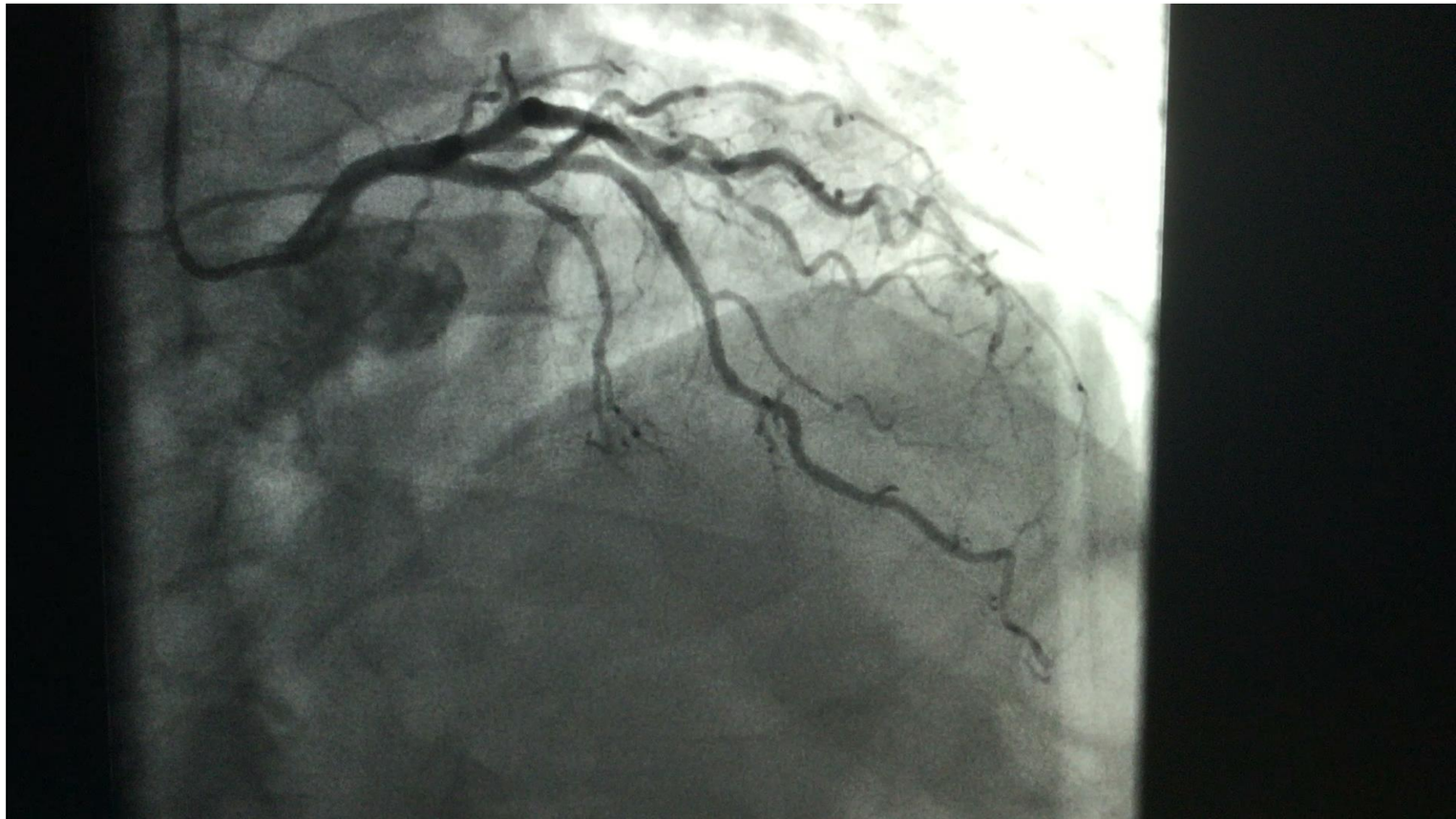
NF-kB

- **Activation of the NF-κB plays a central role in inflammation**
- **Ability to induce transcription of proinflammatory genes**
- **Pathway is activated upon appropriate cellular stimulation**
- **Most often by signals related to pathogens or stress.**

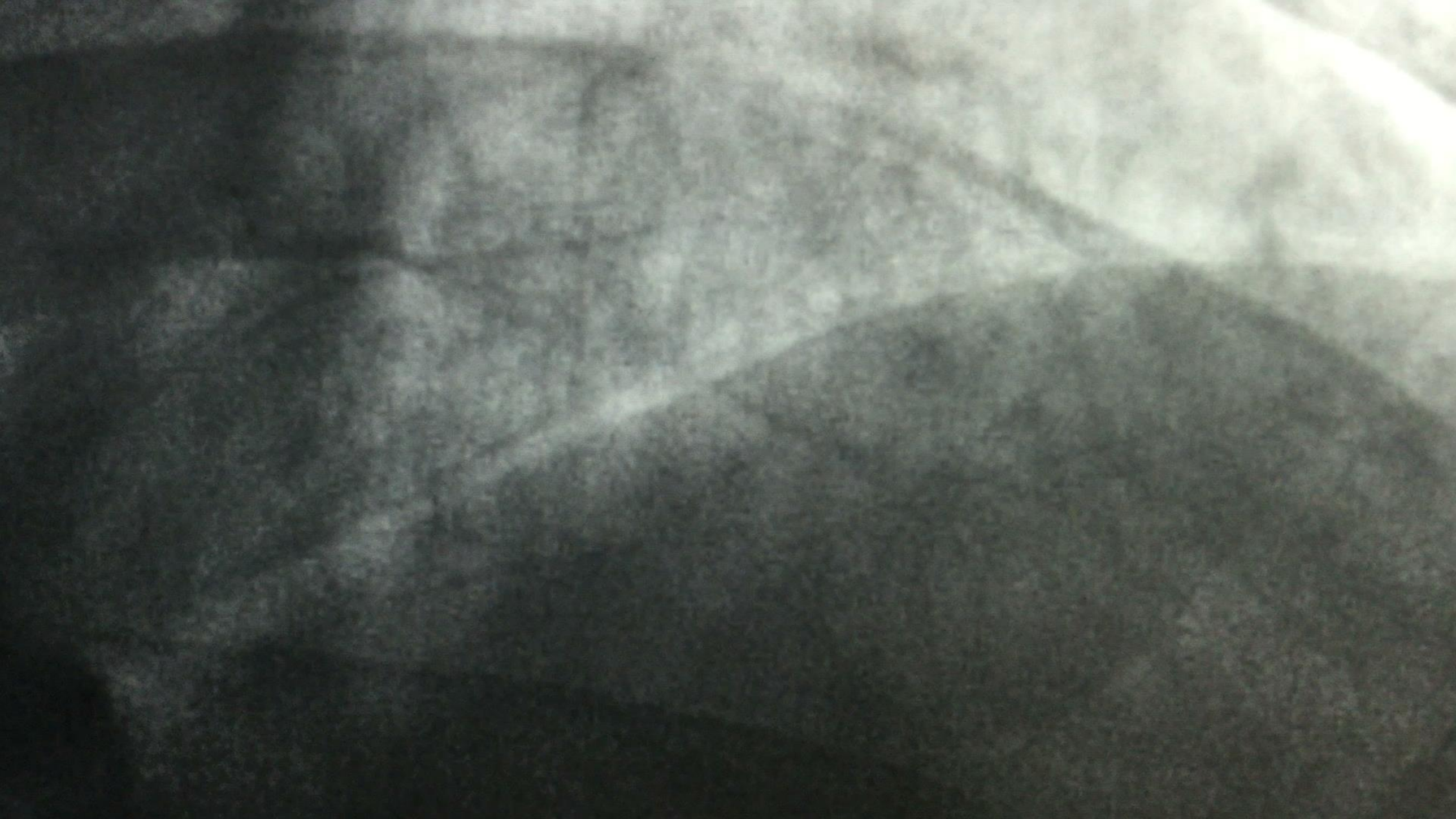
NF-κB (**nuclear factor kappa-light-chain-enhancer of activated B cells**) is a protein complex that controls transcription of DNA, cytokine production and cell survival. NF-κB is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, heavy metals, ultraviolet irradiation, oxidized LDL, and bacterial or viral antigens.[1][2][3][4][5] NF-κB plays a key role in regulating the immune response to infection (κ light chains are critical components of immunoglobulins). Incorrect regulation of NF-κB has been linked to cancer, inflammatory and autoimmune diseases, septic shock, viral infection, and improper immune development. NF-κB has also been implicated in processes of synaptic plasticity and memory.

RHEOLOGY

- The coronary- circulation may be uniquely predisposed to atherosclerosis (804), probably because of high intraluminal pressure and complete flow cessation and possible reversal during systole



- 804. Hunt SC, Hopkins PN, Williams RR. Hypertension: genetics and mechanisms. In: Atherosclerosis and Coronary Artery Disease, edited by Fuster V, Ross R, and Topol EJ. Philadelphia, PA: Lippincott-Raven, 1996, p. 209 –235.



Infection and Atherosclerosis

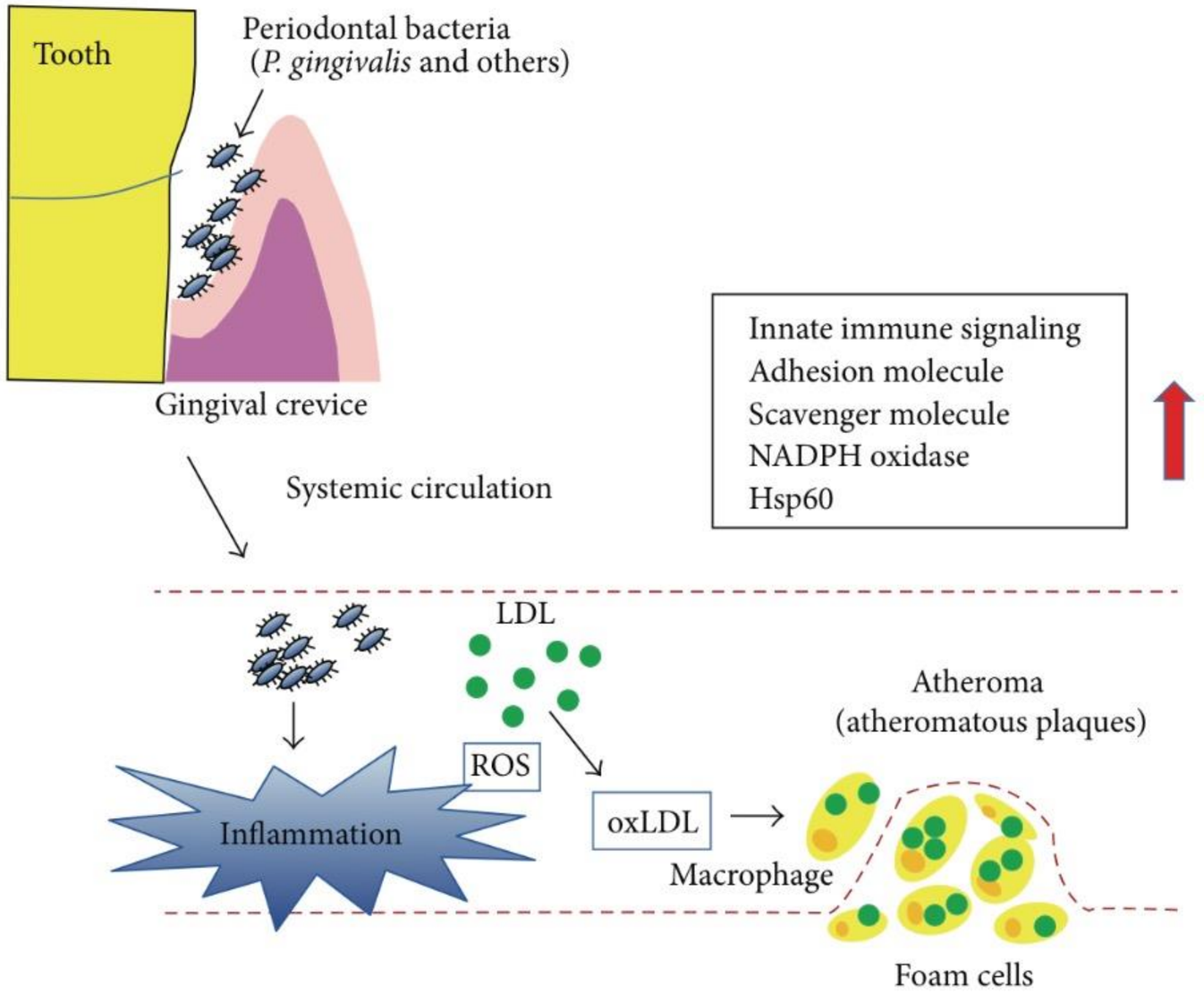

Tooth
Periodontal bacteria
(P. gingivalis and others)
Gingival crevice
Systemic circulation
Innate immune signaling
Adhesion molecule
Scavenger molecule
NADPH oxidase
Hsp60
LDL
ROS
Inflammation
oxLDL
Macrophage
Atheroma
(atheromatous plaques)
Foam cells

FIGURE 1

Porphyromonas gingivalis belongs to the phylum Bacteroidetes and is a nonmotile, Gram-negative, rod-shaped, anaerobic, pathogenic bacterium.

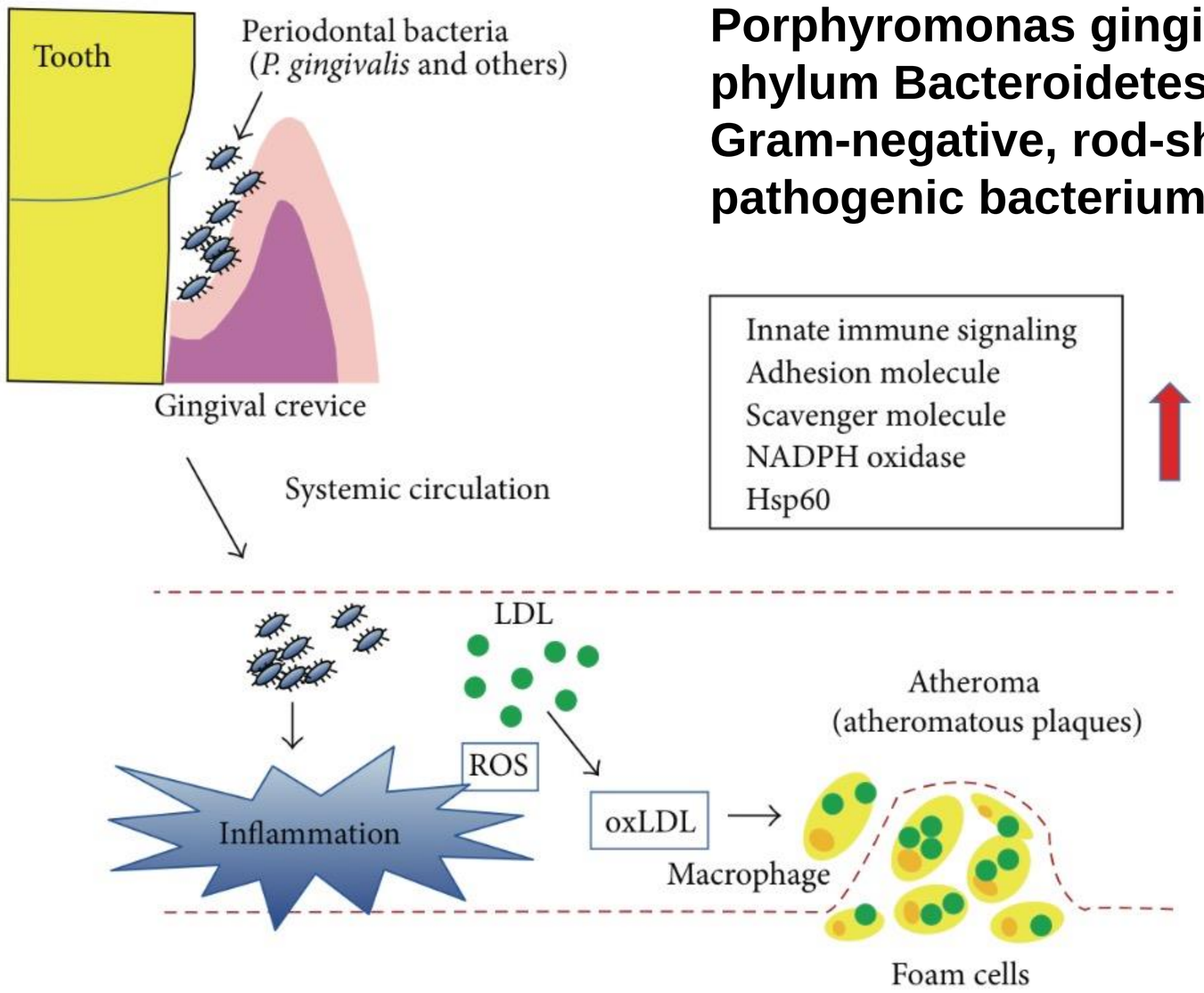
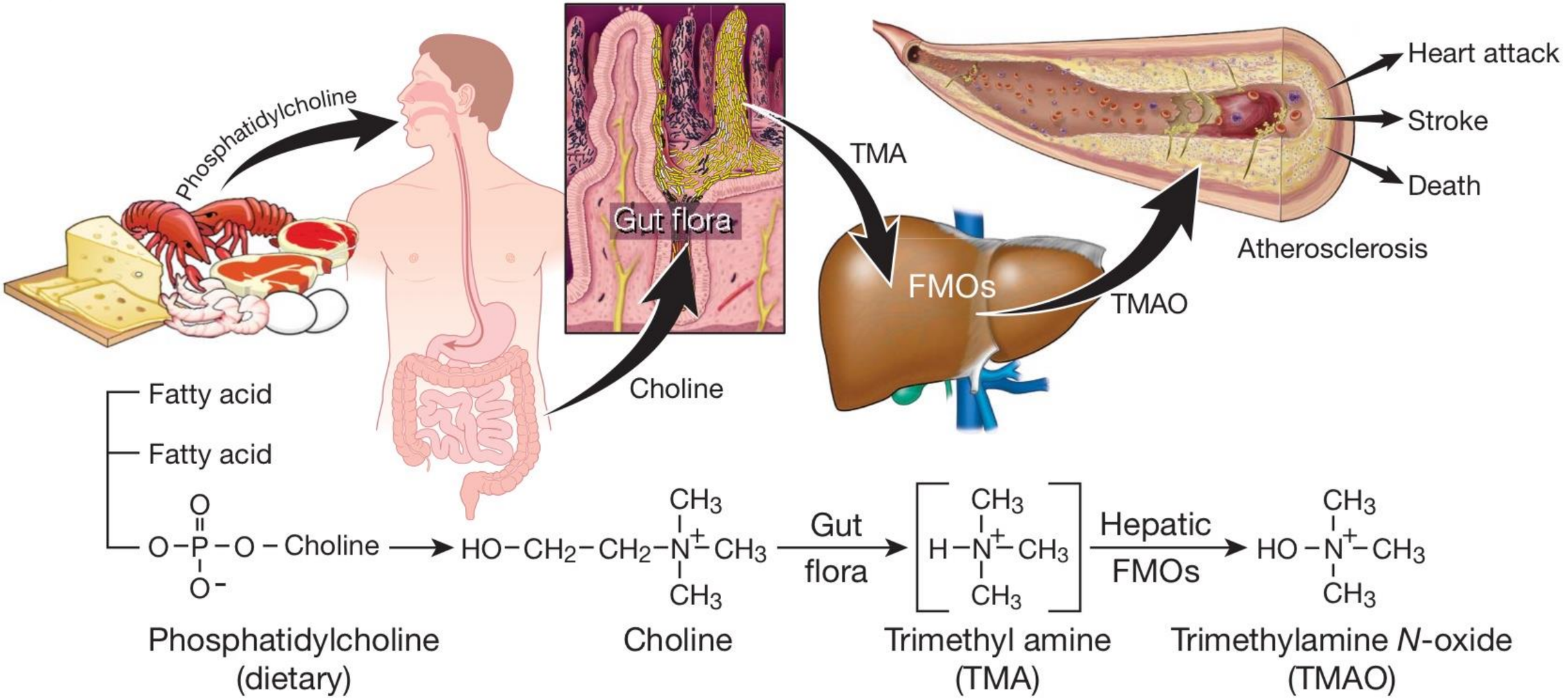
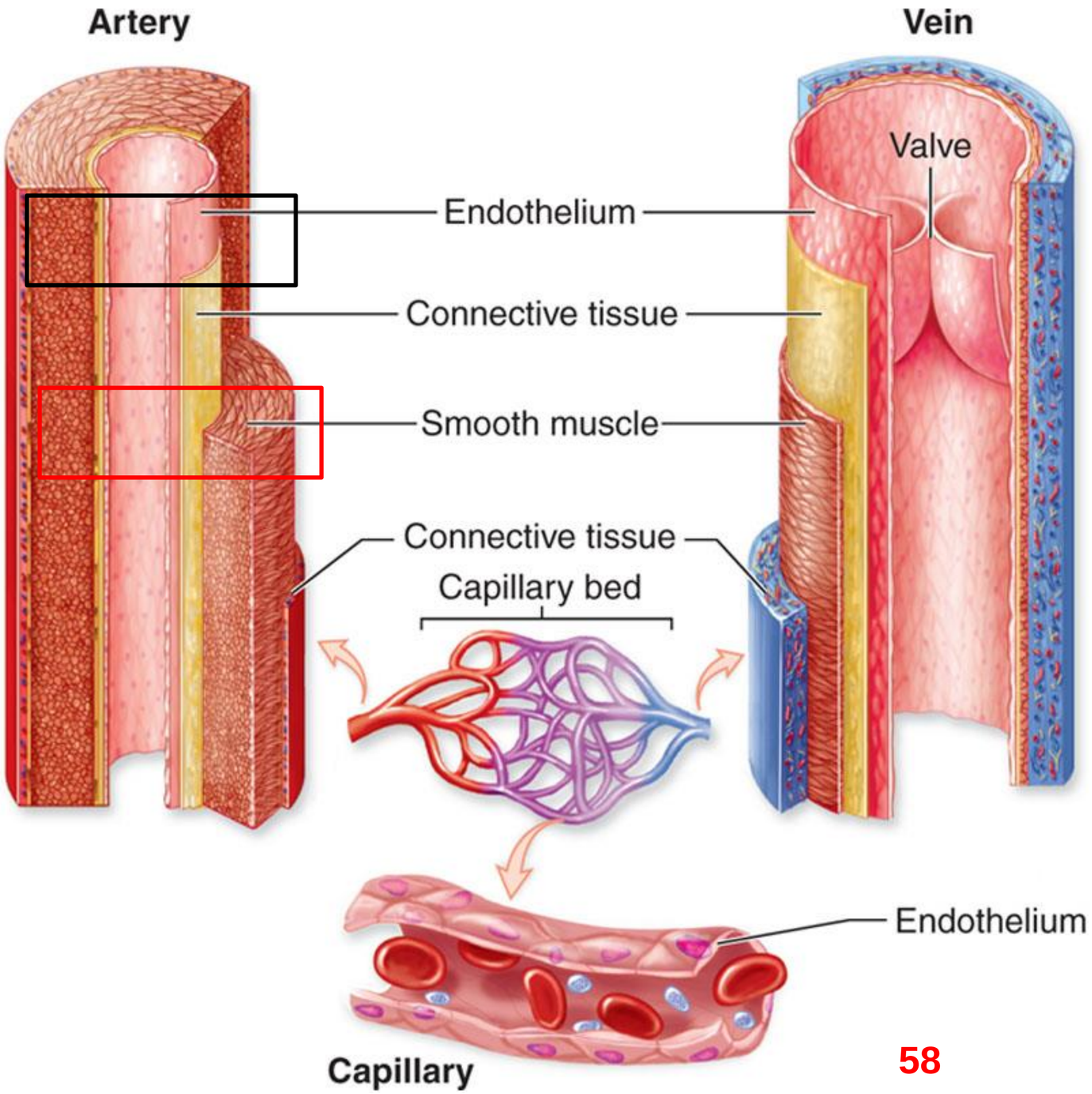


FIGURE 1

Department of Cell Biology, Cleveland Clinic,
Cleveland, OH 44195

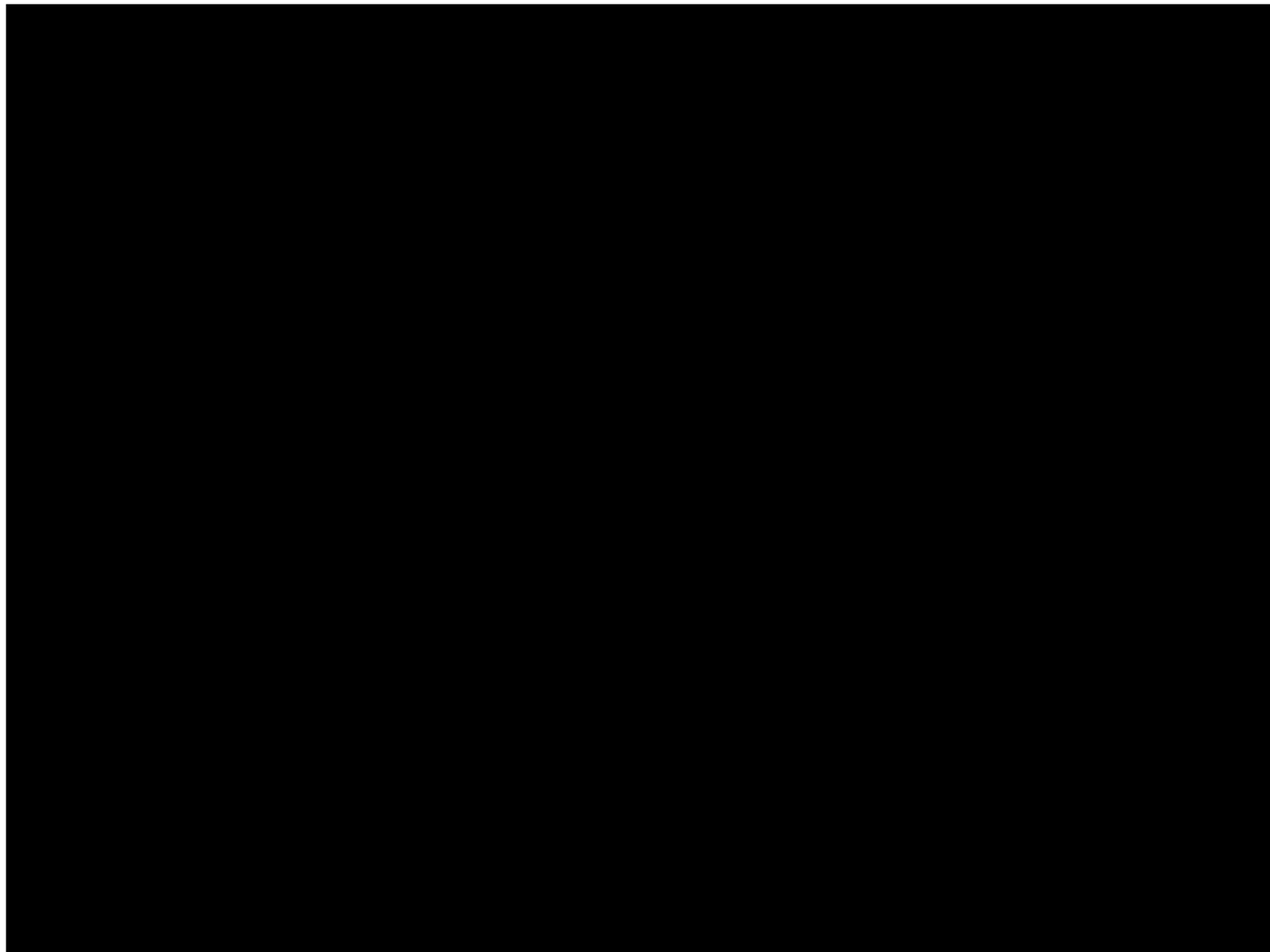


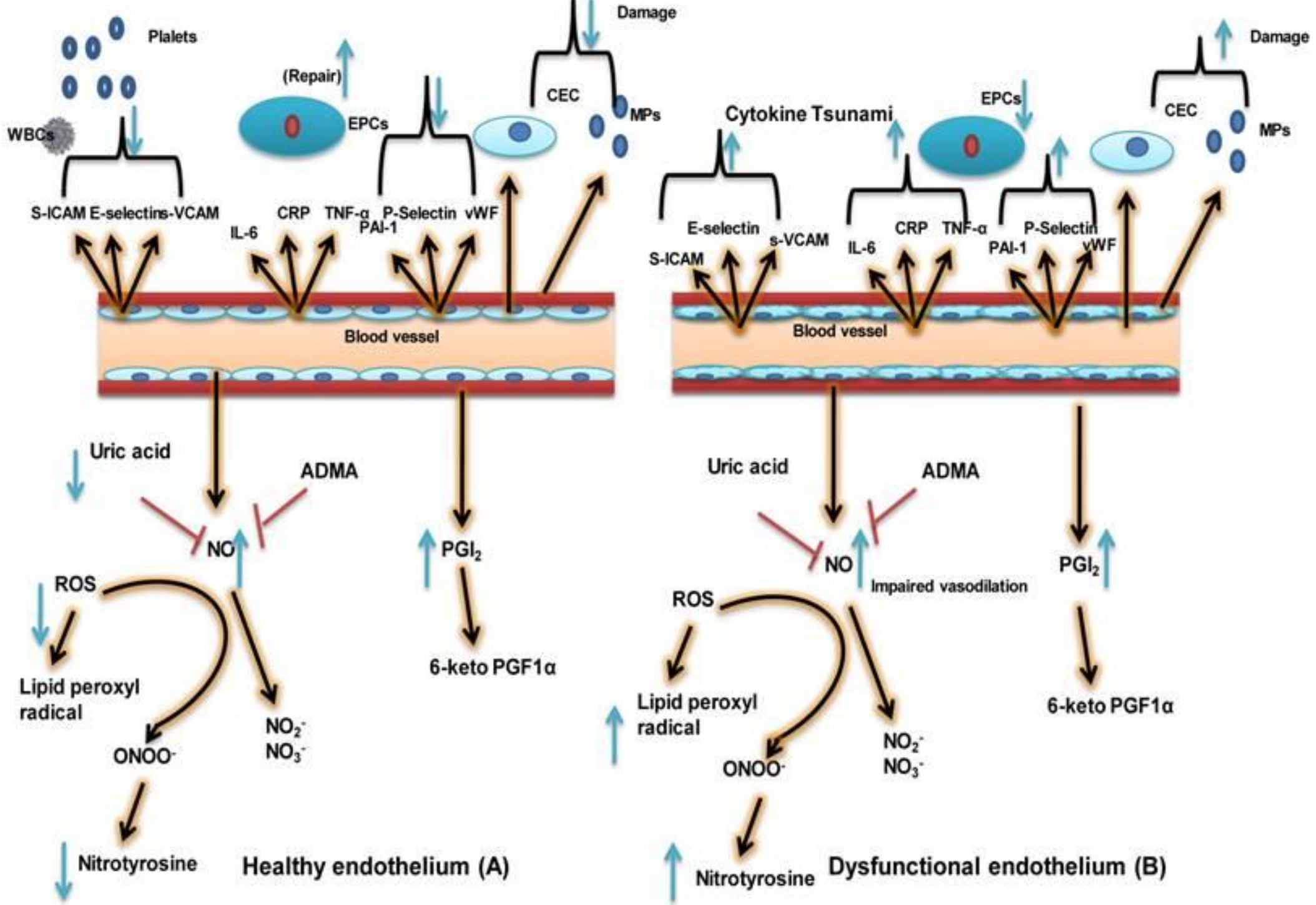


Endothelium actively maintains approximately 60,000 miles of blood vessels in the human body

Clinically manifest atherosclerosis may be viewed as the culmination of four major steps:

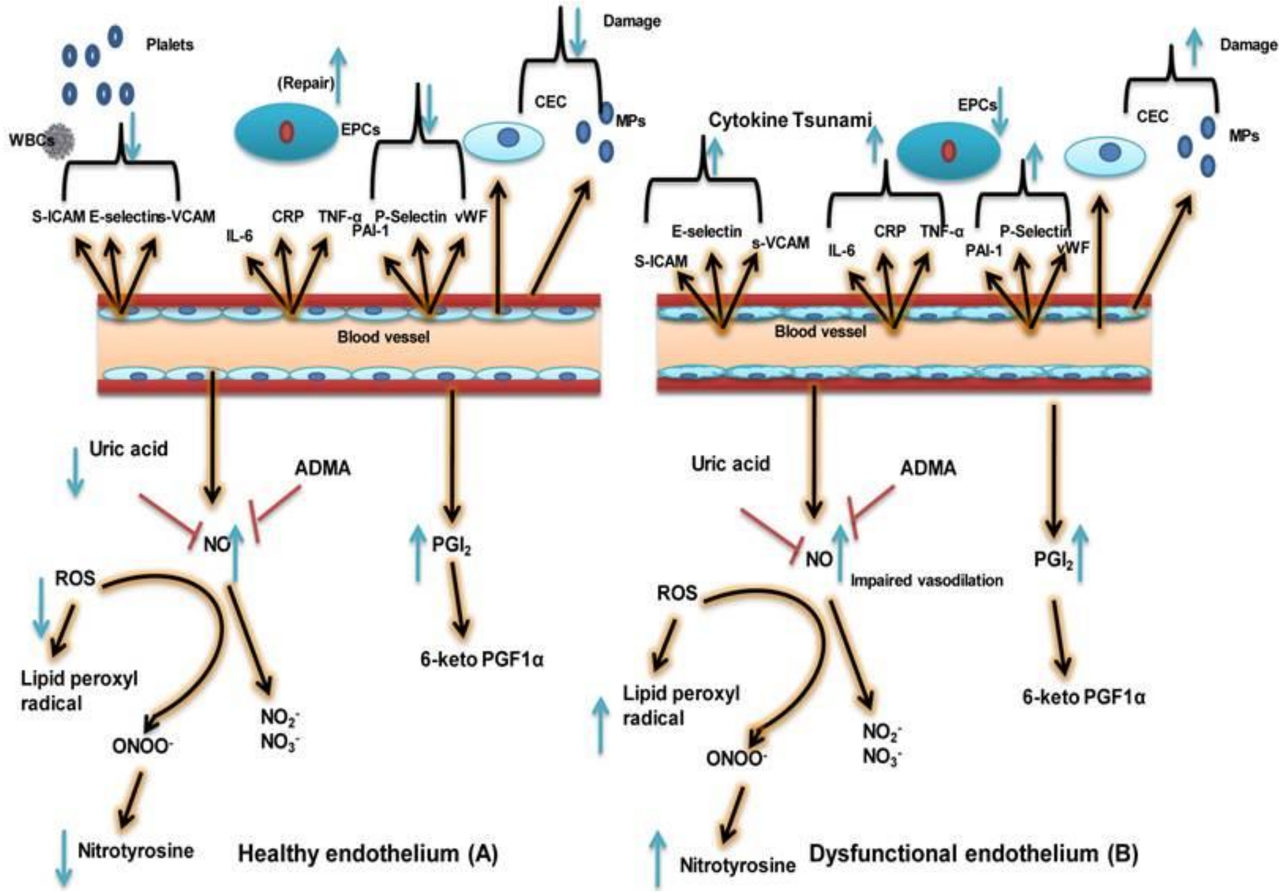
- 1. Initiation of endothelial activation and inflammation
- 2. promotion of intimal lipoprotein deposition, retention, modification, and foam cell formation
- 3. progression of complex plaques by plaque growth, enlargement of the necrotic core, fibrosis, thrombosis, and remodeling
- 4. precipitation of acute events




Plalets
WBCs
(Repair)
EPCs
CEC
Damage
MPs
S-ICAM E-selectins-VCAM
IL-6
CRP
TNF-α
PAI-1
P-Selectin
vWF
Blood vessel
Uric acid
ADMA
NO
ROS
Lipid peroxyl radical
ONOO-
NO2-
NO3-
PGI2
6-keto PGF1α
Nitrotyrosine
Healthy endothelium (A)
Cytokine Tsunami
EPCs
CEC
Damage
MPs
E-selectin
s-VCAM
S-ICAM
IL-6
CRP
TNF-α
PAI-1
P-Selectin
vWF
Blood vessel
Uric acid
ADMA
NO
Impaired vasodilation
ROS
Lipid peroxyl radical
ONOO-
NO2-
NO3-
PGI2
6-keto PGF1α
Nitrotyrosine
Dysfunctional endothelium (B)

Factors involved in Endothelial Function/ Dysfunction

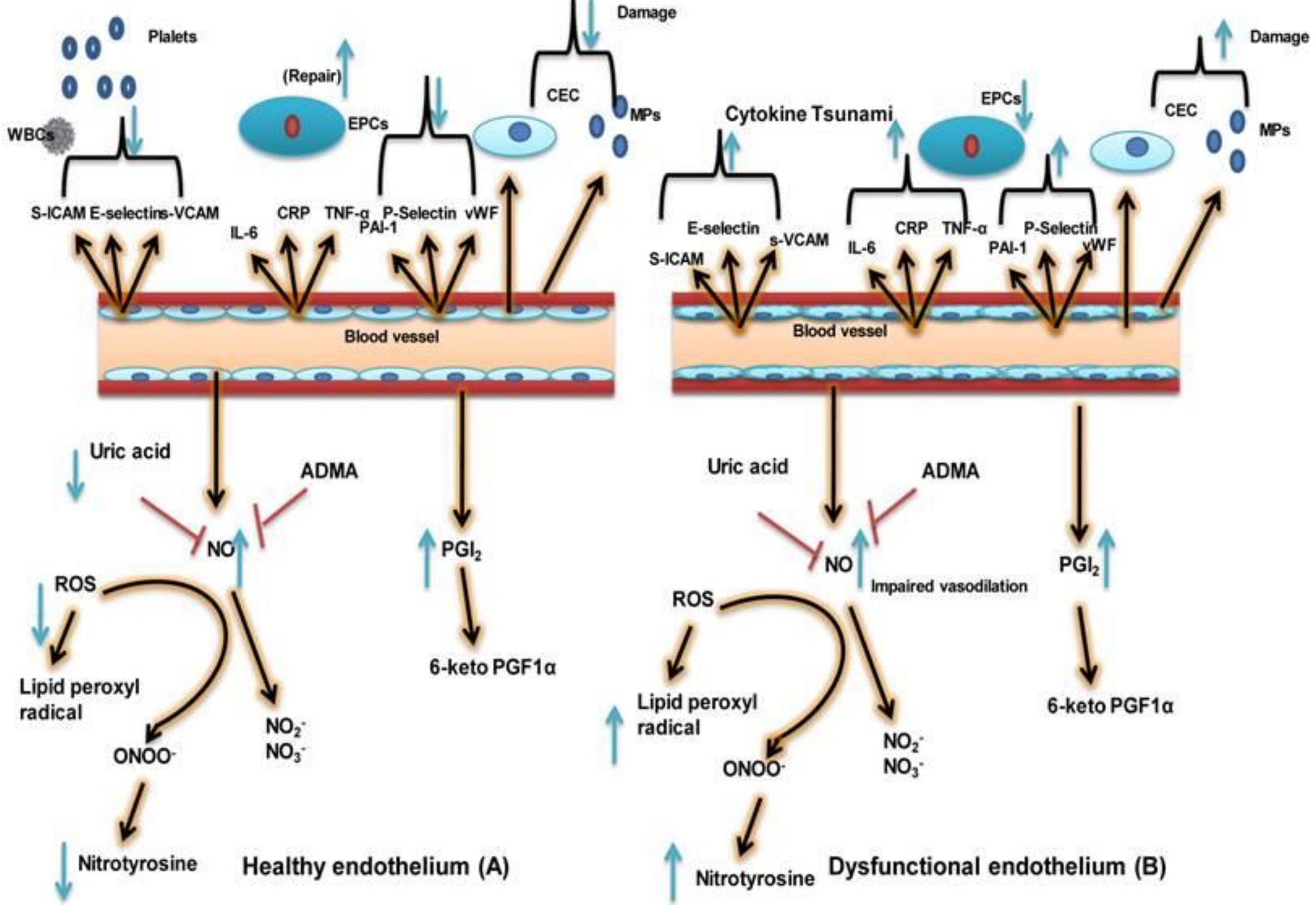
- Soluble intercellular adhesion molecule
- E-selectin (endothelial-leukocyte adhesion molecule)
- Soluble vascular cell adhesion molecule
- Interleukin-6 (IL-6) { important in stimulating immune responses, such as inflammation }
- CRP - an acute-phase protein of hepatic origin that increases following interleukin-6 secretion by macrophages and T cells. Its physiological role is to bind to lysophosphatidylcholine expressed on the surface of dead or dying cells (and some types of bacteria)



Healthy Endothelium

Phenotypic Characteristics

- ***Vasodilatory ,*** **consisting of high levels of vasodilators**
- **Increased levels nitric oxide (NO) and prostacyclin (PGI2)**
- **Decreased levels of reactive oxygen species (ROS) and uric acid**
- ***Anticoagulative***
- **Consisting of low levels of plasminogen activator inhibitor 1 (PAI-1), von Willebrand factor (vWF), and P-selectin.**
- ***Little inflammation***
- **Indicated by low levels of soluble vascular cell adhesion molecule (sVCAM.)**
- **Low levels soluble intercellular adhesion molecule (sICAM), E-selectin, C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6)**
- ***Increased vascular repair capacity***
- **Population of endothelial progenitor cells is high**
- ***Low endothelial stress/damage***
- **Reduced Levels of endothelial microparticles (EMPs) and circulating endothelial cells (CECs)**


Plalets
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Blood vessel
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Healthy endothelium (A)
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Uric acid
ADMA
NO
Impaired vasodilation
ROS
Lipid peroxyl radical
ONOO-
NO2-
NO3-
PGI2
6-keto PGF1α
Nitrotyrosine
Dysfunctional endothelium (B)

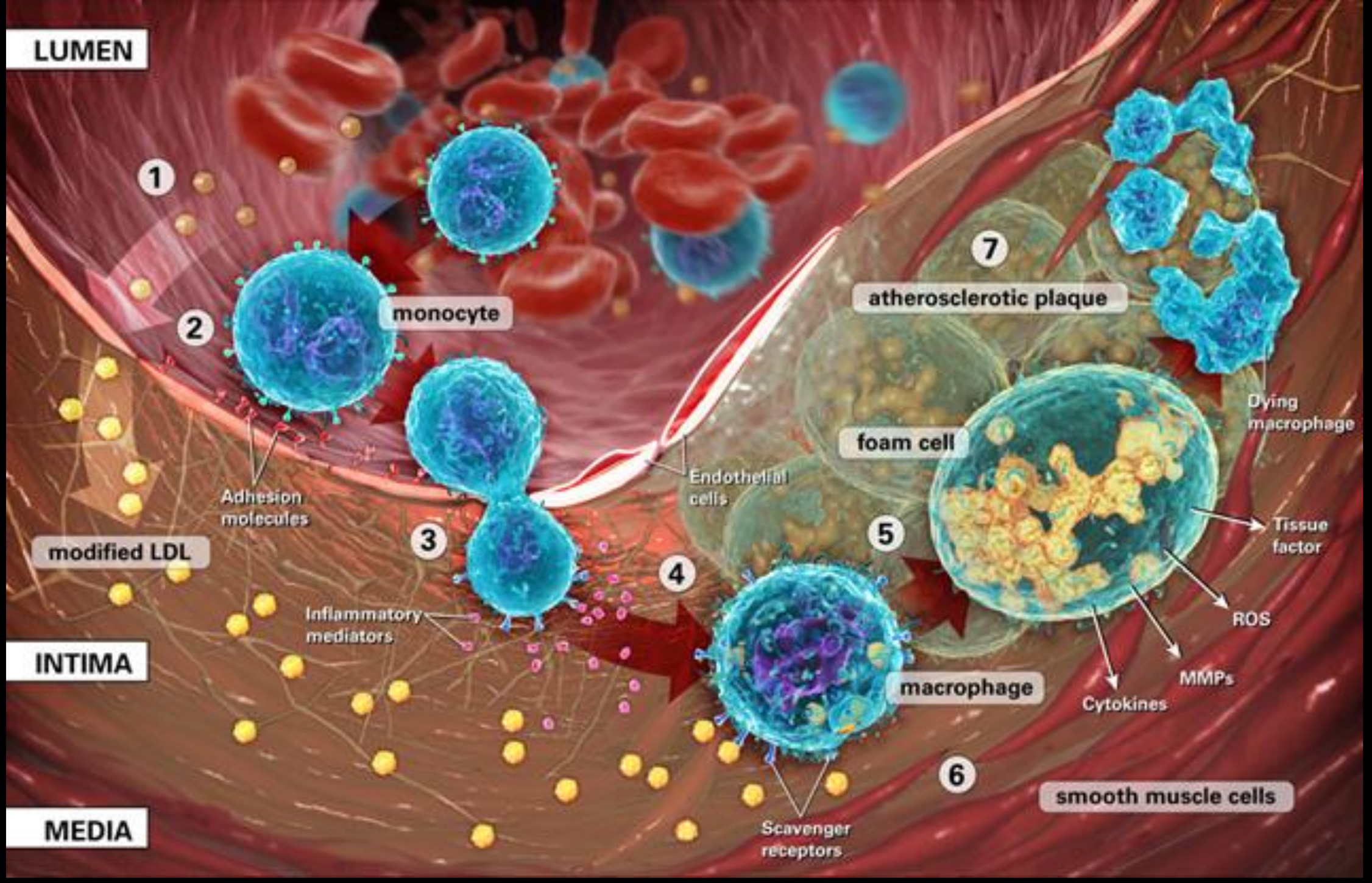
Dysfunctional Endothelium

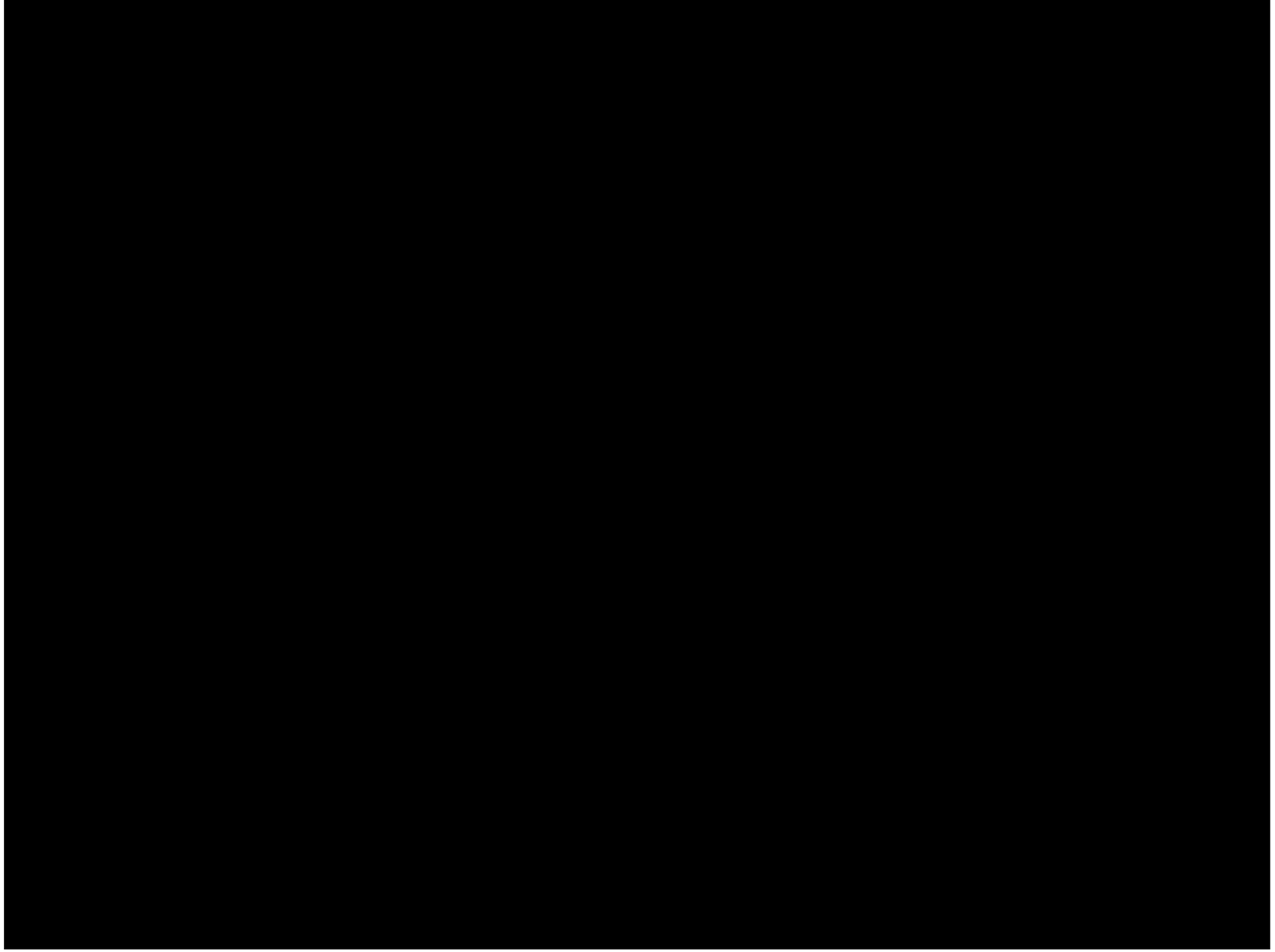
Phenotypic Characteristics

- **Impaired vasodilation**
- **Increased oxidative stress**
- **Uric acid, lipid peroxide radical,Nitrotyrosine and Nitirc oxide**
- **Procoagulant and pro-inflammatory phenotype**
- **Decreased vascular repair capacity**
- **Increased numbers of EMPs and−CECs. 6-keto PGF1α: 6 keto prostaglandin F1-alpha**
- **Increased ADMA; asymmetric dimethyl arginine, inhibitor of NO biosynthesis**
- **Increased EC: endothelial cell**
- **Increased NO2 : nitrite ion, stable degradation product of NO**
- **Increased NO3 nitrate ion, stable degradation product of NO**
- **Increased ONOO− peroxynitrite, the product of superoxide-mediated inactivation of NO**
- **Increased VSMC: vascular smooth muscle cell; WBC: white blood cell. (Modified from Dylan Burger and Rhian MT 2012).**

Cytokines

- ***Cytokines are a broad and loose category of small proteins***
- ***Important in cell signaling.***
- ***Effect on the behaviour of cells around them.***
- ***Cytokines are involved in autocrine signalling, paracrine signalling and endocrine signalling***
- ***Function as immunomodulating agents.***


LUMEN
1
2
monocyte
Adhesion molecules
modified LDL
3
Endothelial cells
4
Inflammatory mediators
INTIMA
MEDIA
Scavenger receptors
5
foam cell
macrophage
6
smooth muscle cells
7
atherosclerotic plaque
Dying macrophage
Tissue factor
ROS
MMPs
Cytokines



The Vunerable Plaque

- **Acute Coronary Syndromes**

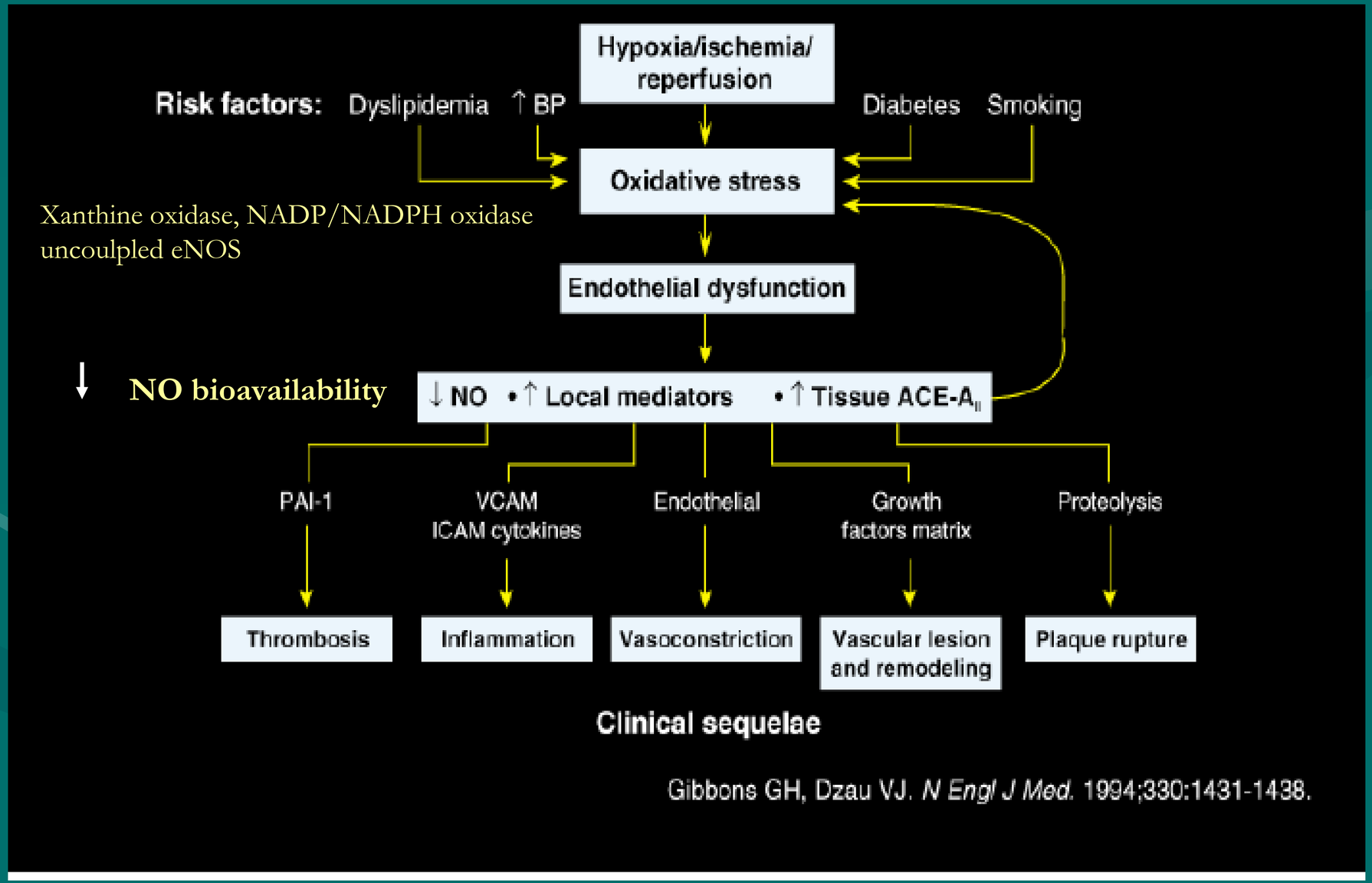
Reported Precipitating Condtions

- **fighting fires (874)**
- **while shoveling snow after a snowstorm (843)**
- **other strenuous exertion, but primarily in those oth- erwise unaccustomed to vigorous exercise (373, 1219)**
- **Earthquakes have been reported to trigger sudden cardiac death (1007).**
- **Increased risks were seen within hours after elevations in air particulates and ozone (481)**
- **Even watching a stressful soccer match (1961)**
- **rooting for the losing Super Bowl team seems to have its risks (920)**
- **Recently, risk of MI or CHD death was found to rise 21-fold during the 24 h following the loss of a spouse or other close loved one (1238)**
- **5.6-fold within the first week after the diagnosis of cancer (499)**
- **The associated risks for such events is not always contingent on preexisting coronary artery dis- ease (CAD).**

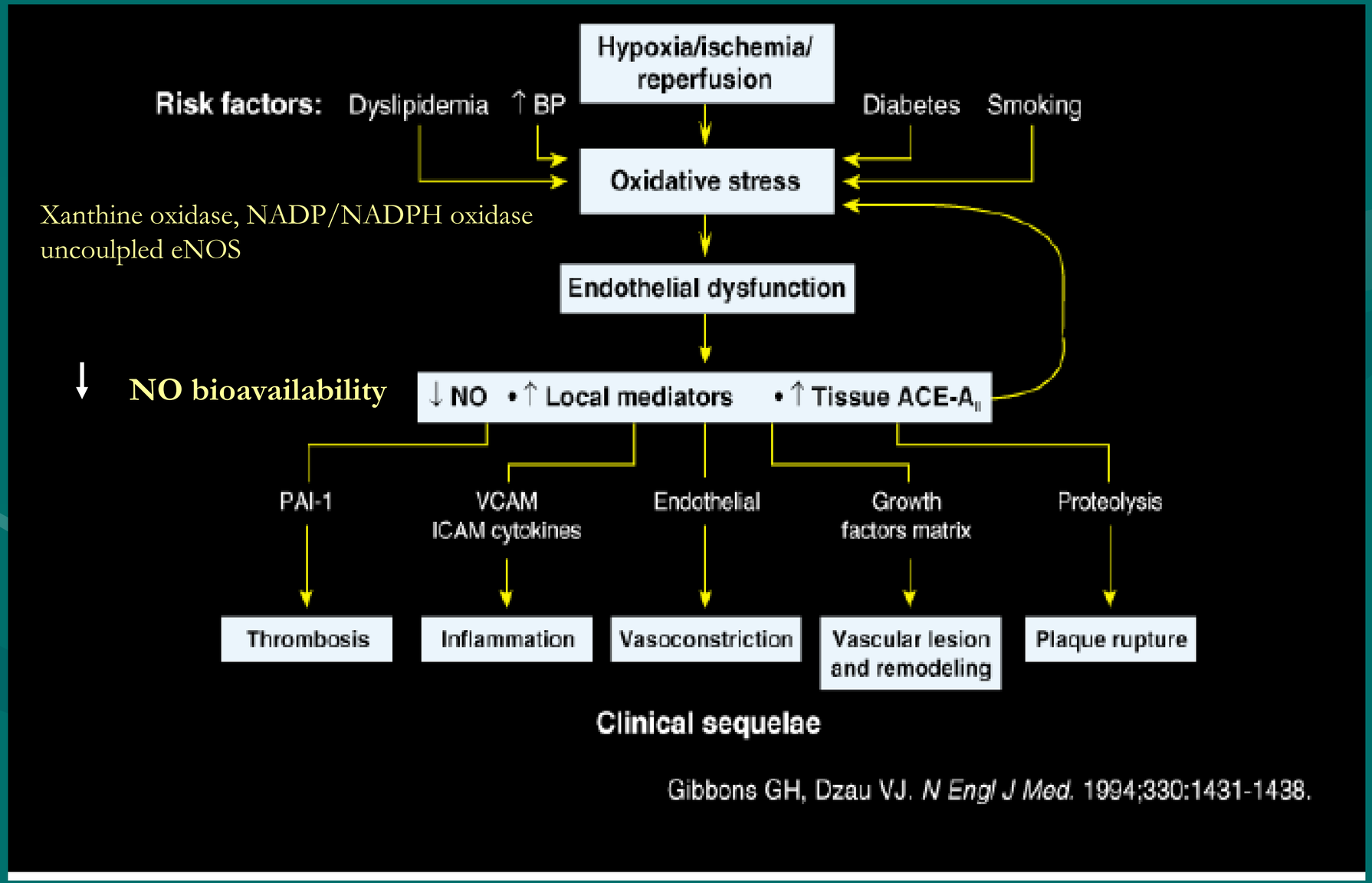
Physiol Rev 93: 1317–1542, 2013
doi:10.1152/physrev.00004.2012

"I want you to keep eating pizza and cheeseburgers. At this point, a salad might shock your system and kill you."

Unifying model: Endothelial dysfunction to CVD

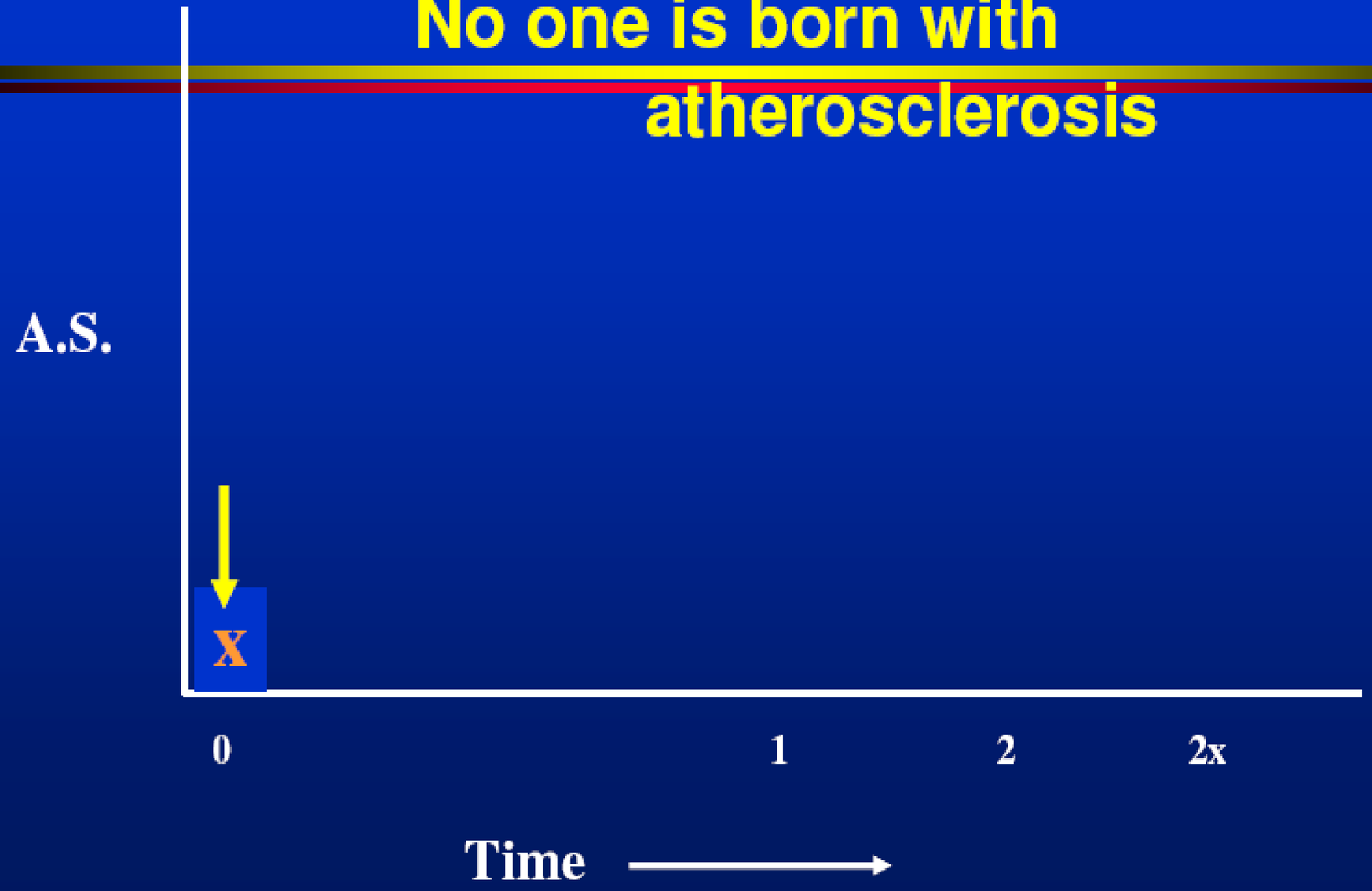


Unifying model: Endothelial dysfunction to CVD

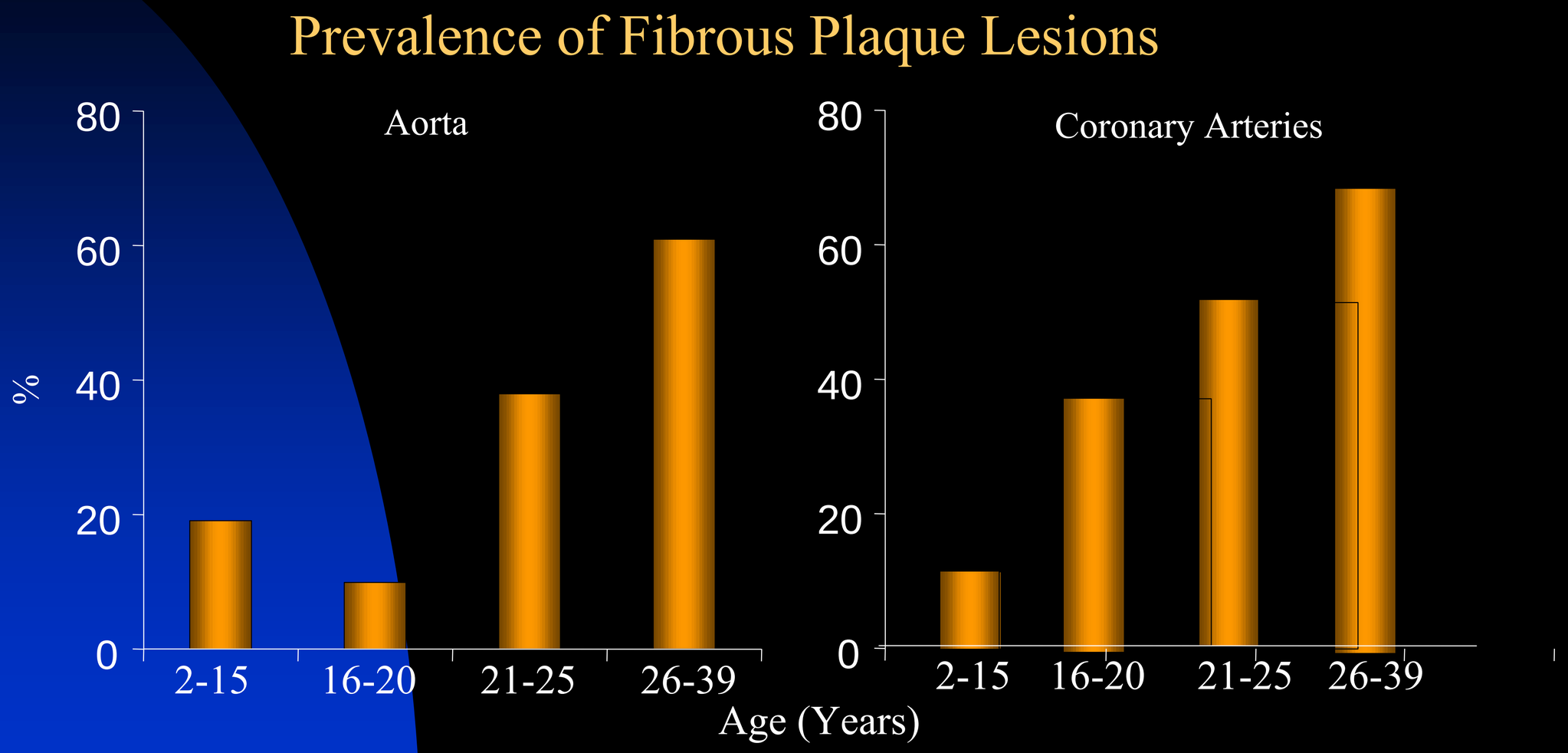


Coronary atherosclerotic burden –

No one is born with atherosclerosis



Early Appearance of Atherosclerosis: Bogalusa Heart Study



p = 0.001 for trend toward increasing prevalence with age in aorta and coronary arteries.

Diet & Free Radicals

Free Radicals are produced in response to many different everyday things, such as:		
Cooked Food (especially animal products (chickens and other birds, cows, pigs, fishes, lambs, eggs, dairy products, animal fats and proteins, and metabolic waste products contained in animal tissues and organs) and refined foods such as white sugar, white flours, hydrogenated oils, etc.) Any foods other than raw foods from the plant kingdom Environmental pollution (from air, water, household chemicals, asbestos, pesticide residues, & other man-made pollutants including the out-gassing of plastic and other synthetics) Preservatives, Colorings, and other food additives Metabolism	Smoking and passive smoke Exposure to excess heat or cold Medical Treatment including medications Alcohol Bacteria Parasites Chemotherapy & Radiation Prescription & Over The Counter Drugs Exercise Lack of Truly Clean & Fresh Air Radiation (including electromagnetic radiation from anything electric such as outside power lines; wires in your home/work, TVs, computer monitors, etc.	Heart Disease & Strokes Computers/Monitors/TVs Use of Ovens **(microwaves are the worst!)** Refrigerators Nutrient deficiencies (major & minor) which can still occur even on the best of diets (even fresh, raw foods contain only as many nutrients as the soil in which they were grown) Sunburn Stress (any) Judgment or any other non-positive mental state Synthetic materials such as Polyester, Acetate, Satin, Plastics, etc. Tap Water, etc.

Diseases Linked with Free Radicals

- Free radicals damage low-density lipoproteins (LDLs), cell proteins, and DNA
- Increase risk for chronic diseases
  - Heart disease
  - Various cancers
  - Diabetes
  - Cataracts
  - Alzheimer's disease
  - Parkinson's disease

Free Radicals….???

- Free radicals are organic molecules responsible for ageing, tissue damage, and possibly some diseases.
- These molecules are very unstable, therefore they look to bond with other molecules, destroying their vigor and perpetuating the detrimental process.
- Antioxidants, present in many foods, are molecules that prevent free radicals from harming healthy tissue.

Genomic Medicine: A Revolution in Medical Practice in the 21st Century

Francis S. Collins, M.D., Ph.D.
National Human Genome Research Institute

World Health Care Congress
April 17, 2006

1990

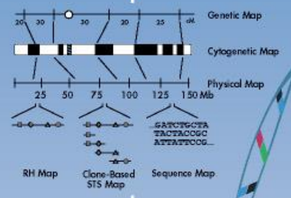
Human Genome Project (HGP) launched in the U.S.

Ethical, Legal, and Social Implications (ELSI) programs founded at NIH and DOE

First gene for breast cancer (BRCA1) mapped

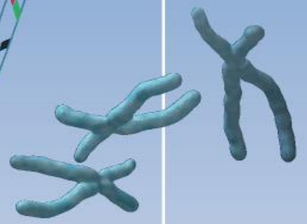
1991

First U.S. Genome Centers established



1992

Second-generation human genetic map developed



Rapid data release guidelines established by NIH and DOE

1993

New five-year plan for the HGP in the U.S. published

Sanger Centre founded (later renamed Wellcome Trust Sanger Institute)

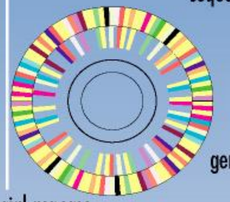
The Wellcome Trust

1994

HGP's human genetic mapping goal achieved

1995

HGP's human physical mapping goal achieved



First bacterial genome (*H. influenzae*) sequenced

U.S. Equal Employment Opportunity Commission issues policy on genetic discrimination in the workplace

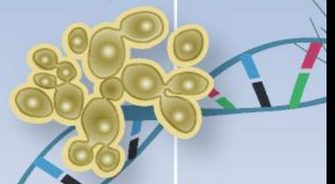
1996

First human gene map established

Pilot projects for human genome sequencing begin in U.S.

First archael genome sequenced

Yeast (*S. cerevisiae*) genome sequenced



HGP's mouse genetic mapping goal achieved

Bermuda principles for rapid and open data release established

World Congress

1997

DOE forms Joint Genome Institute

JGI DOE JOINT GENOME INSTITUTE US DEPARTMENT OF ENERGY OFFICE OF SCIENCE

NCHGR becomes NHGRI

National Human Genome Research Institute

E. coli genome sequenced

Genoscope (French National Genome Sequencing Center) founded

1998

Incorporation of 30,000 genes into human genome map

New five-year plan for the HGP in the U.S. published

RIKEN Genomic Sciences Center (Japan) established

Roundworm (*C. elegans*) genome sequenced

SNP initiative begins

GTGCT
GTCCT

Chinese National Human Genome Centers (in Beijing and Shanghai) established

1999

Full-scale human sequencing begins

Sequence of first human chromosome (chromosome 22) completed

2000

Draft version of human genome sequence completed

President Clinton and Prime Minister Blair support free access to genome information

Fruit fly (*D. melanogaster*) genome sequenced

Mustard cress (*A. thaliana*) genome sequenced

Executive order bans genetic discrimination in U.S. federal workplace

2001

Draft version of human genome sequence published

10,000 full-length human cDNAs sequenced

Mammalian Gene Collection

2002

Draft version of mouse genome sequence completed and published

Draft version of rat genome sequence completed

Draft version of rice genome sequence completed and published

2003

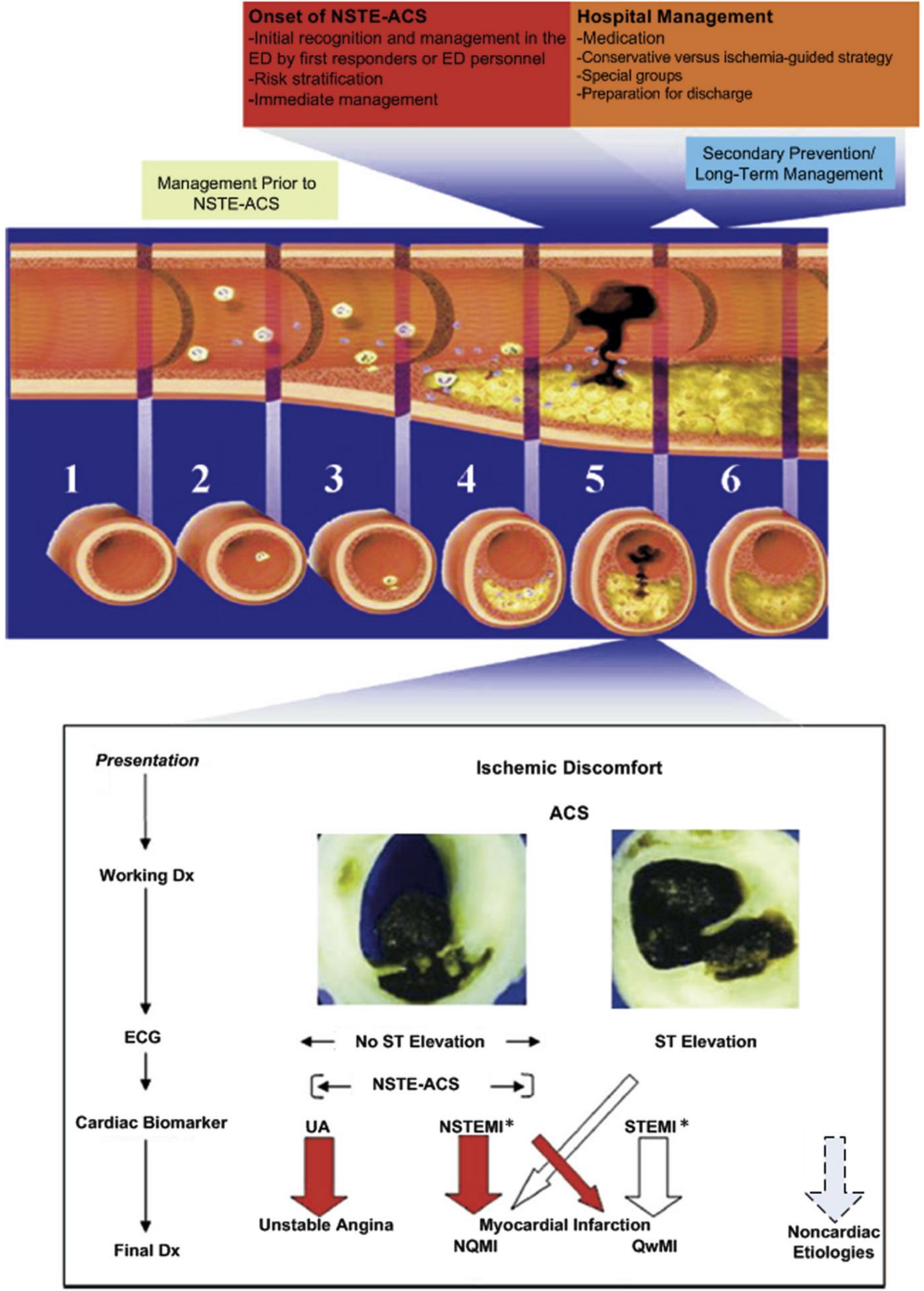
Finished version of human genome sequence completed

HGP ends with all goals achieved

to be continued..

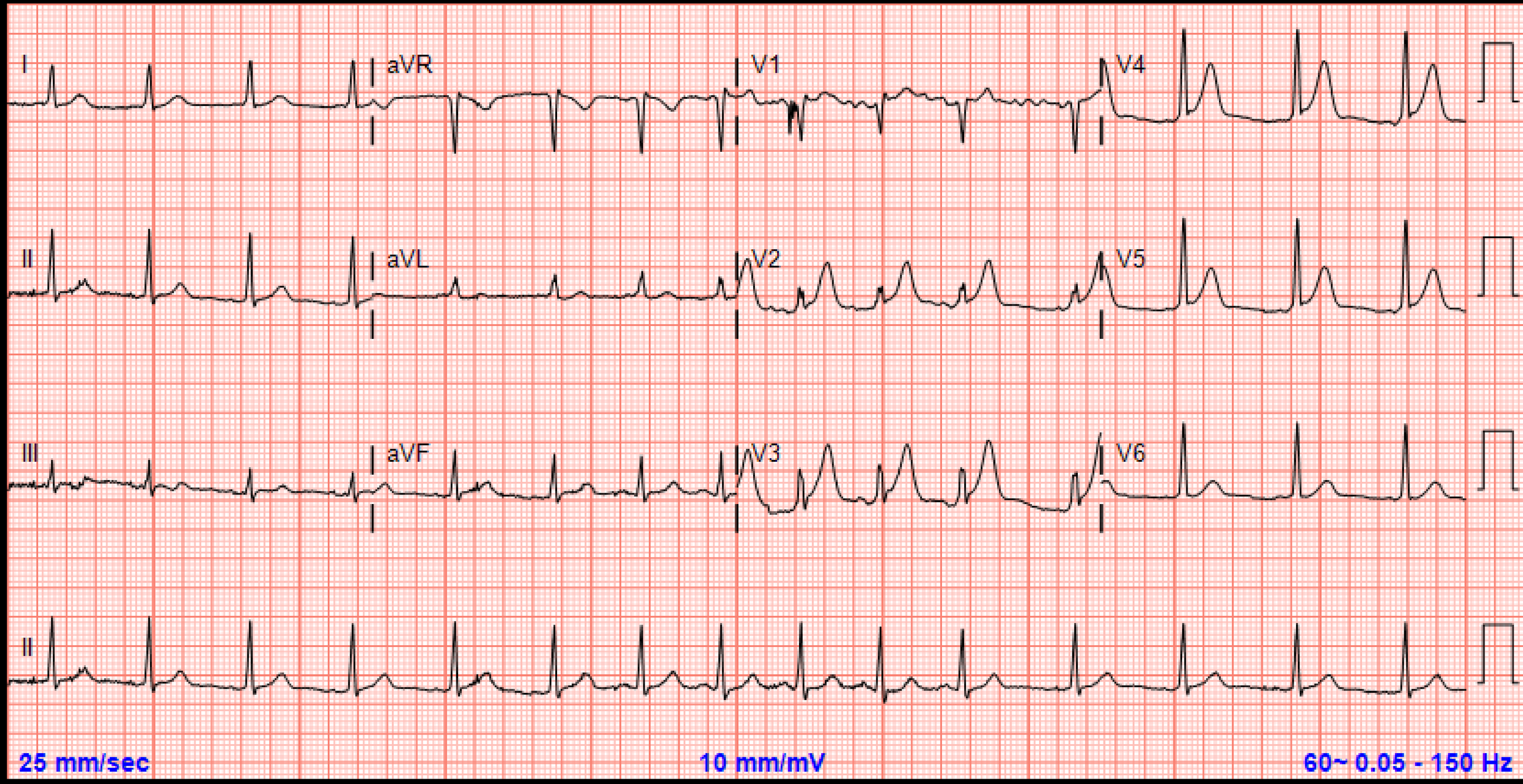
World Congress

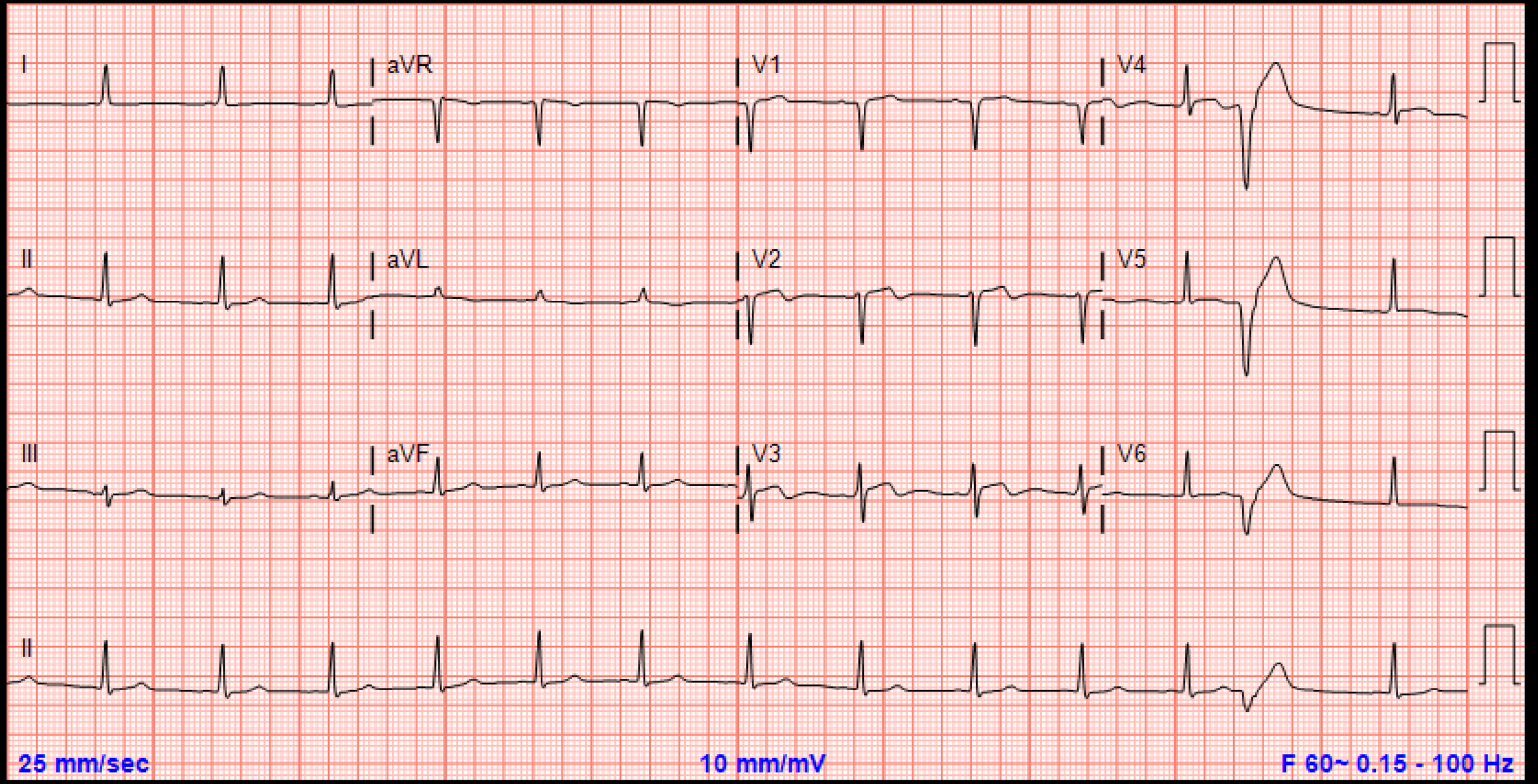
There are an estimated 20,000-25,000 human protein-coding genes. The estimate


Onset of NSTE-ACS
-Initial recognition and management in the ED by first responders or ED personnel
-Risk stratification
-Immediate management
Hospital Management
-Medication
-Conservative versus ischemia-guided strategy
-Special groups
-Preparation for discharge
Secondary Prevention/ Long-Term Management
Management Prior to NSTE-ACS
1
2
3
4
5
6
Presentation
Ischemic Discomfort
ACS
Working Dx
ECG
No ST Elevation
ST Elevation
NSTE-ACS
Cardiac Biomarker
UA
NSTEMI*
STEMI*
Unstable Angina
Myocardial Infarction
NQMI
QwMI
Noncardiac Etiologies
Final Dx

Definitions

- Life Expectancy - Expected # of years of life remaining at a given age.
- Life Span - # of years we live
- Health Span - # of years we live disease free


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
25 mm/sec
10 mm/mV
60~ 0.05 - 150 Hz


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
25 mm/sec
10 mm/mV
F 60~ 0.15 - 100 Hz

Clinically manifest atherosclerosis may be viewed as the culmination of four major steps:

- **1. Initiation of endothelial activation and inflammation**
- **2. promotion of intimal lipoprotein deposition, retention, modification, and foam cell formation**
- **3. progression of complex plaques by plaque growth, enlargement of the necrotic core, fibrosis, thrombosis, and remodeling**
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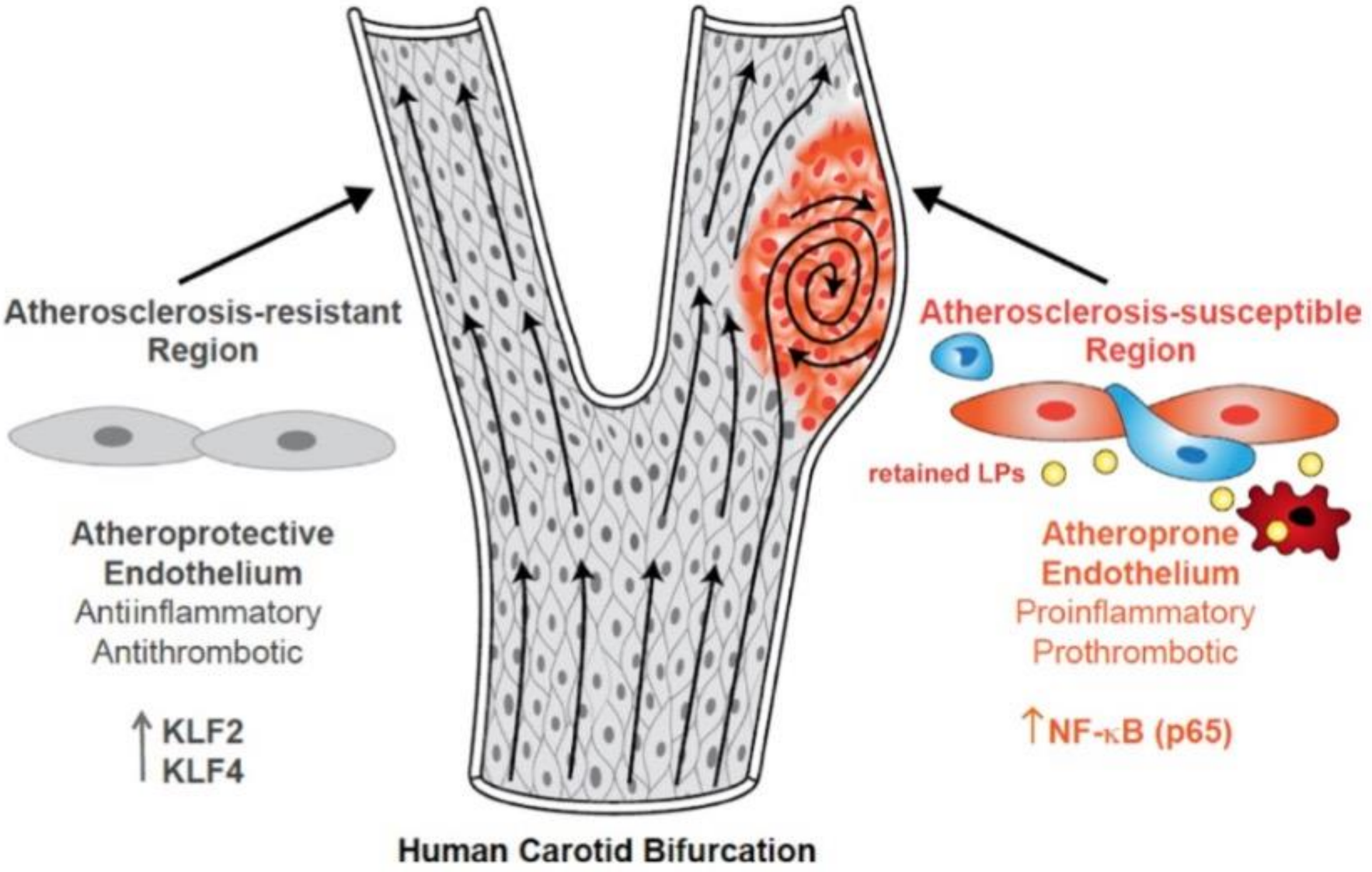

Atherosclerosis-resistant Region
Atheroprotective Endothelium
Antiinflammatory
Antithrombotic
↑ KLF2
KLF4
Atherosclerosis-susceptible Region
retained LPs
Atheroprone Endothelium
Proinflammatory
Prothrombotic
↑ NF-κB (p65)
Human Carotid Bifurcation

RHEOLOGY

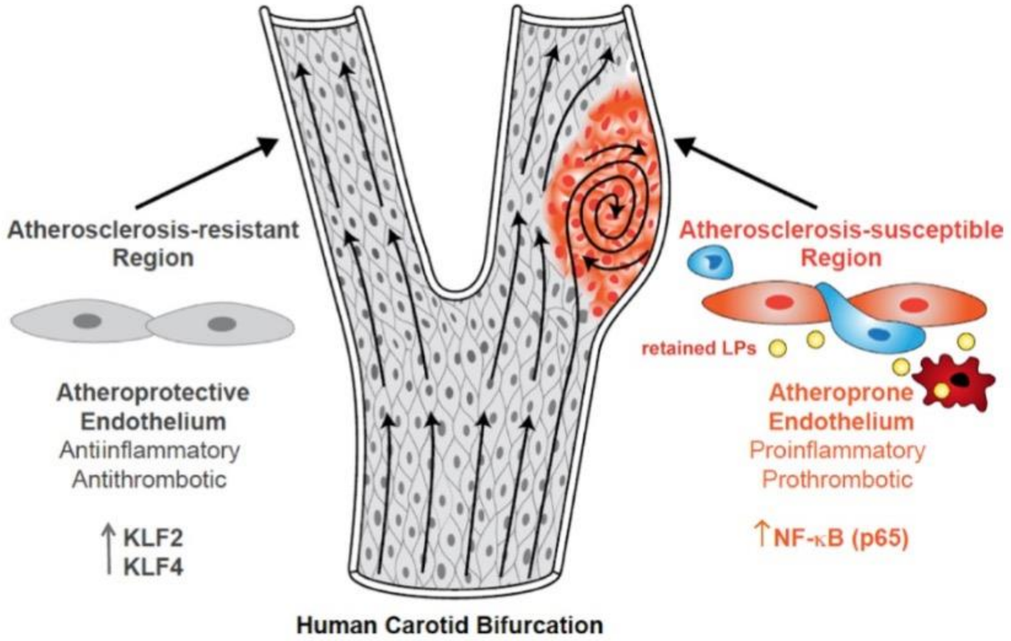
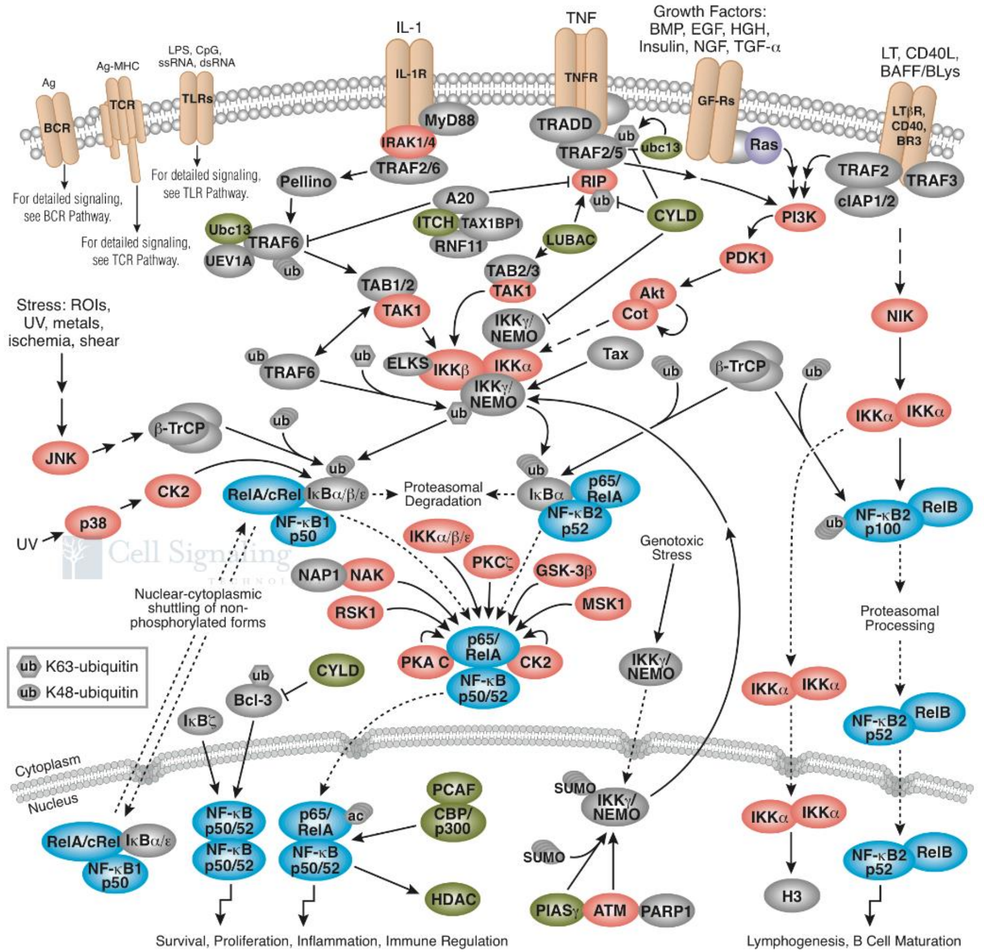


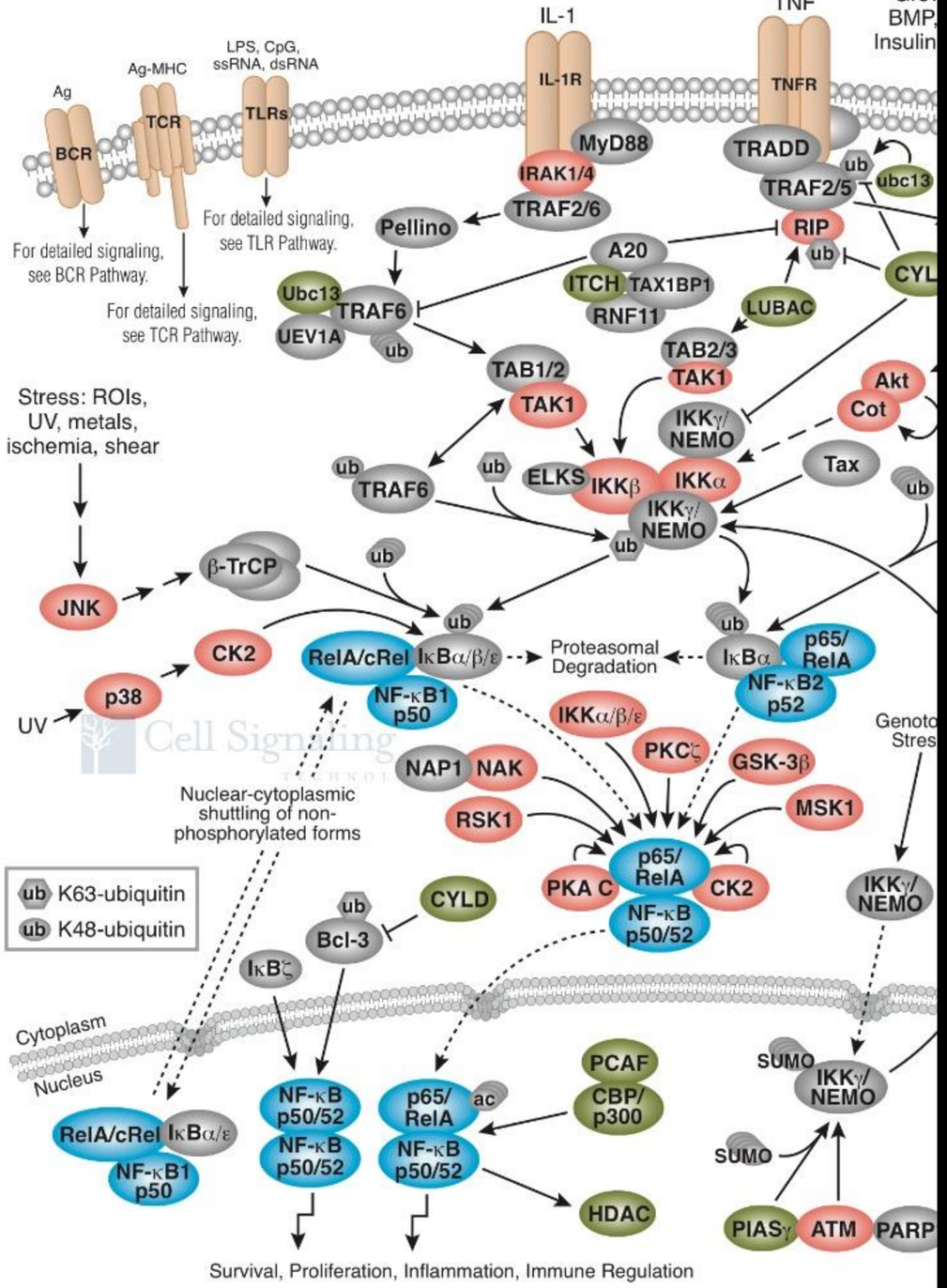
Figure 1. **Vascular endothelial cells and the development of early atherosclerotic lesions.** Early lesions of atherosclerosis in the human carotid artery develop in the area of a major curvature (carotid sinus) exposed to low time-average shear stress, a high oscillatory shear index, and steep temporal and spatial gradients. Endothelial cells at this site display an atheroprone phenotype, which promotes a proinflammatory milieu driven by the priming of the NF-κB signaling pathway, which is then perpetuated in response to subendothelial apoB LPs. NF-κB activation promotes the entry of blood-borne monocytes (blue cells) through the junctions of endothelial cells (orange cells) into the intima, and there, monocytes differentiate into macrophages (red cells). In contrast, arterial geometries that are exposed to uniform laminar flow evoke an atheroprotective endothelial cell phenotype driven by the transcriptional integrators KLF2 and KLF4. This atheroprotective endothelial phenotype, together with a decrease in LP retention, promotes an antiinflammatory and antithrombotic environment that affords relative protection from atherosclerotic lesion development.

NF-κB Signaling



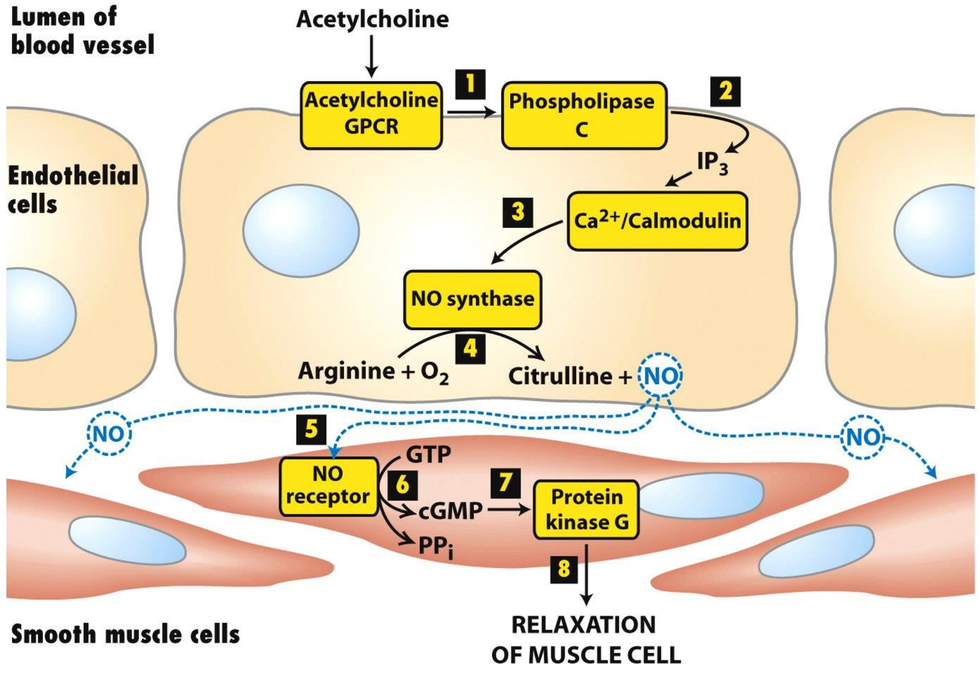
Pathway Diagram Keys

Kinase	Enzyme	G-protein	Direct Inhibitory Modification	Tentative Inhibitory Modification	Translocation
Phosphatase	pro-apoptotic	Acetylase	Multistep Stimulatory Modification	Separation of Subunits or Cleavage Products	Transcriptional Stimulatory Modification
Transcription Factor	pro-survival	Deacetylase	Multistep Inhibitory Modification	Joining of Subunits	Transcriptional Inhibitory Modification
Caspase	GAP/GEF	Ribosomal subunit	Tentative Stimulatory Modification		
Receptor	GTPase	Direct Stimulatory Modification			


IL-1
TNF
BMP,
Insulin
LPS, CpG,
ssRNA, dsRNA
Ag-MHC
Ag
TCR
TLRs
BCR
IL-1R
TNFR
MyD88
TRADD
ub
ubc13
IRAK1/4
TRAF2/5
TRAF2/6
Pellino
RIP
A20
ITCH
TAX1BP1
RNF11
CYL
LUBAC
Ubc13
TRAF6
UEV1A
ub
TAB2/3
TAK1
TAB1/2
TAK1
Akt
Cot
IKKγ/
NEMO
Stress: ROIs,
UV, metals,
ischemia, shear
ub
TRAF6
ELKS
IKKβ
IKKα
Tax
IKKγ/
NEMO
ub
β-TrCP
ub
JNK
ub
CK2
RelA/cRel
IκBα/β/ε
Proteasomal
Degradation
IκBα
p65/
RelA
NF-κB2
p52
NF-κB1
p50
p38
UV
IKKα/β/ε
PKCζ
GSK-3β
Genoto
Stres
NAP1
NAK
RSK1
MSK1
Nuclear-cytoplasmic
shuttling of non-
phosphorylated forms
p65/
RelA
PKA C
CK2
NF-κB
p50/52
ub K63-ubiquitin
ub K48-ubiquitin
CYLD
ub
Bcl-3
IκBζ
IKKγ/
NEMO
Cytoplasm
Nucleus
PCAF
CBP/
p300
SUMO
IKKγ/
NEMO
RelA/cRel
IκBα/ε
NF-κB1
p50
NF-κB
p50/52
NF-κB
p50/52
p65/
RelA
ac
NF-κB
p50/52
HDAC
SUMO
PIASγ
ATM
PARP
Survival, Proliferation, Inflammation, Immune Regulation
For detailed signaling,
see BCR Pathway.
For detailed signaling,
see TLR Pathway.
For detailed signaling,
see TCR Pathway.

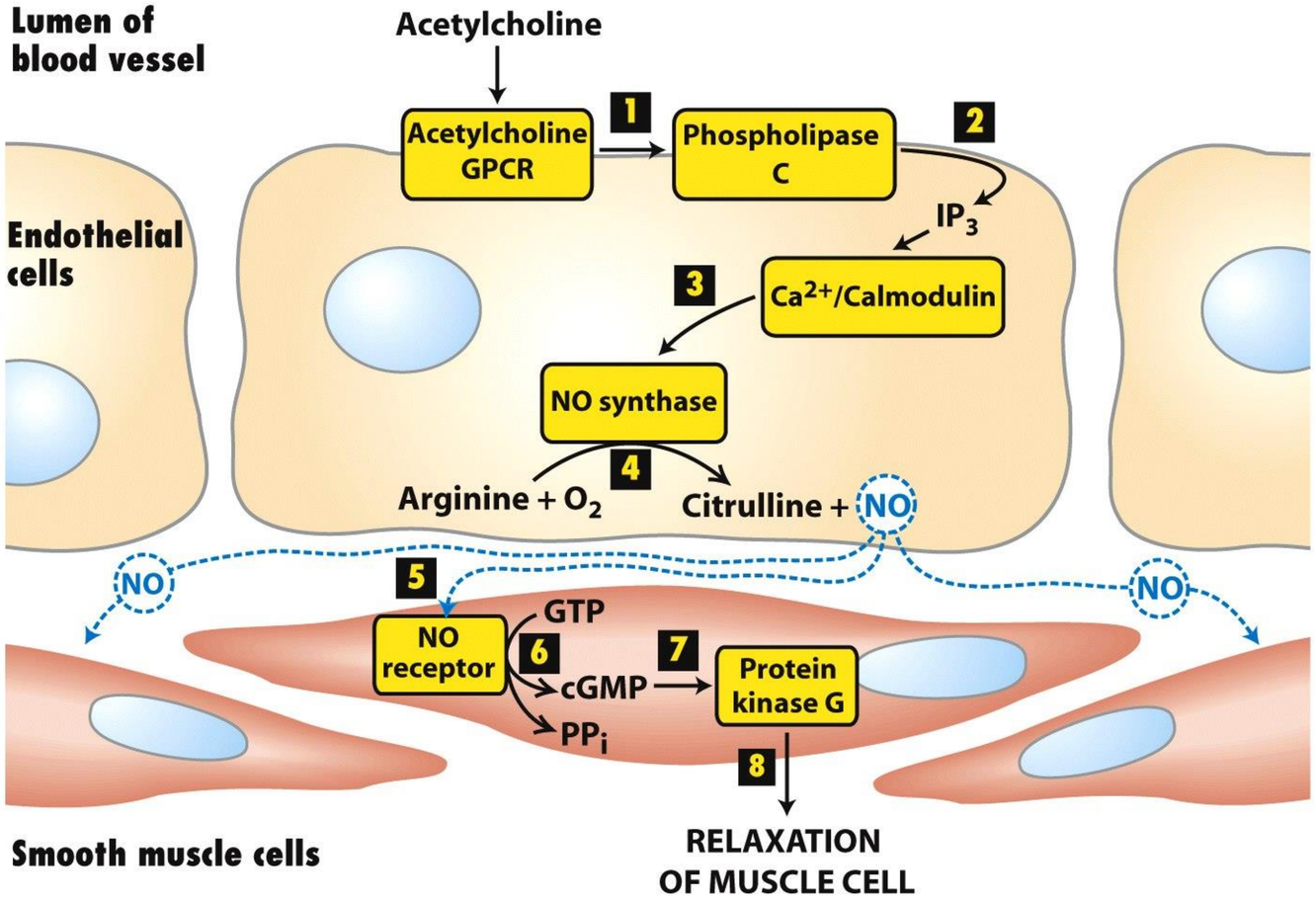
Nitric Oxide (NO)/cGMP Signaling

A related signaling pathway involving phospholipase C operates in vascular endothelial cells and causes adjacent smooth muscle cells to relax in response to circulating acetylcholine (Fig. 15.37). In the NO/cGMP signaling pathway, the downstream target of Ca^{2+}/calmodulin is nitric oxide synthase, which synthesizes the gas NO from arginine. NO diffuses into smooth muscle cells and causes relaxation by activating guanylyl cyclase and increasing [cGMP]. As a result arteries in tissues such as the heart dilate, increasing blood supply to the tissue. NO also is produced from the drug nitroglycerin which is given to heart attack patients and patients being treated for angina.



Nitric Oxide (NO)/cGMP Signaling

A related signaling pathway involving phospholipase C operates in vascular endothelial cells and causes adjacent smooth muscle cells to relax in response to circulating acetylcholine (Fig. 15.37). In the NO/cGMP signaling pathway, the downstream target of Ca^{2+}/calmodulin is nitric oxide synthase, which synthesizes the gas NO from arginine. NO diffuses into smooth muscle cells and causes relaxation by activating guanylyl cyclase and increasing [cGMP]. As a result arteries in tissues such as the heart dilate, increasing blood supply to the tissue. NO also is produced from the drug nitroglycerin which is given to heart attack patients and patients being treated for angina.



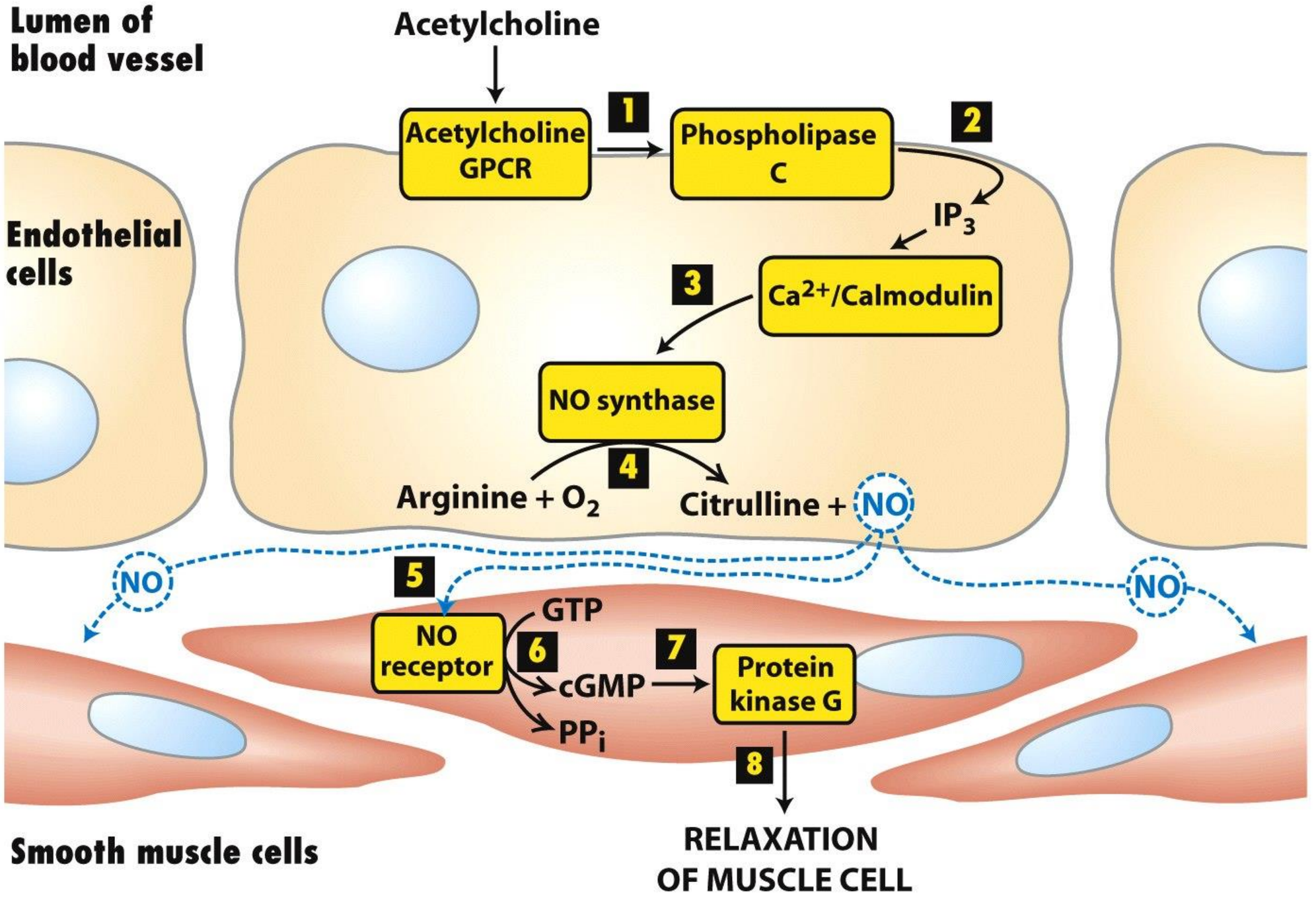
Key Signaling Pathways

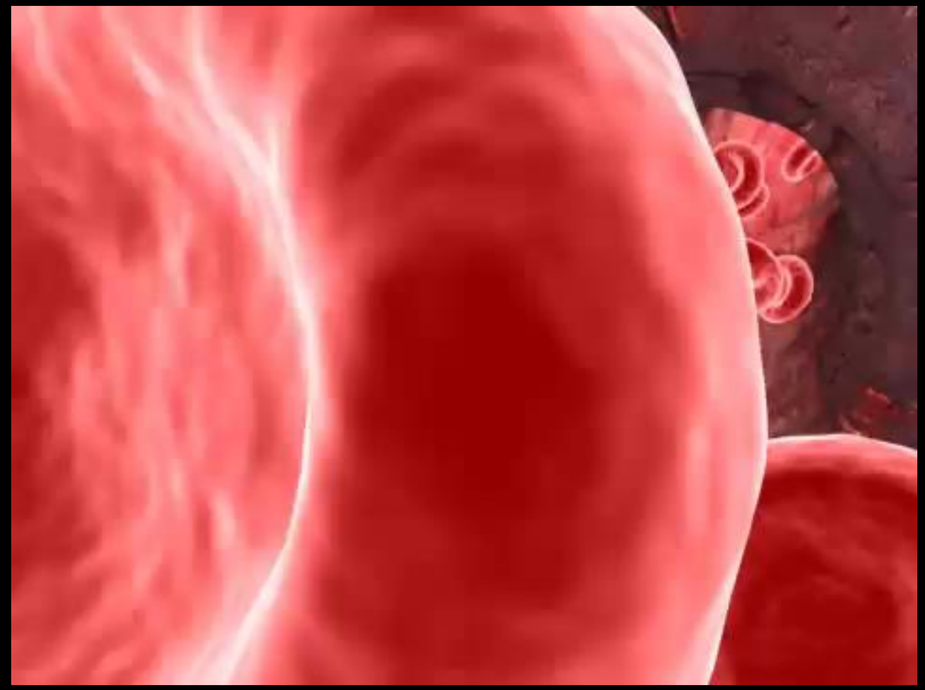
(Relevant to Atherogenesis)

- the insulin receptor (and other receptor tyrosine kinases)
- Ras and MAPK activation
- **TNF- and related family members leading to activation of NF- B**
- effects of reactive oxygen species (ROS) on signaling
- endothelial adaptations to flow including G protein-coupled receptor (GPCR) and integrin-related signaling
- activation of endothelial and other cells by modified lipoproteins
- purinergic signaling
- control of leukocyte adhesion to endothelium, migration, and further activation
- foam cell formation
- macrophage and vascular smooth muscle cell signaling related to proliferation, efferocytosis, and apoptosis.

RHEOLOGY

- The cor- circulation may be uniquely predisposed to atherosclerosis (804), probably because of high intraluminal pressure and complete flow cessation and possible reversal during systole

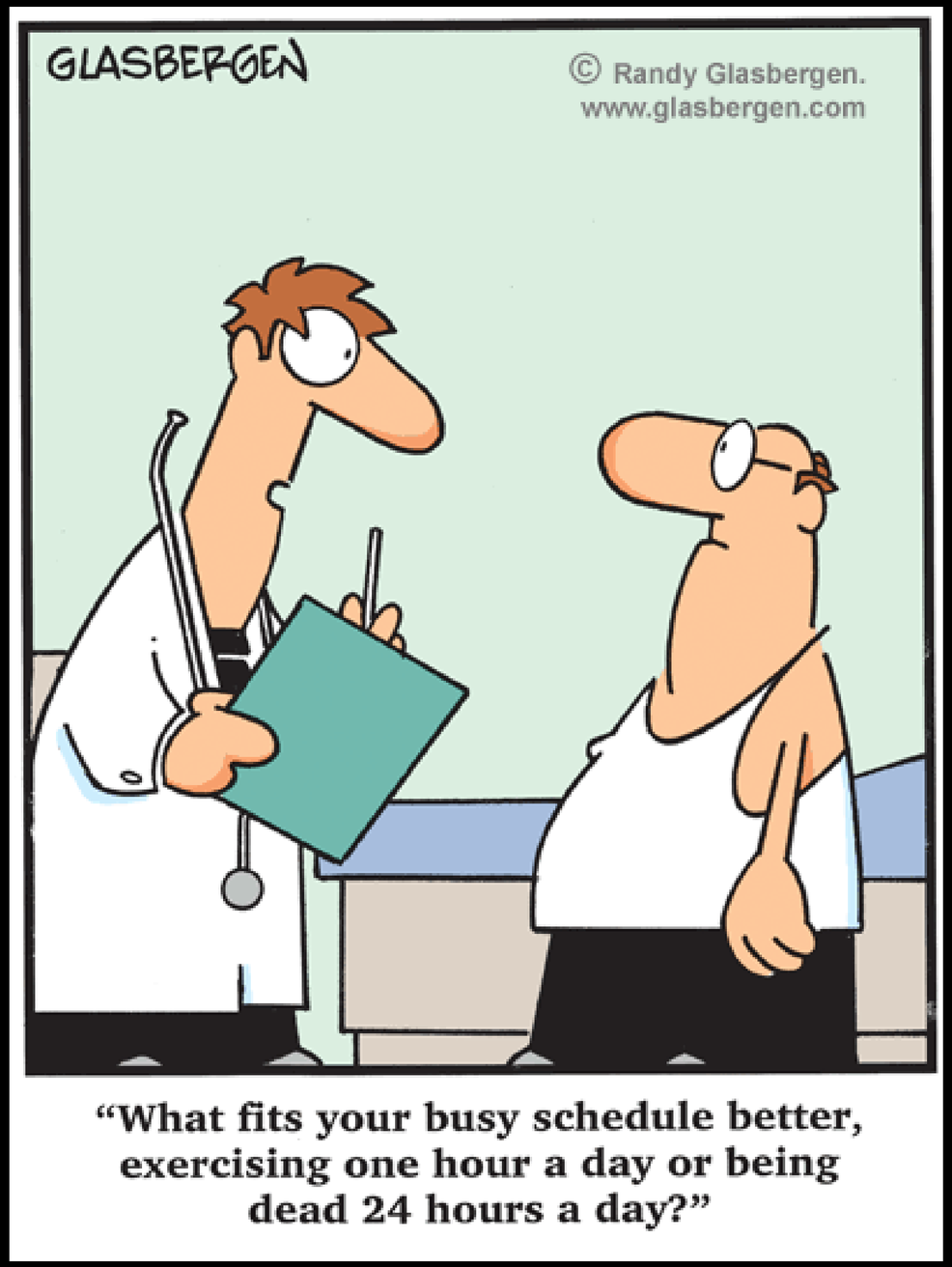

Lumen of blood vessel
Acetylcholine
Acetylcholine GPCR
1
Phospholipase C
2
IP3
Endothelial cells
3
Ca2+/Calmodulin
NO synthase
4
Arginine + O2
Citrulline + NO
NO
NO
5
GTP
NO receptor
6
cGMP
PPi
7
Protein kinase G
8
RELAXATION OF MUSCLE CELL
Smooth muscle cells



Calcification

- **Calcications are common in progressive atherosclerotic lesions and increase with age.**
- **Apoptotic cells, extracellular matrix, and necrotic core material may act as nidus for microscopic calcium granules, which can subsequently expand to form larger lumps and plates of calcium deposits.77,78**
- **The necrotic core can completely calcify with time and calcications can constitute most of plaque volume.17**
- **Osseous metaplasia is sometimes seen in human lesions (versus chondroid metaplasia in mouse models),78,79 but these are rare**

Mechanisms of Plaque Formation and Rupture
Jacob Fog Bentzon, Fumiyuki Otsuka, Renu Virmani, Erling Falk
(Circ Res. 2014;114:1852-1866.)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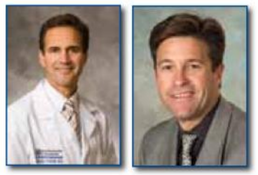
"What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?"

Special Series Preventive Cardiology

Cardiovascular Damage Resulting from Chronic Excessive Endurance Exercise

by Harshal R. Patil, MD, James H. O'Keefe, MD, Carl J. Lavie, MD, Anthony Magalski, MD, Robert A. Vogel, MD & Peter A. McCullough, MD

Chronic, excessive sustained endurance exercise may cause adverse structural remodeling of the heart and large arteries.



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Contact: jokeefe@saint-lukes.org

Abstract

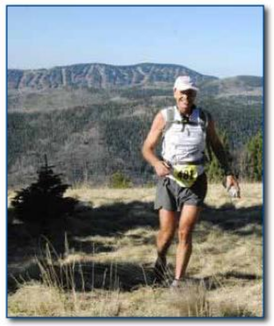
A daily routine of physical activity is highly beneficial in the prevention and treatment of many prevalent chronic diseases, especially of the cardiovascular (CV) system. However, chronic, excessive sustained endurance exercise may cause adverse structural remodeling of the heart and large arteries. An evolving body of data indicates that chronically training for and participating in extreme endurance competitions such as marathons, ultra-marathons, Iron-man distance triathlons, very long distance bicycle racing, etc., can cause transient acute volume overload of the atria and right ventricle, with transient reductions in right ventricular ejection fraction and elevations of cardiac biomarkers, all of which generally return to normal within seven to ten days. In veteran extreme endurance athletes, this recurrent myocardial injury and repair may eventually result in patchy myocardial fibrosis, particularly in the atria, interventricular septum and right ventricle, potentially creating a substrate for atrial and ventricular arrhythmias. Furthermore, chronic, excessive, sustained, high-intensity endurance exercise may be associated with diastolic dysfunction, large-artery wall stiffening and coronary artery calcification. Not all veteran extreme endurance athletes develop pathological remodeling, and indeed lifelong exercisers generally have low mortality rates and excellent functional capacity. The aim of this review is to discuss the emerging understanding of the cardiac pathophysiology of extreme endurance exercise, and make suggestions about healthier fitness patterns for promoting optimal CV health and longevity.

Introduction

Although exercise is not a pharmacologic agent, in many ways its effects resemble those

Pheidippides: First Marathon Runner and Its First Casualty, Too

During the Greco-Persian War in 490 BC, Pheidippides, a 40-year-old Greek herald, presumably a veteran long-distance runner, ran about 150 miles during a 48-hour period to deliver urgent critical military messages. On the third day, he ran the 26 miles from a battlefield near Marathon to Athens to deliver news of a momentous Greek victory. According to legend, upon arriving, Pheidippides exclaimed to the Athenians, "Victory is ours!", then immediately collapsed, and died. Now, 2,500 years later, with the rise in popularity of endurance sports, concerning evidence is mounting suggesting that extreme endurance training and competition may promote adverse cardiac structural remodeling, and predispose to acute and chronic CV problems.[1]



Born to Run

In the best-selling book, Born to Run, (Christopher McDougall, Knopf Publishing, 2009) Micah True is the mythic long distance runner, Caballo Blanco, who runs as far as 100 miles in a day. Recently, this legendary ultra-marathoner died suddenly while out on a routine 12-mile training run March 27, 2012. On autopsy his heart was enlarged and scarred; he died of a lethal arrhythmia.[2] Although speculative, the pathologic changes in the heart of this 58-year-old veteran extreme endurance athlete were likely manifestations of Pheidippides' cardiomyopathy—a condition caused by chronic excessive endurance exercise.[28]

Animal Studies

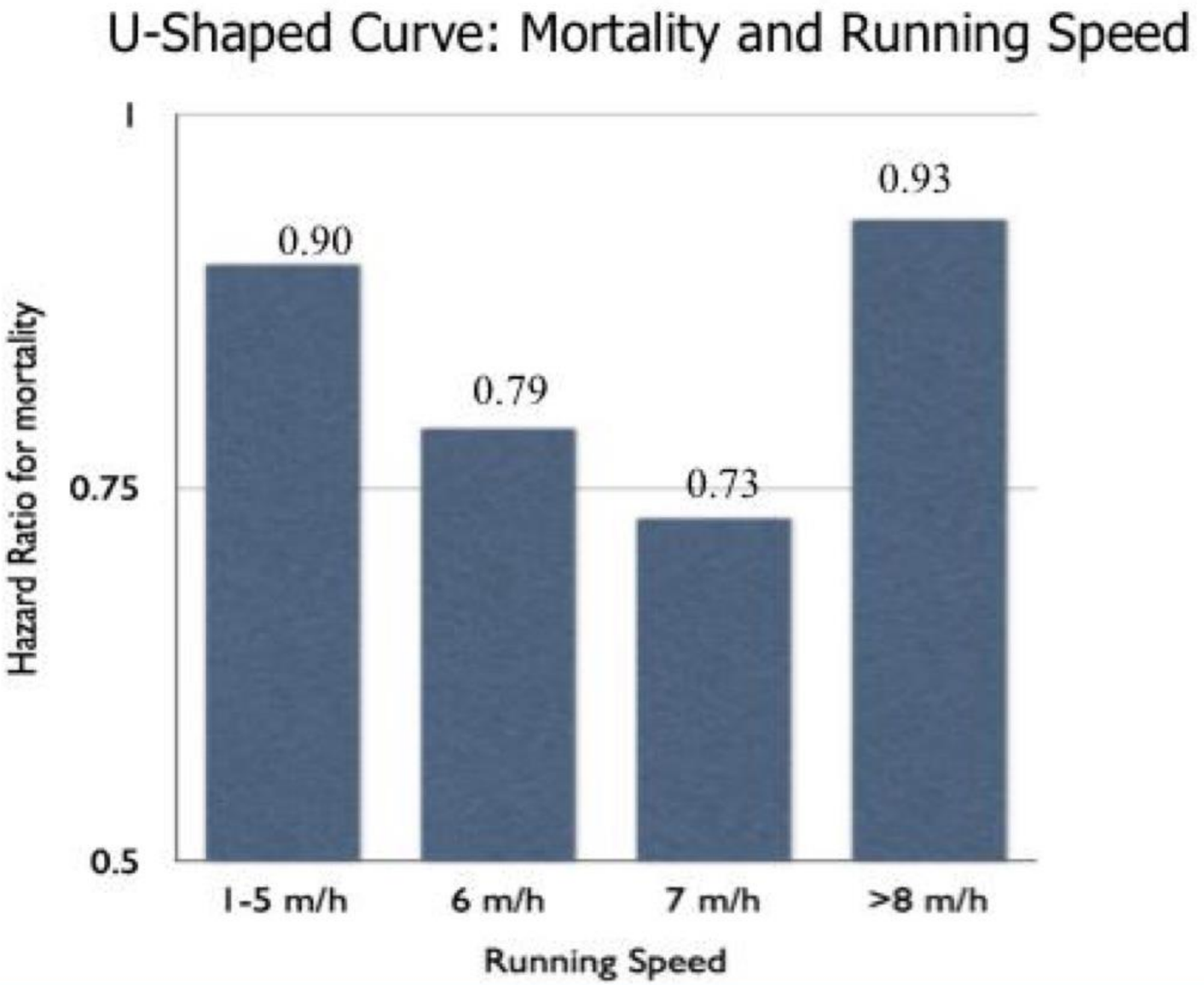
In an animal study Benito et al. compared rats that were trained to run strenuously and without resting for 60 minutes daily for 16 weeks to sedentary rats.[41] The running rats developed bi-ventricular hypertrophy, diastolic dysfunction, bi-atrial dilation and had increased collagen deposition and fibrosis in the RV and in both atria. Ventricular tachycardia was inducible in 42% of the running rats versus only 6% of the sedentary rats ($P=0.05$). Importantly, the fibrotic changes caused by 16 weeks of intensive ET had largely regressed back to normal by eight weeks after the daily running regimen was ceased. Excessive strenuous daily running in this animal study replicated the adverse cardiac structural remodeling and pro-arrhythmia substrate noted in observational studies of extreme endurance human athletes. These findings support the hypothesis that long-term strenuous daily endurance ET such as marathon running or professional long-distance cycling may cause cardiac fibrosis (especially in the atria and the RV), diastolic dysfunction, and increased susceptibility to atrial and ventricular arrhythmias (VA). However, it should be noted that animal studies are of uncertain clinical relevance due to the excessively stressful nature of the imposed exercise.

Biomarker Evidence for Cardiac Damage with Excessive Endurance Exercise

Running is a prototypical natural physical activity and often plays an integral and important role in an active healthy lifestyle.[1,2] However, continuous running such as is required for training and participating in a marathon may be detrimental to cardiovascular health. Several serological markers of cardiac damage

Figure 2

Relationship between running speed and mortality.[10]

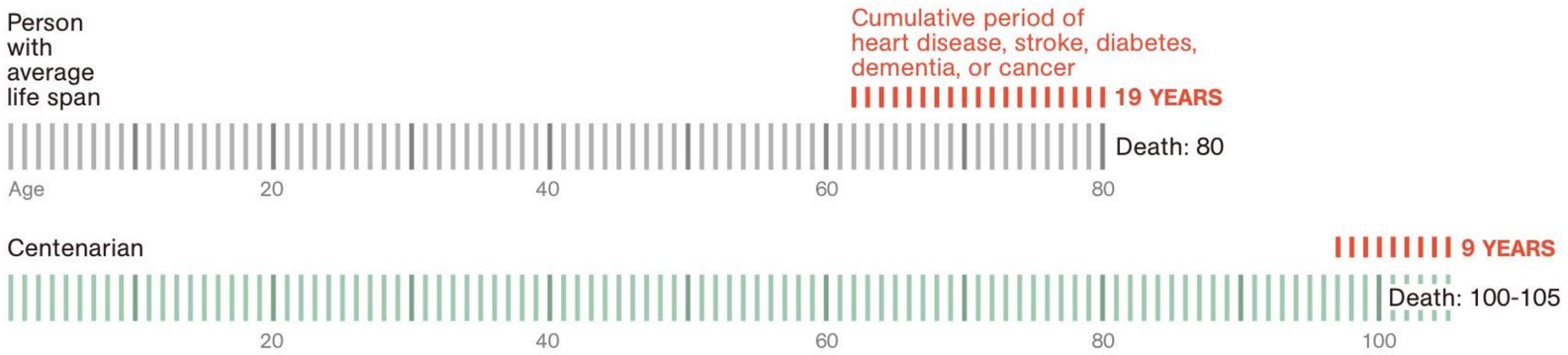


SuperCentarian

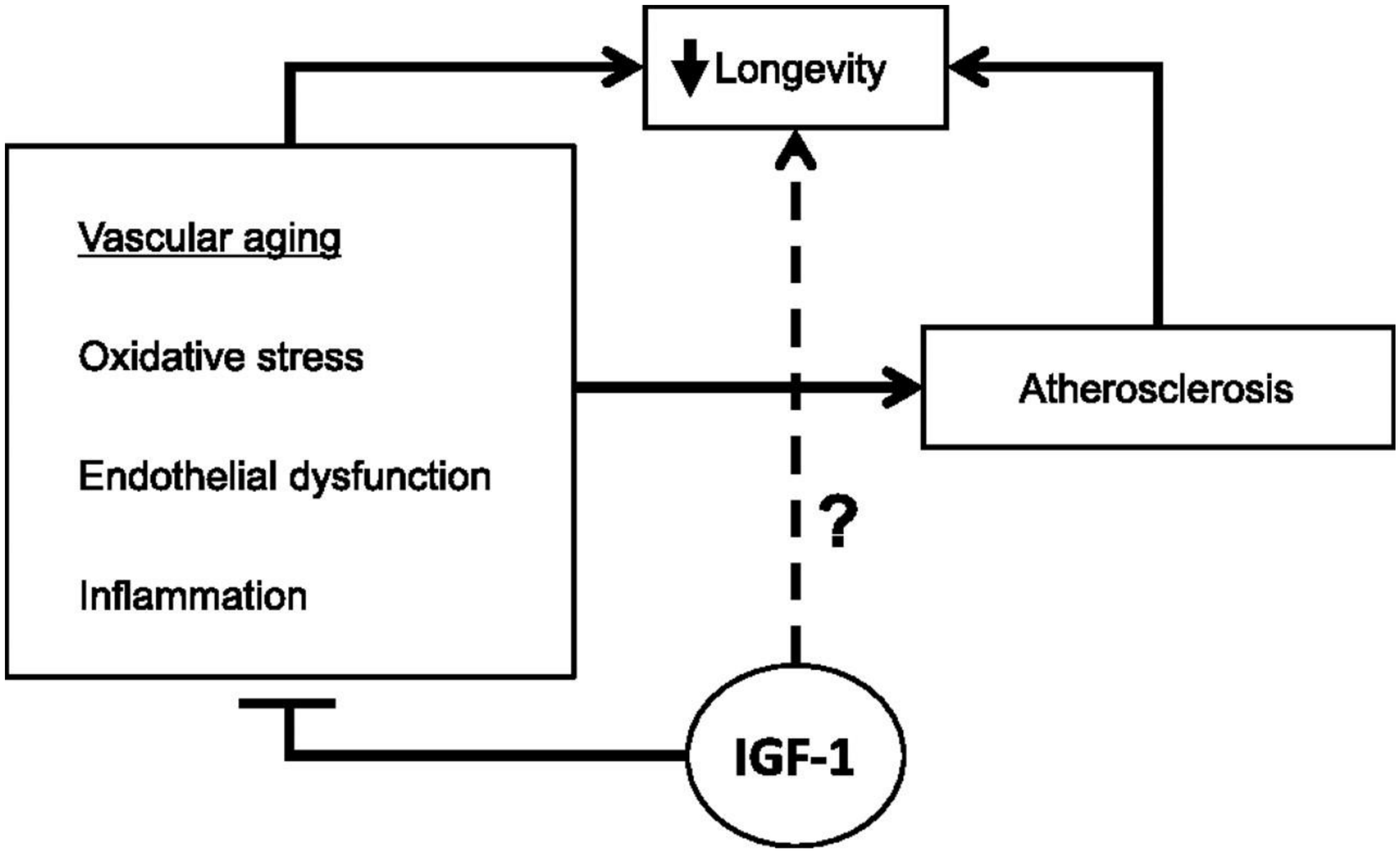
Mme Jeanne Calment, died 1998, aged 122

Getting to 100 candles

Centenarians reach that milestone because they're healthier, by virtue of genetics, common sense, or luck. In people with an average life span, diseases of old age strike earlier and last longer.



Paradoxical effects of insulin-like growth factor (IGF)-1 on atherogenesis and the aging process.



Higashi Y et al. J Gerontol A Biol Sci Med Sci 2012;67A:626-639

the Journals of gerontology Series a

RHEOLOGY

- **Arterial flow patterns** largely determine whether endothelial cells stand poised for facile inflammatory activation or will resist activating signals.

- **Atherosclerosis** develops almost exclusively in areas of slow flow or low shear stress, often with eddy currents

- **Turbulence** is not a feature of flow at these sites. Indeed, turbulence, defined as blood flow exceeding the critical Reynolds number, occurs almost nowhere in the normal human circulatory system.

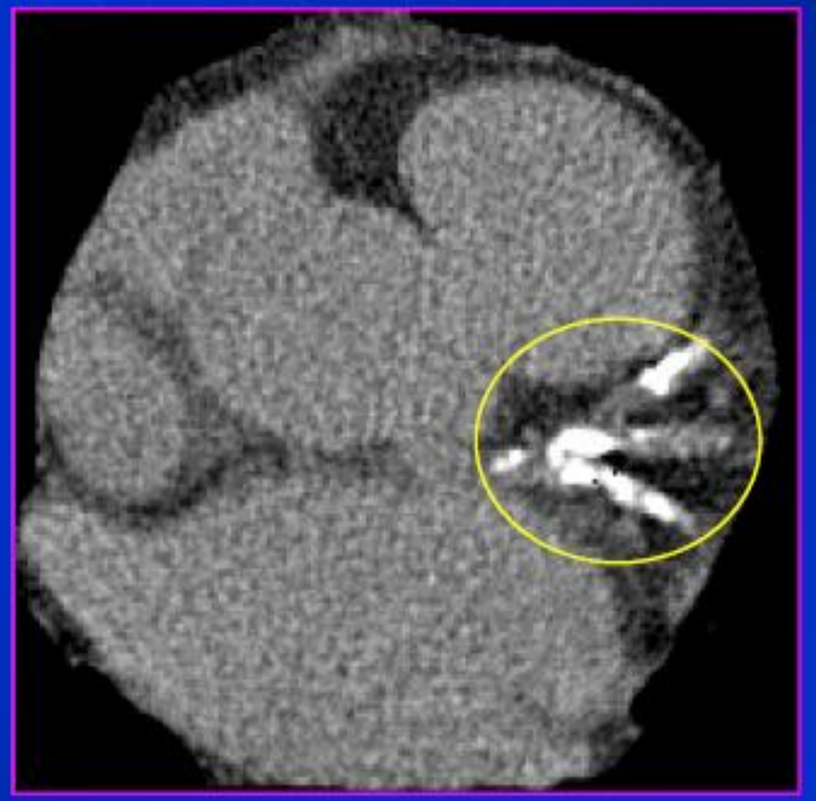
Vascular Endothelial Mediators

Include the following

- Nitric oxide (NO)
- Cycloxygenase (CxO)
- Endothelin-1 (ET-1)
- Endothelium Depolarisation Factor (EDF)
- And many others - thus
- It is the largest endocrine gland

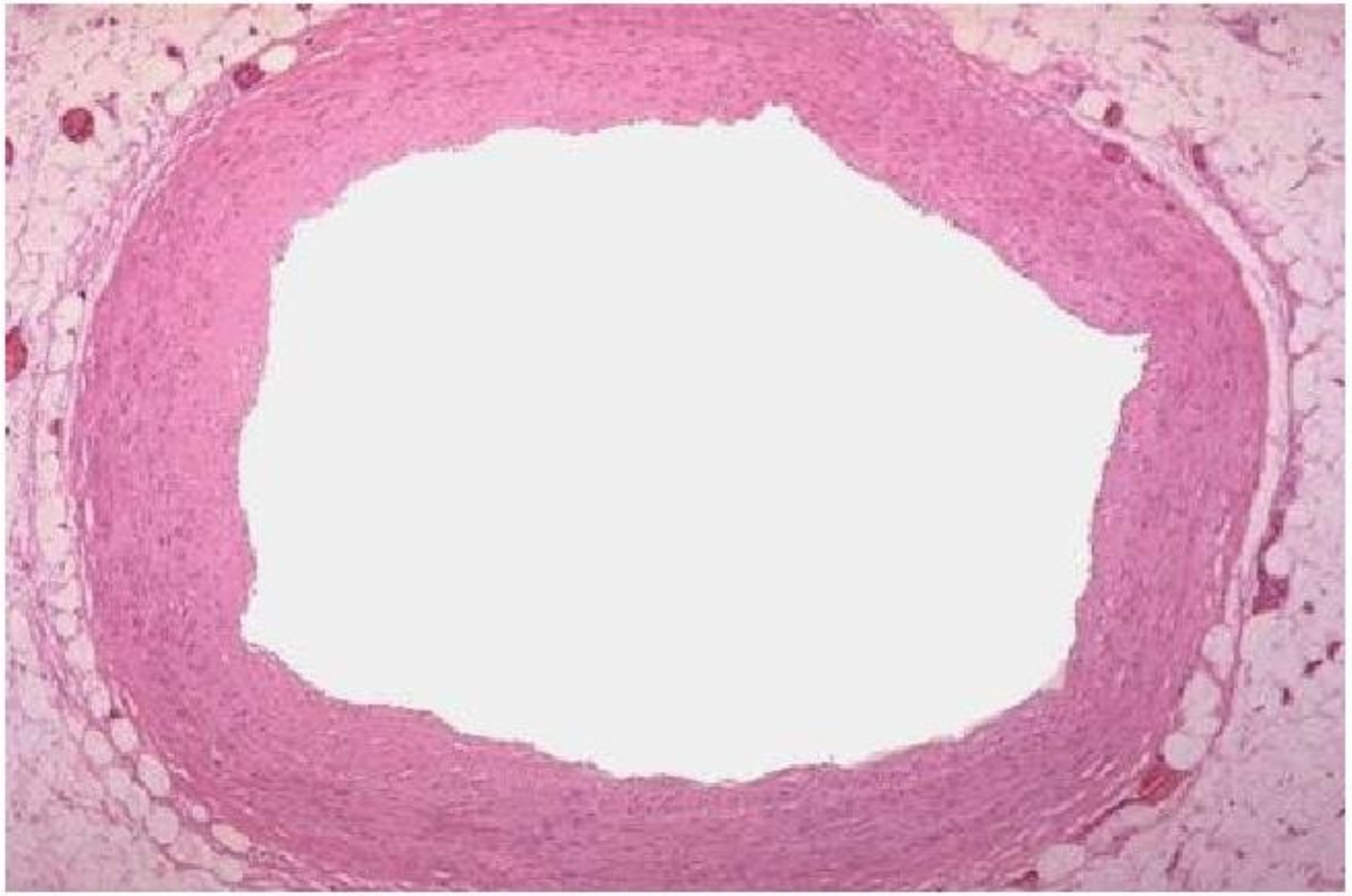
Coronary Artery Scanning

- SEVERE CALCIFICATION



Histology

- the branch of biology dealing with the study of tissues. ... the structure, especially the microscopic structure, of organic tissues.

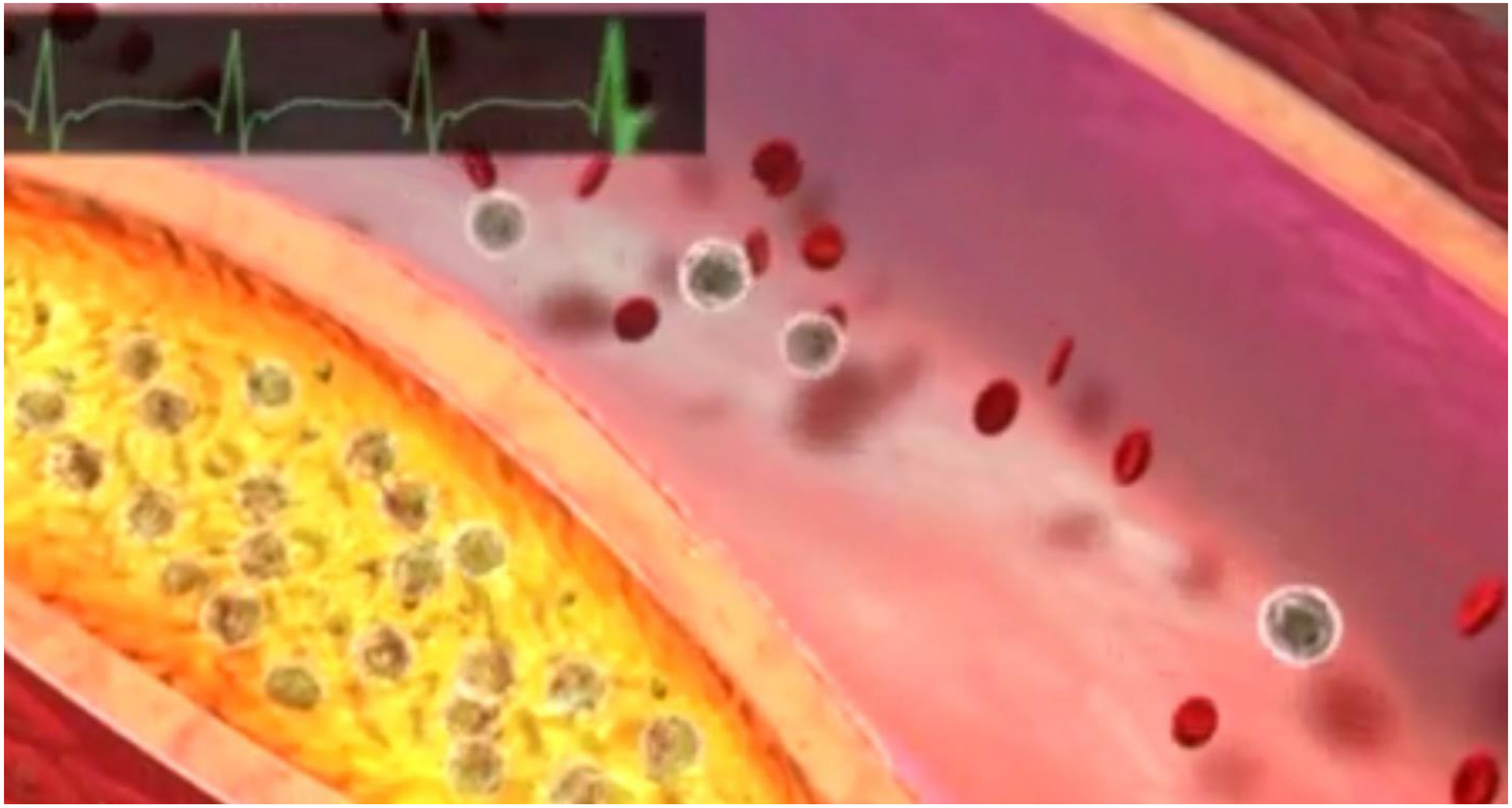


THE REAL NIGHTMARE

CVD

- **KEY FACTS**

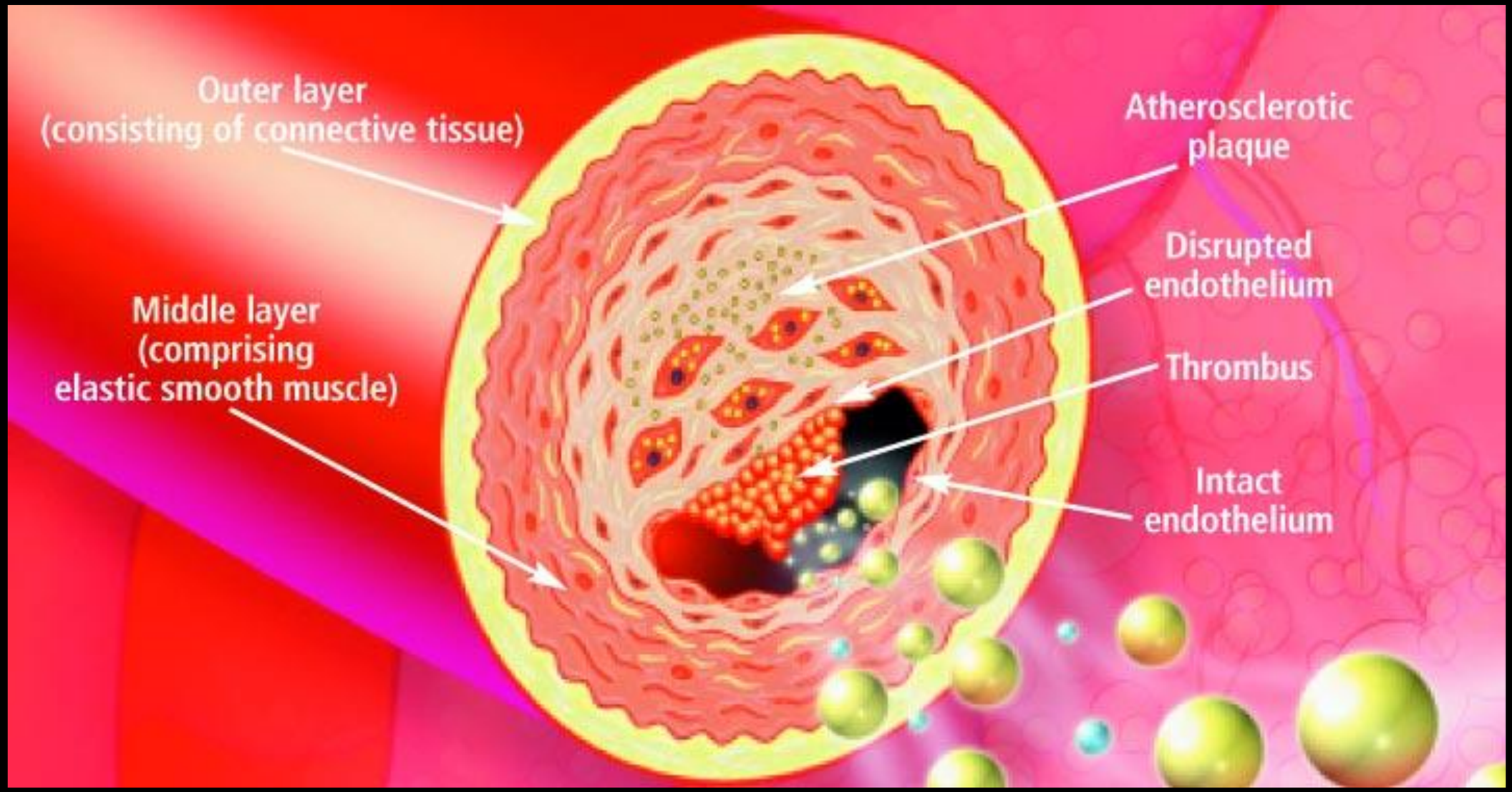
- ***CVDs are the number 1 cause of death globally: more people die annually from CVDs than from any other cause.***
- **An estimated 17.5 million people died from CVDs in 2012, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease and 6.7 million were due to stroke .**
- **Over three quarters of CVD deaths take place in low- and middle-income countries.**
- **Out of the 16 million deaths under the age of 70 due to noncommunicable diseases, 82% are in low and middle income countries and 37% are caused by CVDs.**
- **Most cardiovascular diseases can be prevented by addressing behavioural risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol using population-wide strategies.**
- **People with cardiovascular disease or who are at high cardiovascular risk (due to the presence of one or more risk factors such as hypertension, diabetes, hyperlipidaemia or already established disease) need early detection and management using counselling and medicines, as appropriate.**

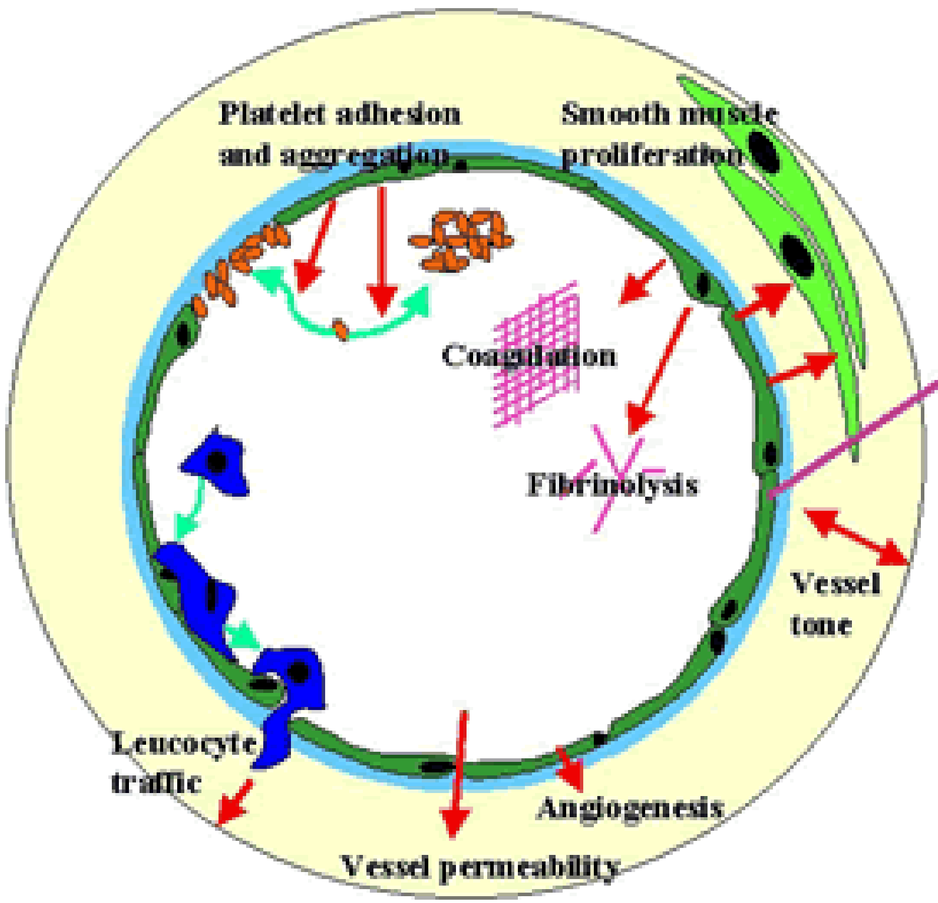


Theories of Atherogenesis

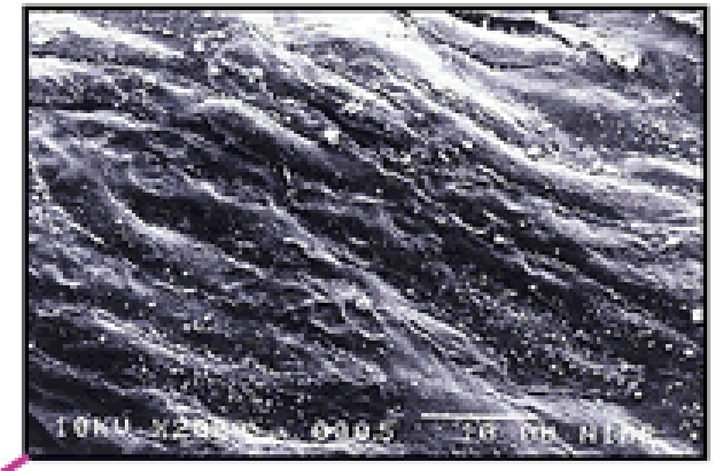
- Virchow - imbibition
  - (lipid theories)

- Rokitansky - encrustation
  - (thrombotic theories)


Outer layer
(consisting of connective tissue)
Middle layer
(comprising
elastic smooth muscle)
Atherosclerotic
plaque
Disrupted
endothelium
Thrombus
Intact
endothelium

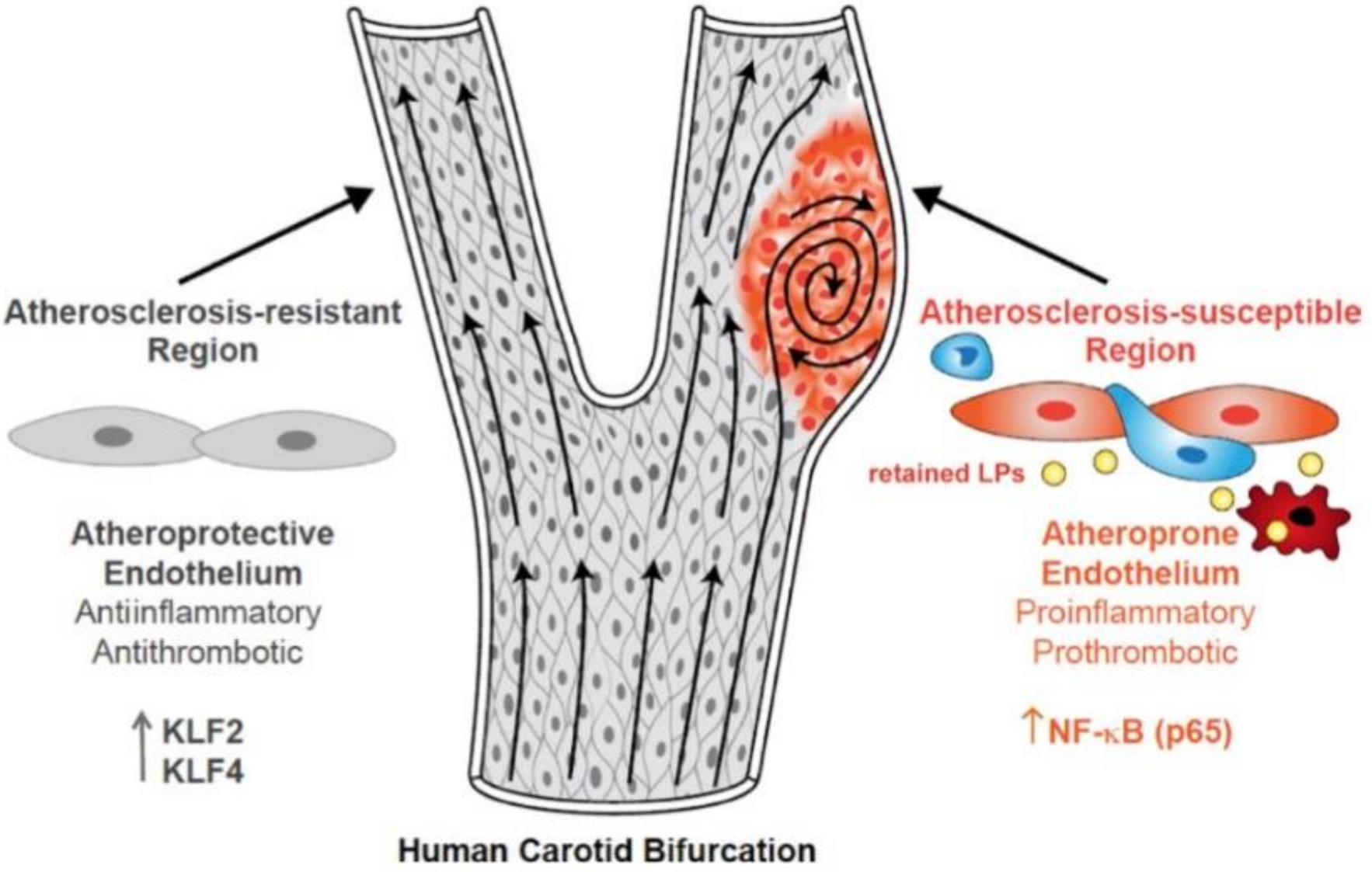


Endothelial cells



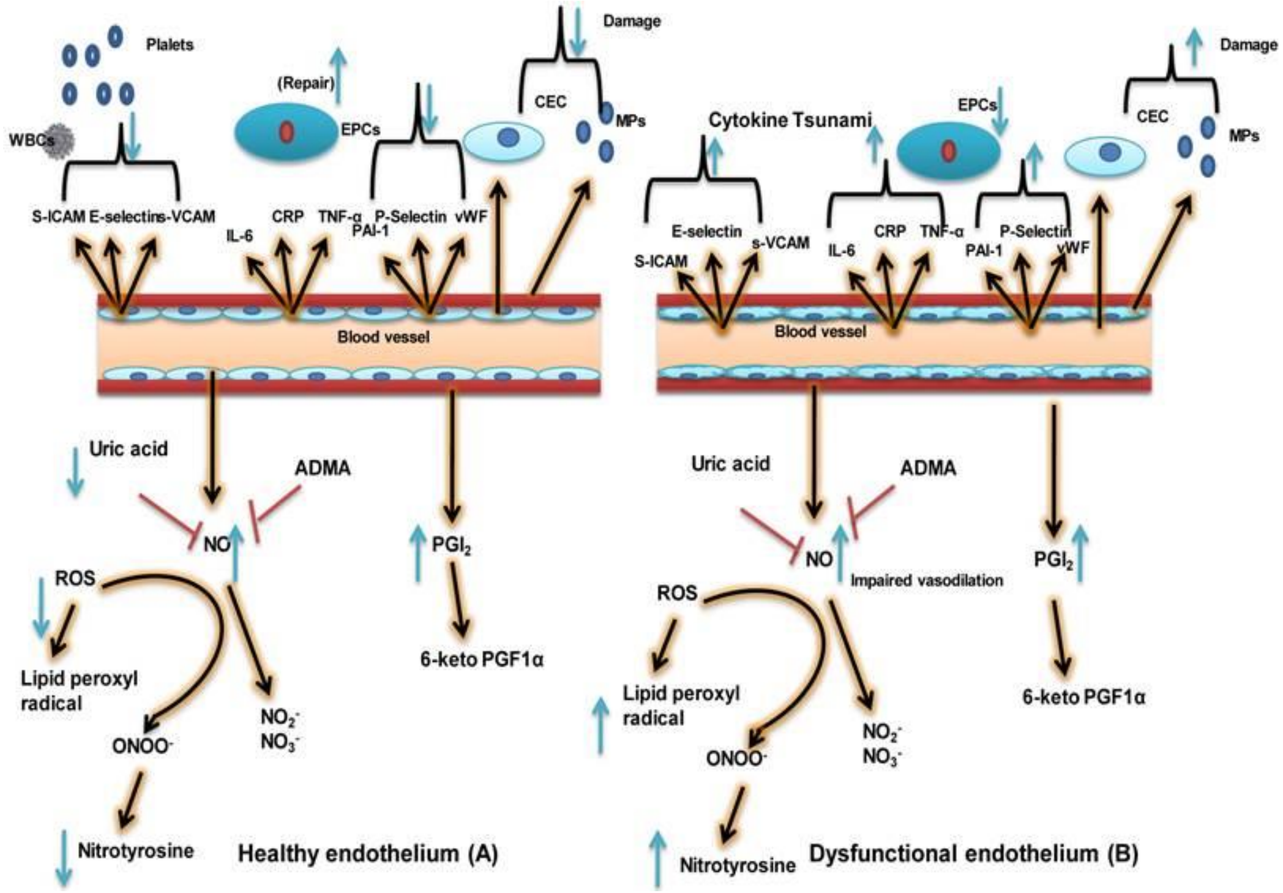
- Barrier between blood and tissues
- Control blood coagulation/fibrinolysis platelet adhesion & aggregation
- Vessel tone & blood flow
- Vessel permeability
- Movement of nutrients and white cells between blood and tissues
- Wound healing and vessel growth

Inflammation and endothelial dysfunction as therapeutic targets in patients with heart failure
Dimitris Tousoulis, , Marietta Charakida and Christodoulos Stefanadis Int J of Cardiology Vol 100 Issue 3 2005


Atherosclerosis-resistant Region
Atheroprotective Endothelium
Antiinflammatory
Antithrombotic
↑ KLF2
KLF4
Atherosclerosis-susceptible Region
retained LPs
Atheroprone Endothelium
Proinflammatory
Prothrombotic
↑ NF-κB (p65)
Human Carotid Bifurcation

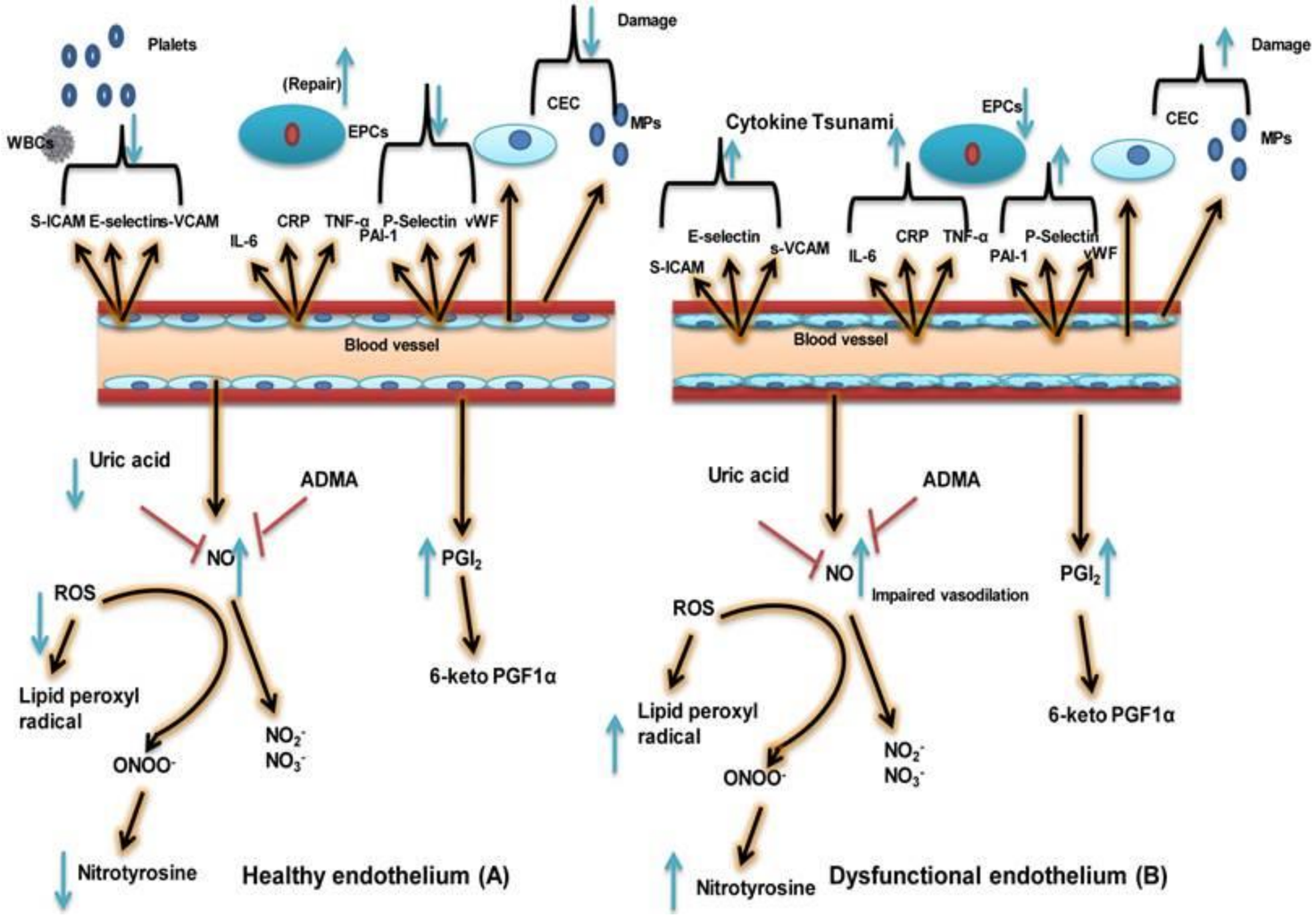
Factors involved in Endothelial Function/ Dysfunction

- Tumor necrosis factor alpha is a cell signaling protein (cytokine) involved in systemic inflammation and is one of the cytokines that make up the acute phase reaction. It is produced chiefly by activated macrophages
- Endothelial progenitor cells- EPCs. Circulating EPCs can secrete microparticles and paracrine growth factors which activate resident ECs to proliferate and regenerate the injured vasculature



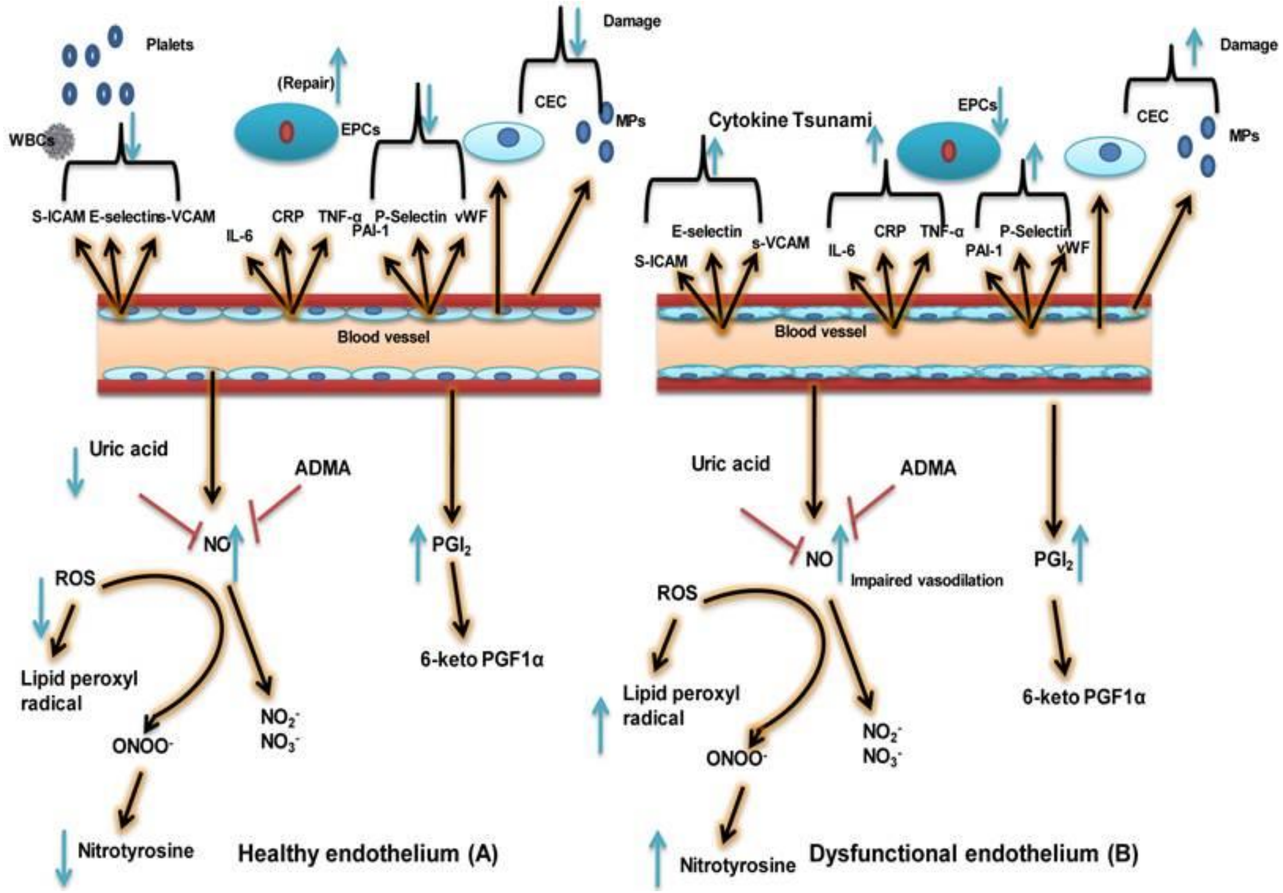
Factors involved in Endothelial Function/ Dysfunction

- EPCs are biomarkers of repair while CEC are biomarkers of damage. They can be distinguished by their different surface markers .



Factors involved in Endothelial Function/ Dysfunction

- P-selectin functions as a cell adhesion molecule (CAM) on the surfaces of activated endothelial cells, and activated platelets.
- Von Willebrand factor (VWF) performs two critical functions in hemostasis: it acts as a bridging molecule at sites of vascular injury for normal platelet adhesion, and under high shear conditions, it promotes platelet aggregation.



Major CHD Risk Factors Other Than LDL-C According to NCEP ATP-III

Positive risk factors

- Age
  - male ≥45
  - female ≥55
- Family Hx of CHD: 1st-degree relative with MI or sudden cardiac death - male relative: <age 55
  - female relative: <age 65
- Current cigarette smoking
- Hypertension: BP ≥140/90 mm Hg or on antihypertensive meds
- Low HDL-C: <40 mg/dL
- Diabetes IS A CHD QUIVALENT IDENTIFYING PT AS HIGH RISK

Negative risk factor

- High HDL-C: ≥60 mg/dL

Other Recognized Risk Factors

- Obesity: traditionally determined by body mass index >30 kg/m^2 with overweighted defined as 25-<30 kg/m^2.
- Abdominal obesity involves waist circumference ≥40 in. in men, ≥35 in. in women
- Physical inactivity: various definitions

Published April 13, 2015

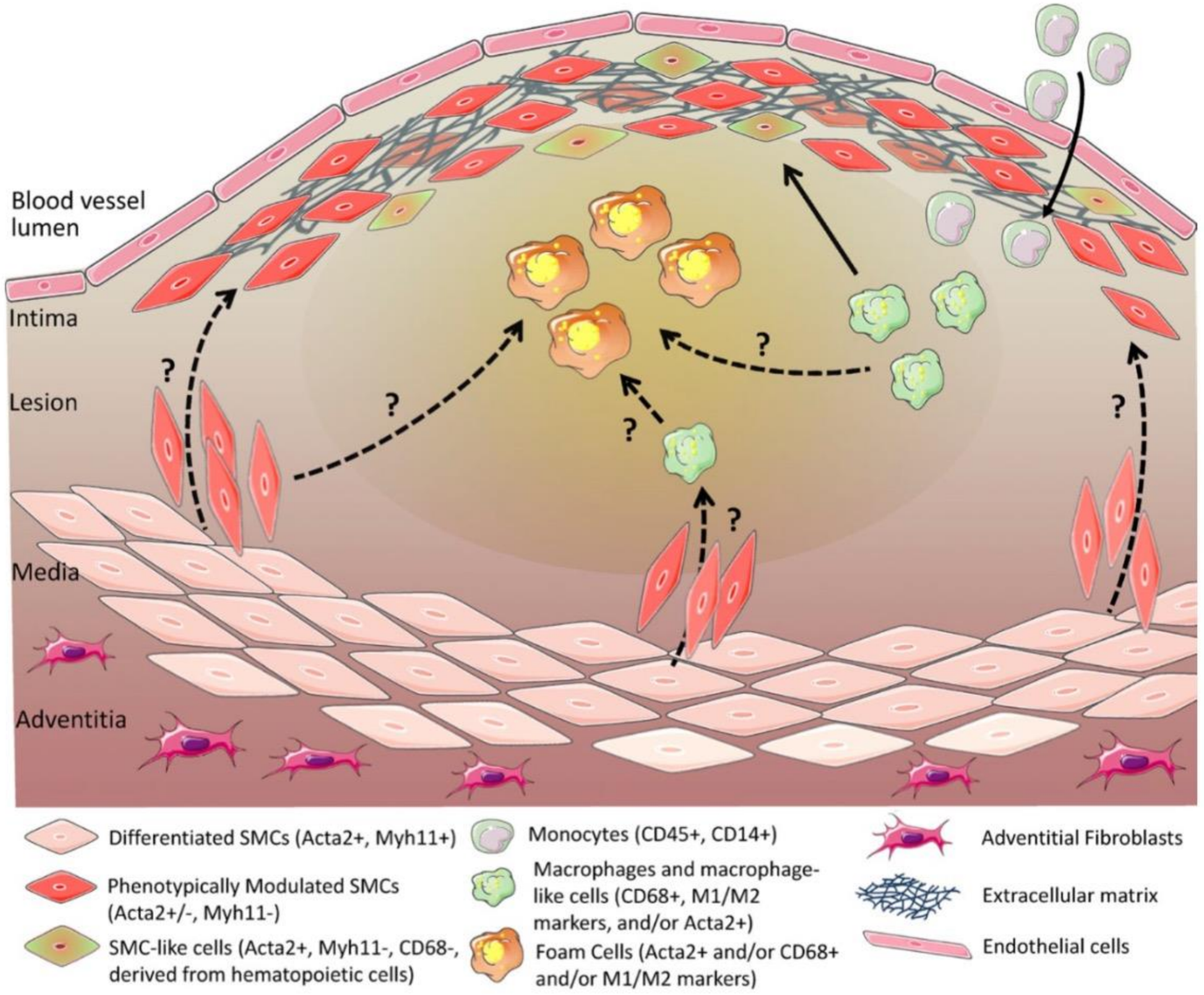


Figure 3. **Ambiguity regarding the identity and origins of SMC, macrophages, and putative derivatives of these cells within advanced human atherosclerotic lesions.** Lesional cells display remarkable heterogeneity as a result of effects of microenvironmental factors, including cytokines, inflammatory lipids, growth factors, dead cell debris, oxygen tension variations, and oxidative stress. For purposes of this figure, we have only considered data in intact human tissue specimens rather than studies in cultured cells or animal models. The solid arrows illustrate known pathways that give rise to lesion cells, whereas the dotted arrows indicate putative pathways not yet directly validated in humans. For example, cross-gender bone marrow transplant Y-chromosome lineage tracing studies provide clear evidence that myeloid cells, presumably monocytes, give rise to $CD68^+$ macrophages but also $Acta2^+$ SMC-like cells within advanced human coronary artery lesions. In contrast, there is no direct evidence that SMCs are the primary source of fibrous cap cells that produce extracellular matrix that stabilizes lesions because $Acta2^+$ cells may be derived from SMCs, macrophages, or other cell types. Similarly, there is evidence that approximately half of the foam cells within advanced human coronary artery atherosclerotic lesions are $Acta2^+$ and $CD68^+$ (Allahverdian et al., 2014), but the origin of these cells is not clear.