

CHAPTER 6

MYOCARDIUM

- Myocyte Necrosis
- No-reflow
- Approaches to Cell Protection
 - § NHE Inhibition.
 - § Complement Inhibition
 - § Others
- Cardiac Remodeling

- The myocardium is the last target of pharmacologic therapy.
- Failing to prevent plaque progression and stabilization and to prevent coronary thrombosis will result in interruption of coronary perfusion and myocardial damage.
- The goals here are to:
 1. Protect the myocardium against:
 - a. Direct myocyte necrosis.
 - b. No reflow.
 - c. Reperfusion damage.
 2. Prevent LV remodeling after MI

MYOCYTE NECROSIS

Mechanisms

- Metabolic changes.
- Ionic shifts.
- Complement activation.
- Generation of cytotoxic substances.
- Inflammation – tissue oedema, apoptosis and matrix degradation.
- Unless interrupted these processes lead to irreversible damage.
- Reperfusion therapy saves life for up to 12 hours after onset of symptoms.
- Extensive necrosis can occur prematurely, despite restoration of blood flow, as a result of No reflow at tissue level.
- Myocyte necrosis is mediated by the cell membrane sodium-hydrogen exchange (NHE) system:
 - NHE transports H^+ in exchange for Na^+
 - It is regulated by the intracellular pH.
 - It protects against acidosis.
 - Driving force is the transmembrane Na^+ gradient.
 - During ischemia Na^+ is exchanged for Ca^{2+} .
- Elevated intracellular Ca^{2+} concentration directly mediates cell death.

NO-REFLOW

Failure of cardiac myocyte perfusion after restoration of epicardial coronary flow following temporary occlusion.

Mechanisms

- *Coronary endothelial injury*; secondary to ischemia.
Endothelial dysfunction results in vasoconstriction, inflammatory reaction and tendency to thrombosis. Formation of platelet-leucocyte aggregates plug small arterioles.
- *Micro embolization* – fragmentation of coronary thrombi in epicardial arteries by natural or pharmacolytic systems or by catheter intervention. Occlusion of the coronary microcirculation will impair myocyte perfusion in spite of adequate epicardial flow.
- *Coronary spasm* – caused by vasoconstrictor substances released from coronary thrombi (thrombin, serotonin and TXA₂) and failure to generate vasodilators (NO, prostacyclin) by the damaged endothelium.
 - No-reflow is responsible for myocyte perfusion failure found by contrast echo imaging in up to 25% of patients receiving thrombolytic therapy after AMI.
 - Extensive necrosis can occur prematurely, despite early restoration of blood flow.

REPERFUSION DAMAGE

- Resumption of blood flow to ischemic myocardium triggers immediate release of free radicals (superoxide anions).
- The introduction of oxygen-containing blood results in a rapid burst of free radicals generation in the vascular bed. The reactive oxygen species produce peroxidation of membrane phospholipids leading to disruption of their function.
- Free radicals have been implicated in endothelial cell membrane injury with subsequent calcium entry, edema, neutrophil activation and infiltration.
- Post ischemic ventricular dysfunction is recognized even after a short period of regional or global myocardial ischemia (5-10 minutes) that does not cause myocardial necrosis.
- During the acute phase of post-ischemic reperfusion, several factors known to induce complement formation, trigger neutrophil adhesion and infiltration and set the stage for the late phase of reperfusion injury which involves myocardial apoptosis and necrosis.
- The late phase of reperfusion damage is manifested within days, weeks or even months.
- Reperfusion washes out the extracellular metabolites to accelerate the ionic exchanges. Ca²⁺ then enters the cell massively to cause reperfusion injury.

APPROACHES TO CELL PROTECTION

1. NHE inhibition.
2. Complement inhibition.
3. Other experimental approaches.

1. NHE Inhibition

- Inhibition of the sodium-hydrogen exchange (NHE):
 - Has the potential of counteracting processes associated with ischemia.
 - Reduces infarct size in experimental animals.
- Drugs used as NHE inhibitors:
 - Cariporide.
 - Eniporide.

Cariporide

- § In patients with AMI undergoing angioplasty. When given before reperfusion it improved LV function.
- § In patients with unstable angina, NSTEMI or high risk coronary angioplasty it did not prevent progression of ischemia to necrosis. However, high dose was of benefit in patients undergoing CABG (GUARDIAN trial).
- § Nearly complete inhibition of NHE activity will probably be required for benefit in humans.

Eniporide

- § In patients with STEMI within six hours of onset administered 10-15 min prior to thrombolysis or prior to primary angioplasty.

Dose: 100mg or 150mg

There was no favorable effect on clinical events. (ESCAMI trial).

It seems that NHE activity is an important determinant of infarct size during ischemia rather than during reperfusion.

2. Complement Inhibition

- Complement activation may mediate myocardial damage during ischemia/reperfusion via multiple inflammatory pathways.
- Drug used for complement inhibition: Pexelizumab.

Pexelizumab

- § In patients with AMI treated with thrombolysis or primary PCI (CARDINAL trials). Pexelizumab was given as bolus and infusion over 20 hours.
 - In the thrombolysis group there was no effect on infarct size or clinical endpoints.
 - In the PCI group there was no effect on infarct size but there was a significant reduction in all cause mortality with bolus plus infusion regimen.
- § In patients undergoing CABG (PRIMO-CABG trial), it reduced early and late post-operative MI. It was safe and well tolerated.

3. Other Experimental Approaches

- Adhesion molecules blockers.
- Supersaturated aqueous oxygen.
- Anti-integrins and anti-selectins.
- Agonists to adenosine receptors: adenosine can preserve energy phosphate stores, inhibit neutrophil activity and free radical formation.
- ATP-sensitive potassium channel openers, which mediate preconditioning.
- Monoclonal antibodies against terminal fraction of the complement system.
- Metabolic interventions:
 - § Reduce free fatty acid level and their oxidation.
 - § Enhance glucose utilization and glycolysis (e.g. glucose- insulin- potassium infusion).

CARDIAC REMODELING

Following AMI, there is:

- Loss of cardiac myocytes.
- A local inflammatory reaction with monocytes / macrophage and fibroblast infiltration.
- Collagen desposition leading to excessive fibrosis and scarring.
- Changes in LV shape (from ellipsoid to spherical), dimensions and structure with dialation, areas of wall thinning and areas of hypertrophy.

The previous processes are called *cardiac remodeling* (Fig 40).

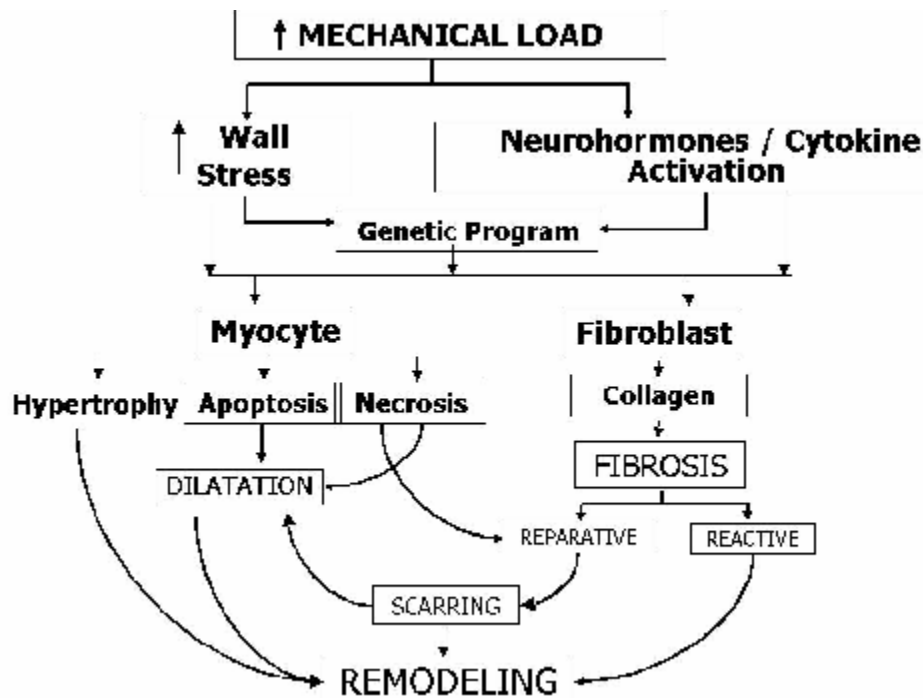


Figure (40): Cardiac remodeling

- Loss of cardiac muscle in MI will increase the mechanical load on the remaining surviving myocardium.
- Increase in the mechanical load will result in: (1) increase in wall stress. (2) neurohormonal and cytokine activation. These events will influence the genetic program of myocardial cells with shift to the fetal form and induce changes in the cellular components of the myocardium i.e. fibroblasts and myocytes.
- Fibroblast activation results in excess collagen formation and production of two forms of fibrosis: reactive fibrosis in the myocardial interstitium and perivascular areas and reparative fibrosis where collagen replaces the lost cardiac myocytes.
- Changes in myocytes include hypertrophy, apoptosis and necrosis. Loss of the myocytes and their replacement with fibrosis tissue (scarring) leads to chamber dilatation.

The main elements of the remodeling process are:

1. Loss of cardiac myocytes.
2. Excess collagen deposition, fibrosis and scarring.
3. Cavity dilatation and change in LV shape (spherical instead of ellipsoid).
4. Myocyte hypertrophy.
5. Change in cardiac genetic program with generation of fetal type of cardiac proteins.

Initiation and Progression of Remodeling

- Neurohormonal activation, cytokine activation and increased wall stress are the initiating events in remodeling (Fig 40).
- Initially the remodeling process is beneficial and compensates for the impaired pumping function. However, when it progresses or becomes excessive it is maladaptive resulting in further deterioration in LV function (Fig 41).
- Macroscopically the LV dilates, hypertrophies and changes from ellipsoid to globular structure. LV dilatation improves pumping function through Frank-Starling mechanism.
- Microscopically there is loss of cardiac myocytes through both necrosis and apoptosis. Both processes are related to excess activation of RAS, adrenergic and other neurohormonal systems (e.g. endothelin). There is increased fibroblast activity resulting in excessive collagen tissue formation and increased myocardial fibrosis.

The Vicious Circle of Cardiac Remodeling (Fig 41)

- LV injury secondary to ischemia, infarction or excessive pressure or volume load will impair LV function. In order to maintain cardiac output and tissue perfusion; a number of compensatory mechanisms are activated which include:
 - (1) Neurohormones (renin-angiotensin-aldosterone system, sympathetic nervous system, arginine-vasopressin, endothelin, etc).
 - (2) Shift of the genetic program to an alternative fetal program which requires less energy at the expense of less power generation, and
 - (3) Chamber remodeling with cavity dilatation that secures an increased force of contraction (Frank-Starling mechanism).
- Neurohormonal activation and alternation in the genetic program contribute to remodeling.
- Furthermore, cavity dilatation and neurohormonal activation result in an increase in wall stress and increase in after-load. These will compromise subendocardial perfusion and induce expression of stretch-activated gene coding for angiotensin II, epinephrine and TNF. The changes result in increased oxidative stress.
- Increased after-load and oxidative stress together with impaired subendocardial perfusion will result in more impairment of LV function.
- Additional deterioration of LV function will activate more compensatory mechanisms and a vicious circle sets in.
- Remodeling begets more remodeling, more dilatation triggering further increase in wall stress and further neurohormonal activation, fibrosis, myocyte loss and a vicious circle of deterioration in LV function sets in.
 - The degree of systolic dysfunction after MI is a key determinant of early and chronic alterations in ventricular shape and remodeling.
 - With severe impairment of LV function, the ability of the remaining viable muscle to compensate is overcome, EF falls and LV dilatation occurs to maintain stroke volume.
 - Significant LV dilatation can begin within three hours from the onset of a first myocardial infarction.

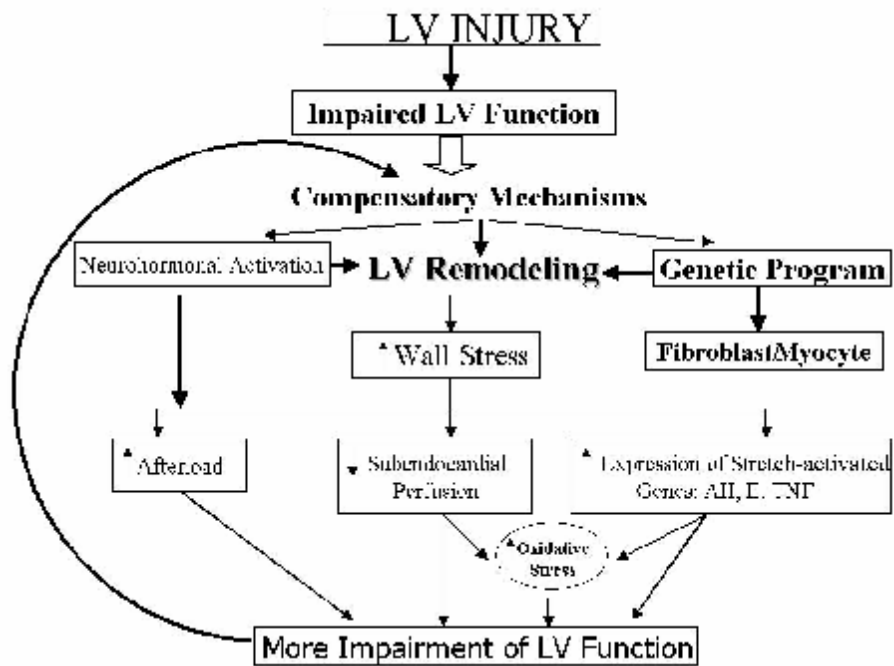


Figure (41): The Vicious Circle of Cardiac Remodeling

Pharmacologic Treatment of Cardiac Remodeling

- Blocking the excessive and inappropriate neurohormonal activation is the main objective of drug therapy for remodeling.
- Three pharmacologic groups proved effective in delaying, stopping and sometimes reversing remodeling. These are:
 - ACE-inhibitors and angiotensin receptor blockers.
 - Beta-adrenergic blockers namely carvedilol, bisoprolol and metoprolol.
 - Aldosterone receptor antagonists: aldactone and eplerenone.
- Regression of cardiac remodeling is translated into reduction in LV cavity dimension, increase in EF and improvement in cardiac morbidity (rate of hospitalization) and mortality.