VLA October 10, 2017

# 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- betwen external surface of external pericardial layer and thoracic wall – primitive thoracic mesenchym –supplied by a. mammaria int.

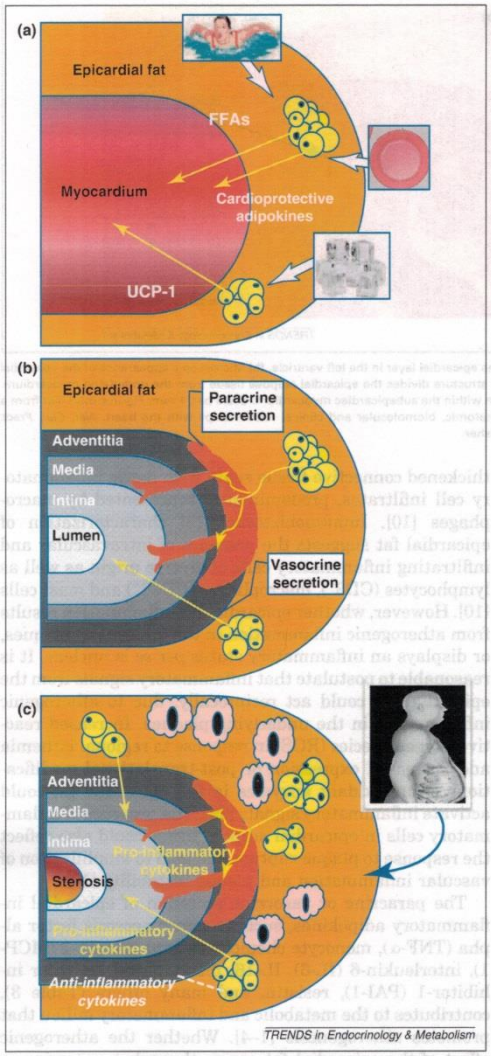



**Figure 2**. Potential physiological, pathophysiological mechanisms and vasocrine/paracrine pathways of epicardial fat. **(a)** Possible physiological roles attributed to the epicardial fat: release of FFAs as energy to the myocardium in condition of high metabolic demand; expression of the thermogenic 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<br>MCP-1 | Adiponectin,<br>Adrenomedullin |
| IL1, IL1β, IL-1Ra, IL6, IL8, IL10<br>CRP<br>PAI-1<br>Prostaglandin D(2), haptoglobin, α1-glycoprotein, JNK<br>sPLA2-IIA, fatty-acid-binding protein 4<br>RANTES<br>ICAM | |
| **Insulin-mimetic, markers of visceral fat** | **Thermogenic** |
| Resistin<br>Visfatin<br>Omentin | UCP 1 |
| **Growth factors** | **Brown fat differentiation transcription factors** |
| NGF<br>FLT1 | PRDM16<br>PGC-1α |
| **Vascular remodeling, blood pressure control, myocardial hypertrophy, adipogenesis** | |
| Angiotensin,<br>Angiotensinogen | |
| Leptin | |
| **Receptors** | |
| Angiotensin II type 1 receptor<br>TLRs<br>PPARγ<br>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.

# EAT AND CORONARY MICROCIRCULATION

- EAT is an ectopic visceral adipose tissue that directly contacts the myocardium and coronary arteries. EAT accumulation is reported to be associated with coronary atherosclerosis and unfavorable cardiovascular outcomes independent of traditional CAD risk factors.
- Pericoronary fat volume was positively associated with the presence of plaque independent of total EAT volume .
- CFR (coronary flow reserve) is dependent on the combined effects of epicardial coronary stenosis and microvascular dysfunction. There is  the possibility of a paracrine role of periventricular EAT on the coronary microcirculation.

# PERIVENTRICULAR EAT AND DIASTOLIC FUNCTION

- Obesity is an important risk factor for LV diastolic dysfunction, which has been shown to be a predictor of heart failure development. However, the underlying mechanism linking obesity to LV diastolic dysfunction has not been fully elucidated.
- Increased periventricular EAT volume seems to be 1 of the important causes of diastolic dysfunction and impaired CFR may be involved in the association between periventricular EAT and diastolic dysfunction.
- Periventricular EAT may affect LV relaxation but not LV compliance. Periventricular EAT may serve as a potential therapeutic target for diastolic dysfunction.

# ATHEROSCLEROSIS DEVELOPMENT

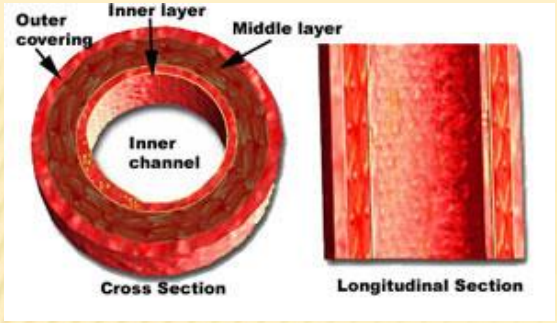
- Initiation
- Inflammation
- Fibrous cap formation
- Plaque rupture
- Thrombosis

# FUNCTIONAL ENDOTHELIUM

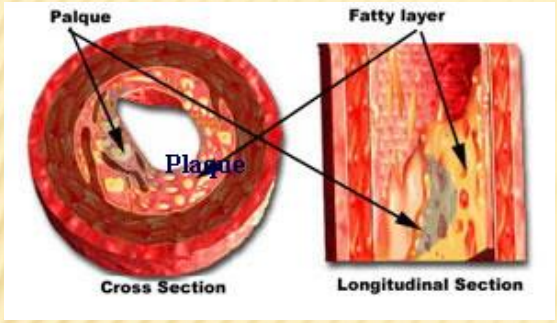
- *Constant vasodilation*
- *Antiadhesive state* (NO, PGI2)
- *Constant local anticoagulation and fibrinolytic state* (increase of AT III, protein C, protein S, tPA, PAI-1)

# ENDOTHELIAL DYSFUNCTION- CAUSES

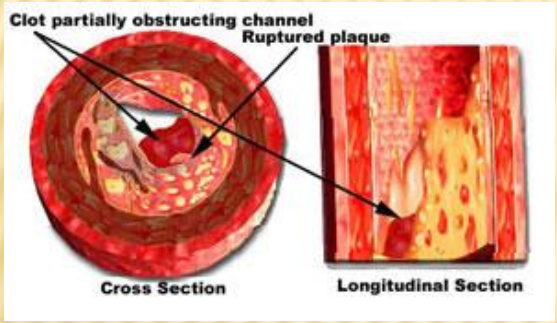
- *LDL modification* (oxidation, glycation, immune complex formation).
- *Expression of adhesive molecules*
- *Cytokines release* (attraction and migration of proinflammatory cells to subendothelial space).
- *Prothrombotic phenotype of* dysfunctional endothelium



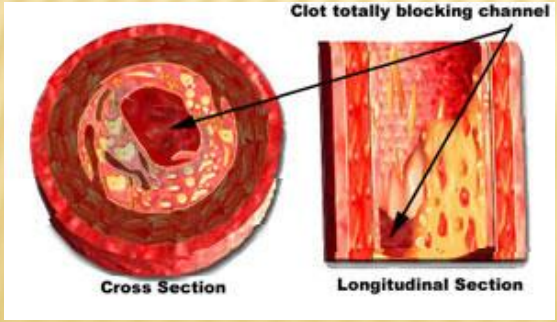

Crossection of normal vessel




Stable angina pectoris




Unstable angina pectoris




Myocardial infarction

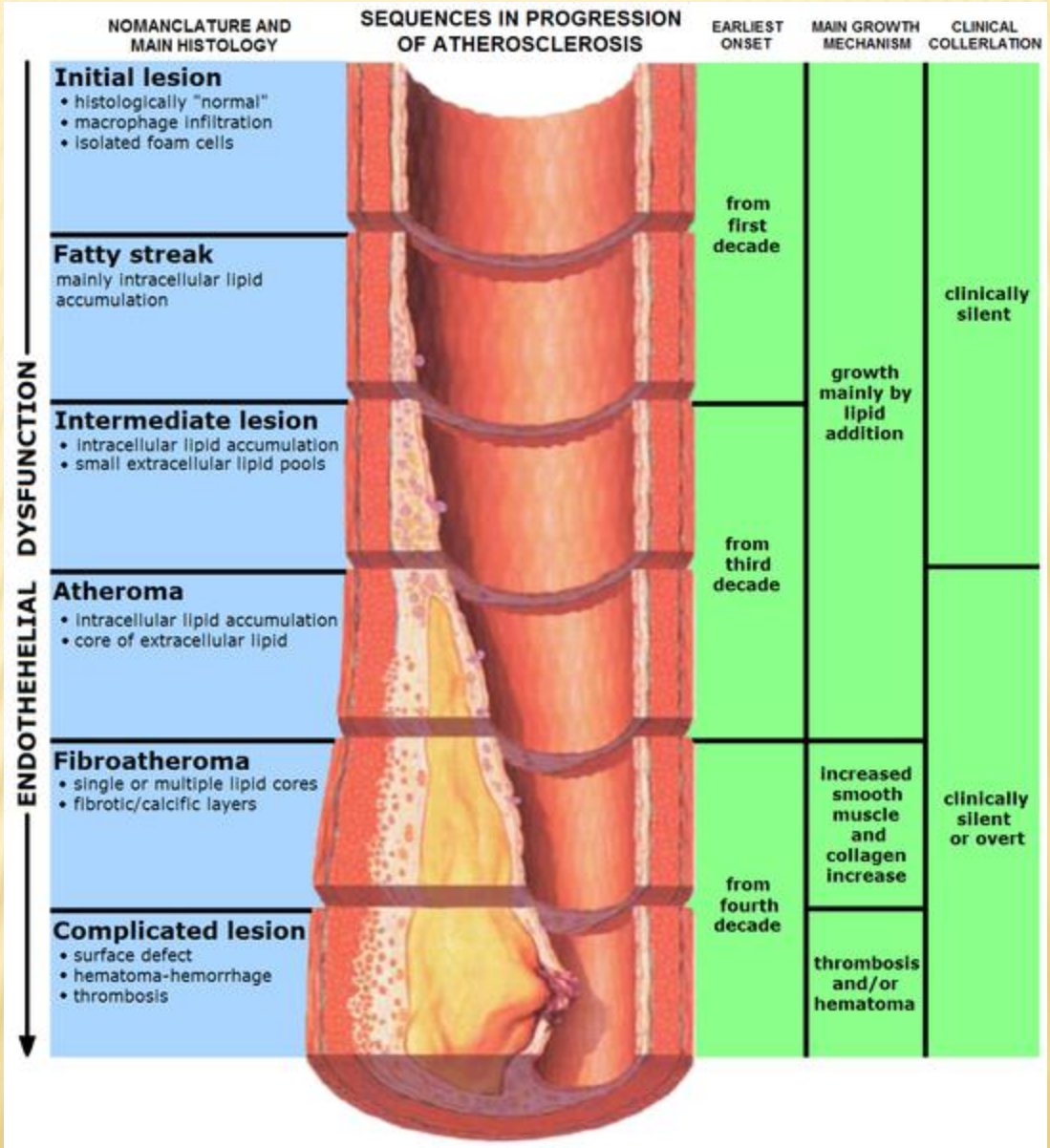
Decreased blood flow

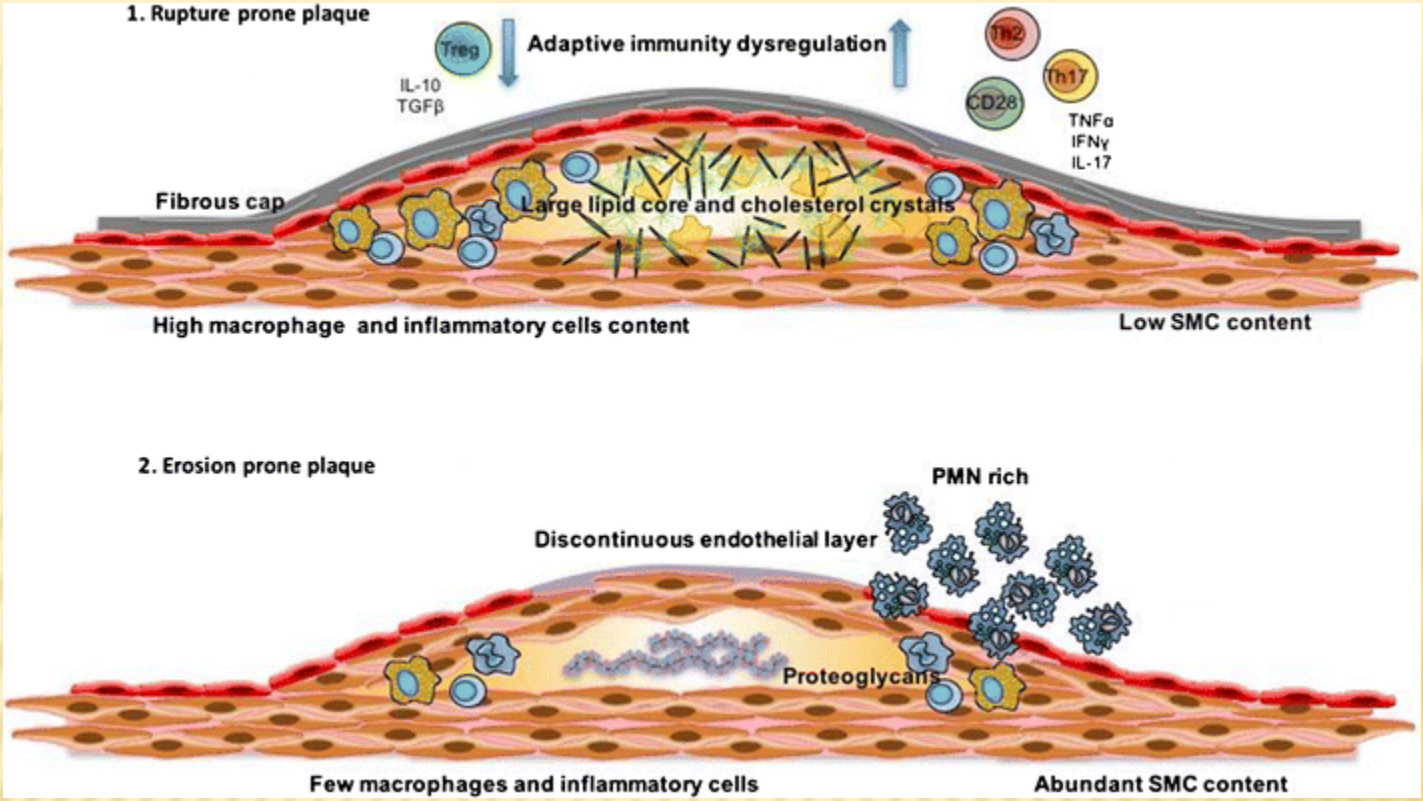
# „RESPONSE-TO-RETENTION“ MODEL OF ATHEROGENESIS

- 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




Plaque rupture and plaque erosion in ACS. (Modified from: Crea F, Liuzzo G: J Am Coll Cardiol. 2013;61(1):1-11)

Current Cardiology Reports
September 2017, 19:84

# INFLAMMATION AND PLAQUES

Inflammation contributes to many of the characteristics of plaques implicated in the pathogenesis of acute coronary syndromes (ACS).

Two major mechanisms precipitate most ACS:

- a rupture of the plaque fibrous cap, which causes most fatal acute myocardial infarctions (higher degree of inflammation), and
- a superficial erosion of the intima (lower degree of inflammation)

Thin fibrous caps, measured in many studies at ≈ 60 to 70 μm, are one of the most studied characteristics of plaques that cause ACS. Inflammatory signals, such as the T helper 1 (TH1) cytokine γ-interferon, impair the ability of the smooth muscle cell (SMC), to synthesize new collagen required to repair and maintain the extracellular matrix of the fibrous cap. On the other hand, matrix-degrading proteinases, tightly regulated by inflammatory mediators, strongly contribute to the dissolution of interstitial collagen that weakens the fibrous cap and hence renders a plaque susceptible to rupture.

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# INFLAMMATION AND PLAQUES

- A dysregulation of adaptive immunity is a major feature of ACS. The abnormalities of $CD4^+$helper T-cell subpopulations are also associated with worse outcomes, especially in patients with diabetes mellitus. Such alterations characterize about half of ACS patients, and may concern the number or the function of T-cells with a differentiation oriented toward aggressive effector phenotypes and/or defective regulatory T-cells that are involved in the suppression of an excessive immune response. This imbalance might contribute to plaque destabilization through multiple pathways, among which the alteration of the normal biological outcome of immune responses seems to be the most relevant.

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# INFLAMMATION AND PLAQUES

- A marked increase in Th1 frequency and increased expression of Th1-related cytokines such as IFN-γ were reported. By releasing their signatory cytokine IFN-γ, Th1 cells contribute to increase the fragility of the fibrous cap, as well as the thrombogenic potential of the plaque. Indeed, IFN-γ is involved in the recruitment and activation of macrophages, in the reduction of collagen synthesis, and in the increase of extracellular matrix-degrading proteins. Among helper T-cells, $CD4^{+}CD28^{null}$ T-cells might be considered a different lymphocyte subset for several aspects. This subpopulation of T-cells, with increased resistance to apoptosis and a wide range of pro-inflammatory properties (above all increased production of IFN-γ and TNF-α), is strongly associated with ACS; since $CD4^{+}CD28^{null}$ T-cells are present preferentially in unstable ruptured atherosclerotic plaques and their frequency shows a direct relation with the risk of ACS.

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# INFLAMMATION AND PLAQUES

- Recently, the introduction of a T-cell subset, Th17, characterized by the expression of a different transcription factor (retinoid-related orphan receptor, ROR-γt), and by the production of IL-17, was reported.
- IL-17 seems to be predominantly pro-atherogenic. Increased levels of Th17 and Th17 associated cytokines, such as IL-17, IL-21 and IL-23, have been described in atherosclerotic carotid artery plaques and found to be associated with the progression of atherosclerotic disease and with plaque vulnerability.

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# INFLAMMATION AND PLAQUES

- Indeed, Th17 cells with features overlapping both inducible Tregs (IL-17/IL-10 dual producing T cells) and Th1 (IL-17/IFNγ dual producing T cells) have been described. On the other hand, the role of Treg in the atherosclerotic disease is well known. This T-cell subpopulation inhibits atherosclerosis development and progression by suppressing effector T-cell responses.
- ACS patients show low levels of circulating Treg, a reduced suppressive efficiency of Treg and an increased Treg susceptibility to apoptosis. ACS patients have a lower induction of Treg after T-cell receptor (TCR) in vitro stimulation. Moreover, Treg from unstable plaque shows a restricted TCR diversity, suggesting an increased antigen-specific Treg redistribution between the peripheral blood and local sites of inflammation.

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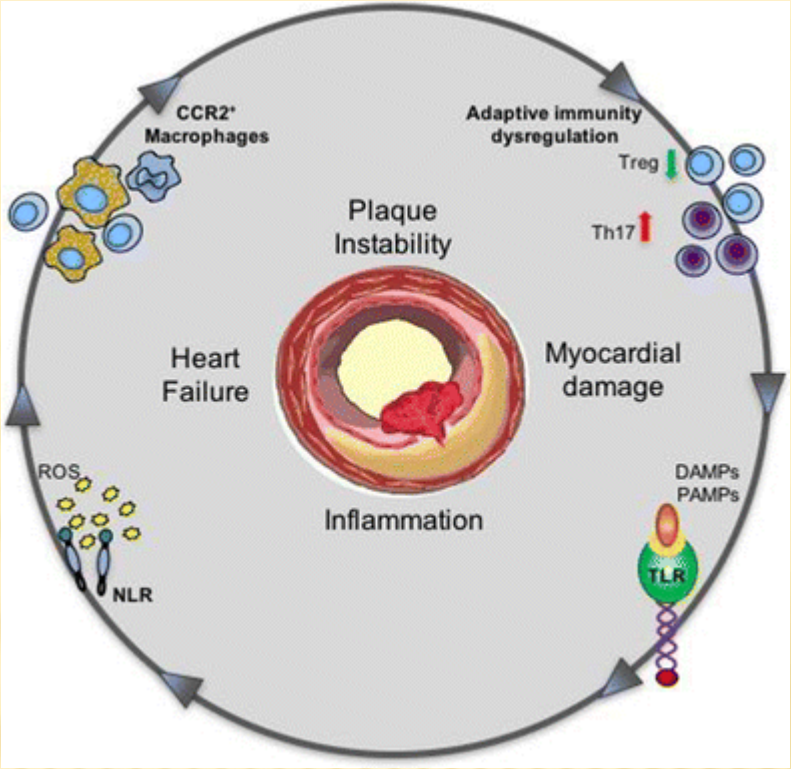


Role of inflammation in heart failure development and plaque instability. (Modified from: Crea F, Liuzzo G: J Am Coll Cardiol. 2013;61(1):1-11)

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# INFLAMMATION AND HEART FAILURE

- One of the first steps of the relationship between inflammation and heart failure is the dysregulation of autophagy and subsequent accumulation of reactive oxygen species (ROS), leading to activation of Toll-like receptors (TLR-s) signaling pathways. In particular, there is evidence that the impairment of dysfunctional mitochondrial autophagy (called mitophagy) can lead to low-grade release of DAMPs, important triggers of pathological inflammation.

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# INFLAMMATION AND HEART FAILURE

- Mitochondrial DNA (mtDNA) can be released into the circulation by injured cells (secondary to impairment in mitophagy) and then recognized by TLR9 of polymorphonuclear neutrophils (PMNs), with subsequent proinflammatory cytokines production (TNF-α, IL-1β, and IL-6).
- Direct activation of NLRP3 inflammasome by oxidized mitochondrial DNA, a key element of inflammatory response in acute coronary syndrome and heart failure was shown.

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# DAMPS, PAMPS, AND TLR-4 SIGNALING ACTIVATION

- It is known that Toll-like receptor 4 (TLR4) plays a pivotal role in atherosclerosis development through activation of interleukin-1 receptor associated kinases (1, 2, and 4) and the transcription factor nuclear factor-κB (NF-κB), leading to the expression of a wide range of inflammatory genes. Moreover, TLR-4 signaling involves downregulation of the sterol transporters ABCA1 and ABCG1 in macrophages and upregulation of very low density lipoprotein receptor, and adiponectin receptor 2, thus increasing foam cells formation, and mediates activation of metalloproteinases with plaque destabilization.
- A similar role for TLR-4 inflammatory pathway involved in the establishment and progression of chronic HF was shown.

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# DAMPS, PAMPS, AND TLR-4 SIGNALING ACTIVATION

- TLRs recognize specific ligands, termed damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), from damaged host cells and pathogens, respectively. During cardiac stress, above all ischemic injury or hypertension and metabolic syndrome, a conspicuous release of DAMPs by cardiomyocytes has been described, such as high-mobility group box 1 (HMGB1)and heat shock protein 60 (HSP 60).
- As for DAMPs, pathogen-associated molecular patterns (PAMPs) can also promote activation of TLRs signaling, determining transition from viral myocarditis to heart failure.
- High doses of LPS induce production of several proinflammatory cytokines in macrophages through marked activation of TLR-4, nuclear factor κB, and the NOD-like receptor family pyrin domain–containing protein 3 (NLRP3) inflammasome, leading to ongoing inflammatory signaling and eventually to LV dysfunction.

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# DIFFERENT MACROPHAGES LINEAGE AS PROTAGONISTS OF ONGOING INFLAMMATION IN HEART FAILURE AND THE CONTRIBUTION OF NLRP-3 INFLAMMASOME

- Recently, distinct cardiac macrophage subsets were identified, which have their own separate origins and function.
- Total cardiac macrophage numbers expanded through two different pathways: C-C motif chemokine receptor 2 (CCR2)-mediated monocyte recruitment and local proliferation of resident macrophages. These two macrophage lineages are characterized by different properties and may exert different roles in the complex interplay of pathological and physiological inflammation at the base of heart failure development. Resident macrophages are enriched in reparative genes expressions, while recruited CCR2+ macrophages are enriched in inflammatory genes, in particular the NOD-like receptor family pyrin domain–containing protein 3 (NLRP3) inflammasome pathway. The activated inflammasome is a powerful mediator of the immune response via caspase-1 activation of IL-1β and IL-18. Moreover, the NLRP3 inflammasome can also induce pyroptosis in a caspase-1-dependent manner, leading to loss of cardiomyocytes and subsequent reduction of contractile reserve leading to HF progression. Usually, pyroptosis is a highly inflammatory form of programmed cell death that occurs upon infection with intracellular pathogens and is likely to form part of the antimicrobial response .

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# DIFFERENT MACROPHAGES LINEAGE AS PROTAGONISTS OF ONGOING INFLAMMATION IN HEART FAILURE AND THE CONTRIBUTION OF NLRP-3 INFLAMMASOME

- In this context, the initiation of pyroptosis in macrophages may be caused by the recognition of pathogen-associated molecular patterns (PAMPs) by NOD-like receptors (NLRs) secondary to various microbial triggers, such as viral myocarditis or LPS released by gut microbiota in metabolic syndrome, associated with heart failure development.
- Furthermore, in the setting of diabetic cardiomyopathy inflammasome activation dependent on the combination of oxidative stress and reactive oxygen species production, because of mitochondrial dysfunction was shown, leading to increased susceptibility to atherosclerosis, dyslipidemia, hypertension, and the prothrombotic state, which ultimately can lead to heart failure development.
- Finally, another contribution to the establishment of heart failure comes from the profibrotic pathways elicited by recruited cardiac macrophages, which play a pivotal role in the transdifferentiation of fibroblasts to myofibroblasts through expression of transforming growth factor (TGF)-β. Also in this setting, NLRP3 was found to represent a key element through regulation of mitochondrial ROS (mROS) production and Smad signaling, ultimately leading to profibrotic gene expression.

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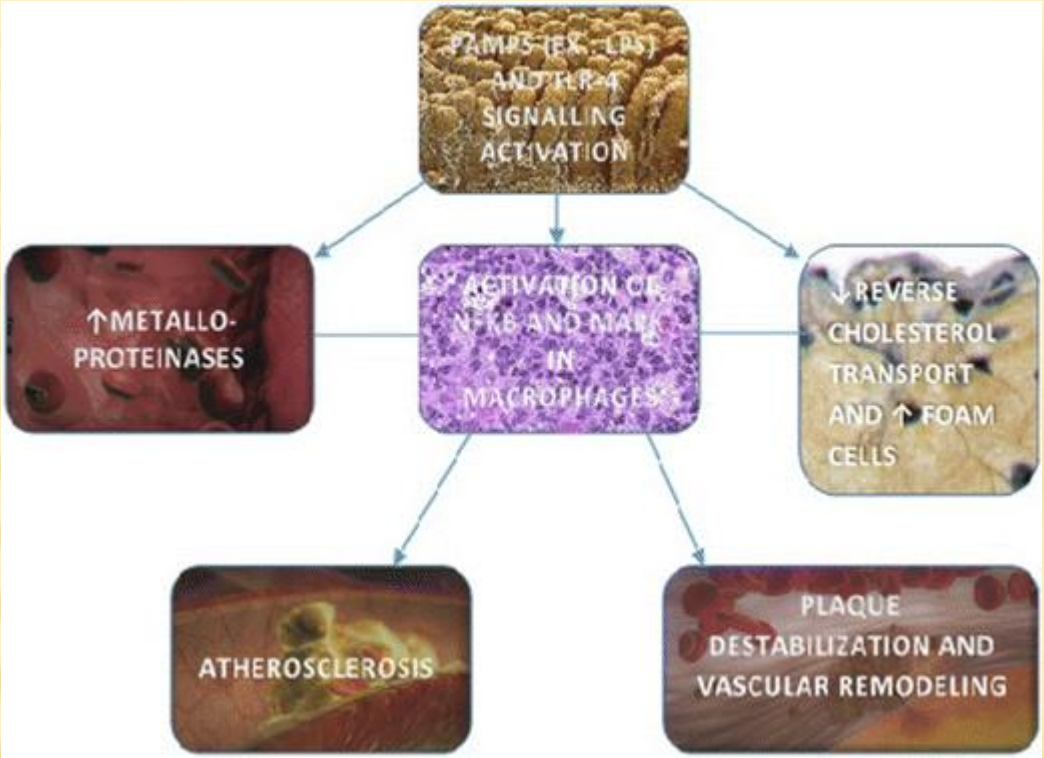


Role of PAMPs in the inflammatory atherosclerotic burden. (Modified with permission from: La Rosa G, Biasucci LM. Cardio Innov Appl. 2016;1(4):433-442(10);

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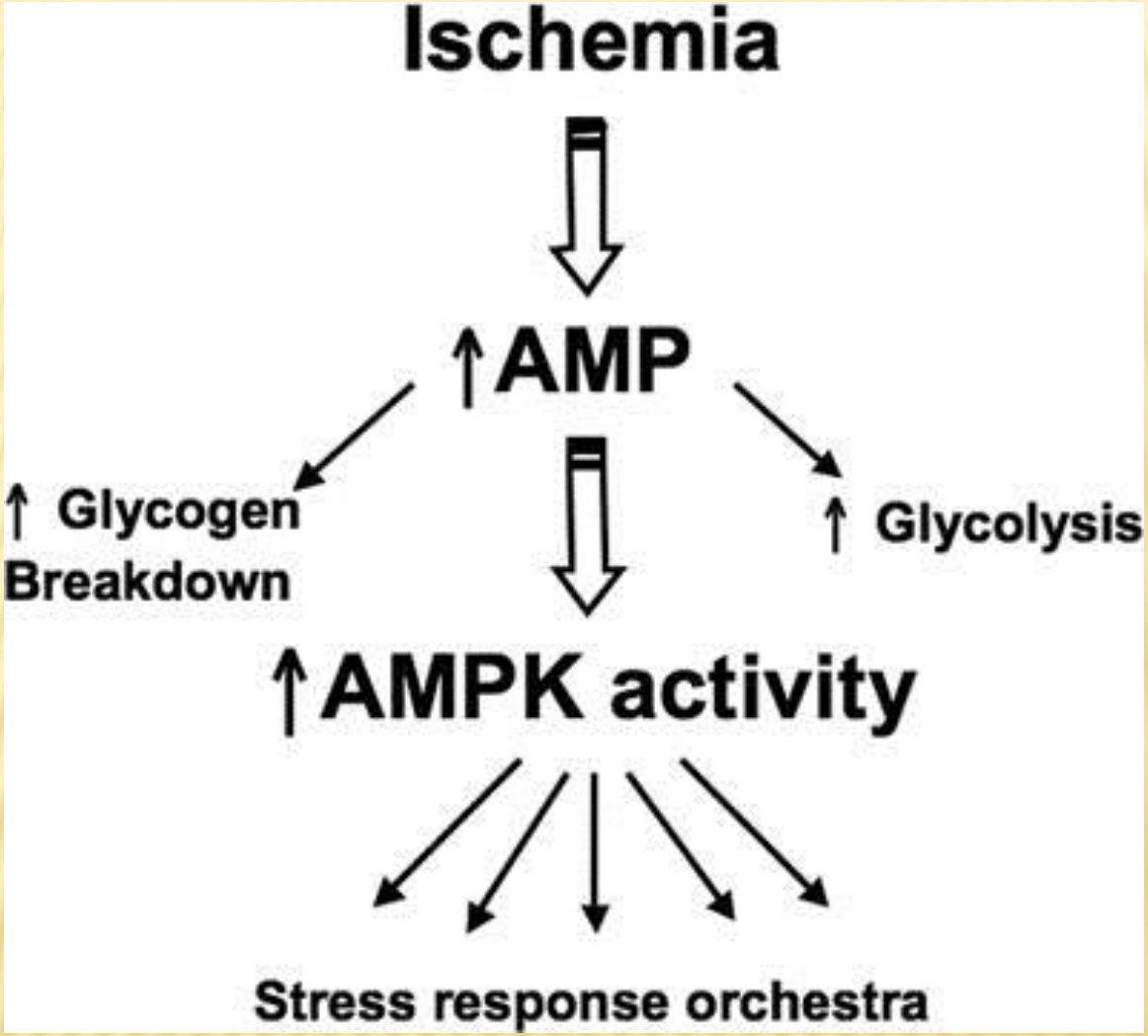
# MYOCARDIAL ISCHEMIA

- 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 (mitoptosis).
- 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%).

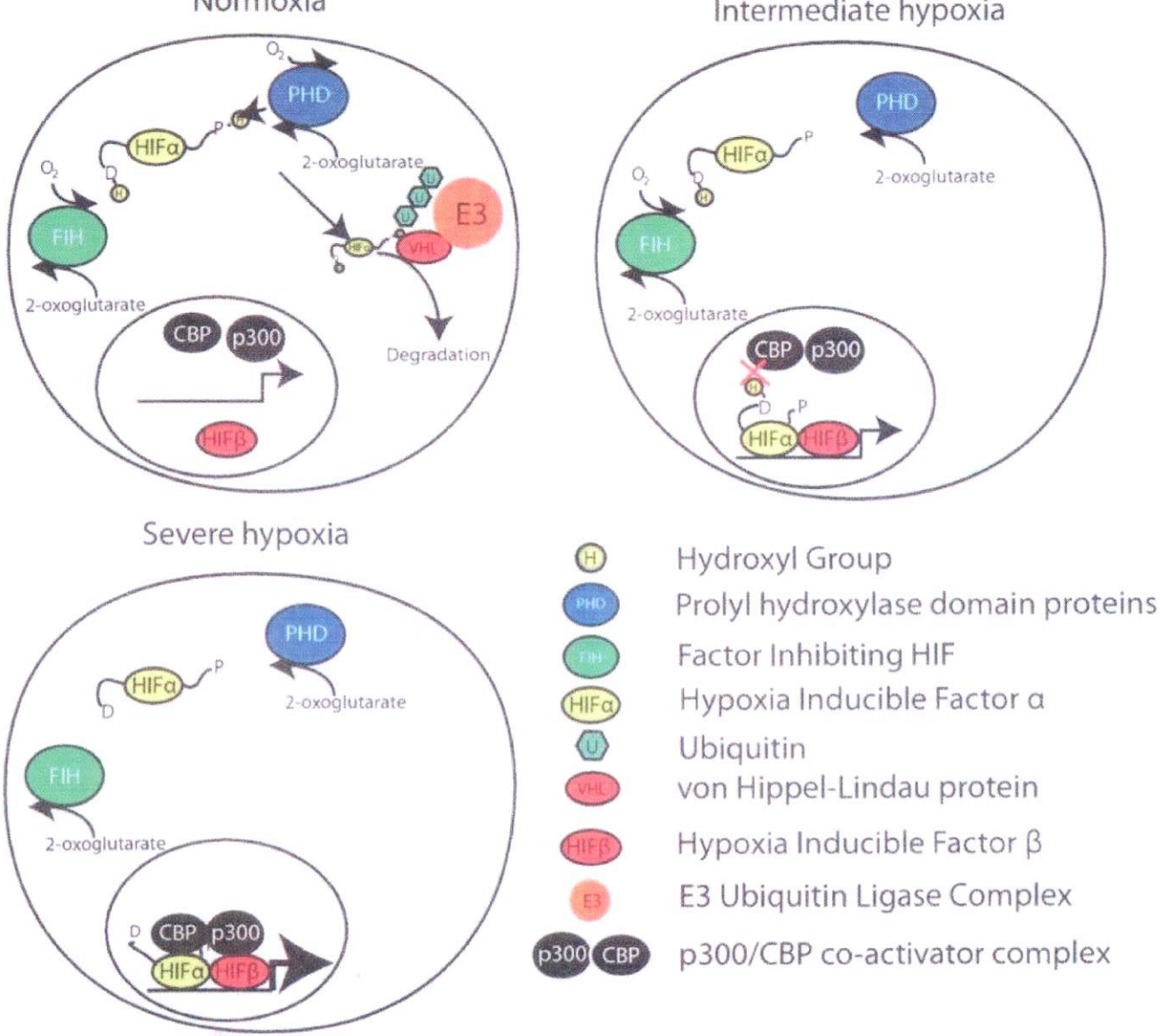



**Figure 1. Mechanism of HIF activity.** Under normoxic conditions, HIFα subunits are hydroxylated on proline residues. Hydroxylated prolines are recognised by the von Hippel-Lindau protein, ubiquinated by the E3 ubiquitin ligase, and targeted for proteosomal degradation. As oxygen levels fall, HIFα 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.

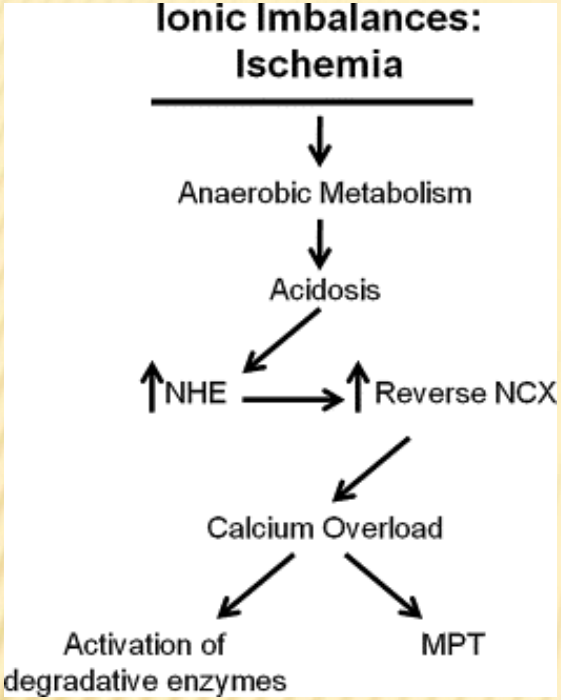
doi:10.1371/journal.pbio.1001116.g001

# 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. It can improved by ghrellin.

# 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.

Adam J. Perricone , Richard S. Vander Heide

**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

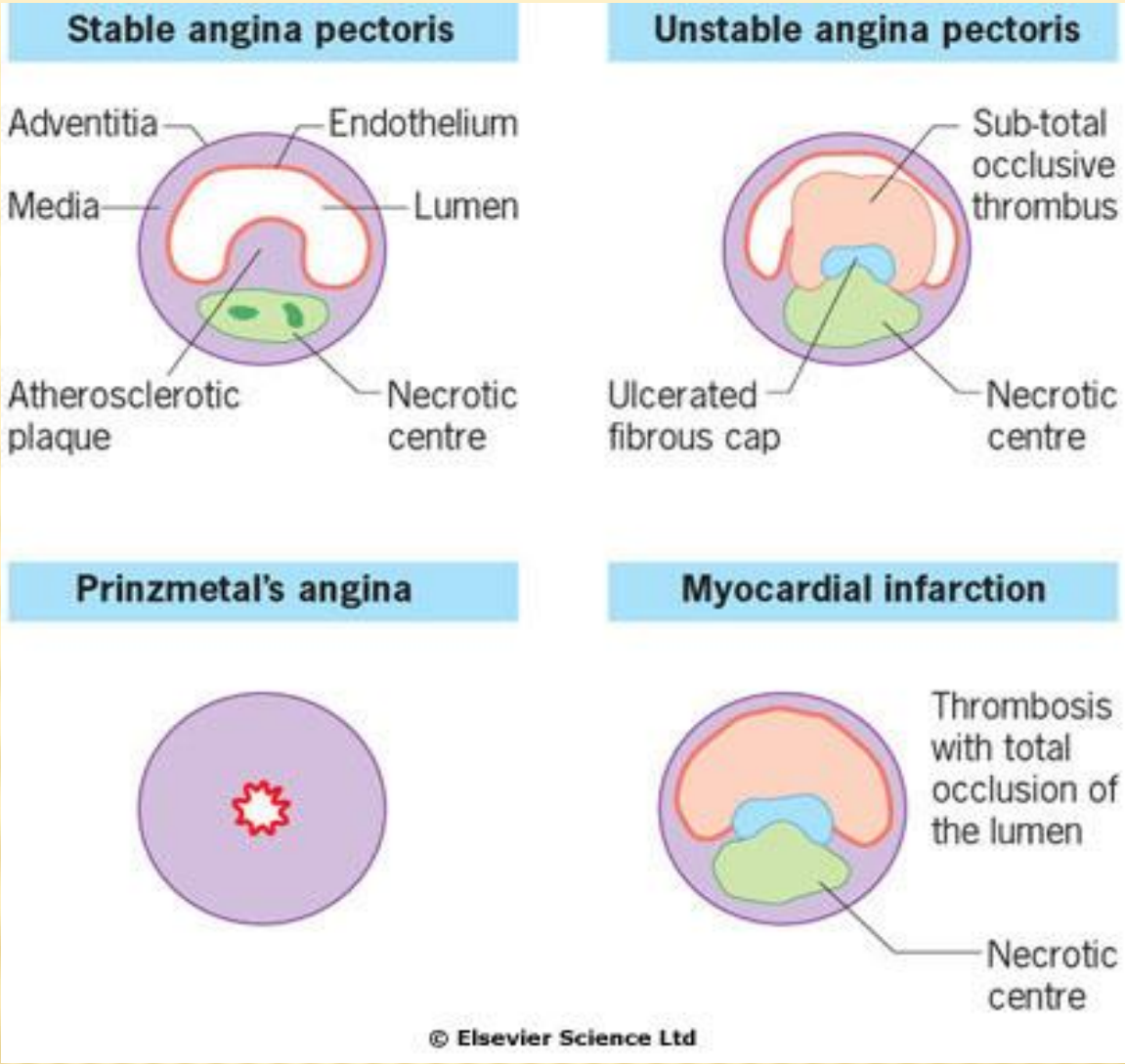
**Fixed**
Age
Male sex
Positive family history
Deletion polymorphism in the ACE gene (DD)

**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.

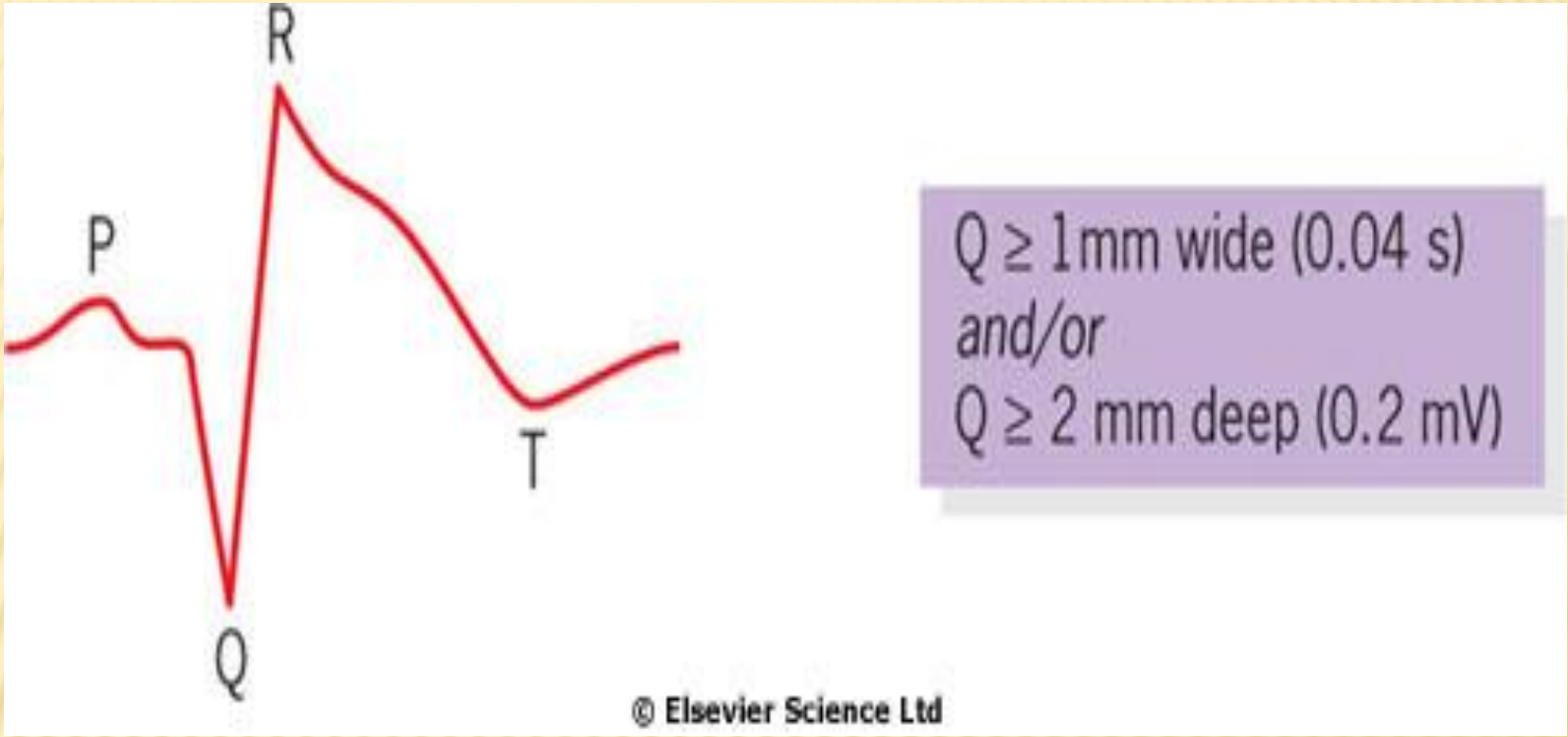
# MYOCARDIAL INFARCTION

- 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

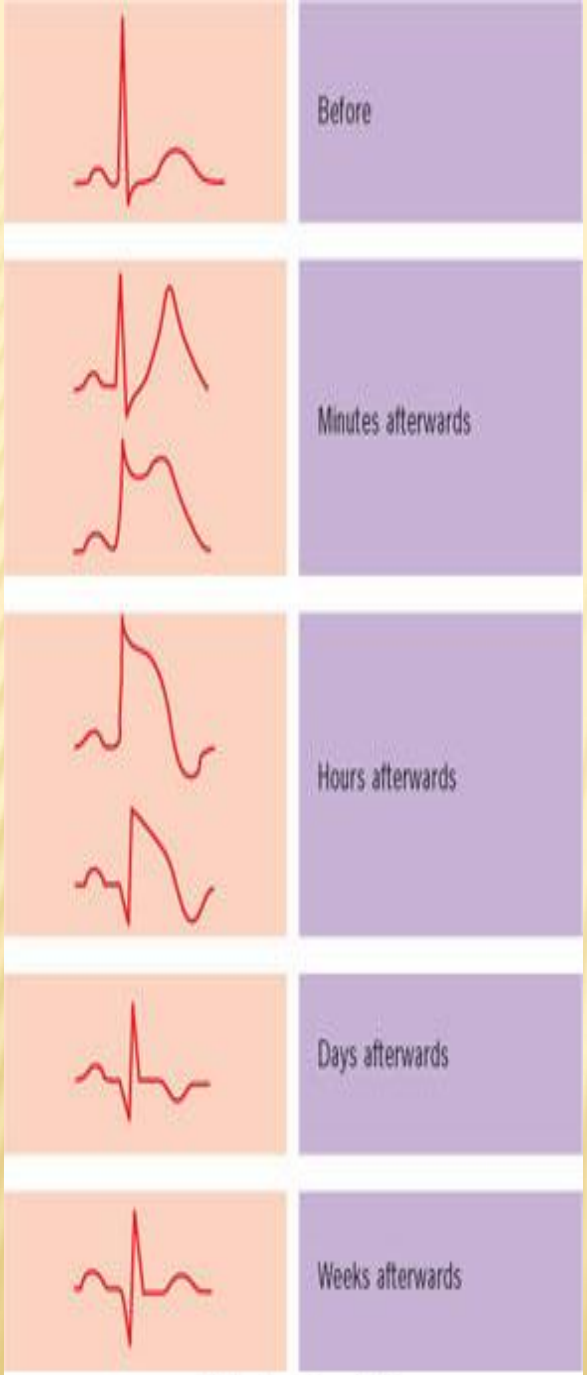
At least two signs:

- 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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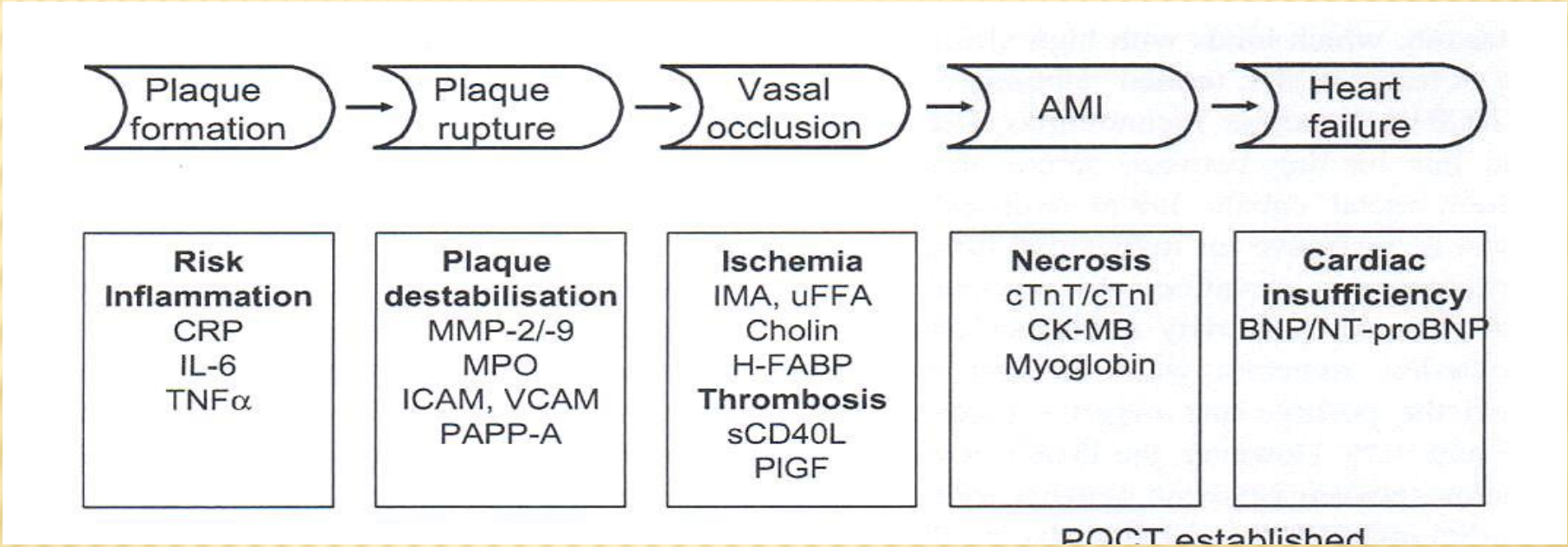
## Table 13.29

### 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



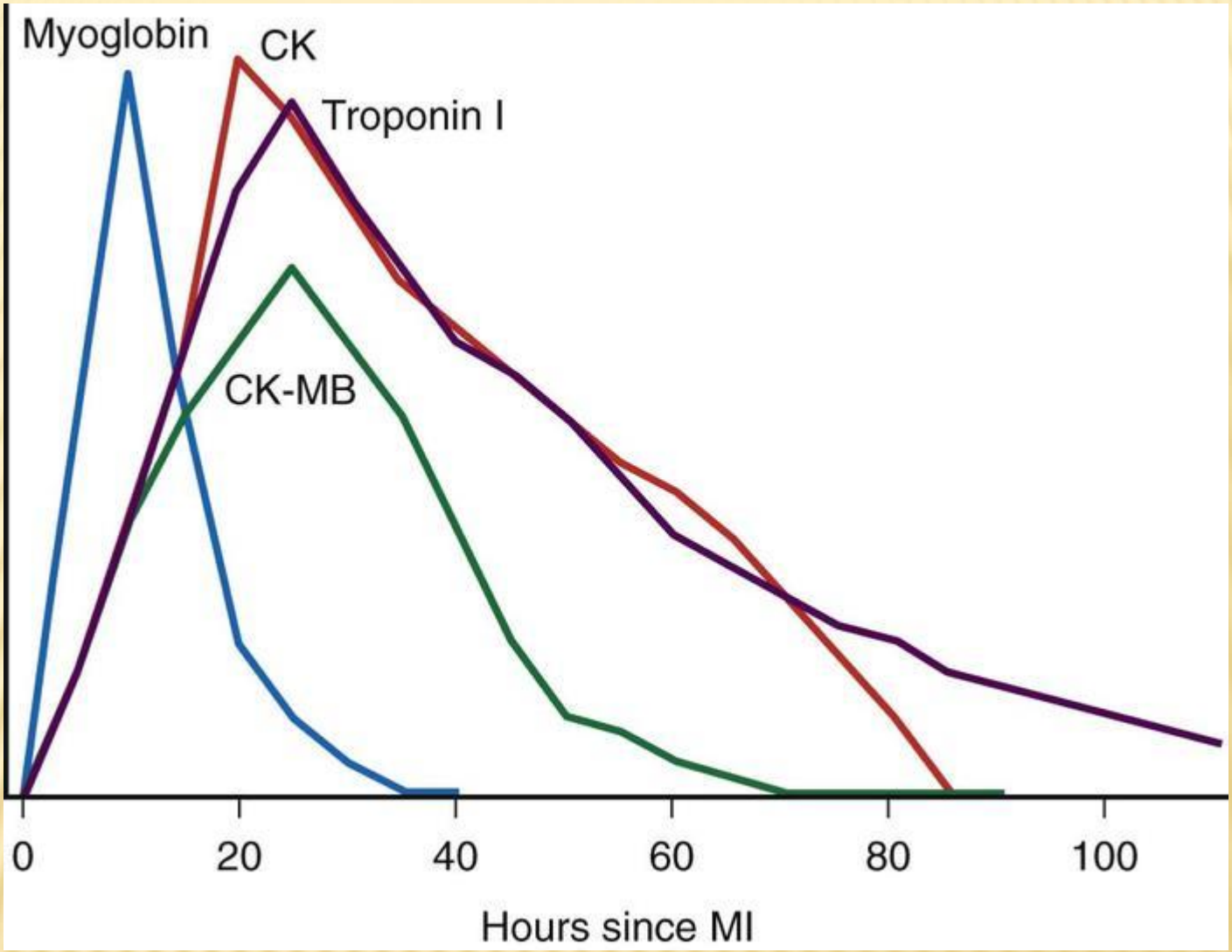
# Another markers of acute coronary syndrome

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.

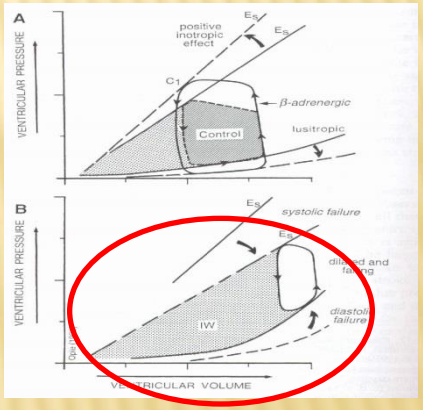
Generally, the more proximal the coronary occlusion, the more extensive the amount of myocardium that will be at risk of necrosis. The larger the myocardial infarction, the greater the chance of death because of a mechanical complication or pump failure. The longer the period of vessel occlusion, the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