VLA November 1, 2016

METABOLISM OF MYOCARDIUM ISCHEMIC HEART DISEASE MYOCARDIAL INFARCTION

METABOLISM OF THE HEART

- The heart is an omnivore organ, which utilizes a diverse set of fuel substrates, including lactate, glucose, amino acids, ketones, and particularly free fatty acids.
- Newborns –preferentially-glucose (Fas with a long chains are needed for myelinisation)
- Healthy adults - lipids
- Ischemic adults - anaerobic glycolysis only (↓ATP)
- Diabetic adults – also ketones
- Patients with heart failure - toxic effects of both glucose and lipid metabolism

EPICARDIAL ADIPOSE TISSUE

Epicardial portion – between inner surface of visceral layer of pericardium and myocardium (without fascia- common microcirculation)- origin-splanchnopleuric mesoderm- supplied by aa. coronarie. Similar to brown tissue (high expression UCP-1, modulation of the heat production for heart during changes of thermoregulation, protection against effects of ischemia/ hypoxia with great hemodynamical effects, maybe characteristics of beige fat)

EPICARDIAL ADIPOSE TISSUE

- Pericardial (paracardial) portion- betwwen external surface of external pericardial layer and thoracic wall – primitive thoracic mesenchym –supplied by a. mammaria int.

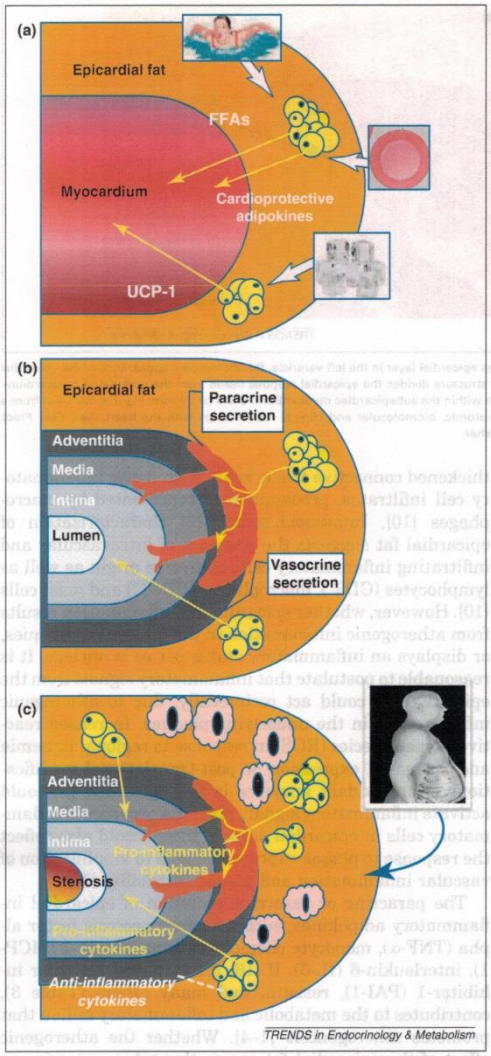


Figure 2. Potential physiological, pathophysiological mechanisms and vasocrine/paracrine pathways of epicardial fat. **(a)** Possible physiological roles attributed to the epicardial fat: release of FFAs as energy to the myocardium in condition of high metabolic demand; expression of the thermogenic protein UCP-1 in response of cold exposure; expression and secretion of cardioprotective factors in conditions of normal coronary and local circulation. **(b)** Putative mechanisms by which adipokines might reach the coronary artery lumen from the epicardial fat. Adipokines from periadventitial epicardial fat could traverse the coronary wall by diffusion from outside to inside, via a paracrine mechanism. Adipokines might also be released from epicardial tissue directly into the vasa vasorum and be transported downstream into the arterial wall via a vasocrine mechanism. **(c)** Putative pathophysiological role of epicardial fat in CAD: proinflammatory cytokines are highly expressed and secreted into the coronary lumen; anti-inflammatory adipokines are thought to be downregulated. In high-risk subjects, as well as those with metabolic syndrome and excessive visceral fat accumulation, epicardial fat increases in size and cellularity, exhibiting an elevated number of macrophages.

Table 3. Epicardial adipose tissue bioactive molecules

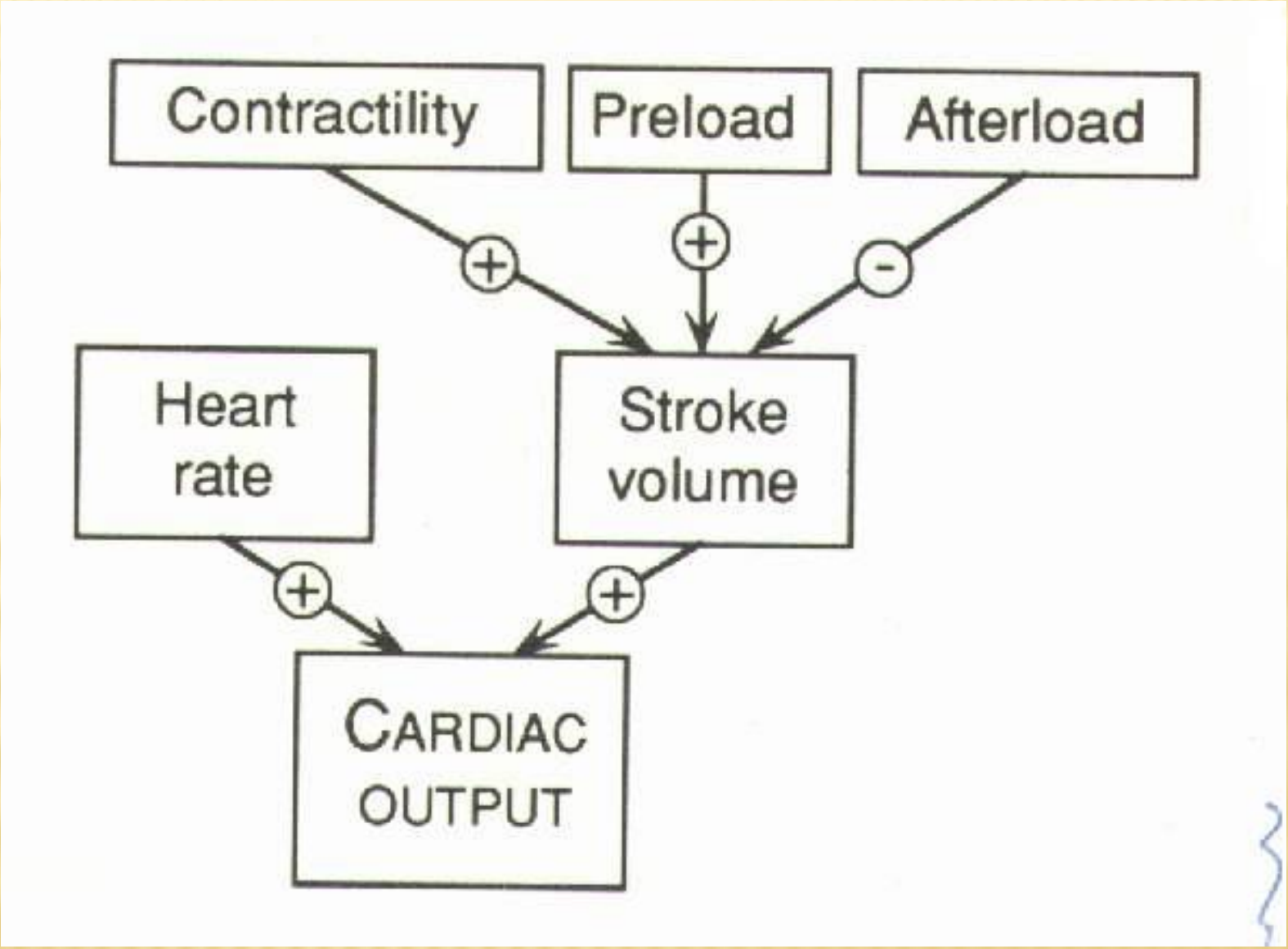
Proinflammatory, proatherogenic	**Anti-inflammatory, anti-atherogenic**
TNF-α MCP-1	Adiponectin, Adrenomedullin
IL1, IL1β, IL-1Ra, IL6, IL8, IL10 CRP PAI-1 Prostaglandin D(2), haptoglobin, α1-glycoprotein, JNK sPLA2-IIA, fatty-acid-binding protein 4 RANTES ICAM	
Insulin-mimetic, markers of visceral fat	**Thermogenic**
Resistin Visfatin Omentin	UCP 1
Growth factors	**Brown fat differentiation transcription factors**
NGF FLT1	PRDM16 PGC-1α
Vascular remodeling, blood pressure control, myocardial hypertrophy, adipogenesis	
Angiotensin, Angiotensinogen	
Leptin	
Receptors	
Angiotensin II type 1 receptor TLRs PPARγ GLUT-4	

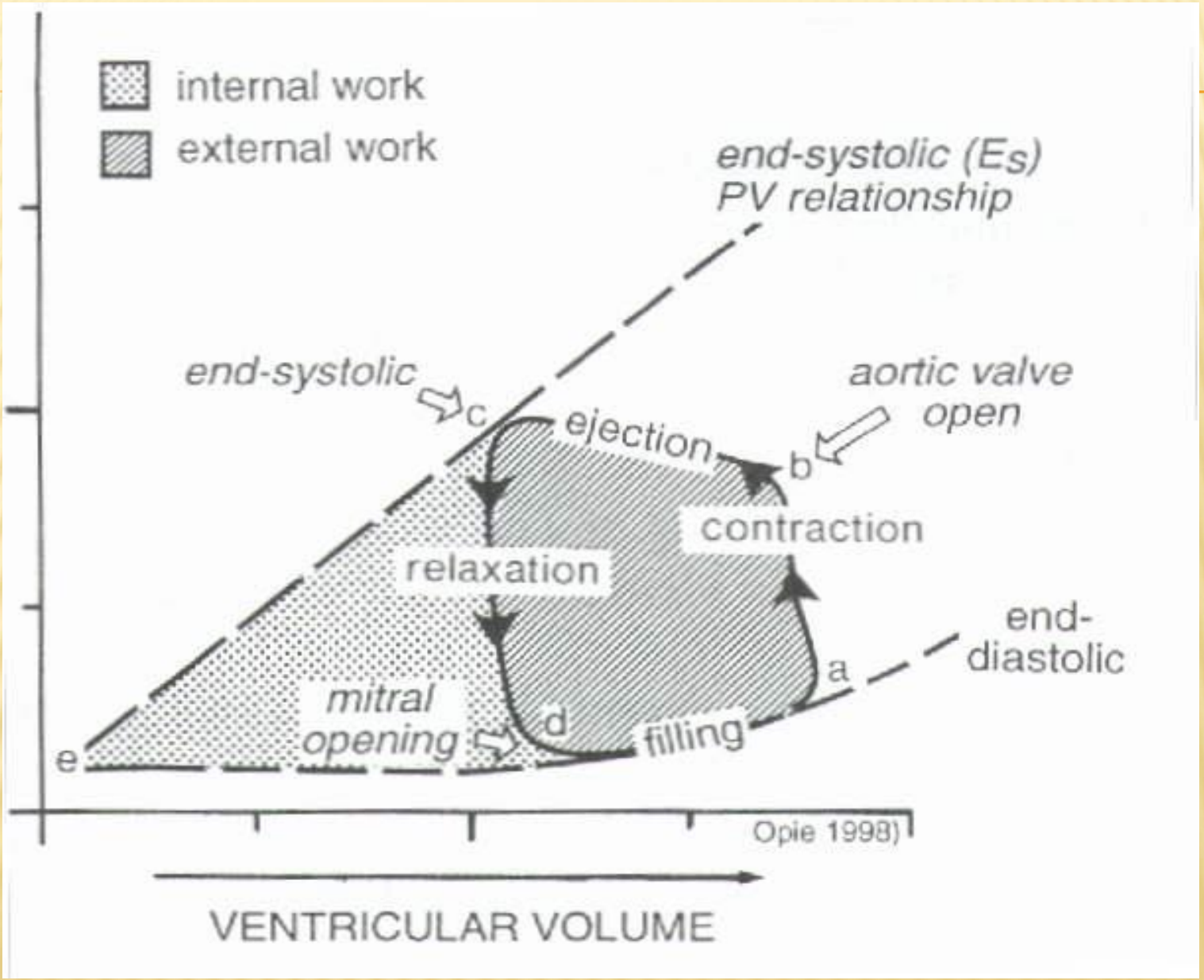
Abbreviations: CRP, C-reactive protein; FLT1, soluble vascular endothelial growth factor receptor; GLUT-4, glucose transporter-4; ICAM, soluble intercellular adhesion molecule; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; JNK, c-Jun N-terminal kinase; MCP-1, monocyte chemoattractant protein-1; NGF, nerve growth factor; PAI-1, plasminogen activator inhibitor-1; PGC-1α, PPAR-γ coactivator-1α; sPLA2-IIA, secretory type II phospholipase A2; PPAR-γ, peroxisome-proliferator-activated receptor γ; PRDM16, brown adipocyte differentiation transcription factor PR-domain-missing16; RANTES, regulated upon activation normal T cell and secreted; TLRs, toll-like receptors; TNF-α, tumor necrosis factor-alpha; UCP1, uncoupling protein-1.

NORMAL CARDIAC FUNCTION

- Cardiac Output = Heart rate x Stroke volume
- Heart rate – controled by SNS and PNS
- Stroke – dependent on preload, afterload and contractility
- Preload = LVEDP and is measured as PCWP (Pulmonary Capillary Wedge Pressure)
- Afterload = SVR (Systemic Vascular Resistance)
- Contractility: ability of contractile elements to interact and shorten against a load

  (+ inotropy - inotropy)

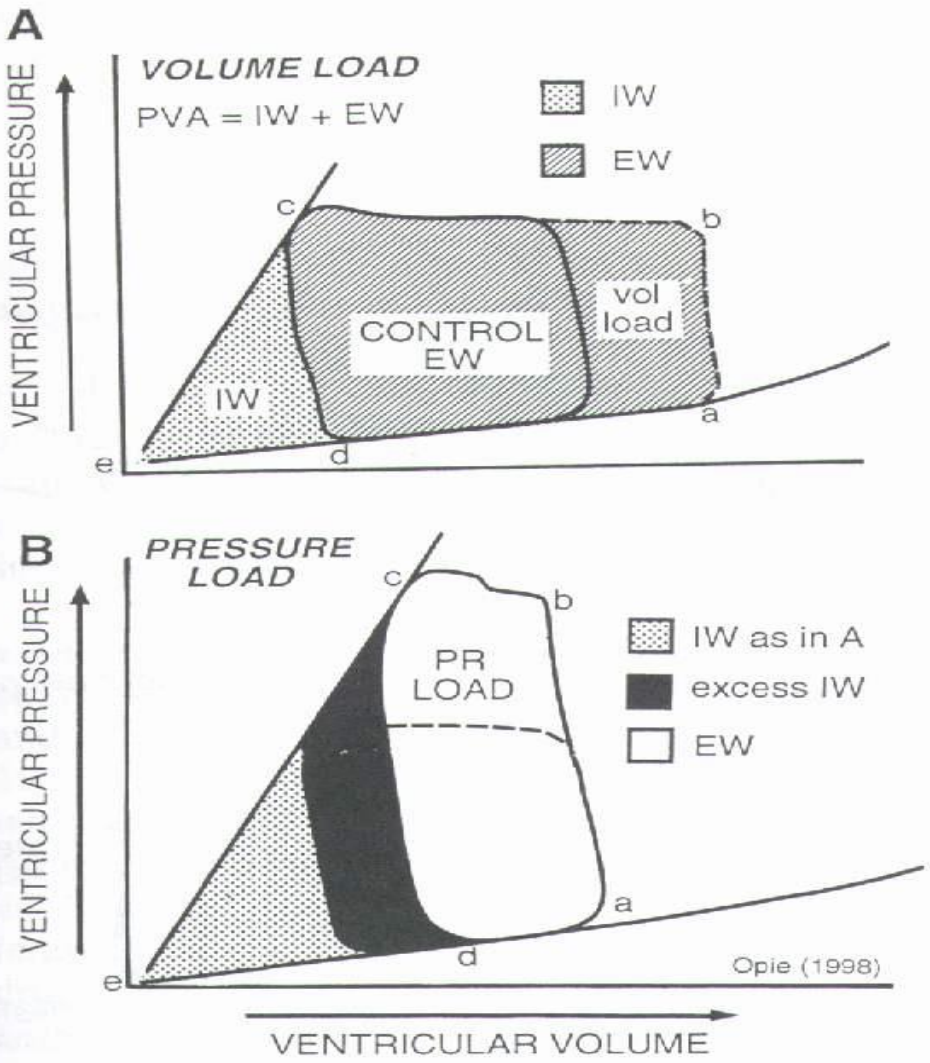

Contractility
Preload
Afterload
+
+
-
Heart rate
Stroke volume
+
+
CARDIAC OUTPUT



Working diagram

Sum of the external and internal work represents the total mechanical work of contraction and this is directly proportional to oxygen consumption of the myocardium.

Pressure work of the heart consumes more oxygen than volume work, so that the effectivity of the former is lower than that of the latter.

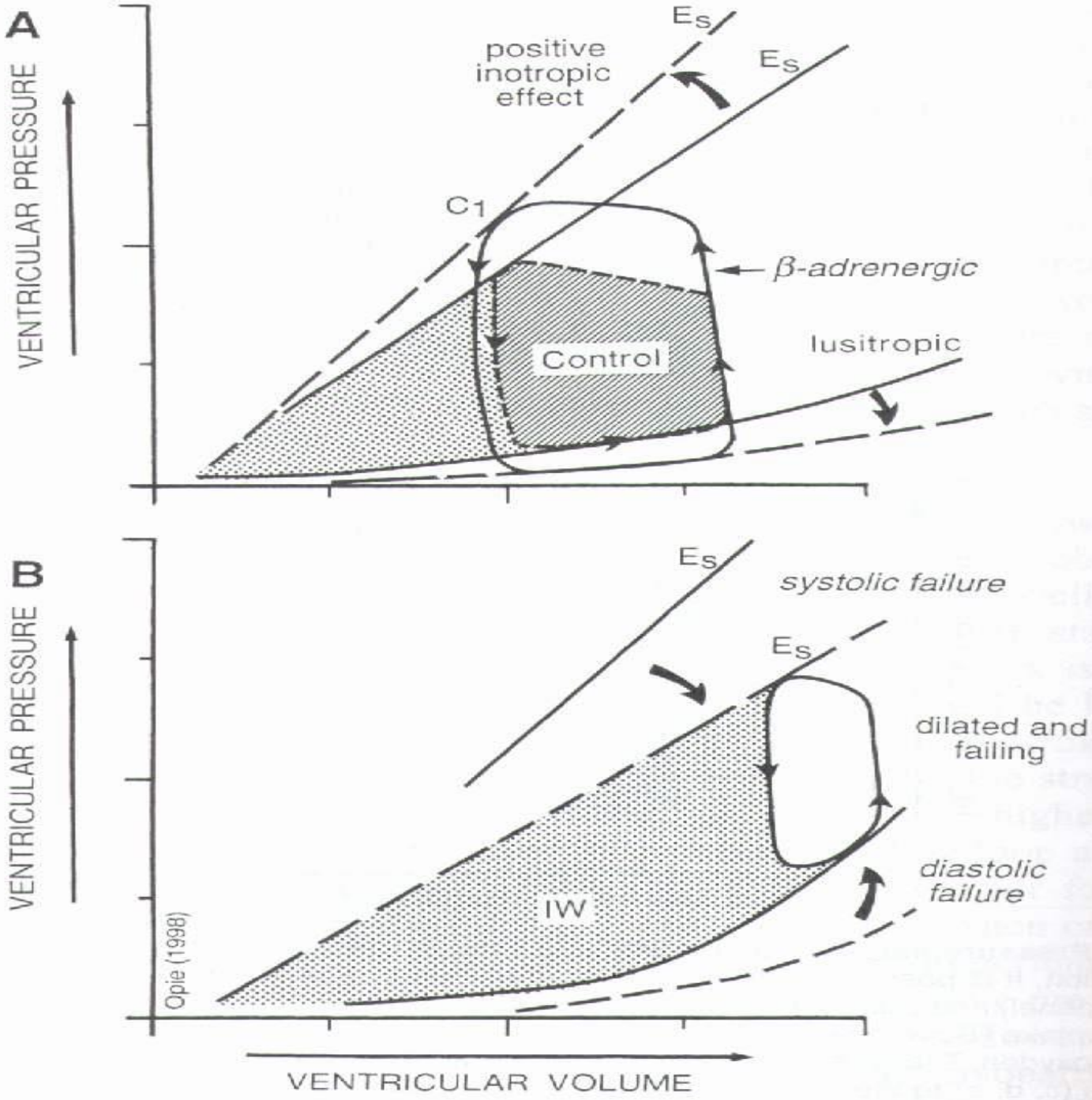

A
VOLUME LOAD
PVA = IW + EW
IW
EW
VENTRICULAR PRESSURE
c
b
CONTROL EW
vol load
IW
a
e
d
B
PRESSURE LOAD
c
b
PR LOAD
IW as in A
excess IW
EW
a
e
d
Opie (1998)
VENTRICULAR VOLUME

SYSTOLIC DYSFUNCTION

- Impairment of the contraction of the left ventricle leads to reduction of stroke volume (SV) for any given end-diastolic volum (EDV)
- Ejection fraction (EF) is reduced (below 40-45%)
- EF=SV/EDV

DIASTOLIC DYSFUNCTION

- Ventricular filling rate and the extent of filling are reduced or a normal extent of filling is associated with an inappropriate rise in ventricular diastolic pressure.


A
VENTRICULAR PRESSURE
positive
inotropic
effect
Es
Es
C1
β-adrenergic
Control
lusitropic
B
VENTRICULAR PRESSURE
Es
systolic failure
Es
dilated and
failing
diastolic
failure
IW
Opie (1998)
VENTRICULAR VOLUME

COMPENSATORY MECHANISMS FOR DECREASED CARDIAC OUTPUT

- Increased SNS activity

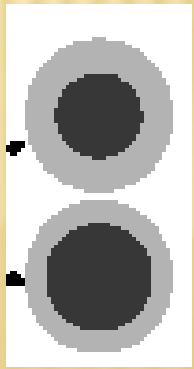
  Increase HR and SVR which increases BP

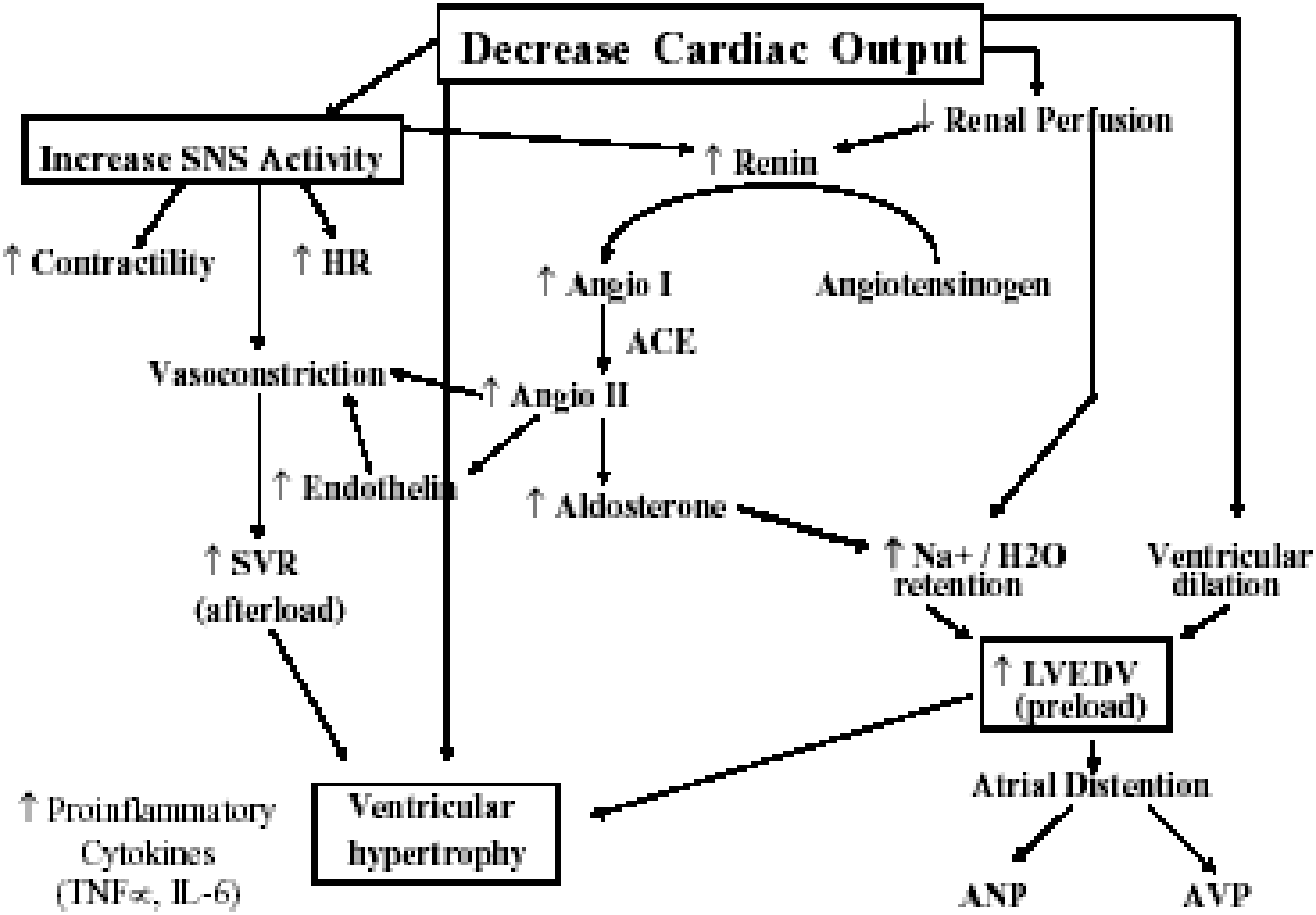
- Frank-Starling mechanism:

  ⇑ LVEDP = ⇑ SV

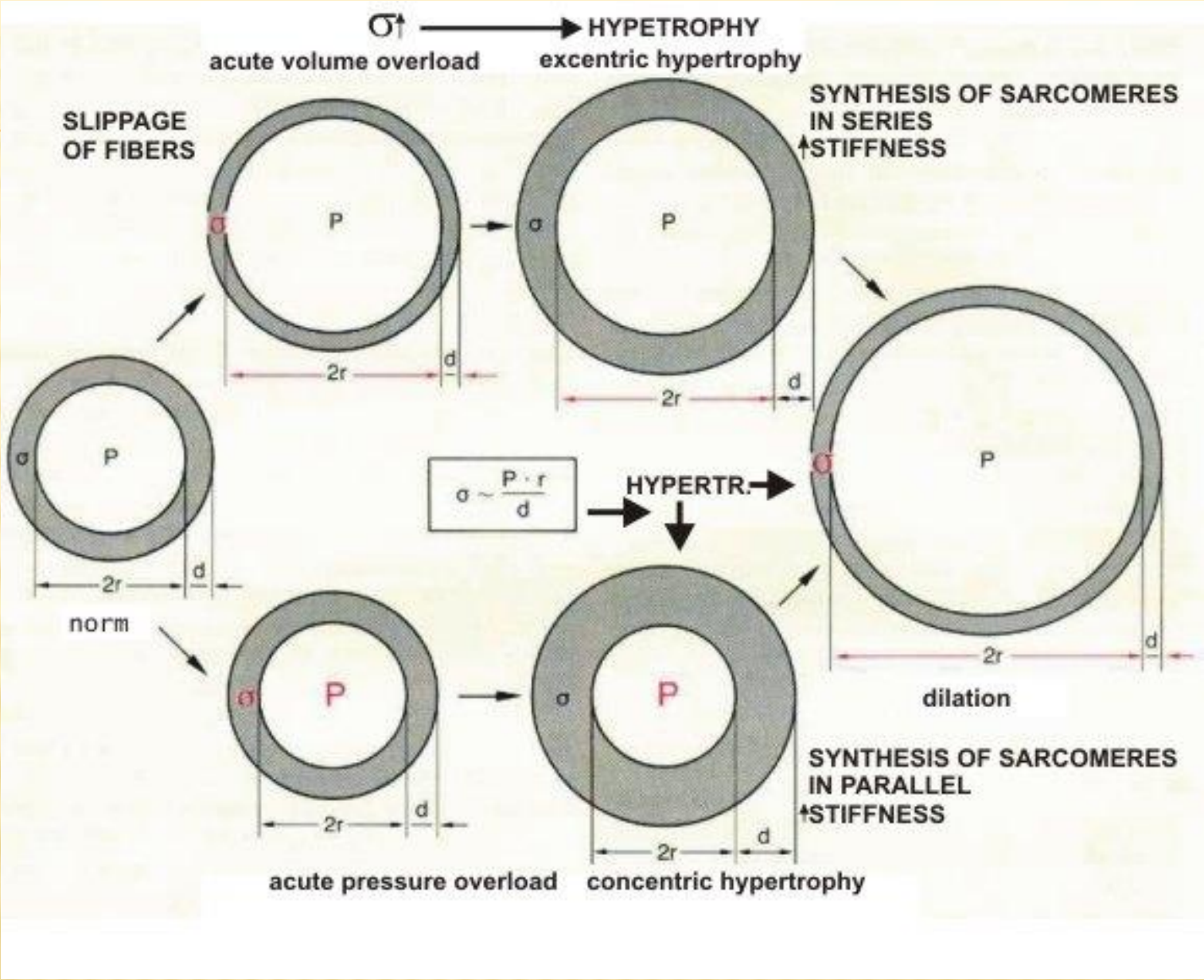
- Activation of renin-angiotensin-aldosterone
- system (RAAS)
- Myocardial remodeling

  - Concentric hypertrophy
  - Eccentric hypertrophy




Decrease Cardiac Output
Increase SNS Activity
↓ Renal Perfusion
↑ Renin
↑ Contractility
↑ HR
↑ Angio I
Angiotensinogen
ACE
Vasoconstriction
↑ Angio II
↑ Endothelin
↑ Aldosterone
↑ SVR
(afterload)
↑ Na+ / H2O
retention
Ventricular
dilation
↑ LVEDV
(preload)
↑ Proinflammatory
Cytokines
(TNFα, IL-6)
Ventricular
hypertrophy
Atrial Distention
ANP
AVP

Pat


σ↑ → HYPETROPHY
acute volume overload
excentric hypertrophy
SLIPPAGE OF FIBERS
SYNTHESIS OF SARCOMERES IN SERIES
↑STIFFNESS
σ
P
2r
d
$\sigma \sim \frac{P \cdot r}{d}$
HYPERTR.
norm
dilation
SYNTHESIS OF SARCOMERES IN PARALLEL
↑STIFFNESS
acute pressure overload
concentric hypertrophy

ATHEROSCLEROSIS DEVELOPMENT

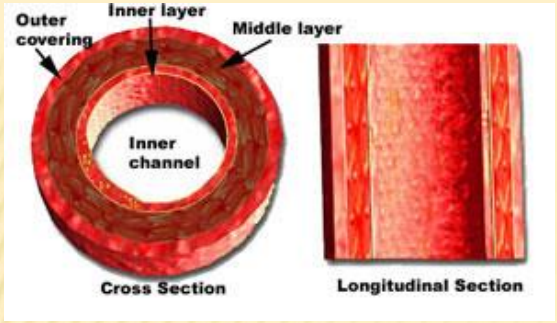
- Initiation
- Inflammation
- Fibrous cap formation
- Plaque rupture
- Thrombosis

FUNCTIONAL ENDOTHELIUM

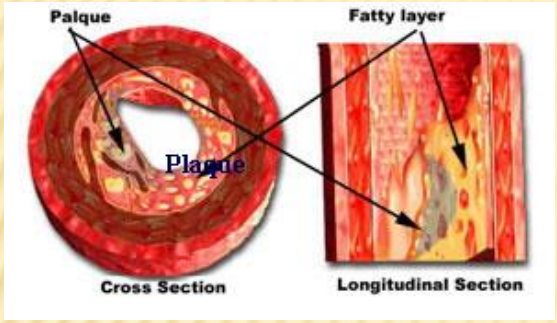
- *Constant vasodilation*
- *Antiadhesive state* (NO, PGI2)
- *Constant local anticoagulation and fibrinolytic state* (increase of AT III, protein C, protein S, tPA, PAI-1)

ENDOTHELIAL DYSFUNCTION- CAUSES

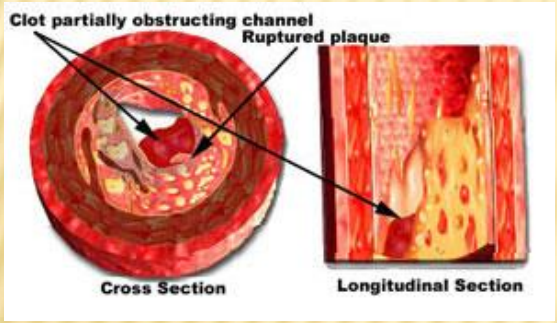
- *LDL modification* (oxidation, glycation, immune complex formation).
- *Expression of adhesive molecules*
- *Cytokines release* (attraction and migration of proinflammatory cells to subendothelial space).
- *Prothrombotic phenotype of* dysfunctional endothelium



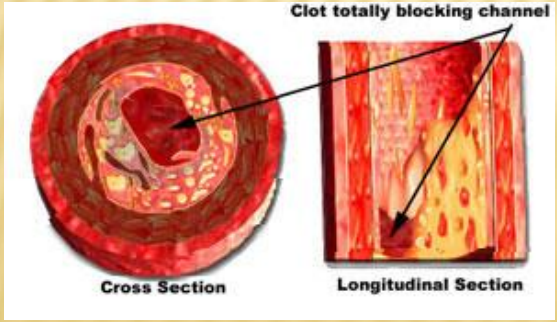
Crossection of normal vessel



Stable angina pectoris



Unstable angina pectoris



Myocardial infarction

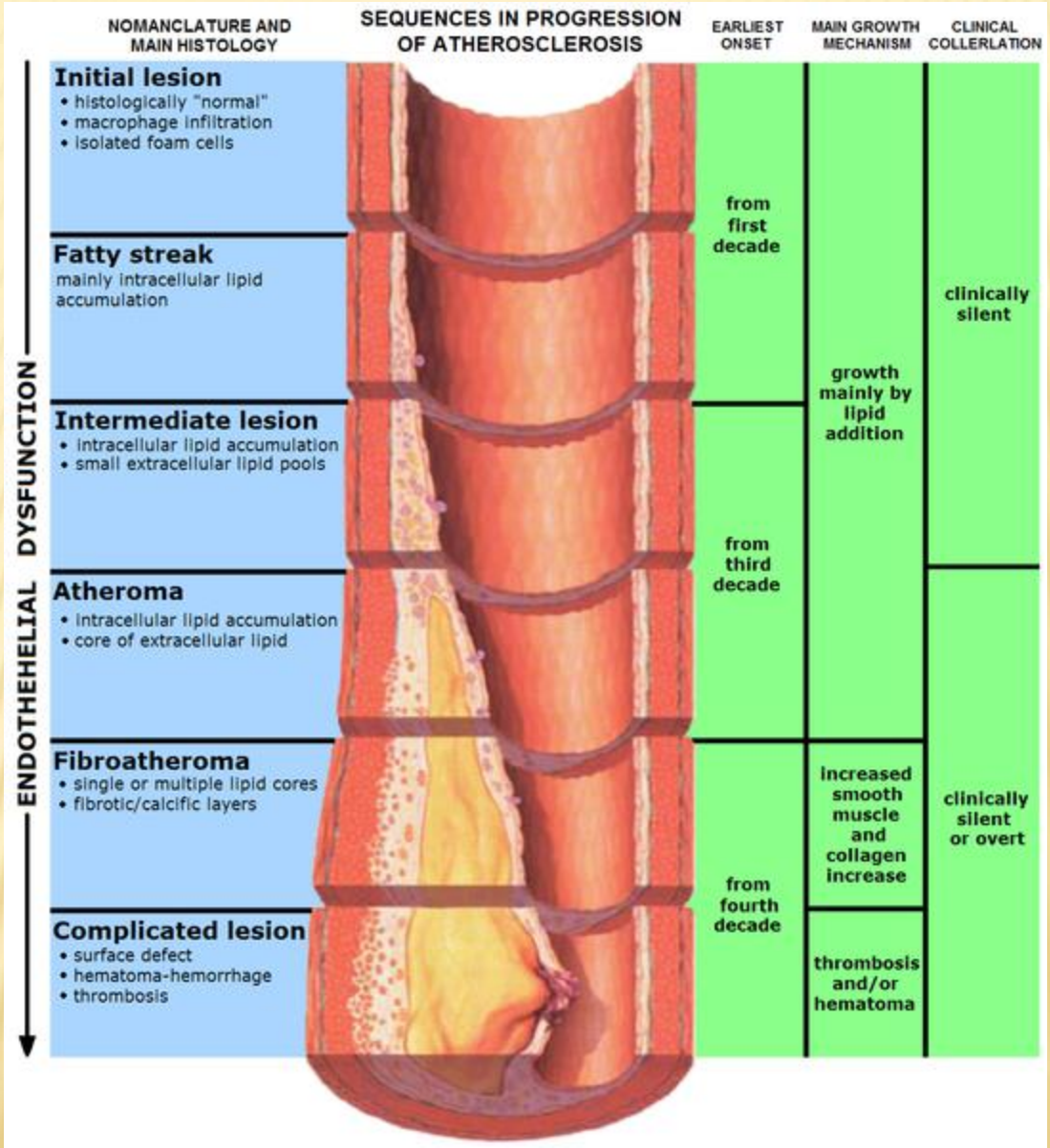
Decreased blood flow

„RESPONSE-TO-RETENTION“ MODEL OF ATHEROGENESIS

- Atherogenesis is initiated by focal retention of *ApoB* on molecules of subendothelial matrix, especially on proteoglycans.
- Adherent lipoproteins are modified (by aggregation and/ or oxidation), which lead to maladaptive inflammatory response. Monocytes enter subendothelial space, differentiate to macrophages and that phagocyte adherent and modified lipoproteins. They become gradually foam cells. Another cells as T-lymphocytes, mast cells and other ones enter the developing lesion and take part in maladaptive inflammatory response. The process is accelerating by increased retention of lipoproteins in atherosclerotic plaques.
- Smooth muscle cells (SMCs) migrate to intima and support production of collagen fibrous cap which seems to be remodelling response of vascular wall (similar to scar) to damage.
- During atherosclerotic lesion progression focal necrotic lesions with death macrophages are formed. In these lesions accumulation of extracellular debris, cholesterol crystals, proteases and procoagulation/ trombogenic material can be observed. This leads to attenuation of fibrous cap, erosion and/ or rupture of the plaque and development of acute thrombotic vascular event *(MI, cerebral stroke)*.

„RESPONSE-TO-RETENTION“ MODEL OF ATHEROGENESIS

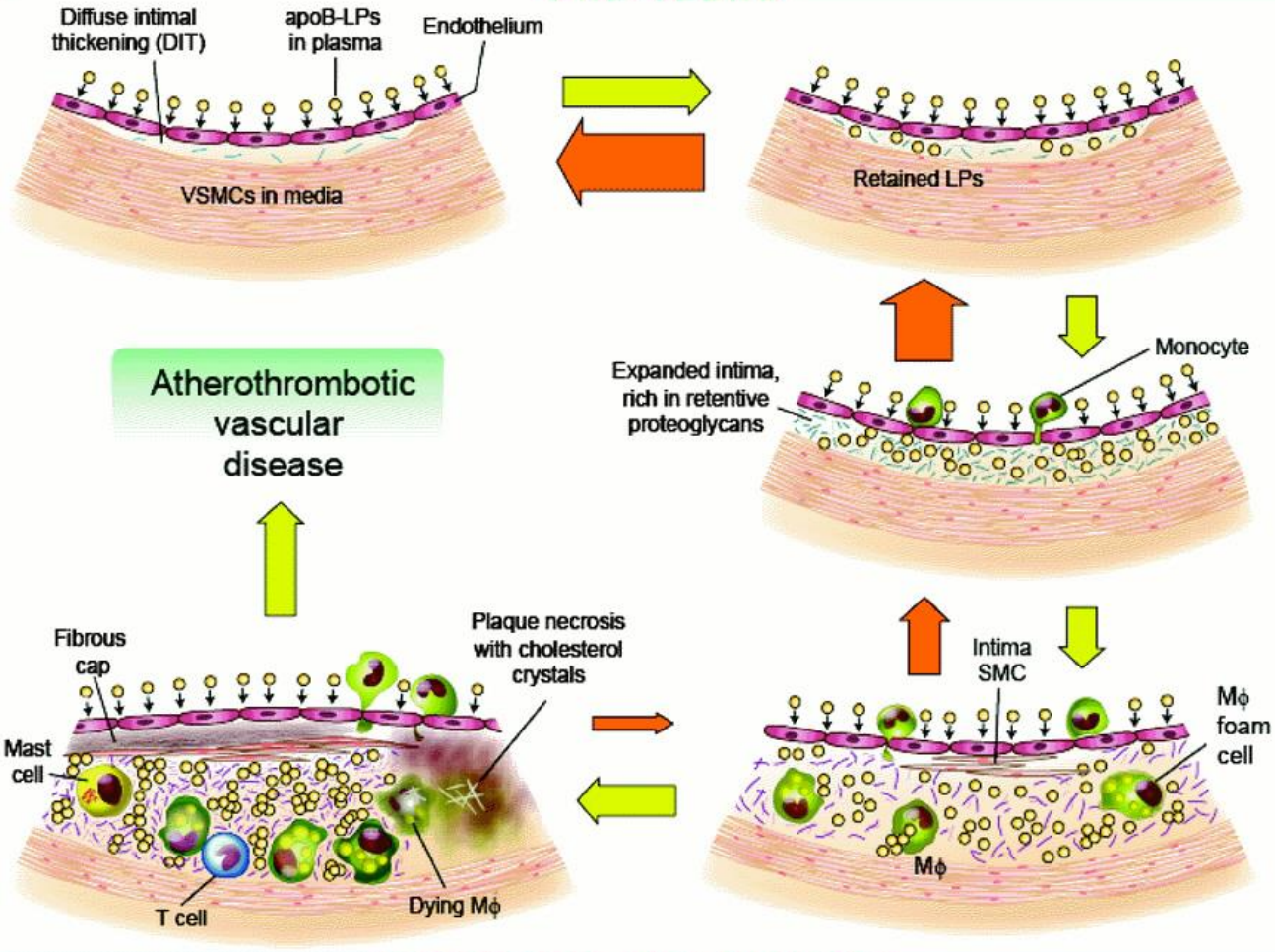
- Cytokine release (platelet-derived growth factor a transforming growth factor-β (TGF-β) from monocytes, macrophages and/ or damaged endothelial cells support further accumulation of macrophages and migration and proliferation of smooth muscle cells


NOMANCLATURE AND MAIN HISTOLOGY
SEQUENCES IN PROGRESSION OF ATHEROSCLEROSIS
EARLIEST ONSET
MAIN GROWTH MECHANISM
CLINICAL COLLERLATION
ENDOTHEHELIAL DYSFUNCTION
Initial lesion
• histologically "normal"
• macrophage infiltration
• isolated foam cells
Fatty streak
mainly intracellular lipid accumulation
Intermediate lesion
• intracellular lipid accumulation
• small extracellular lipid pools
Atheroma
• intracellular lipid accumulation
• core of extracellular lipid
Fibroatheroma
• single or multiple lipid cores
• fibrotic/calcific layers
Complicated lesion
• surface defect
• hematoma-hemorrhage
• thrombosis
from first decade
from third decade
from fourth decade
growth mainly by lipid addition
increased smooth muscle and collagen increase
thrombosis and/or hematoma
clinically silent
clinically silent or overt

- Pre-lesional susceptible area of the arterial wall with diffuse intimal thickening (DIT)
- Lowering plasma apoB LPs and decreasing risk factors will prevent future vascular disease

- Early lipoprotein retention
- Lowering plasma apoB LPs and decreasing risk factors will readily promote removal of atherogenic components and prevent maladaptive responses and future disease

PRE-TEENS



TEENS

- Early responses to LP retention, *e.g.*, monocyte entry
- Lowering plasma apoB LPs and decreasing risk factors will readily promote removal of atherogenic components and prevent further responses and future disease
- Future strategies to prevent LP retention are likely to be most feasible up to this stage

TWENTIES AND BEYOND

- Advanced responses to LP retention, including maladaptive inflammation, Mϕ death, and plaque necrosis
- LP retention continues to accelerates
- Lowering plasma apoB LPs and reducing risk factors can promote removal of atherogenic components and promote regression, but reversal is more difficult and prolonged, and vascular disease may still develop

- Continued responses to LP retention, e.g., Mϕ foam cell formation and SMC migration
- LP retention starts to accelerate
- Lowering plasma apoB LPs and other risk factors can still promote removal of atherogenic components, promote regression, and prevent further responses and future disease

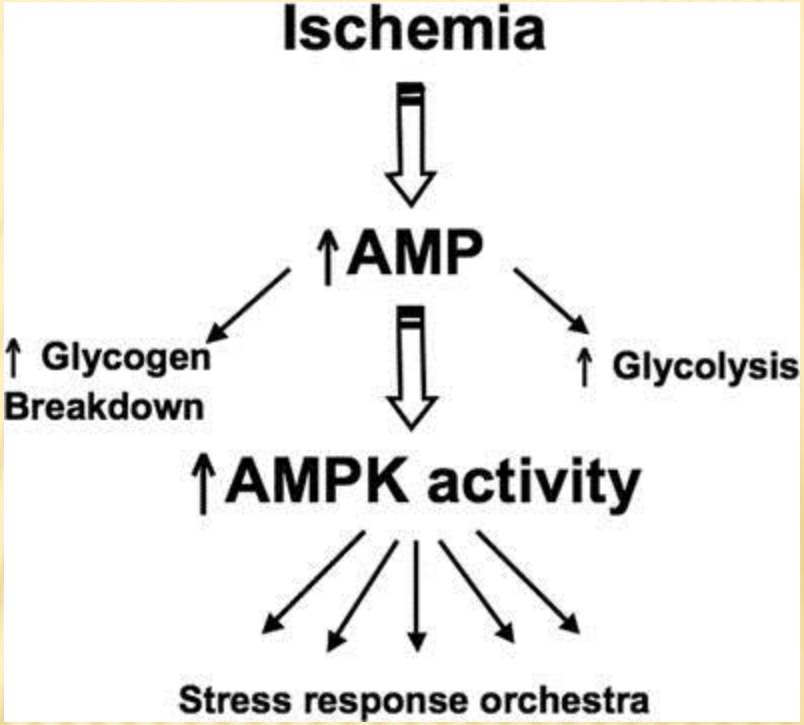
Tabas: Circulation, 116, 2007: 1832-1844

MYOCARDIAL ISCHEMIA

- Myocardial ischemia results in numerous deleterious consequences at the level of the cardiac myocyte that, if left uncorrected, culminate in necrotic cell death.
- A major consequence of myocardial ischemia is the depletion of adenosine triphosphate (ATP) and other high energy phosphates due to cessation of aerobic metabolism and oxidative phosphorylation. Because the continually contracting myocardium is highly dependent on aerobic metabolism, ATP depletion occurs rapidly in the ischemic heart and contractility is halted within 60 s.
- ATP depletion is leading to: decreased relaxation of myofilaments, glycogen depletion, disruption of ionic equilibrium and cell swelling.

MYOCARDIAL ISCHEMIA

- Nevertheless, these effects can be reversed and normal myocyte contractile function restored if the duration of ischemia is sufficiently brief (generally considered to be less than 20 min of severe ischemia).
- If the ischemia is prolonged, irreversible injury will develop, which is characterized by damage and/or disruption of the myocyte sarcolemmal membrane.
- Plasma membrane damage leads to loss of osmotic balance and the leakage of cellular metabolites into the extracellular space.
- Damage to the mitochondrial membranes compromises the cell's ability to generate ATP upon reperfusion, as well as results in release of mitochondrial proteins that can directly stimulate the apoptotic cell death pathway.
- Disruption of lysosomal membranes is especially dire, as this can lead to the release of degradative enzymes capable of digesting essentially all cellular constituents, invariably leading to cellular necrosis.


Ischemia
↑AMP
↑ Glycogen Breakdown
↑ Glycolysis
↑AMPK activity
Stress response orchestra

ACUTE MYOCARDIAL ISCHEMIA

- Acute myocardial ischemia was find to induce early increases (10 min) of circulating glucose, lactate, glutamine, glycine, glycerol, phenylalanine, tyrosine, and phosphoethanolamine; decreases in choline-containing compounds and triacylglycerols; and a change in the pattern of total, esterified, and nonesterified fatty acids. Creatine increased 2 h after ischemia.
- Using multivariate analyses, a biosignature was developed that accurately detected patients with MIS both in the setting of angioplasty-related MIS (area under the curve 0.94) and in patients with acute chest pain (negative predictive value 95%).

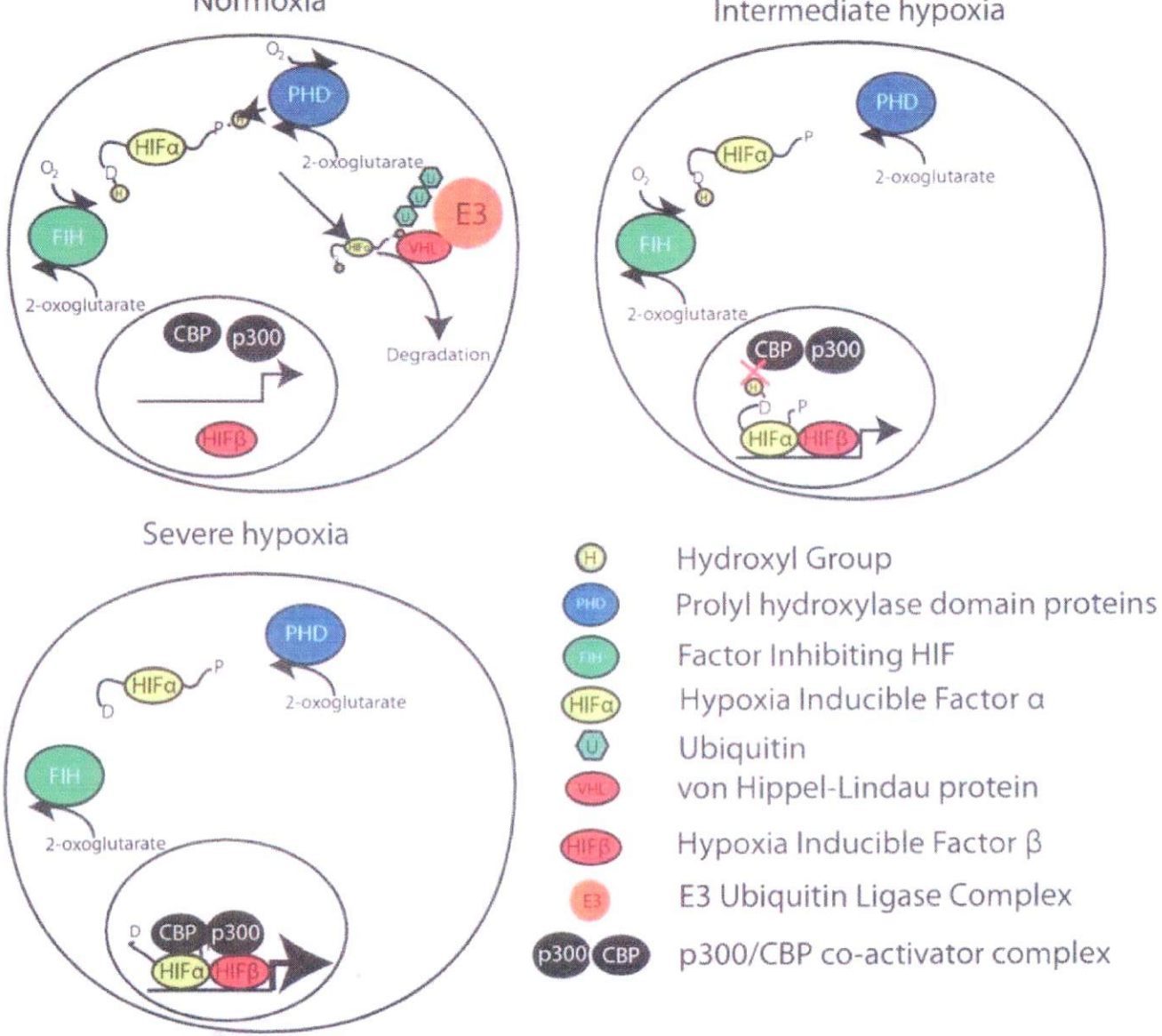


Figure 1. Mechanism of HIF activity. Under normoxic conditions, HIFα subunits are hydroxylated on proline residues. Hydroxylated prolines are recognised by the von Hippel-Lindau protein, ubiquinated by the E3 ubiquitin ligase, and targeted for proteosomal degradation. As oxygen levels fall, HIFα is stabilised and enters the nucleus to form a transcriptional complex with HIFβ subunits. FIH activity is maintained at lower oxygen levels than PHDs and remains active, hydroxylating asparagines. Hydroxylation of asparagines by FIH prevents association of the CBP/p300 coactivator complex with the HIFα/HIFβ transcriptional dimer. Under very low oxygen conditions, FIH becomes inactive and maximal HIF transcriptional activity is promoted.

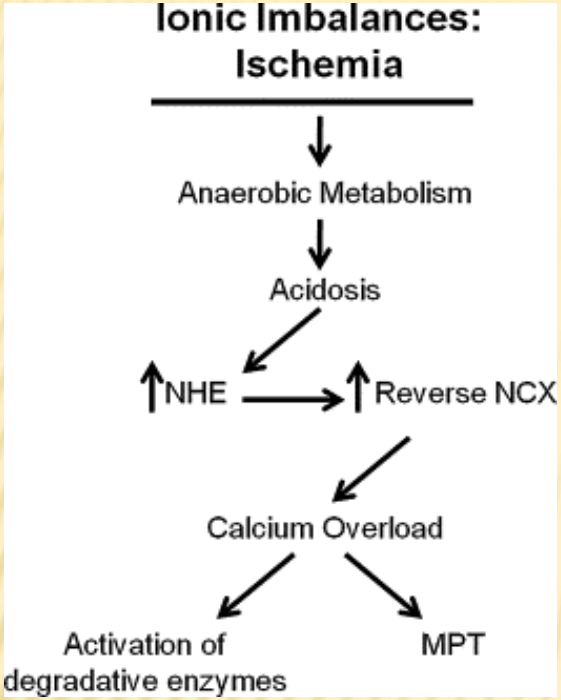
doi:10.1371/journal.pbio.1001116.g001

ISCHEMIA/REPERFUSION-INDUCED CELL DEATH

- In addition to necrosis, apoptosis also contributes significantly to myocyte death during ischemia/reperfusion-induced cell death (IR). While apoptotic myocyte death is most pronounced in the reperfused myocardium, apoptosis has also been shown to contribute to cell death in ischemic-only hearts.
- In addition, a more recently defined form of cell death known as necroptosis or "programmed necrosis," a form of cell death with characteristics of both necrosis and apoptosis, has been suggested to contribute to myocyte death during IR.

MYOCYTE CALCIUM HOMEOSTASIS

- Loss of myocyte calcium homeostasis results in a number of cellular changes that predispose the myocyte to irreversible injury.
- Mitochondrial calcium overload is the primary stimulus for mitochondrial permeability transition (MPT), a stress response mediated by the opening of a high conductance pore located on the inner mitochondrial membrane. While enhanced intracellular calcium concentration is capable of directly stimulating apoptosis, elevated calcium levels can also stimulate the activation of numerous intracellular degradative enzymes with the potential to damage several different cellular structures and precipitate cell death, including phospholipases, proteases and endonucleases. Activation of phospholipases can lead to the damage of cellular membranes which, as described above, can lead to necrotic cell death as a consequence of disruption of cellular osmotic balance and the release of lysosomal enzymes in the cytoplasm. The ionic imbalances have further consequences.



Causes and consequences of ionic imbalances during ischemia.

Ischemia results in a cessation of aerobic metabolism and a reliance on anaerobic metabolism, resulting in cellular and tissue acidosis. Accumulation of intracellular H^+ stimulates NHE, resulting in accumulation of intracellular Na^+. Accumulation of intracellular Na^+, in turn, stimulates reverse activity of the NCX, resulting in intracellular Ca^{2+} accumulation. If ischemia is sustained, cellular Ca^{2+} overload may develop, resulting in activation of degradative enzymes (*e.g.*, proteases, phosphatases and endonucleases), and stimulation of MPT, culminating in myocyte death. NHE, Na^+/H^+ exchanger; NCX, Na^+/Ca^{2+} exchanger; MPT, mitochondrial permeability transition.

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Novel therapeutic strategies for ischemic heart disease

Pharmacological Research, Volume 89, 2014, 36 - 45

http://dx.doi.org/10.1016/j.phrs.2014.08.004

METABOLISM OF THE HEART IN ISCHEMIC CONDITIONS

- Dramatic and immediate changes take place in cardiac and global metabolism as a consequence of insufficient blood flow to meet the myocardium energy needs and secondary to the subsequent stress response.
- These mechanisms include a decrease of β-oxidation and an increase of glycolysis and lactate release among others.

CORONARY ARTERY DISEASE (CAD)

- Multifactorial etiology, frequent risk factors
- *Uninfluenced*: genetics, age, sex, rase, family history, low socioeconomic state (?)
- *Influenced*: total cholesterol, smoking, diabetes mellitus, hypertension, life style,
- We can observe patients with CAD without these risk factors.

Table 13.25
Risk factors for coronary disease

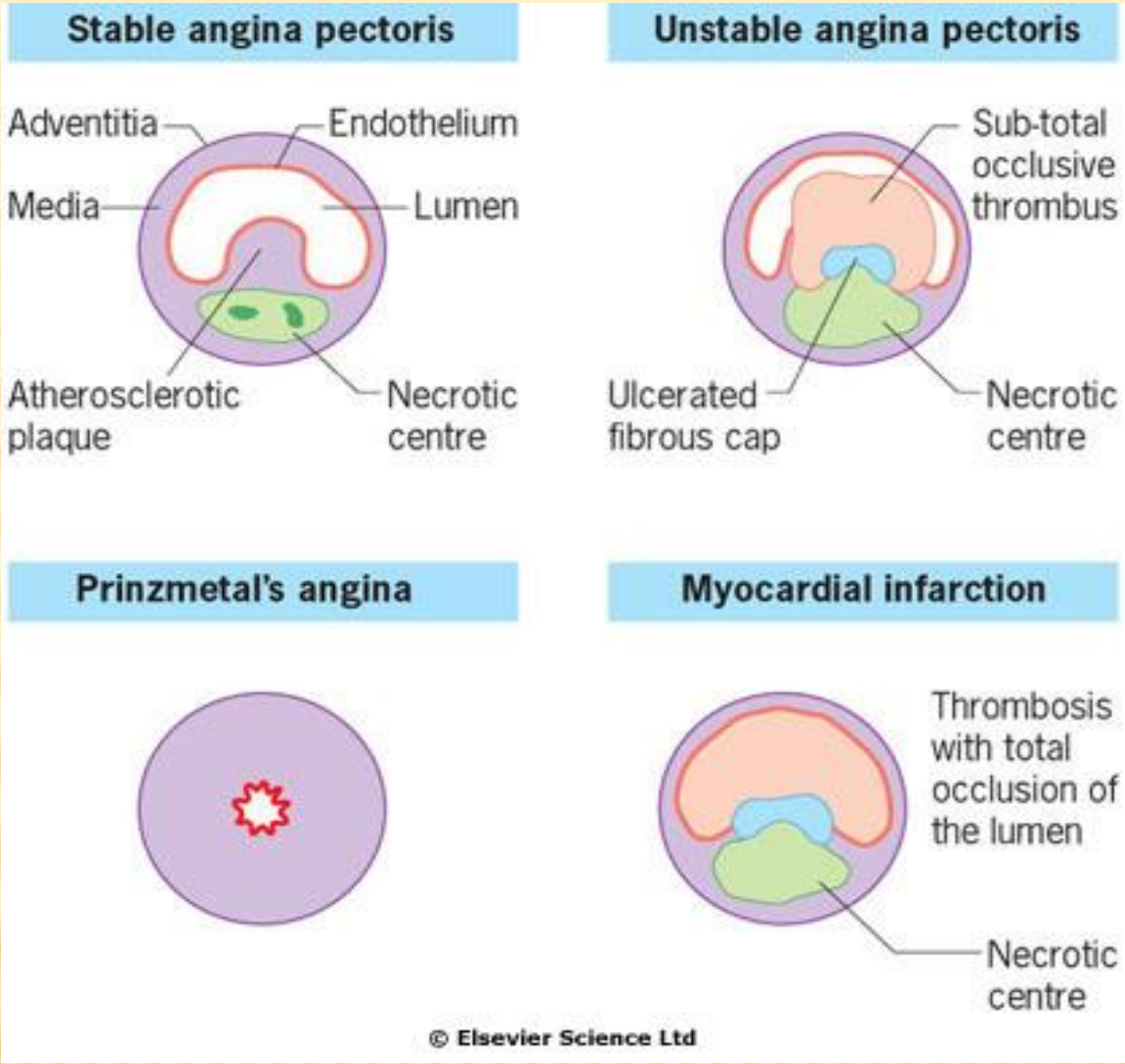
Fixed
Age
Male sex
Positive family history
Deletion polymorphism in the ACE gene (DD)

Potentially changeable with treatment
Hyperlipidaemia
Cigarette smoking
Hypertension
Diabetes mellitus
Lack of exercise
Blood coagulation factors – high fibrinogen, factor VII
C-reactive protein
Homocysteinaemia
Personality
Obesity
Gout
Soft water
Contraceptive pill
Heavy alcohol consumption

ACE, angiotensin-converting enzyme

ACUTE AND CHRONIC ISCHEMIC HEART DISEASES

- Acute coronary syndrom – generally related to unstable angina pectoris- myocardial infarction
- Stable angina pectoris – chest pain during exercise
- Unstable angina pectoris – chest pain in rest conditions
- Prinzmetal´s angina pectoris – due to spasms



Relations among coronary arteries state and clinical syndrome.

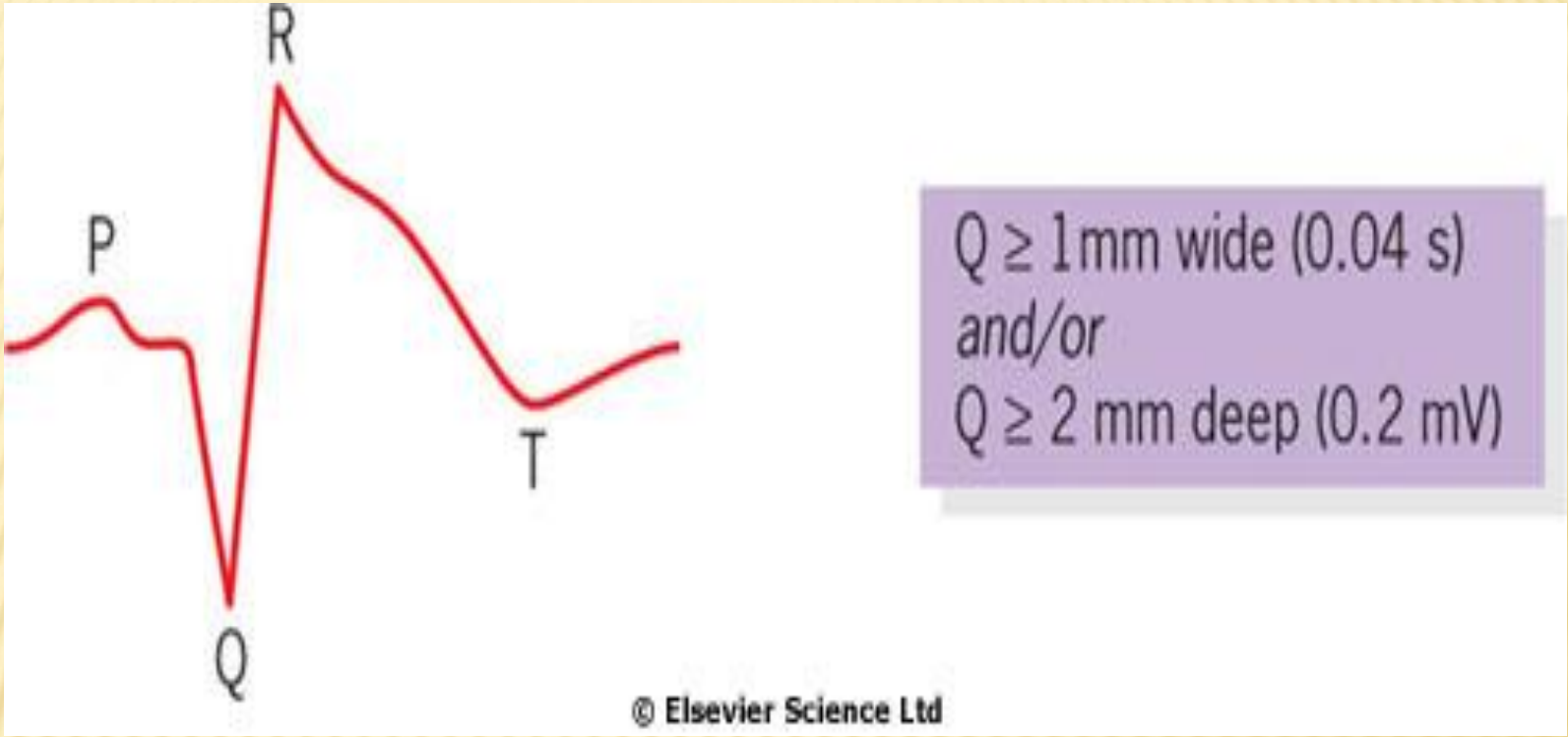
MYOCARDIAL INFARCTION

- Clinical signs:
- *Pain,* angina-like after exercise. Brief onset, during rest, several hours. Pain intensity oscillating, in 20% patients without pain feeling. S.c. ‚silent' MI usually in diabetic patients and older individuals.
- *Vegetative nerve system activation*: sweat, nausea, vomiting, fatique, unrest,
- Patents pale, grey, sweaty
- *Sinus tachykardia* (sympathetic nerve systém activation)
- *Slight fever* (to 38°C) during 5 first days

DIAGNOSIS OF MI

At least two signs:

- Chest pain
- Corresponding changes on ECG
- Increase of cardiac biomarkers



MI Signs on ECG
Q wave, ST elevation, T wave inversion

MI on ECG

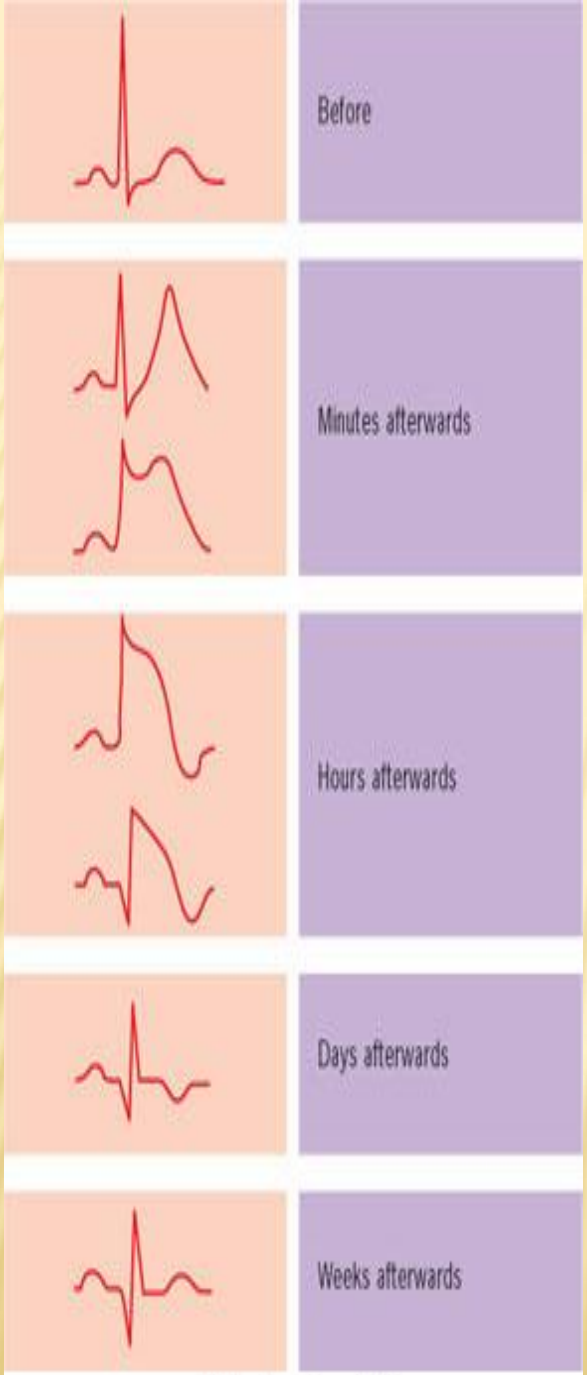

Before
Minutes afterwards
Hours afterwards
Days afterwards
Weeks afterwards
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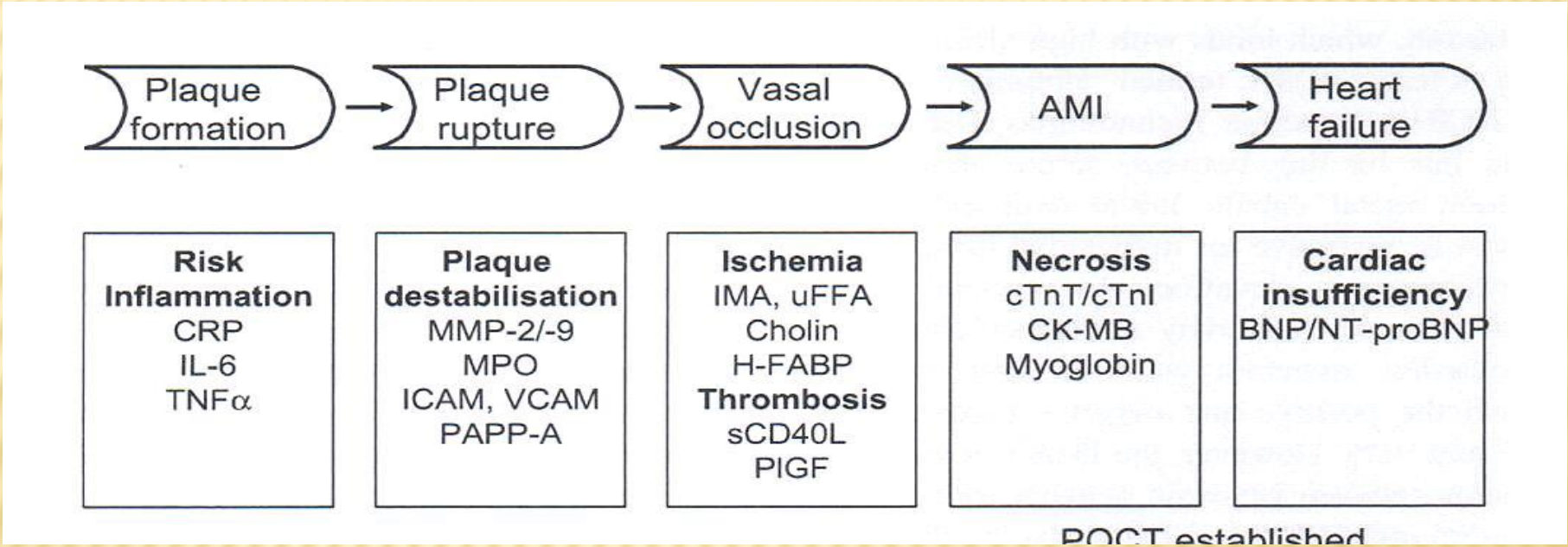
Table 13.29

Typical ECG changes in myocardial infarction

Infarct site	Leads showing main changes
Anterior	
Small	V_3–V_4
Extensive	V_2–V_5
Anteroseptal	V_1–V_3
Anterolateral	V_4–V_6, I, AVL
Lateral	I, II, AVL
Inferior	II, III, AVF
Posterior	V_1, V_2 (reciprocal)
Subendocardial	Any lead
Right ventricle	VR_4

HEART BIOMARKERS



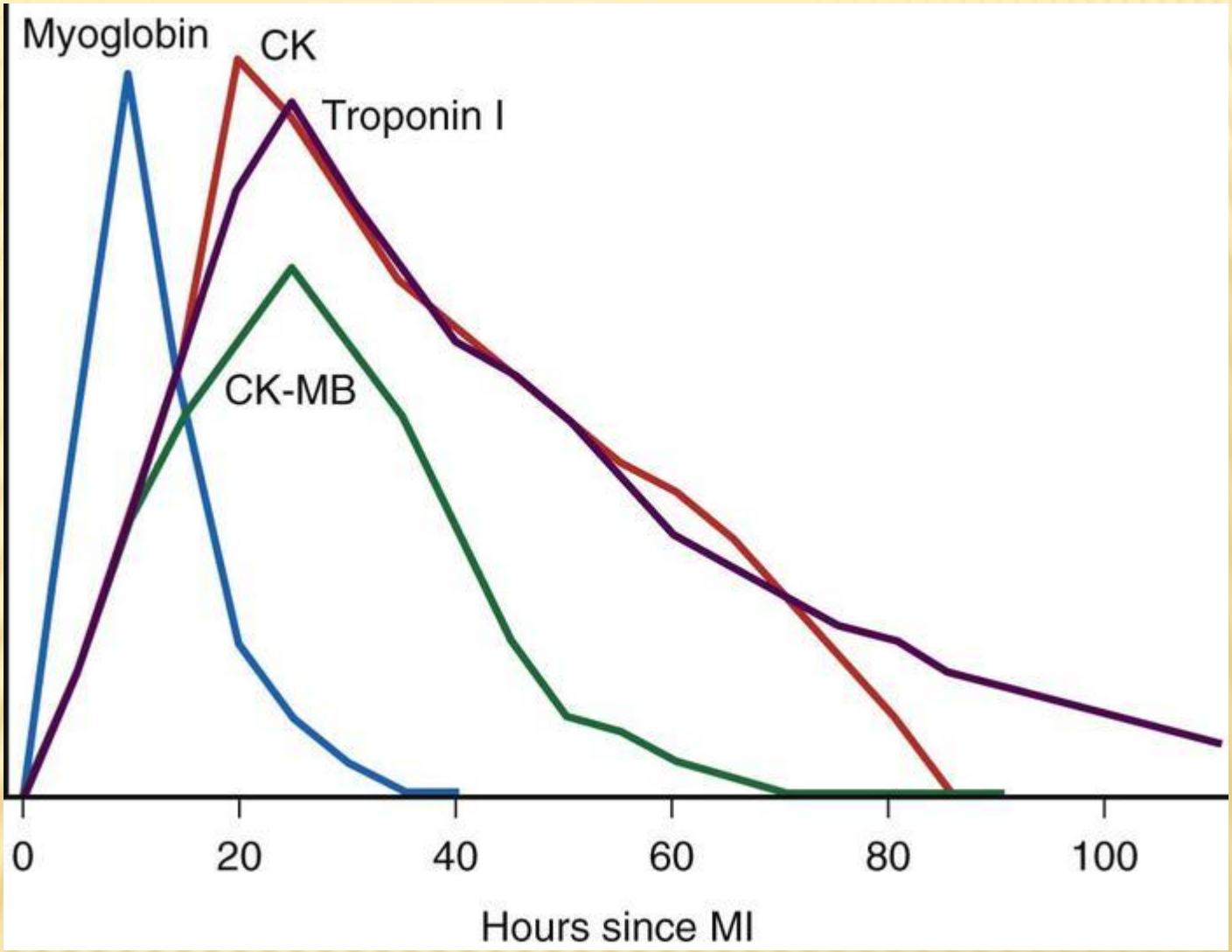
Another markers of acute coronary syndrome

sensitive markers would be particularly useful if they were N-terminus of albumin, as well as the release of copper

Table 3 Additional biomarkers of acute coronary syndrome (*ACS*) and AMI currently under evaluation

hs-CRP	Elevated hs-CRP at admission and at hospital discharge indicates worse short- and long-term prognosis in patients with NSTEMI, whereas it has no predictive value in STEMI (reviewed in [2, 27, 32])
MMP-2, MMP-9	Increased MMPs in patients with ACS compared with patients with stable angina or with controls [43, 44]
MPO	Elevated plasma MPO in patients with ACS is associated with increased frequency of AMI or cardiovascular death independently of cardiac troponin or sCD40L levels [45]
PAPP-A	In ACS an elevated level of serum PAPP-A identifies patients at high risk for AMI or cardiovascular death independently of the levels of cardiac troponins [50]
sCD40L	In patients with ACS elevated plasma sCD40L levels reflect a prothrombotic state [46] and indicate an increased risk for future cardiovascular events and recurrent AMI [47, 48]
IMA	Early marker of myocardial ischemia; predictor of subsequent troponin level elevation in AMI [35, 36]; poor discriminator of AMI and other tissue ischemia
Cholin	Predictor of high-risk unstable angina and of AMI in the follow-up phase [40]
uFFA	Early marker of myocardial ischemia [37, 38]
H-FABP	Exclusion of AMI by a negative result; early indicator of myocardial ischemia [41, 58]
NT-pro-BNP/ BNP	Elevated serum levels are associated with risk of new or recurrent AMI and with higher cardiovascular and overall mortality [51–56]

hs-CRP high-sensitivity C-reactive protein, *NSTEMI* non-ST-segment-elevation myocardial infarction, *STEMI* ST-segment-elevation myocardial infarction, *MMP* metalloproteinase, *MPO* myeloperoxidase, *sCD40L* soluble CD40 ligand, *PAPP-A* pregnancy-associated plasma protein A, *IMA* ischemia-modified albumin, *uFFA* unbound free fatty acids, *H-FABP* heart-type-isoform fatty acid binding protein, *NT-pro-BNP* N-terminal pro-B-type natriuretic peptide fragment, *BNP* B-type natriuretic peptide


Myoglobin
CK
Troponin I
CK-MB
0
20
40
60
80
100
Hours since MI

SIGNS AND SYMPTOMS

Acute MI can have unique manifestations in individual patients. The degree of symptoms ranges from none at all to sudden cardiac death. An asymptomatic MI is not necessarily less severe than a symptomatic event, but patients who experience asymptomatic MIs are more likely to be diabetic. Despite the diversity of manifesting symptoms of MI, there are some characteristic symptoms.

- Chest pain described as a pressure sensation, fullness, or squeezing in the midportion of the thorax
- Radiation of chest pain into the jaw or teeth, shoulder, arm, and/or back
- Associated dyspnea or shortness of breath
- Associated epigastric discomfort with or without nausea and vomiting
- Associated diaphoresis or sweating
- Syncope or near syncope without other cause
- Impairment of cognitive function without other cause

An MI can occur at any time of the day, but most appear to be clustered around the early hours of the morning or are associated with demanding physical activity, or both. Approximately 50% of patients have some warning symptoms (angina pectoris or an anginal equivalent) before the infarct.

PATHOPHYSIOLOGY SUM OF MI

- Most myocardial infarctions are caused by a disruption in the vascular endothelium associated with an unstable atherosclerotic plaque that stimulates the formation of an intracoronary thrombus, which results in coronary artery blood flow occlusion. If such an occlusion persists for more than 20 minutes, irreversible myocardial cell damage and cell death will occur.
- flow, an MI can result.

PATHOPHYSIOLOGY SUM OF MI

- The development of atherosclerotic plaque occurs over a period of years to decades.
- The two primary characteristics of the clinically symptomatic atherosclerotic plaque are a fibromuscular cap and an underlying lipid-rich core. Plaque erosion can occur because of the actions of matrix metalloproteases and the release of other collagenases and proteases in the plaque, which result in thinning of the overlying fibromuscular cap. The action of proteases, in addition to hemodynamic forces applied to the arterial segment, can lead to a disruption of the endothelium and fissuring or rupture of the fibromuscular cap. The loss of structural stability of a plaque often occurs at the juncture of the fibromuscular cap and the vessel wall, a site otherwise known as the *shoulder region*. Disruption of the endothelial surface can cause the formation of thrombus via platelet-mediated activation of the coagulation cascade. If a thrombus is large enough to occlude coronary blood flow, an MI can result.

PATHOPHYSIOLOGY SUM OF MI

- The death of myocardial cells first occurs in the area of myocardium most distal to the arterial blood supply: the endocardium. As the duration of the occlusion increases, the area of myocardial cell death enlarges, extending from the endocardium to the myocardium and ultimately to the epicardium. The area of myocardial cell death then spreads laterally to areas of watershed or collateral perfusion.
- Generally, after a 6- to 8-hour period of coronary occlusion, most of the distal myocardium has died. The extent of myocardial cell death defines the magnitude of the MI. If blood flow can be restored to at-risk myocardium, more heart muscle can be saved from irreversible damage or death.

PATHOPHYSIOLOGY SUM OF MI

- The severity of an MI depends on three factors:
- the level of the occlusion in the coronary artery,
- the length of time of the occlusion, and
- the presence or absence of collateral circulation.

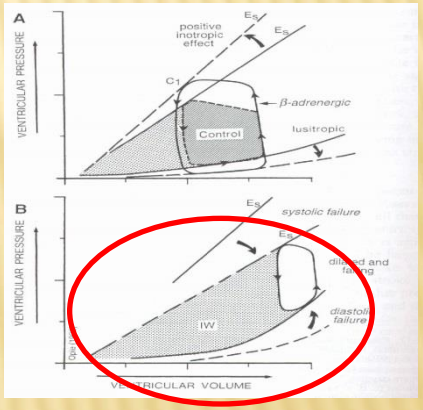
Generally, the more proximal the coronary occlusion, the more extensive the amount of myocardium that will be at risk of necrosis. The larger the myocardial infarction, the greater the chance of death because of a mechanical complication or pump failure. The longer the period of vessel occlusion, the greater the chances of irreversible myocardial damage distal to the occlusion.

STEMI (=MI with ST elevation) is usually the result of complete coronary occlusion after plaque rupture. This arises most often from a plaque that previously caused less than 50% occlusion of the lumen.

NSTEMI (= MI without ST-elevation) is usually associated with greater plaque burden without complete occlusion. This difference contributes to the increased early mortality seen in STEMI and the eventual equalization of mortality between STEMI and NSTEMI after 1 year.

PRECIPITATING CAUSES OF HEART FAILURE

1. ischemia
2. change in diet, drugs or both
3. increased emotional or physical stress
4. cardiac arrhythmias (eg. atrial fib)
5. infection
6. concurrent illness
7. uncontrolled hypertension
8. new high output state (anemia, thyroid)
9. pulmonary embolism
10. mechanical disruption (sudden MR…)



NYHA FUNCTIONAL CLASSIFICATION

- **Class I**: *patients with cardiac disease but no limitation of physical activity*
- **Class II**: *ordinary activity causes fatigue, palpitations, dyspnea or anginal pain*
- **Class III**: *less than ordinary activity causes fatigue, palpitations, dyspnea or angina*
- **Class IV**: symptoms even at rest conditions

STAGES OF HEART FAILURE

- Stage A
  - High risk for development of heart failure
- Stage B
  - Structural heart disease
  - No symptoms of heart failure
- Stage C
  - Symptomatic heart failure
- Stage D
  - End-stage heart failure

DÍKY ZA POZORNOST