Pathobiology of Heart Failure
Molecular and Cellular Mechanism

Jonathan Leor

Neufeld Cardiac Research Institute

Tel-Aviv University

Sheba Medical Center, Tel-Hashomer

שאלה 1

התא הנפוץ ביותר (~75%) בלב הוא:

- א. פיברובלסט
- ב. קרדיומיוציט
- ג. אנדותל
- ד. שריר חלק

Pathobiology of Heart failure:

- **Braunwald Heart Disease: Textbook of Cardiovascular Medicine 2001:**

- **Normal and abnormal cardiac function. Pp 443-461**
- Contractile proteins.
- Calcium ion influxes.
- Sarcolemmal control of calcium and sodium ions.
- Receptors and signal systems.
- Inhibitory signal systems.

- **Pathophysiology of heart failure. Pp 506-517**
- Short-term adaptive mechanism.
- Chronic myocardial remodeling.
- Molecular mechanisms of myocardial remodeling and failure.

- **Review papers: 1.** *St John Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: Pathophysiology and Therapy. Circulation 2000; 101:2981-2988.*
- ***2.** Mann DL. Mechanisms and models in heart failure. Circulation 1999;100:999-1008.*
- ***3**. Towbin & Bowles. The failing heart. Nature 2002;415:227.*

Myocardium

1. Cardiomyocytes and non-myocyte cells
2. Extracellular Matrix
3. Vessels

Myocardial Cells

TABLE 1. Myocytes and Nonmyocytes in the Myocardium

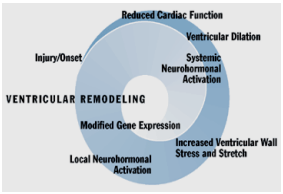
Group	By Cell No.	By Cell Volume	By Cell Mass
Cardiomyocyte	25%[16]	~75%[16]	...
	30–35% [19]	~67%[6]	~90%[17,20]
	33% [6]	67%[22]	...
		80%[23]	...
Nonmyocyte	75%*[18]	~33%[6]	~10%[17,20,21]
	65–70% [19]	33%†[22]	(90–95% fibroblasts)‡[17,20]
	67% [6]	20% (13% vascular§[23]	...

*Connective tissue nuclei.
§Includes lumen (volume fraction).
†Mostly fibroblasts.
‡Fibroblasts as % of nonmyocyte fraction.

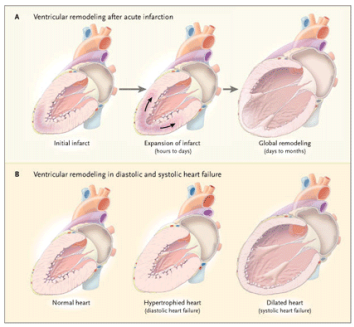
Jugdutt & al. Circulation 2003

Cardiac Remodeling Cycle

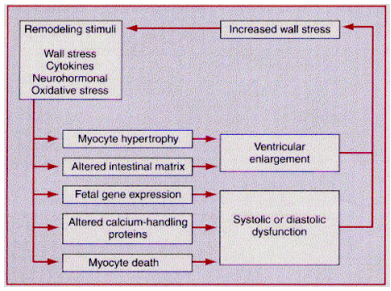
- Molecular, cellular and interstitial changes manifested clinically as changes in size, shape and function of the heart resulting from cardiac load or injury
- A determinant of the clinical course of heart failure
- Influenced by hemodynamic load, neurohormonal activation and other factors still under investigation.



Ventricular Remodeling after Infarction (Panel A) and in Diastolic and Systolic Heart Failure (Panel B)



The Cycle of Myocardial Remodeling



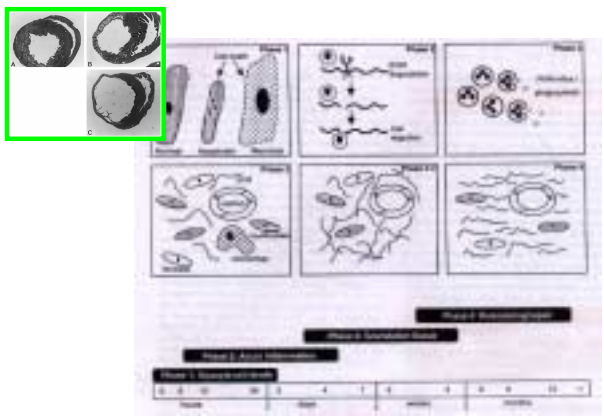
Braunwald Chapter 16 (Fig. 16–9).

Heart Failure — A Complex Cascade

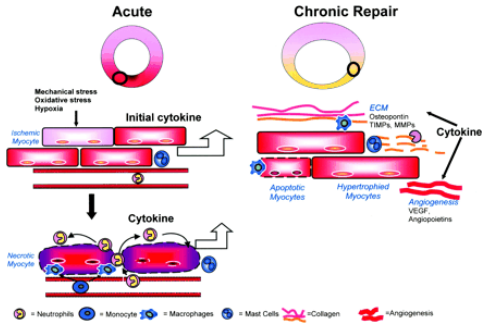
Myocardial Events in Response to Ischemic Injury

Acute phase
- Myocyte cell death (apoptosis/necrosis)
- Inflammation

Chronic phase
- Myocyte hypertrophy
- Extracellular matrix remodeling

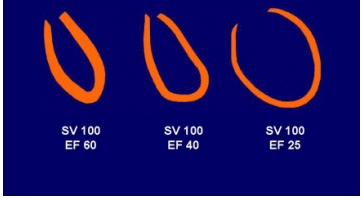


The induction of inflammatory cytokines after myocardial ischemia and their effect on acute and chronic cardiac remodeling postinfarction.

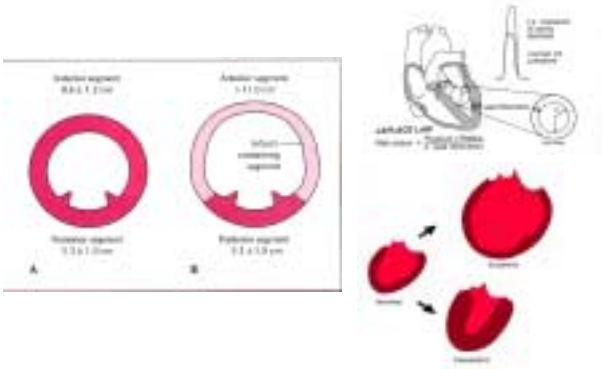


Nian & al. Circ Res 2004

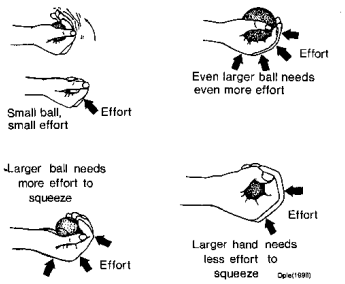
Left Ventricular Remodeling



LV Remodeling and Hypertrophy



LV Dilatation



Consequences of Left Ventricular Remodeling

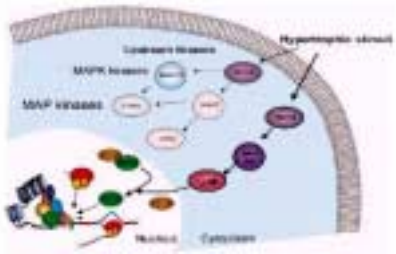
- Increased systolic wall tension/stress
- Increased MVO_2
- Reduced myocyte shortening
- Increased diastolic wall tension/stress
- Reduced subendocardial perfusion
- Dysynchronous depolarization/contraction
- Mitral regurgitation
- Ventricular arrhythmias
- Ventricular fibrillation

Cardiac Support Device

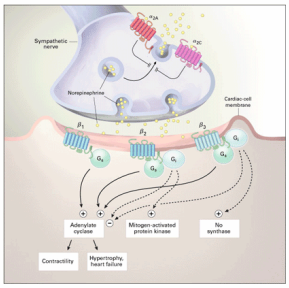
Savedra & al. JACC 2002;39:2069-76

Heart Failure — A Complex Cascade

Signal Transduction of **Hypertrophy**



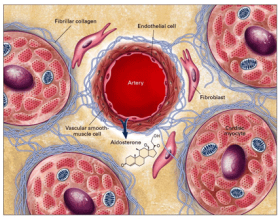
Beta Receptors



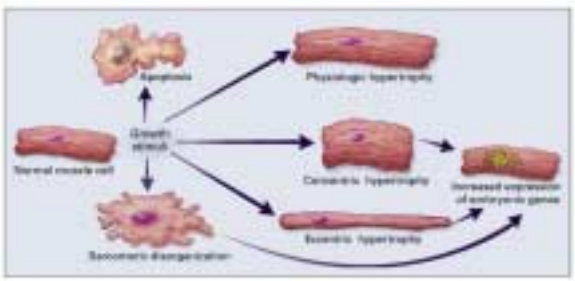
Hypertrophy

Mechanism of LVH

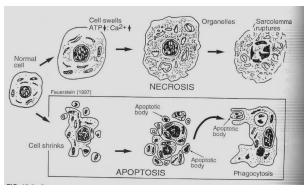
1. Cardiac myocytes increased in size
2. Fibroblast proliferation
3. Fibrosis
4. Apoptosis

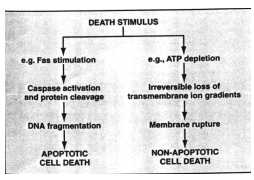


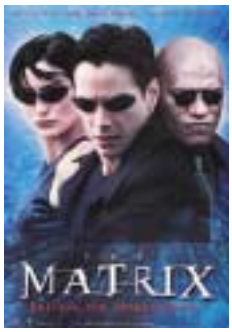
Cellular Hypertrophy



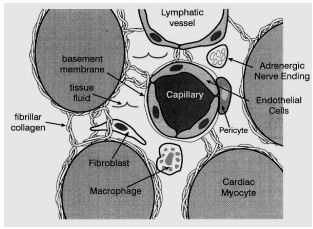
Comparison of Apoptosis and Necrotic Cell Death

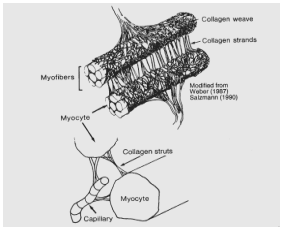






Extra Cellular Matrix





•

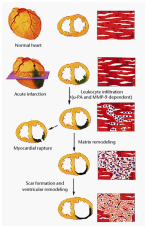
Extracellular Matrix

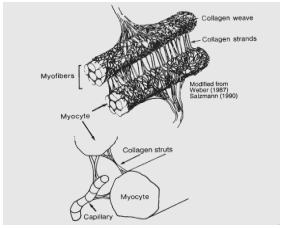
TABLE 4. Main Components and Function of Myocardial Extracellular Matrix

Component	Main Function
Collagen fibrils (types I and III)	• Structural support, maintain shape • Transmission of force • Tensile strength (type I); resilience (type III)
Elastin	• Resilience; vessel wall stretch; cardiac wall stretch and relaxation
Cells	
Fibroblasts	• Produce fibrillar collagens • Convert to myoFbs after injury
Macrophages	• Phagocytosis; inflammatory response • Monocytes
Plasma cells	• Immune defense
Other cells	• Endothelial cells; smooth muscle cells; pericytes; neurons
Gel matrix (ground substance)	• Viscous gel-type fluid; bathe cells and fibrils
Hydrophilic glycosaminoglycans	• Diffusion of nutrients, metabolites, growth factors, cytokines, drugs, etc.
Glycoproteins	• Myocyte nutrition; lubricant
Integrins (matrix receptors)	• Myocyte-fibroblast interactions; matrix remodeling
Fibronectin and laminin	• Mainly noncollagen adhesive fibrous proteins

Jugdutt & al. Circulation 2003

MMP activity site

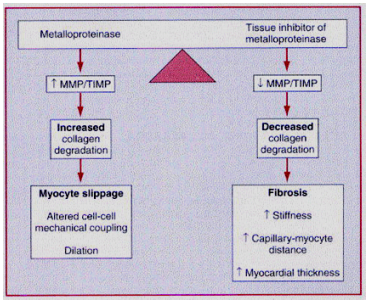


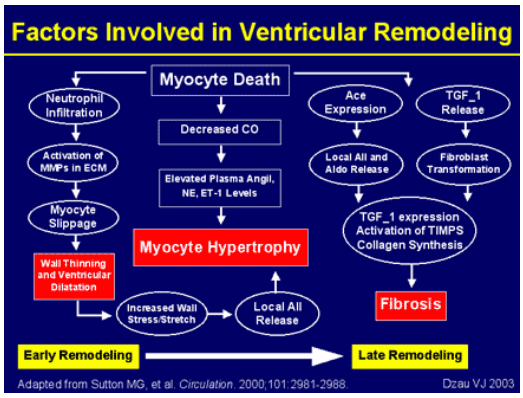


- Extra cellular matrix degradation causes
  - cardiomyocyte realignment
  - wall thinning
  - LV dilatation
  - heart failure

•

MMP/TIMP Balance





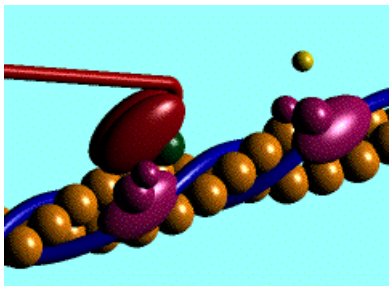
LV Remodeling
at the molecular and cellular level

1. Myocyte growth or hypertrophy.
2. Changes in myocyte phenotype with reexpression of fetal gene programs.
3. Alterations in proteins involved in excitation-contraction coupling and contraction.
4. Myocyte death due to necrosis and apoptosis
5. Changes in the extracellular matrix.
6. Abnormalities in energetics.

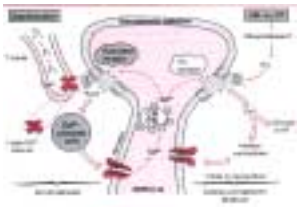
Braunwald Chapter 16 (Fig. 16–9).

Processes Occurring in Ventricular Remodeling (2)

- Continued expansion of infarct zone
- Dilation and reshaping of the left ventricle
- Myocyte hypertrophy
- Ongoing myocyte loss
- Excessive accumulation of collagen in the cardiac interstitium

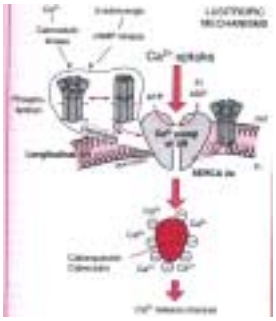


Ca Uptake into the SR



Braunwald p 453

Ca Uptake



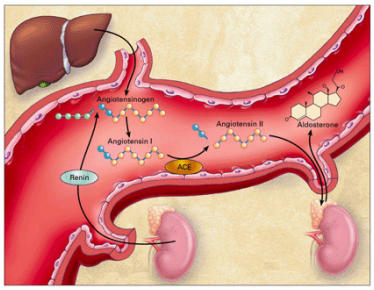
Braunwald 453

Calcium Hemostasis in Failing Human Myocardium

- **<u>Intracellular Calcium levels</u>**
- Basal (diastolic) ↑
- Peak (systolic) ↓
- Rate of fall with diastole ↓

From Braunwald pp 513

Renin Angiotensin System Activation

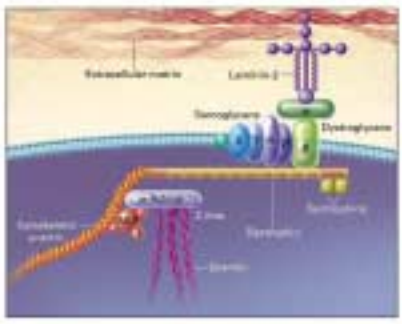


Angiotensin II and Myocardium

- Myocyte hypertrophy
- Myocyte apoptosis
- Fibrosis
- Matrix remodeling (collagen deposition)
- Inflammation
- Oxidative stress

Cytoskeleton **Proteins and Cardiomyopathy**

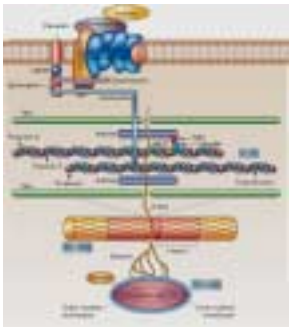
Proteins that Connect the Contractile Proteins to the Cell Membrane



The Failing Heart

Towbin & Bowles, Nature 2002;415:227

Proteins and Genes Involved in the Development of Cardiomyopathy



- **DCM**: sarcoglycan, dystrophin, desmin, laminin A/C
- **HCM** or **DCM**: Sarcomeric actin, b-MHC, tropomyosin,
- **HCM**: troponin I, titin, MLC
- **LV noncompaction**: Dystrobrevin

Towbin & Bowles, Nature 2002;415:227

Stem cells

- Ability to divide for indefinite periods in culture.
- Give rise to specialized cells.

http://www.nih.gov/news/stemcell/primer.htm

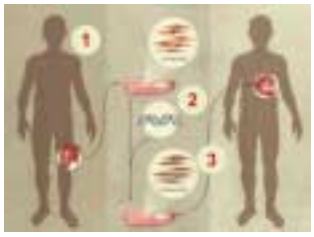
Stem Cells – Summary Points

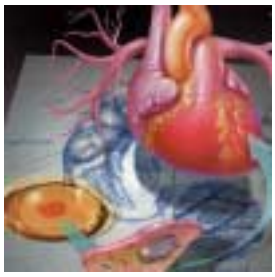
1. Pluripotent embryonic stem cells divide indefinitely and ostensibly generate all cell types.
2. Stem cells from adults regenerate their resident tissue but may have broader potential for differentiation (multipotential).
3. Further work must establish the broad differentiation and functional potential of stem cells from adults.
4. Clinical utility of all stem cells awaits further validation and development .

Kuehnle & Goodell BMJ 2002

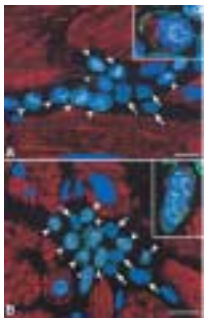
Stem Cell Therapy

Bone Marrow or Skeletal Progenitors



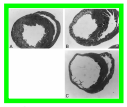


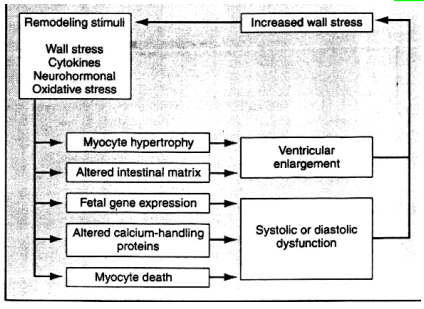
The Future – Myocardial Regeneration



Sleeping Student: Take home message

Sleeping Student: Take home message





Braunwald Chapter 16 (Fig. 16–9).