

שינויים מולקולאריים ומבניים  
באי ספיקת לב  
אפשרויות לטיפול עתידי

פרופ יהונתן ליאור

# Braunwald's Heart Disease 8<sup>th</sup> Edition

## Chapter 21 Mechanisms of Cardiac Contraction and Relaxation

## Chapter 22 Pathophysiology of Heart failure


## Chapter 29 Emerging therapies

braunwald Online

**BRAUNWALD'S HEART DISEASE 7<sup>th</sup> EDITION** Edited by Drs. Douglas P. Zipes, Peter Libby, Robert O. Bonow and Eugene Braunwald

Visit your other e-ditions preferences help log out

HOME IMAGE LIBRARY UPDATES ABSTRACTS FOCUSED REVIEWS LATE-BREAKING CLINICAL TRIALS



**! We have been unable to display the page you requested**

Please try reloading by right-clicking and choosing "Refresh"/"Reload (This Frame)". If the problem persists, please contact [online.help@elsevier.com](mailto:online.help@elsevier.com).

- ▶ I General Considerations of Cardiovascular Disease
- ▶ II Examination of the Patient
- ▼ III Heart Failure
  - ▶ 19 Mechanisms of Cardiac Contraction and Relaxation
  - ▶ 20 Assessment of Normal and Abnormal Cardiac Function
  - ▼ 21 Pathophysiology of Heart Failure
    - Short-Term Adaptive Mechanisms
    - Chronic Myocardial Remodeling
    - Molecular Mechanisms of Myocardial Remodeling and Failure
    - Role of Calcium in Excitation-Contraction Coupling
    - Reduction of Myosin Adenosine Triphosphatase Activity
    - Pathophysiology of Diastolic Heart Failure
    - Neurohormonal, Autocrine, and Paracrine Adjustments
  - ▶ 22 Clinical Aspects of Heart Failure: Pulmonary Edema, High-Output Failure
  - ▶ 23 Drugs in the Treatment of Heart Failure

## 21 Pathophysiology of Heart Failure

Wilson S. Colucci  
Eugene Braunwald

Heart (or cardiac) failure is the pathophysiological state in which the heart is unable to pump blood at a rate commensurate with the requirements of the metabolizing tissues or can do so only from an elevated filling pressure. The American College of Cardiology/American Heart Association Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult defined heart failure as a "complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood."<sup>1</sup> It is often, but not always, caused by a defect in myocardial contraction, that is, by *myocardial failure*.<sup>2,3</sup> However, in some patients with heart failure a similar clinical syndrome is present without a detectable abnormality of *myocardial* function. In many such cases, heart failure is caused by conditions in which the normal heart is suddenly presented with a load that exceeds its capacity<sup>4</sup> or in which ventricular filling is impaired.<sup>1</sup> Heart failure may be caused by myocyte death, myocyte dysfunction, ventricular remodeling, or some combination. Abnormal energy utilization, ischemia, and neurohormonal disturbances can lead to the progression of heart failure (see also [Chap. 23](#)).<sup>2,5-8</sup> *Heart failure* should be distinguished from *circulatory failure*, in which an abnormality of some component of the

ספרות

# Cardiac Plasticity

*Joseph A. Hill, M.D., Ph.D., and Eric N. Olson, Ph.D*  
*N Eng J Med* Volume 358:1370-1380 **March 27, 2008**



The NEW ENGLAND  
JOURNAL of MEDICINE

FREE NEJM E-TOC

[HOME](#) |

[SUBSCRIBE](#) |

[CURRENT ISSUE](#) |

[PAST ISSUES](#) |

[COLLECTIONS](#) |

[SEARCH](#)

[Advanced Search](#)

Institution: TEL AVIV UNIV | [Sign In as Individual](#) | [Contact Subscription Administrator at Your Institution](#) | [FAQ](#)

## REVIEW ARTICLE

### MECHANISMS OF DISEASE

[◀ Previous](#)

Volume 358:1370-1380

March 27, 2008

Number 13

[Next ▶](#)

## Cardiac Plasticity

*Joseph A. Hill, M.D., Ph.D., and Eric N. Olson, Ph.D.*

# שאלה

מדידה שלו בדם 6 שעות מהסמנים מנבאת פרוגנוזה  
לאחר אוטם שריר הלב  
(ברנוולד פרק 22)

1. טרופונין T
2. טרופונין I
3. נטרירורטיק פפטיד (ANP)
4. קולגן

# שאלה

מתן מעכבי ACE לרמודלינג של הלב יעכב הכל

למעט (סמן תשובה לא נכונה)

- Beta-adrenergic desensitization** 1.
- Fetal gene expression** 2.
- Myocyte necrosis** 3.
- MMP activation** 4.
- E-C coupling** 5.

# שאלה

• מיוציטים עלולים למות מכל הנ"ל למעט (תשובה לא נכונה):

1. נקרודיס
2. אפופטודיס
3. אטופאגי
4. אטרופי

# Main Topics

1. LV remodeling -cellular and molecular level
2. Extracellular matrix
3. Regeneration



# 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% <sup>18</sup>	≈ 75% <sup>18</sup>	...
	30–35% <sup>19</sup>	≈ 67% <sup>6</sup>	≈ 90% <sup>17,20</sup>
	33% <sup>6</sup>	67% <sup>22</sup>	...
		80% <sup>23</sup>	...
Nonmyocyte	75%* <sup>18</sup>	≈ 33% <sup>6</sup>	≈ 10% <sup>17,20,21</sup>
	65–70% <sup>19</sup>	33%† <sup>22</sup>	(90–95% fibroblasts)‡ <sup>17,20</sup>
	67% <sup>6</sup>	20% (13% vascular)§ <sup>23</sup>	...

\*Connective tissue nuclei.

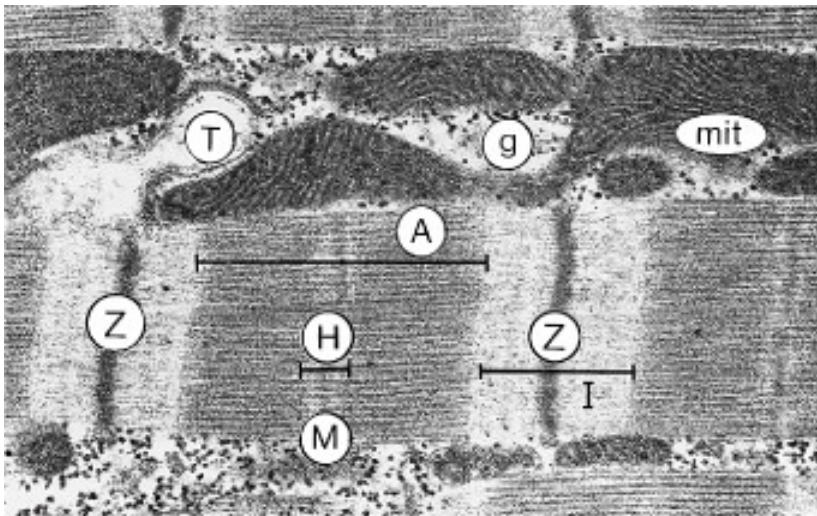
§Includes lumen (volume fraction).

†Mostly fibroblasts.

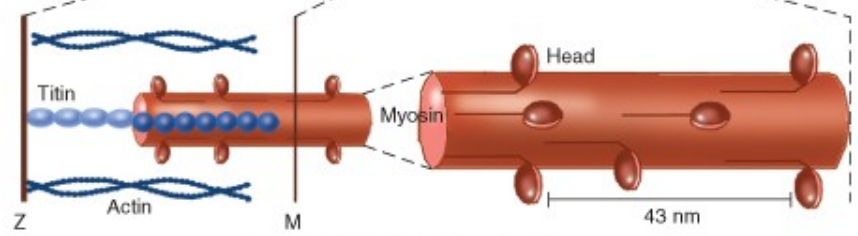
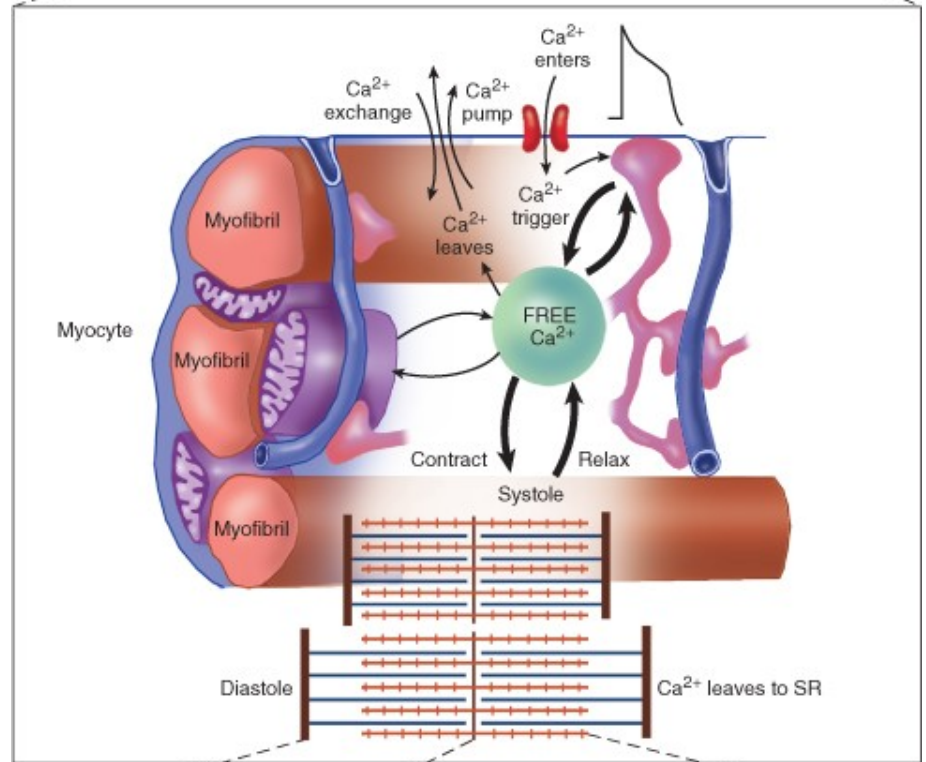
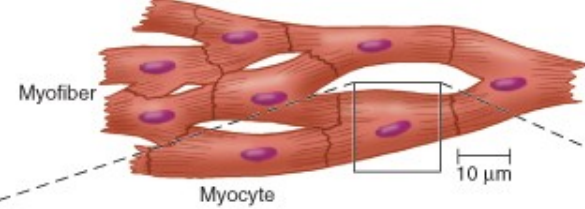
‡Fibroblasts as % of nonmyocyte fraction.

Jugdutt & al. Circulation 2003

# The Sarcomere

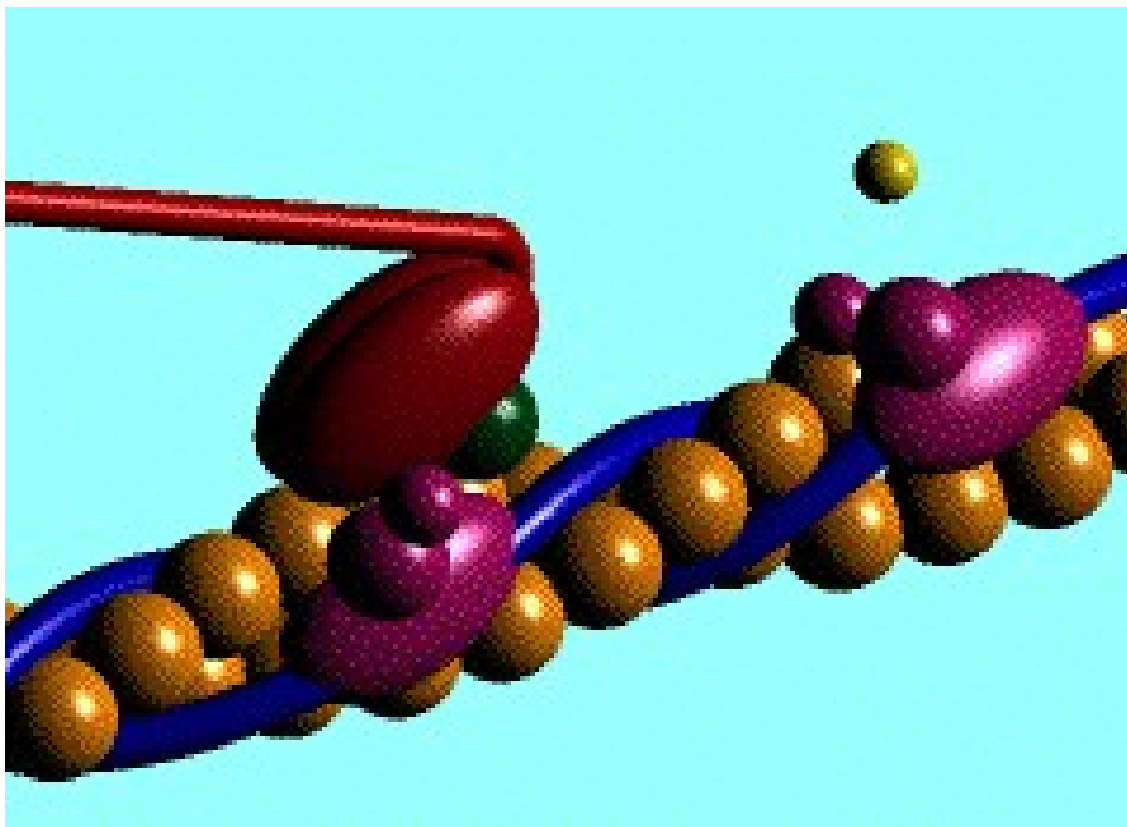


Copyright 2005 by Elsevier Science

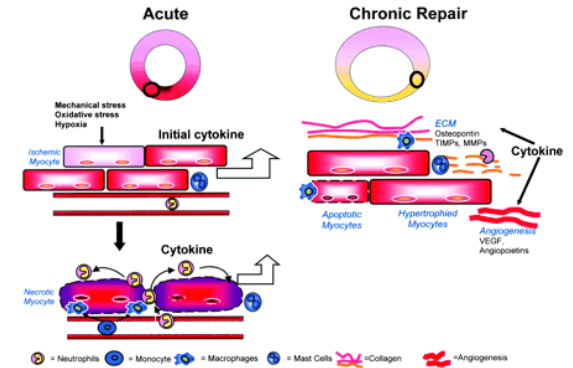


Copyright 2005 by Elsevier Science

Figure 19-1 Braunwald 2005 Prof. Jonathan Leor, NCRI

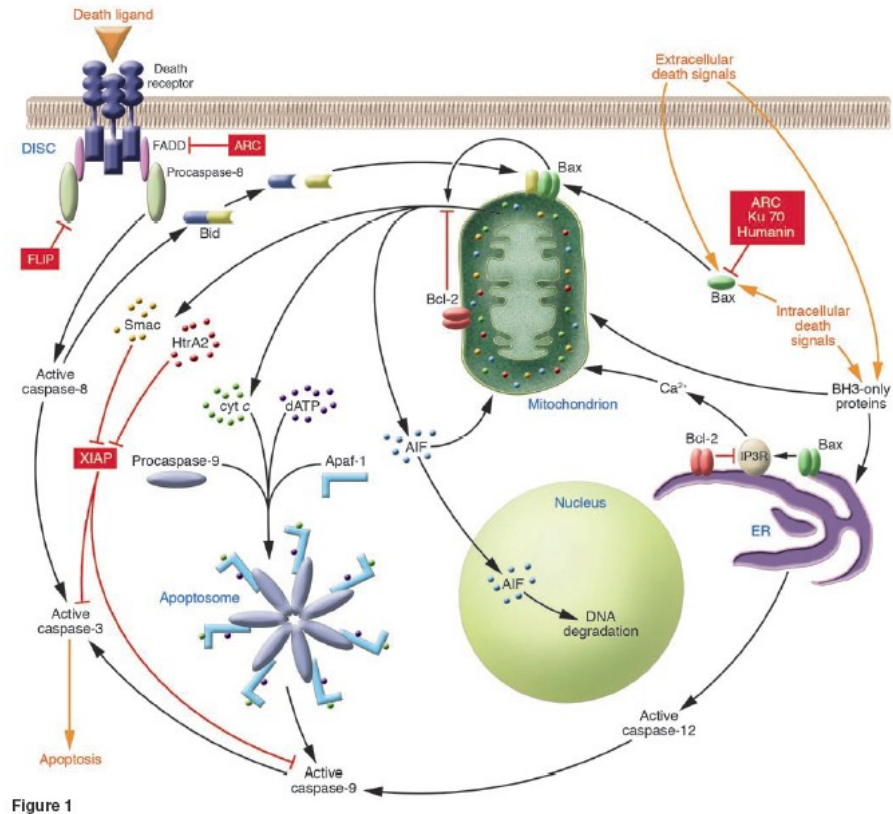


# Cardiac Damage and Repair



# Myocyte Cell Death

- Necrosis
- Apoptosis
- Autophagy





# Healing Nomenclature

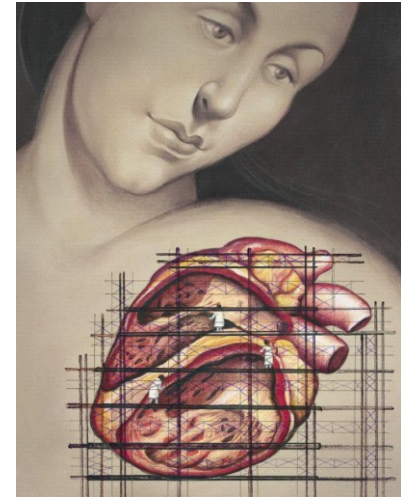
- **Regeneration**

Damaged tissue is replaced from parenchyma.



- **Repair**

Damaged tissue is replaced by fibrous scar tissue.



**Ventricular remodeling**, comprising changes in mass, volume, shape, and composition, constitutes one of the principal mechanisms by which the heart compensates for an increased load



Copyright 2005 by Elsevier Science

Prof. Jonathan Leor, NCRI

## Left Ventricular Remodeling



SV 100  
EF 60



SV 100  
EF 40



SV 100  
EF 25



# Pathogenesis of heart failure

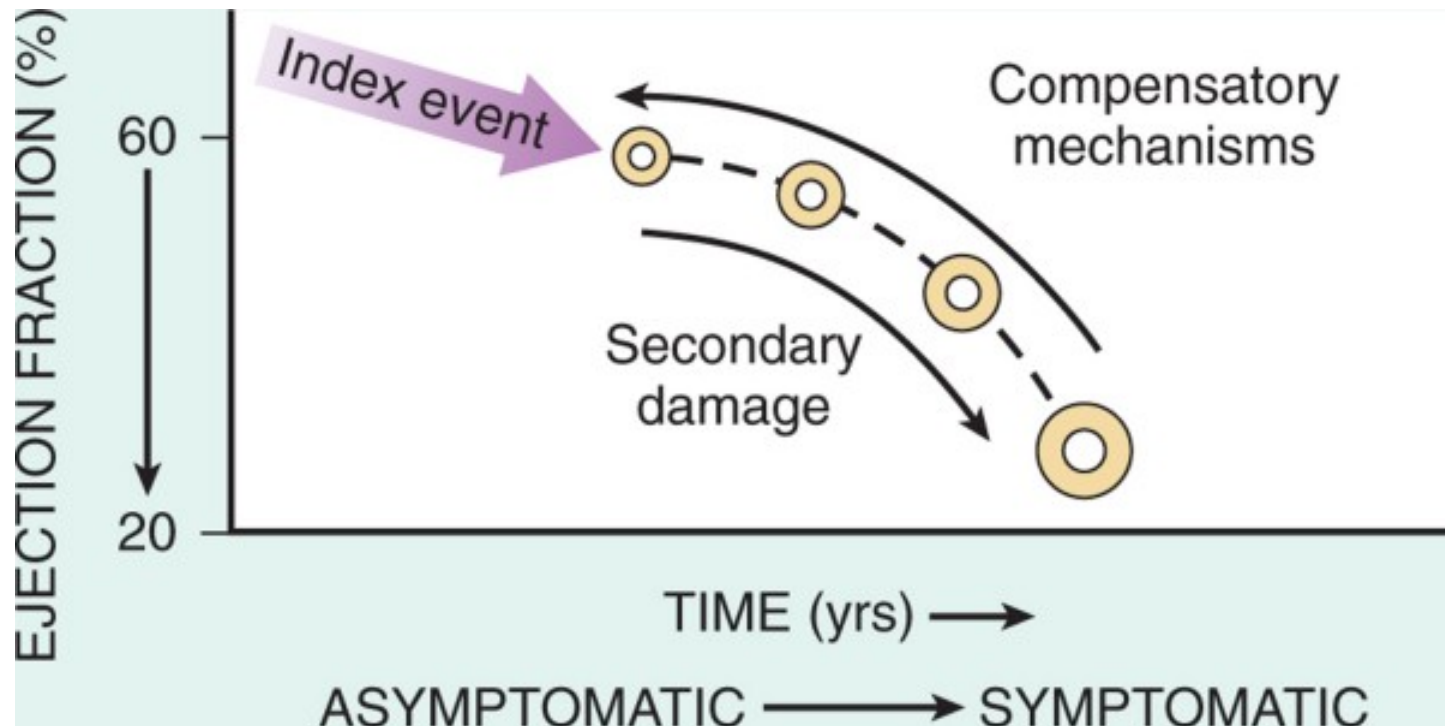
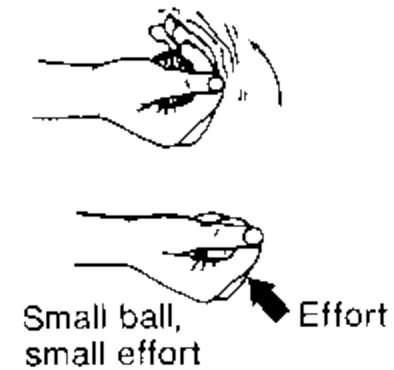
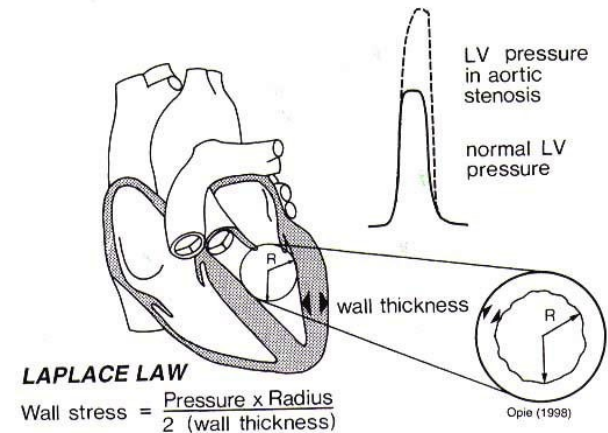
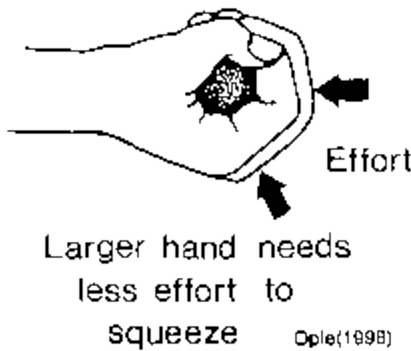
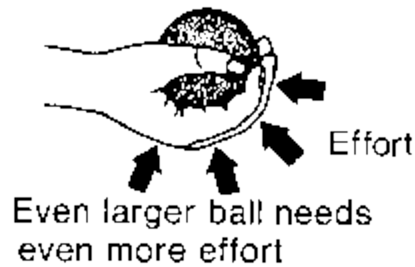


FIGURE 22-1

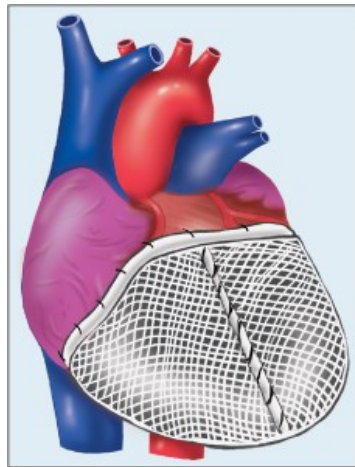
# LV Dilatation



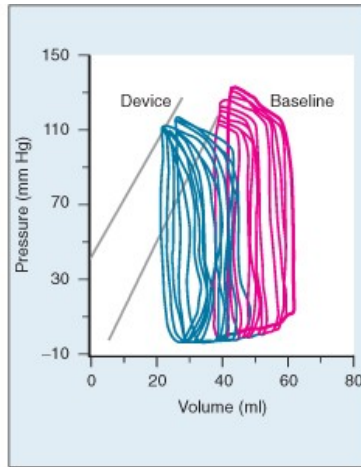
Larger ball needs more effort to squeeze



# Cardiac Support Device

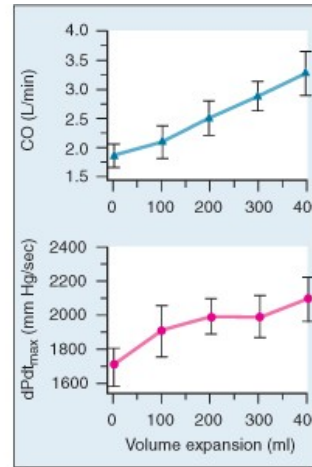


A



B

Copyright 2005 by Elsevier Science



C

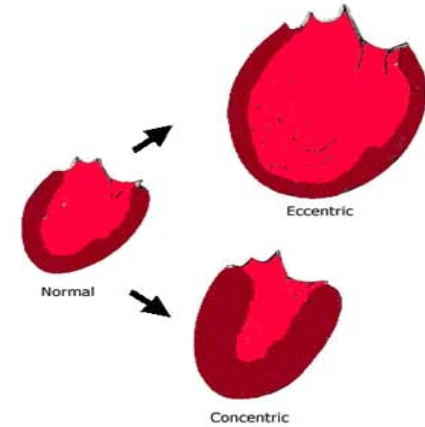


Figure 20-1



**TABLE 22-1****Overview of Left Ventricular (LV)  
Remodeling****Alterations in Myocyte Biology**

Excitation contraction coupling  
Myosin heavy chain (fetal) gene expression  
Beta-adrenergic desensitization  
Hypertrophy  
Myocytolysis  
Cytoskeletal proteins

**Myocardial Changes**

Myocyte loss  
    Necrosis  
    Apoptosis  
    Autophagy  
Alterations in extracellular matrix  
    Matrix degradation  
    Myocardial fibrosis

**Alterations in Left Ventricular Chamber Geometry**

LV dilation  
Increased LV sphericity  
LV wall thinning  
Mitral valve incompetence



# Overview of the pathophysiology of myocardial remodeling

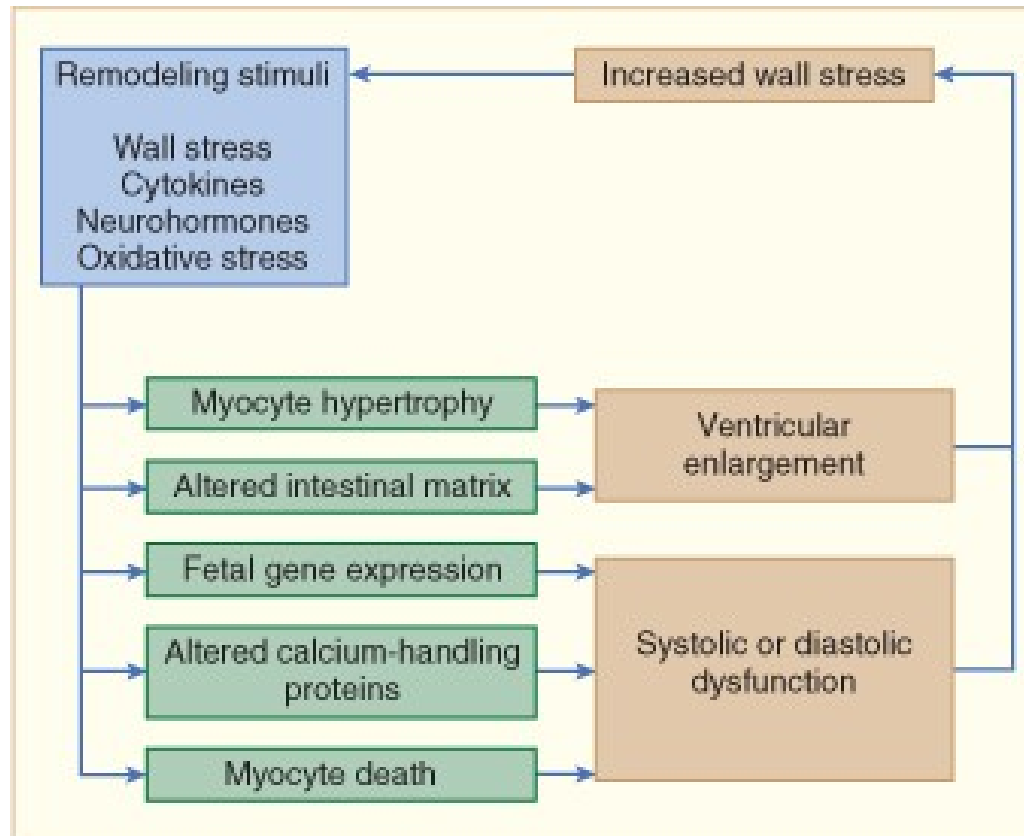
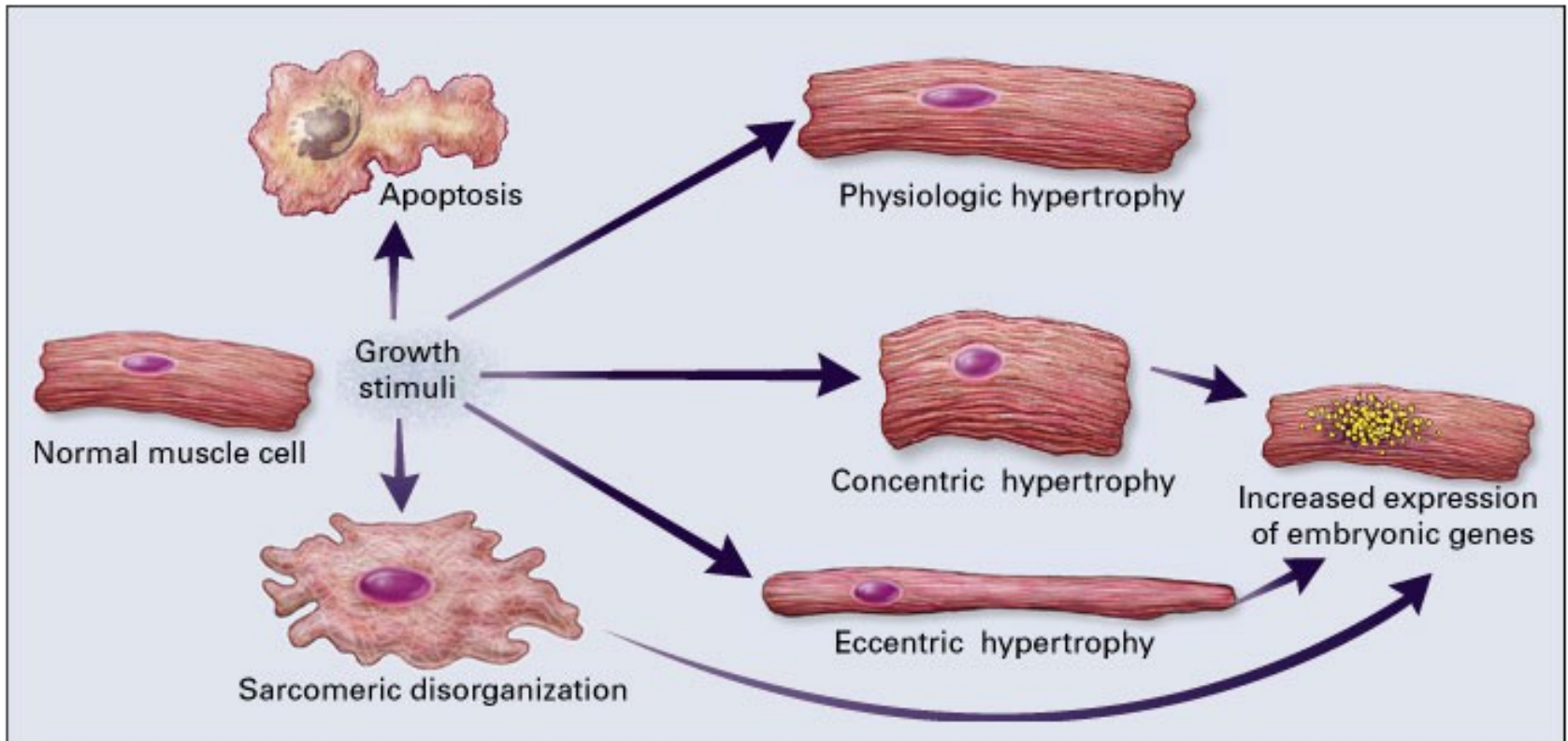
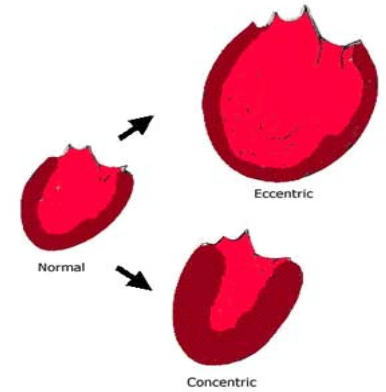


Figure 21-10

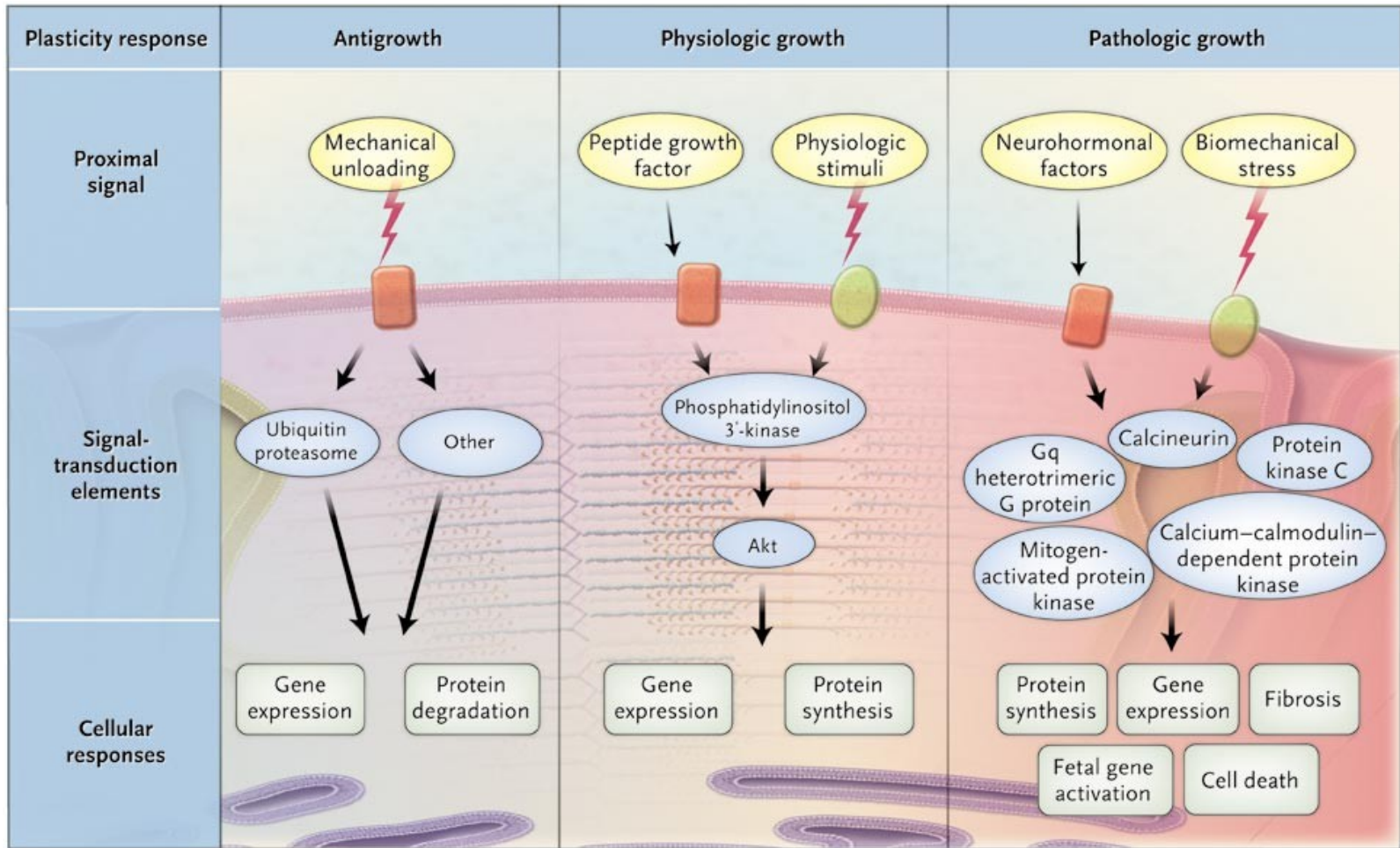
Copyright 2005 by Elsevier Science

# Cellular Hypertrophy





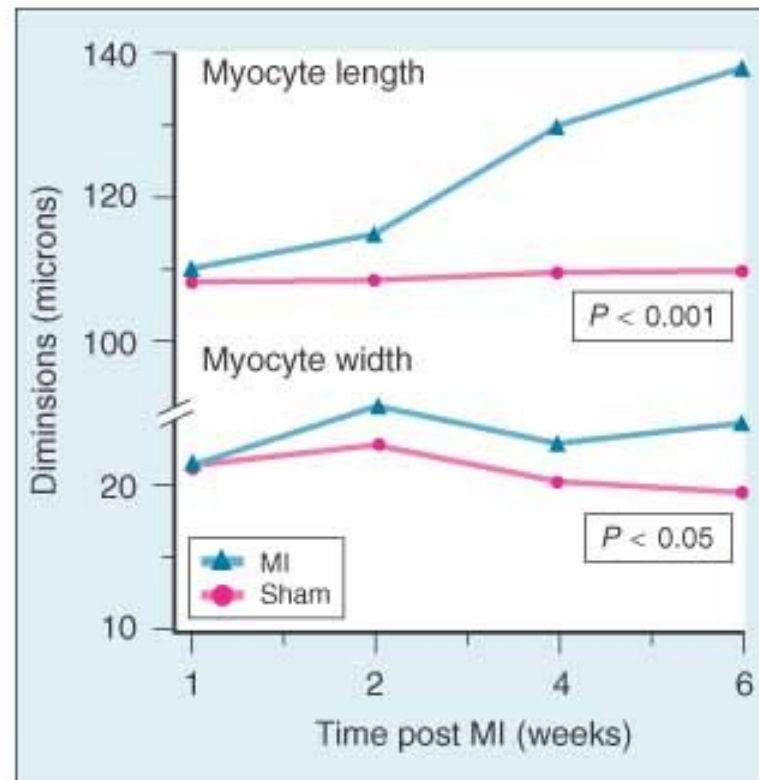
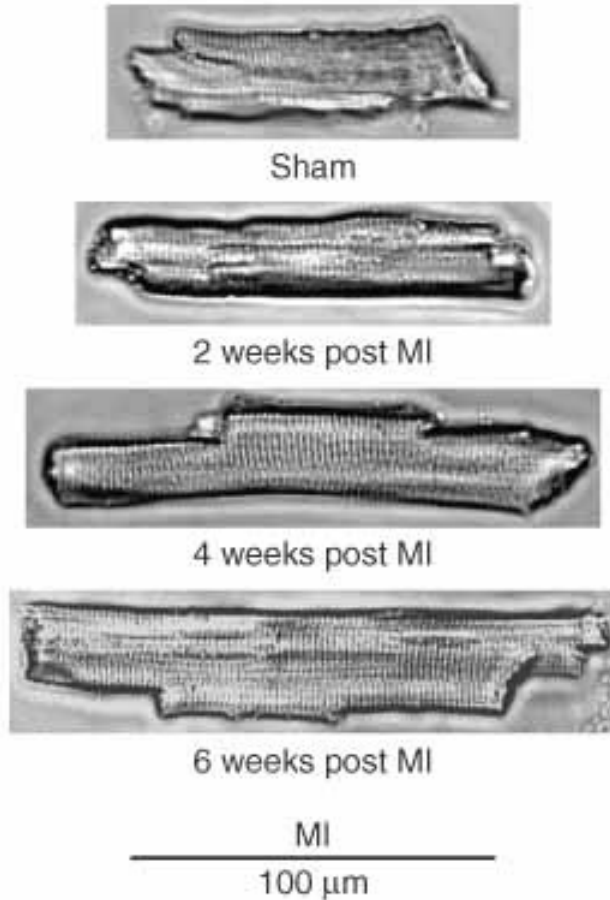
# Extracellular Signals Triggering Intracellular Events in the Cardiac Myocyte



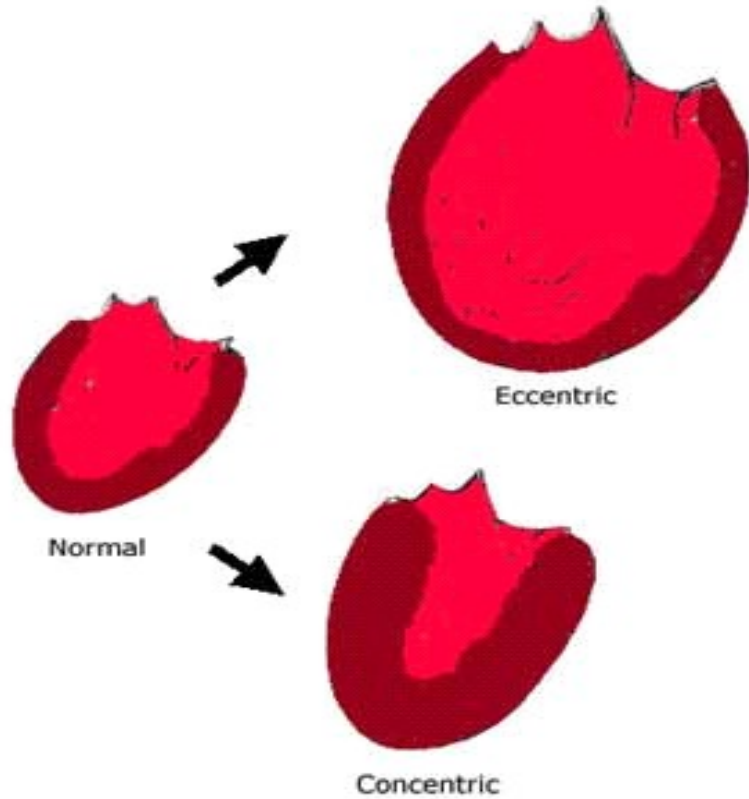


# Cardiac myocyte remodeling

## Increased myocyte length and width



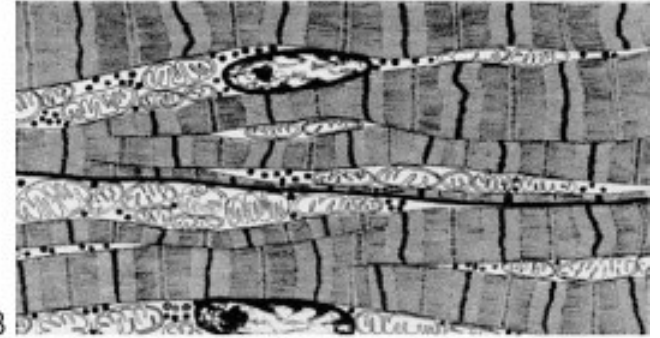
# cardiac hypertrophy



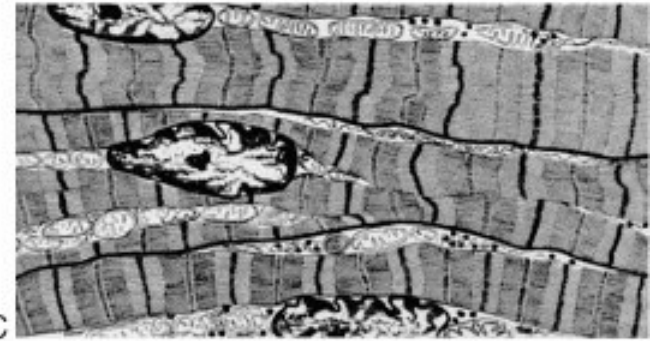
A



B



C



D

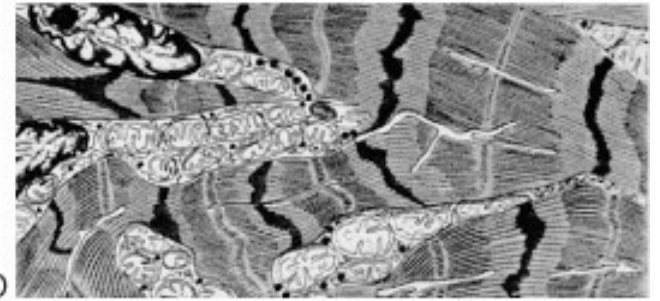
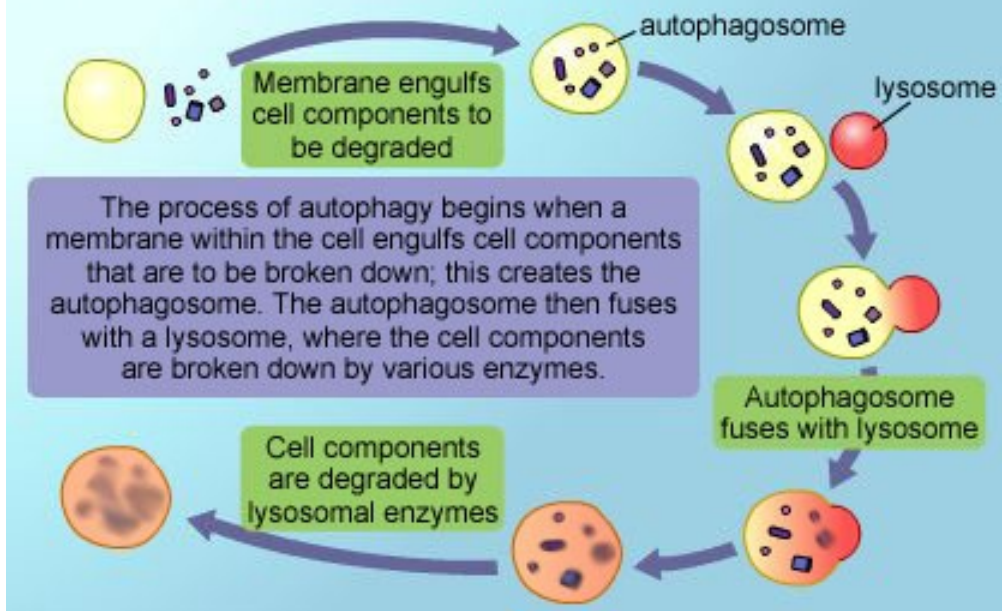


Figure 21-8

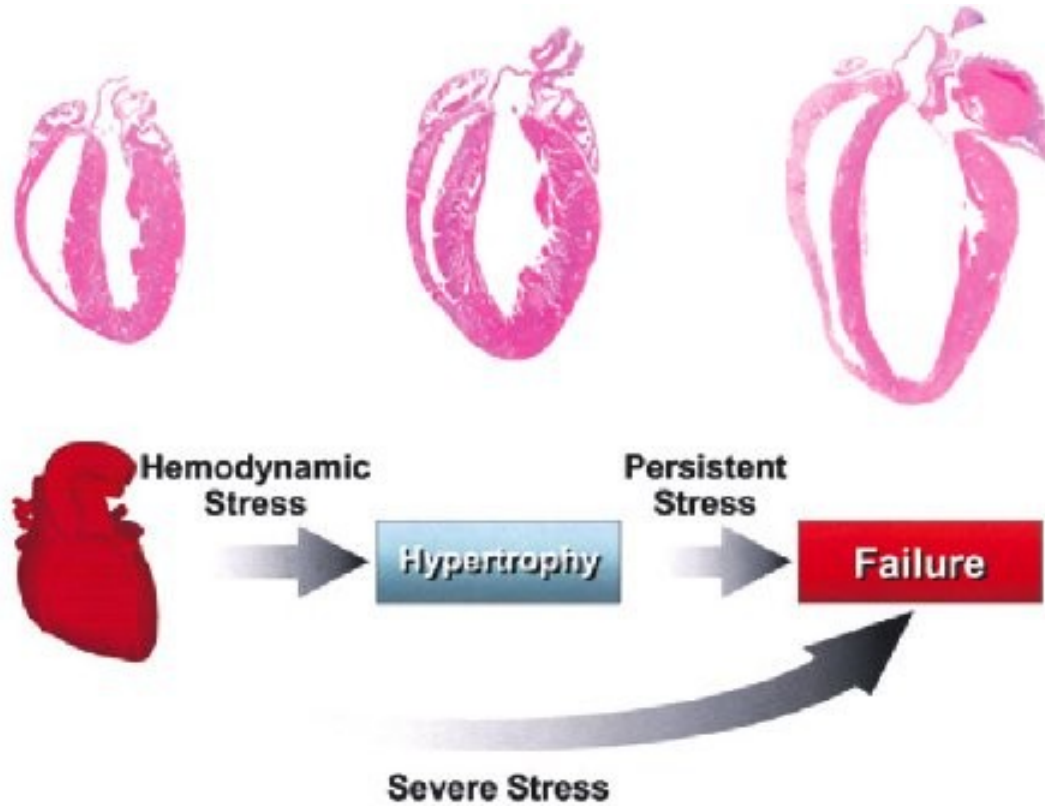
Prof. Jonathan Leor, NC

# Autophagy

Figure H-3: The Process of Autophagy



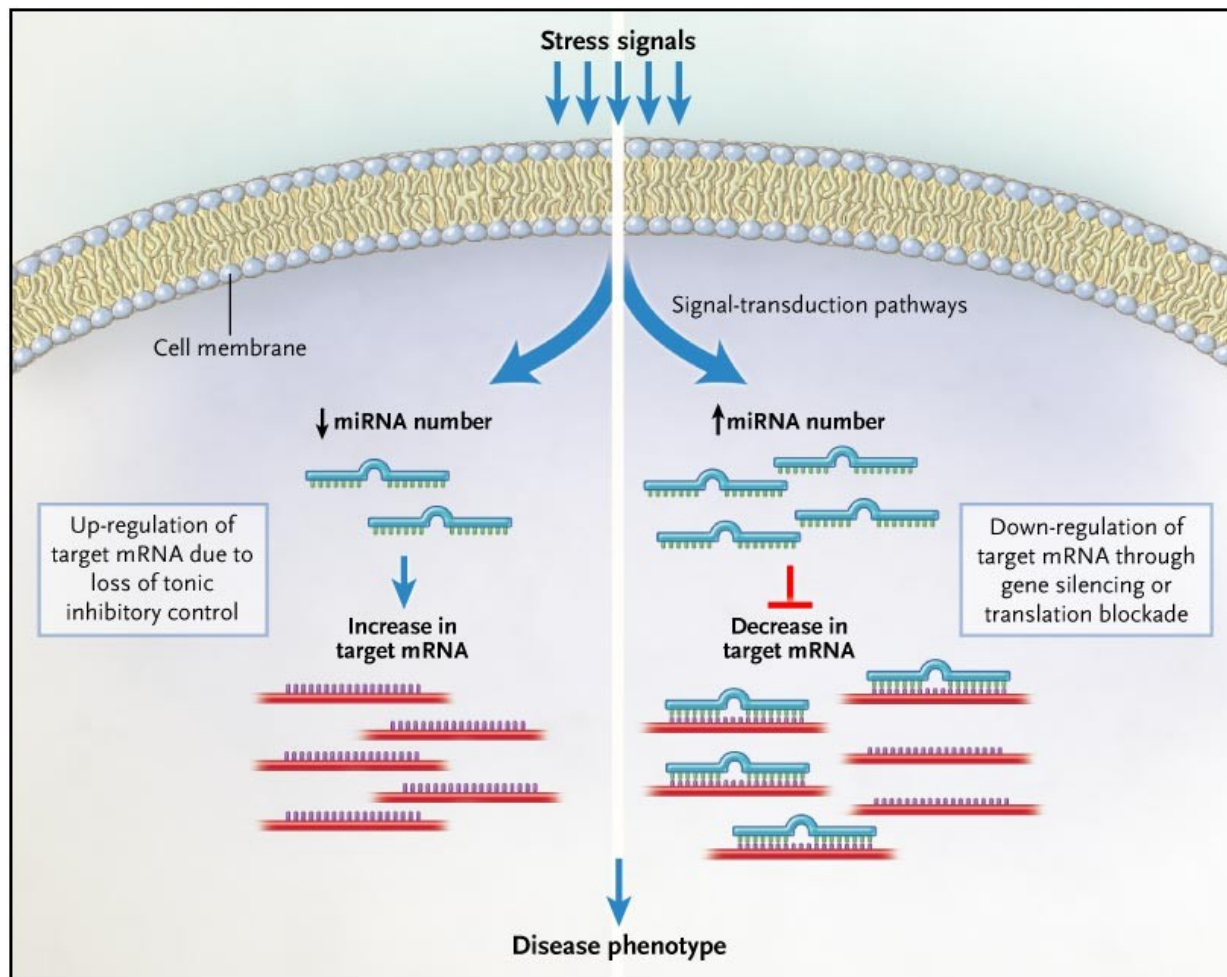
# Small RNAs in a big heart



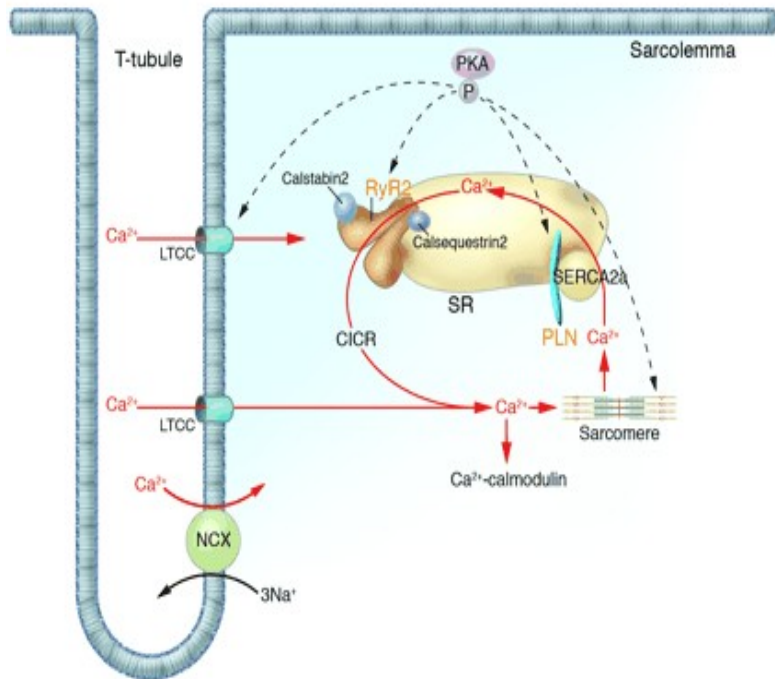


## MicroRNAs as Mediators

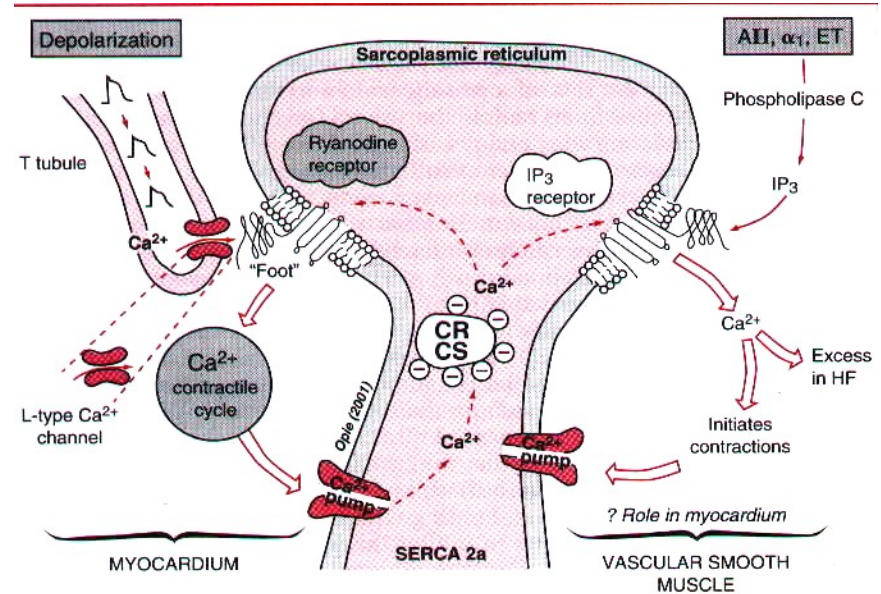
# MicroRNAs as Mediators



# Human mutations affecting Ca<sup>2+</sup> cycling proteins



*J. Clin. Invest.* **115**:518-526 (2005)

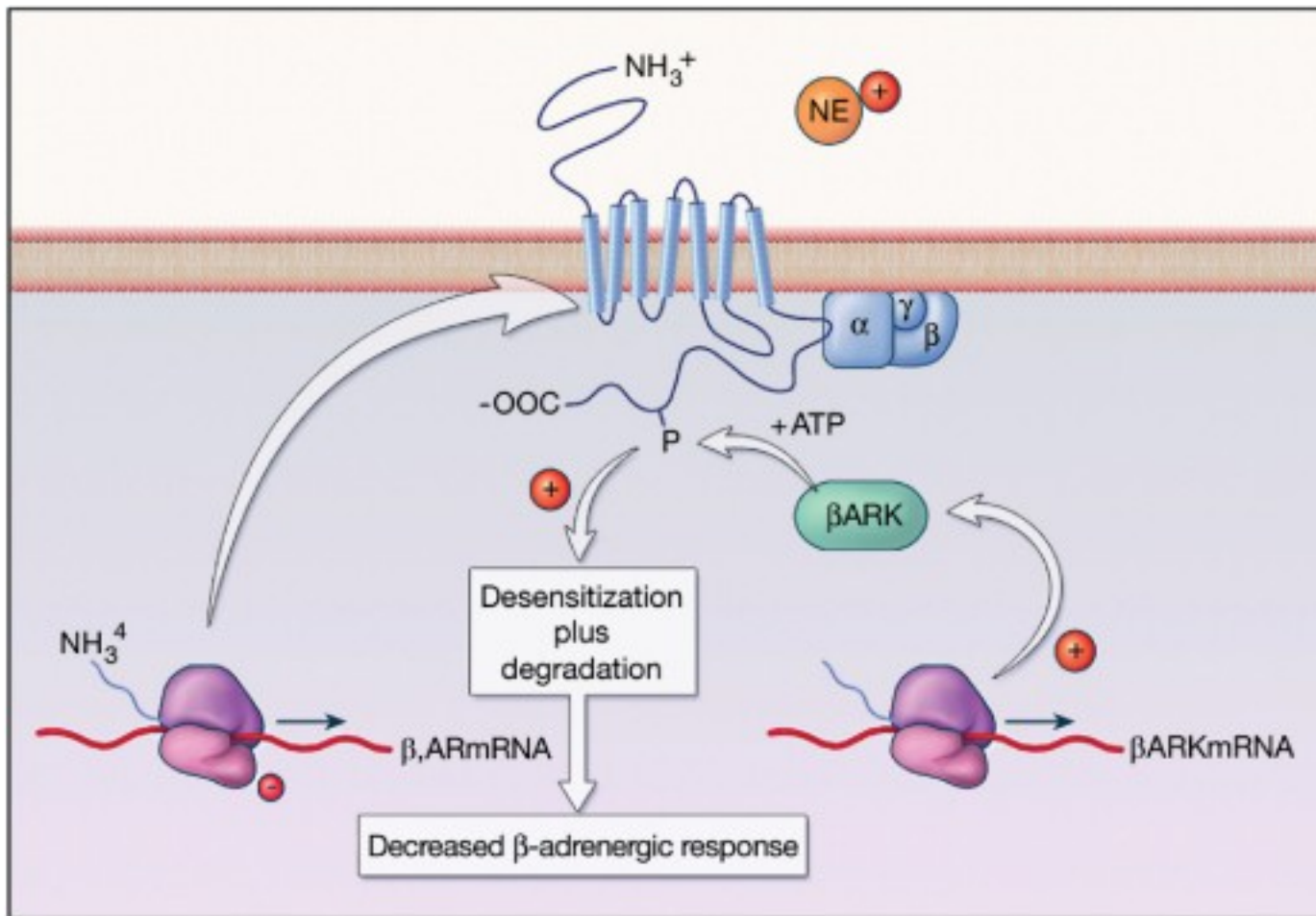


Braunwald p 453

# Calcium Hemostasis in Failing Human Myocardium

- Intracellular Calcium levels
- Basal (diastolic) ↑
- Peak (systolic) ↓
- Rate of fall with diastole ↓

# Alterations in beta-adrenergic pathways in the failing heart





# Braunwald Table 29-5

**TABLE 29-5 -- Potential Therapeutic Targets for Gene Therapy in Heart Failure**

Target	Function
Beta-adrenergic receptor kinase inhibitor ( $\beta$ ARKct)	Inhibits phosphorylation of $\beta$ -adrenergic receptor thus preventing its desensitization
Adenylyl cyclase (AC)	Synthesizes cAMP to activate PKA, which then phosphorylates substrates to regulate calcium handling
Sarcoplasmic reticulum $Ca^{2+}$ ATPase (SERCA2)	Responsible for the reuptake of calcium from cytoplasm into the SR lumen. Critical determinant of both relaxation and contractility via calcium sequestration into SR and via controlling SR calcium loading, respectively
Phospholamban (PLN)	Inhibits SERCA2, inactivated by phosphorylation by PKA and CaMKII
Parvalbumin (Parv)	Rapidly removes calcium in myofilaments, naturally abundant in skeletal muscle (not cardiac); results in enhanced relaxation
S100 protein	A calcium binding protein, a positive inotropic regulator of cardiac function that

**TABLE 22-4****Effects of Inflammatory Mediators on Left Ventricular Remodeling****Alterations in the Biology of the Myocyte**

- Myocyte hypertrophy
- Fetal gene expression
- Negative inotropic effects
- Increased oxidative stress

**Alterations in the Biology of the Nonmyocytes**

- Conversion of fibroblasts to myofibroblasts
- Upregulation of AT<sub>1</sub> receptors on fibroblasts
- Increased matrix metalloproteinase secretion by fibroblasts
- Alterations in the extracellular matrix
- Degradation of the matrix
- Myocardial fibrosis

**Progressive Myocyte Loss**

- Necrosis
- Apoptosis



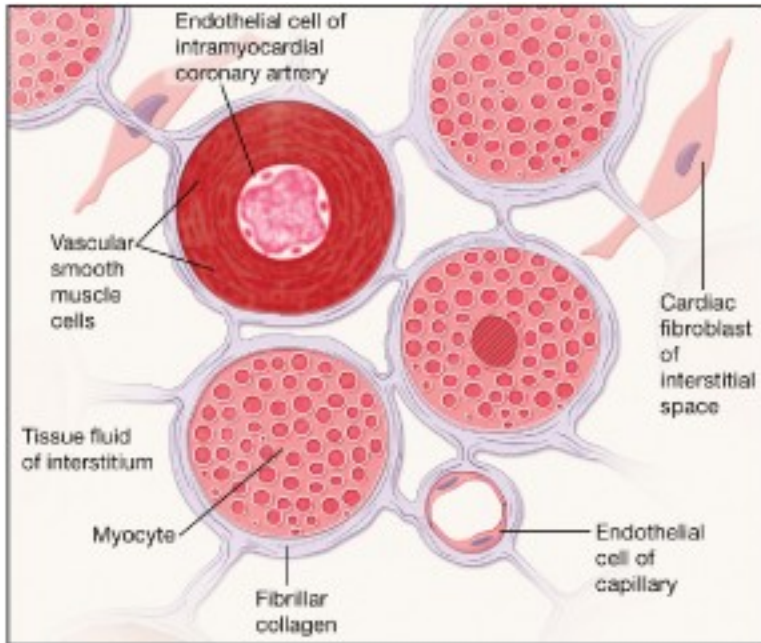
**TABLE 22-4** Effects of Inflammatory Mediators on Left Ventricular Remodeling.

# **Braunwald Table 29-6**

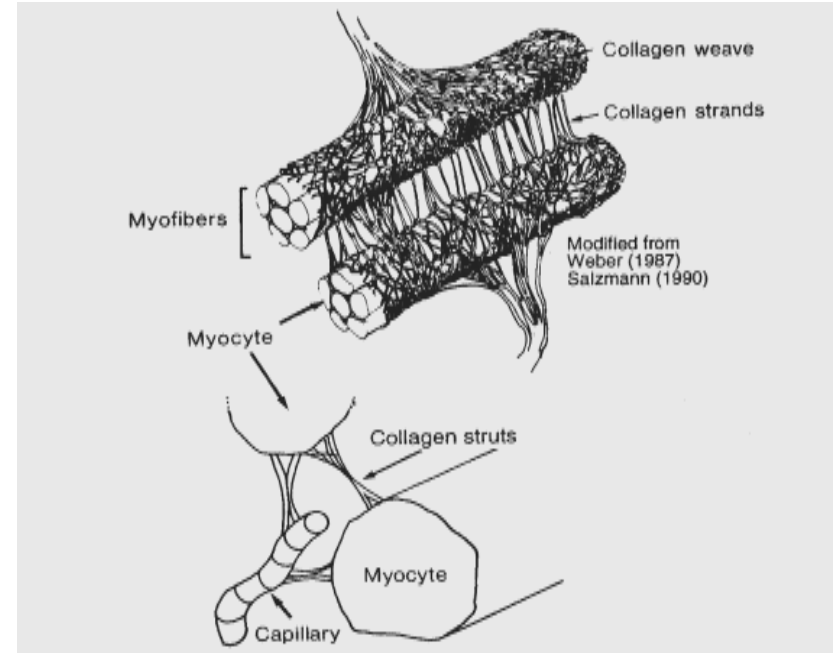
## **Effect of Gene Polymorphisms on the Pharmacological Treatment of Heart Failure**



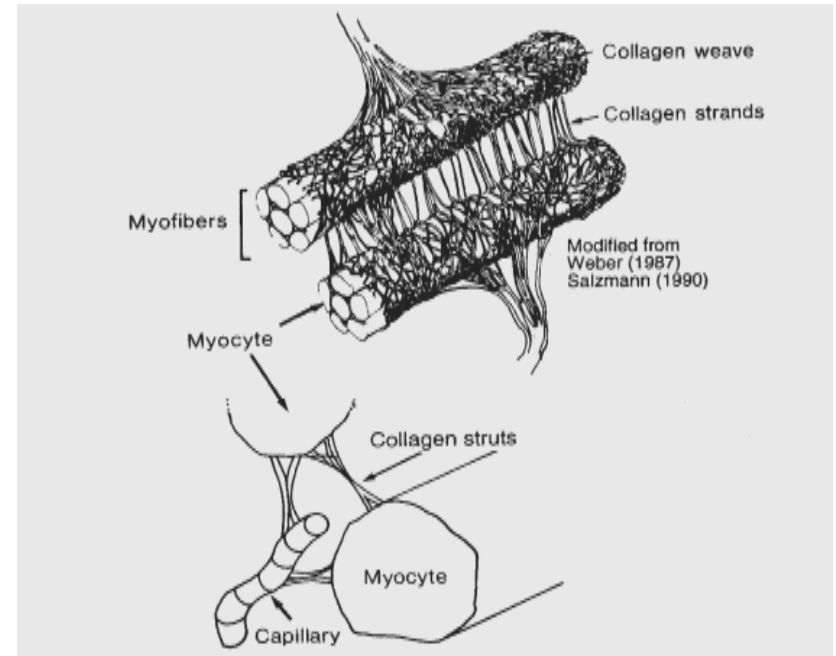
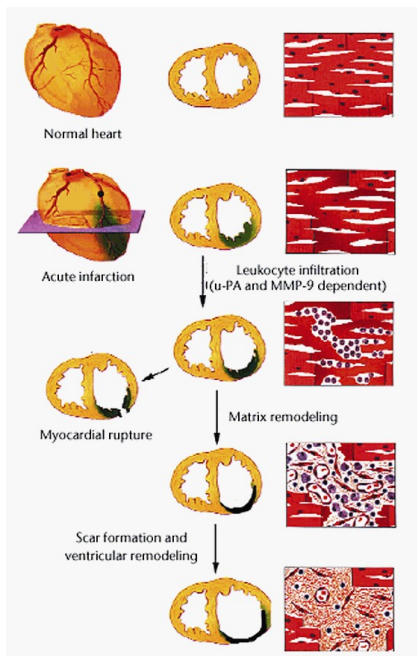
# Extra Cellular Matrix



Copyright 2005 by Elsevier Science

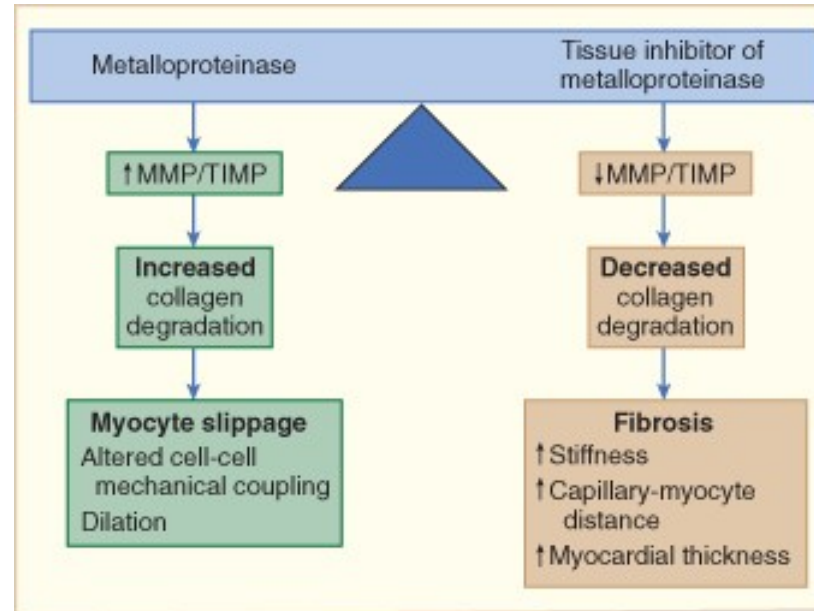


# MMP activity site



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

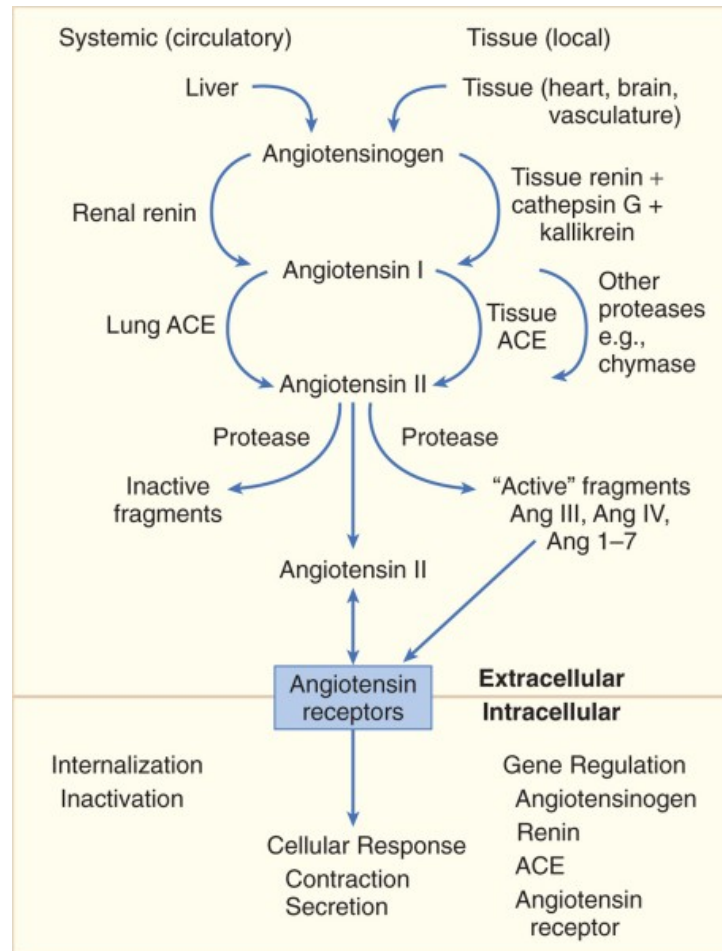
# The regulation of extracellular matrix degradation



Copyright 2005 by Elsevier Science

Figure 21-18

# FIGURE 22-4 The systemic and tissue components of the renin-angiotensin system





# Angiotensin II and Myocardium

1. Myocyte hypertrophy
2. Myocyte apoptosis
3. Fibrosis
4. Matrix remodeling (collagen deposition)
5. Inflammation
6. Oxidative stress

# Summary

## 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.

# Processes Occurring in Ventricular Remodeling (2)

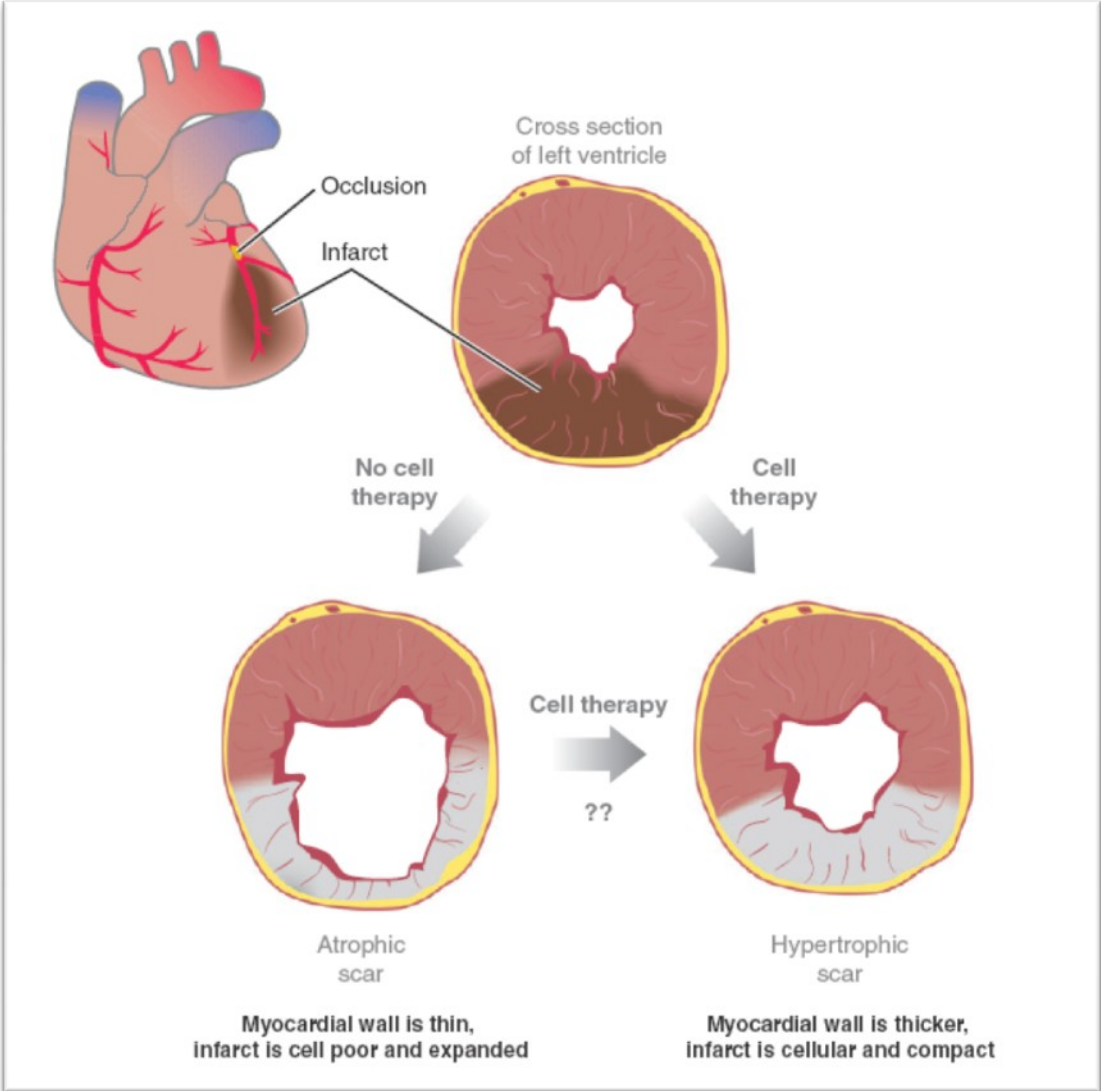
1. Continued expansion of infarct zone
2. Dilation and reshaping of the left ventricle
3. Myocyte hypertrophy
4. Ongoing myocyte loss
5. Excessive accumulation of collagen in the cardiac interstitium

# Table 22-5

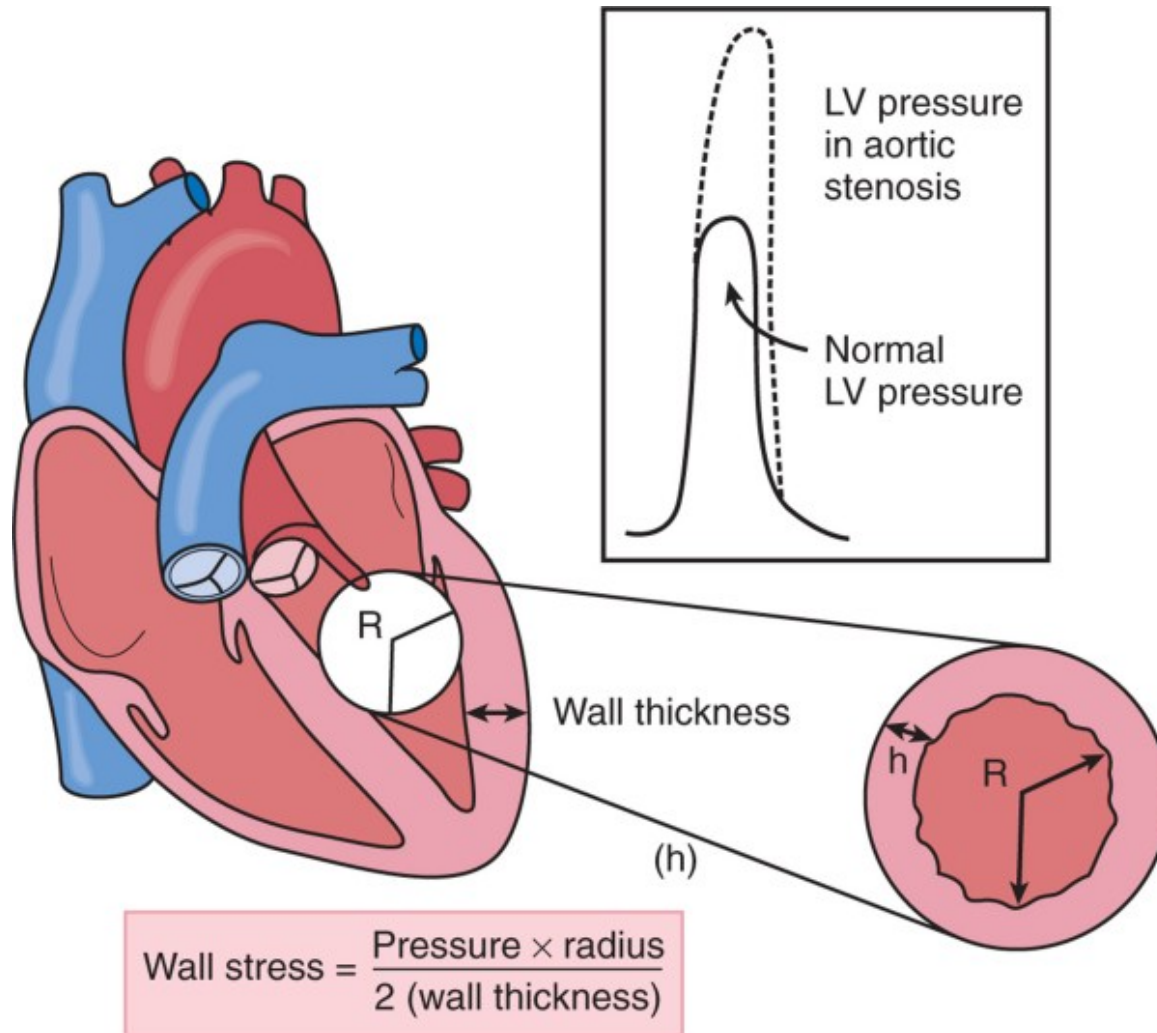
**TABLE 22-5 -- Cellular and Molecular Determinants of Myocardial Recovery**

	ACE Inhibitor	Beta Blocker	LVAD	CSD
<b>Myocyte Defects</b>				
Hypertrophy	Decreased	Decreased	Decreased	Decreased
Myocytolysis	ND	Decreased	Decreased	ND
E-C coupling	Increased	Increased	Increased	Increased
Fetal gene expression	Decreased	Decreased	Decreased	Decreased
Beta-adrenergic desensitization	Decreased	Decreased	Decreased	Decreased
Cytoskeletal proteins	ND	ND	Increased	ND
Myocyte contractility	ND	Increased	Increased	Increased
<b>Myocardial Defects</b>				
Myocyte necrosis	Decreased	Decreased	Decreased	ND
Myocyte apoptosis	Decreased	Decreased	Decreased	Decreased
MMP activation	Decreased	Decreased	Decreased	Decreased
Fibrosis	Decreased	Decreased	Decreased	Decreased
<b>LV Dilation</b>	Stabilized	Decreased	Decreased	Decreased

# Cell therapy for heart repair



# The rationale



# Stem Cell

- Self renewal
- Give rise to specialized cells.

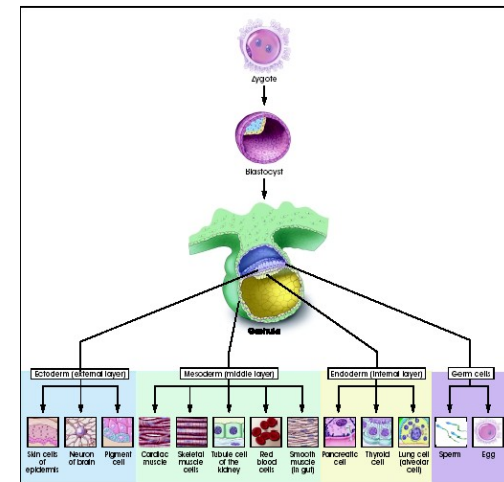
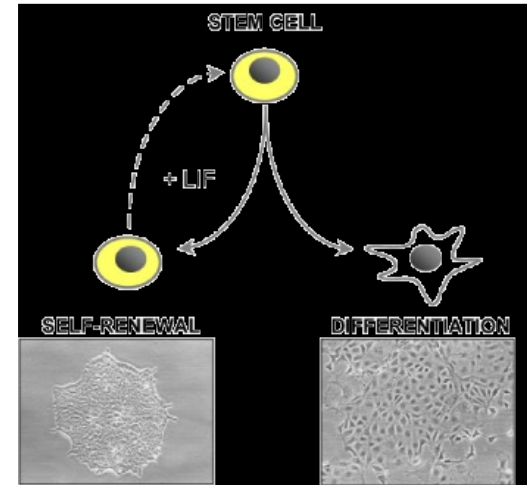
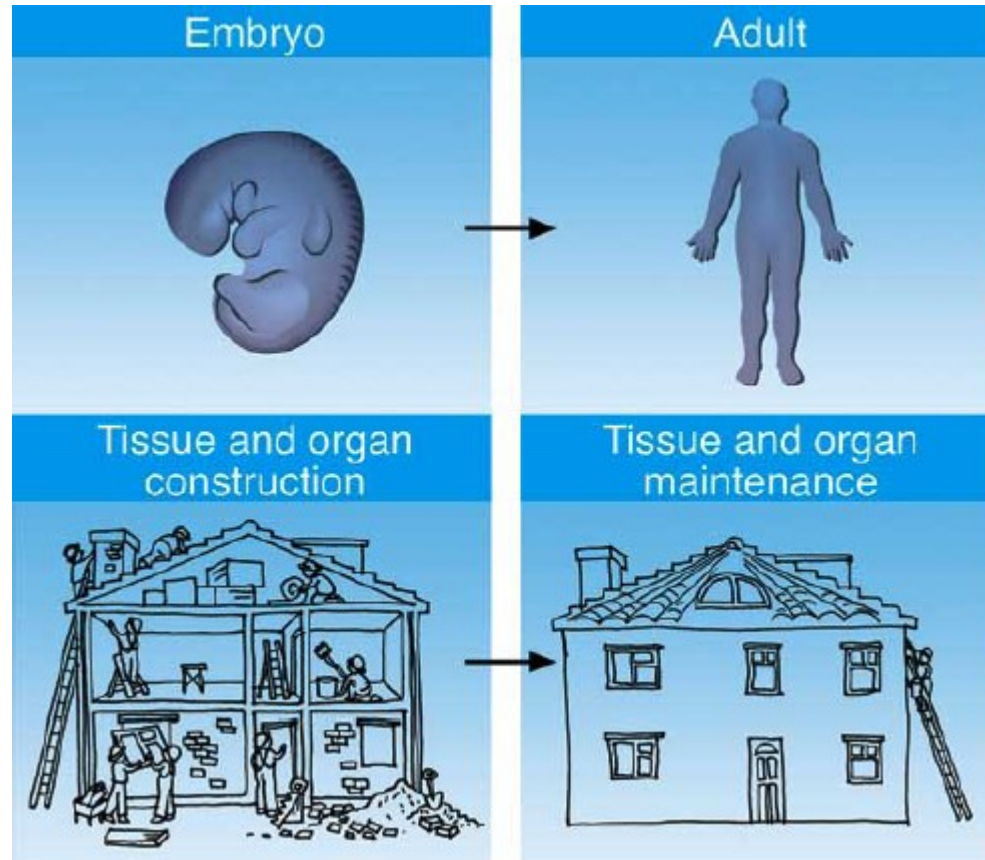


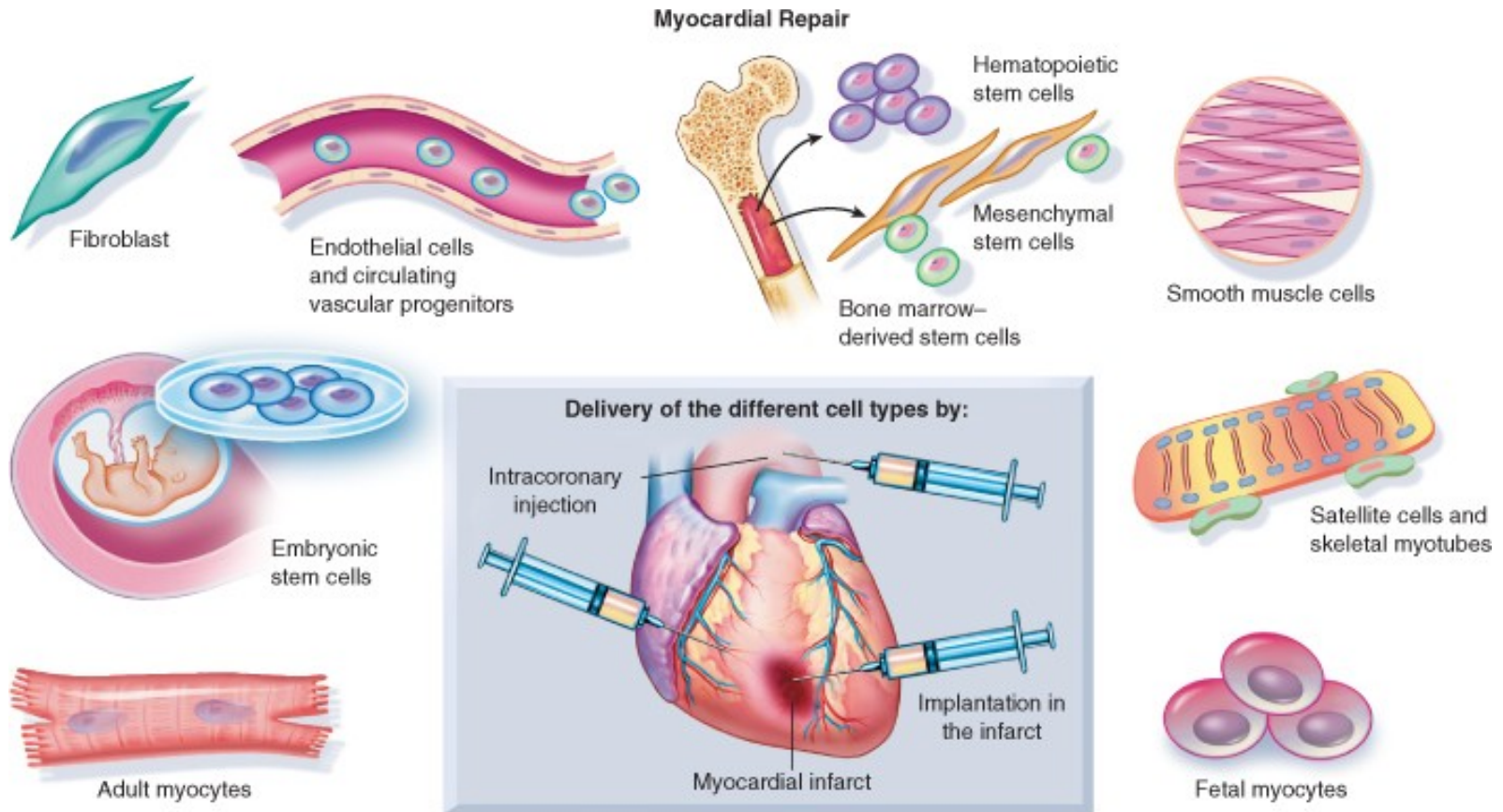
Figure 1.1. Differentiation of Human Tissues.

# Embryonic and Adult Stem Cells





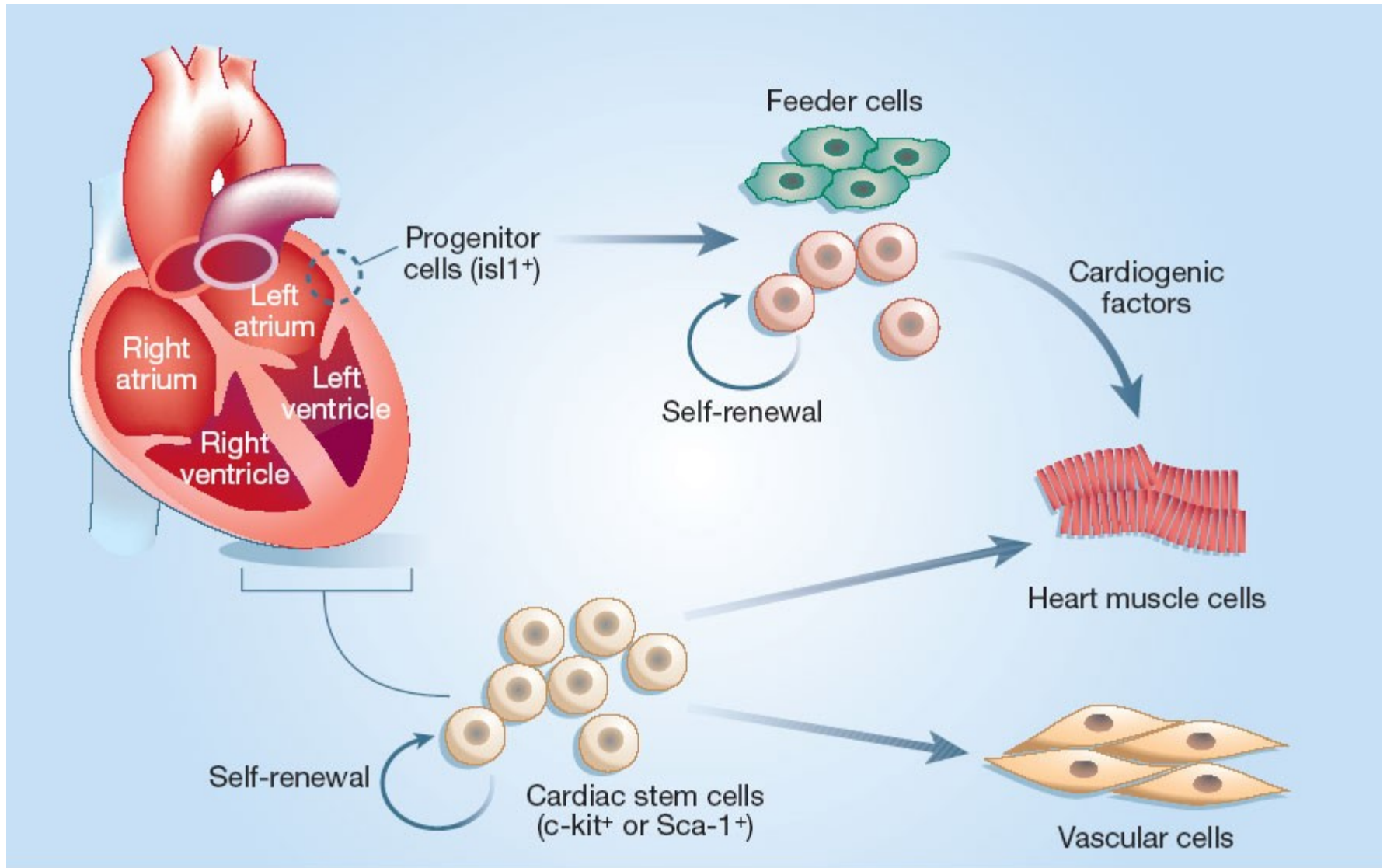
# Myocardial repair



Copyright 2005 by Elsevier Science

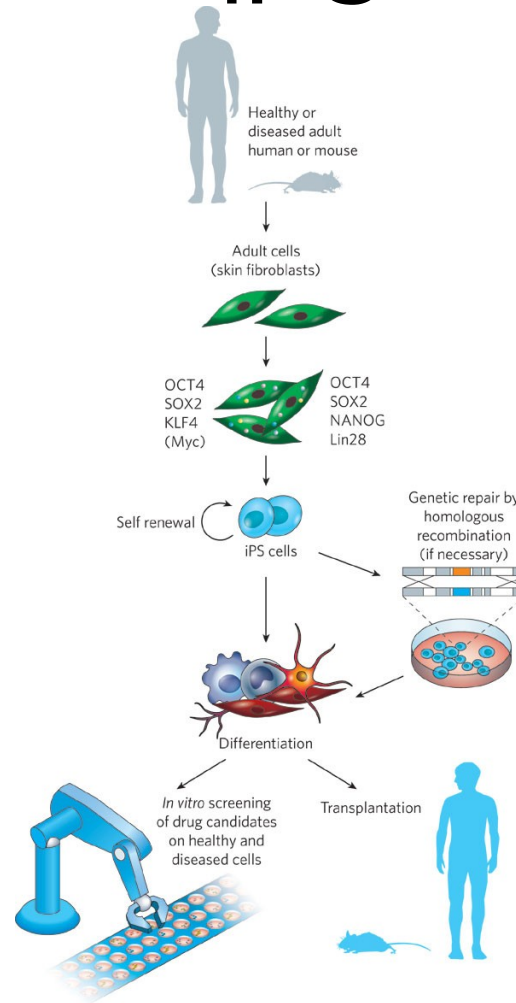
Figure 71-1

# Cardiac Stem cells

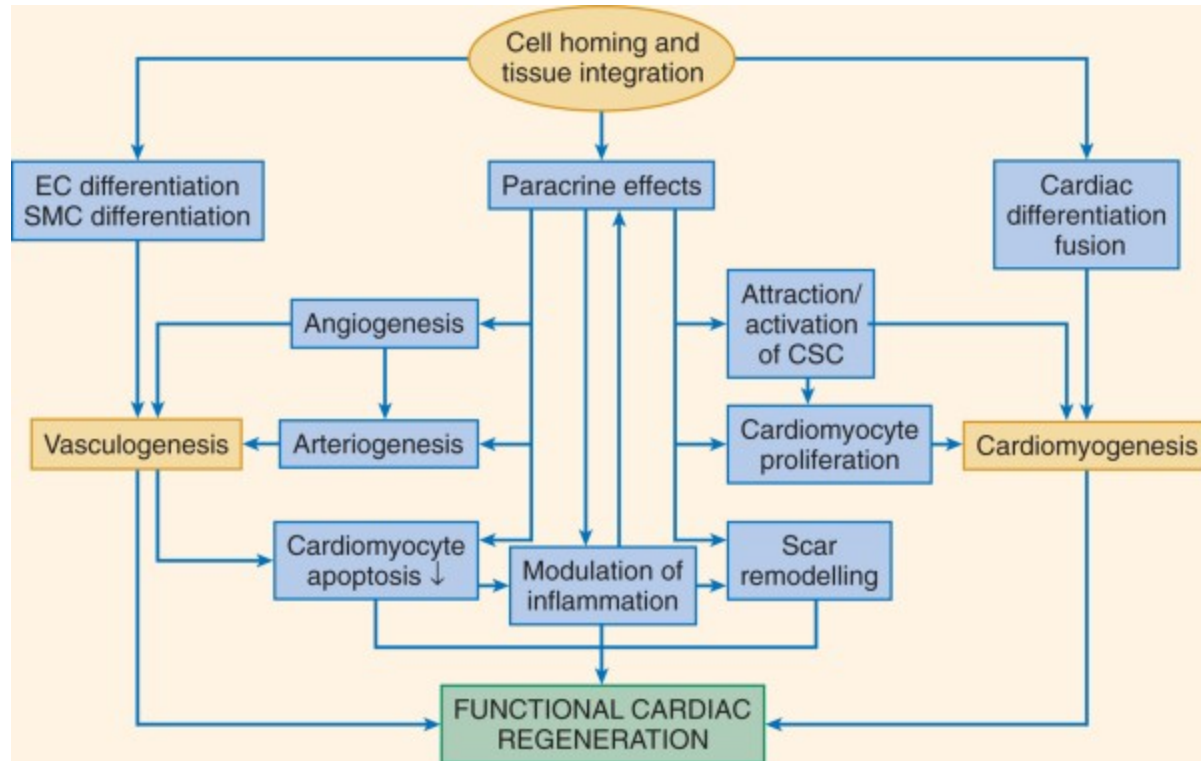


# Induced Pluripotent Stem cells

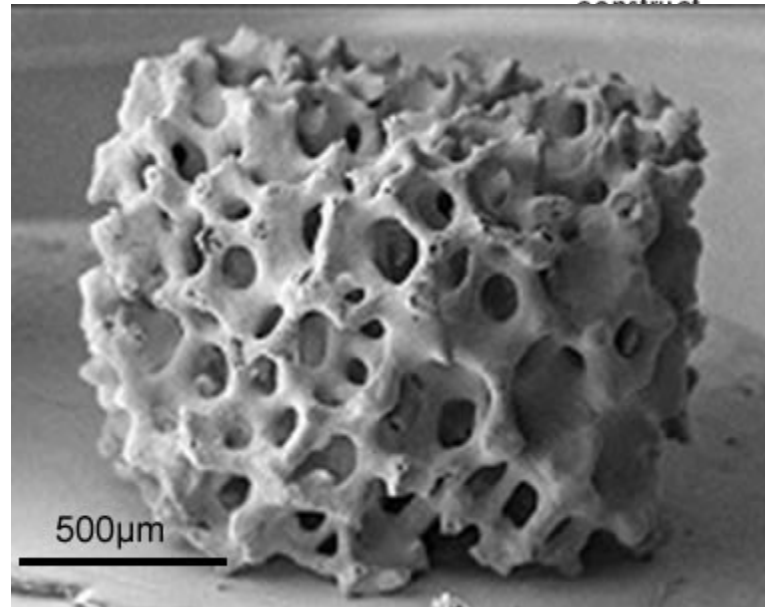
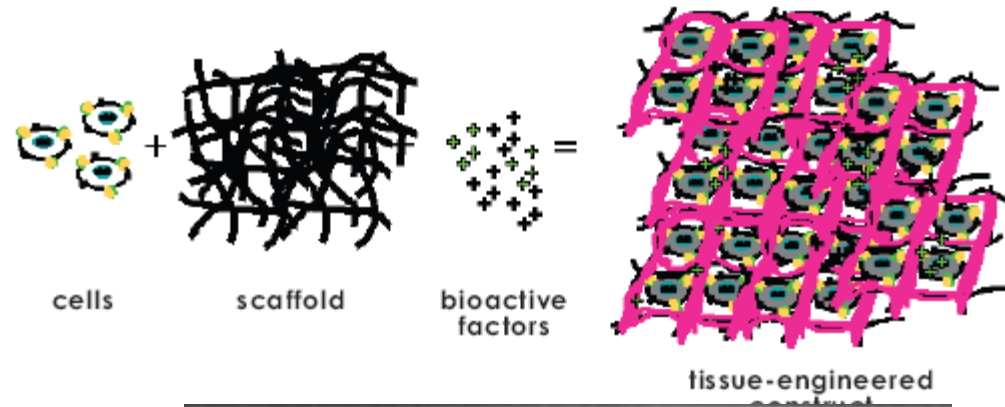
## iPS



# FIGURE 29-3 Proposed mechanisms of action of stem/progenitor cells in cardiovascular repair.



# Cardiac Tissue Engineering





# Cardiac tissue engineering in pig

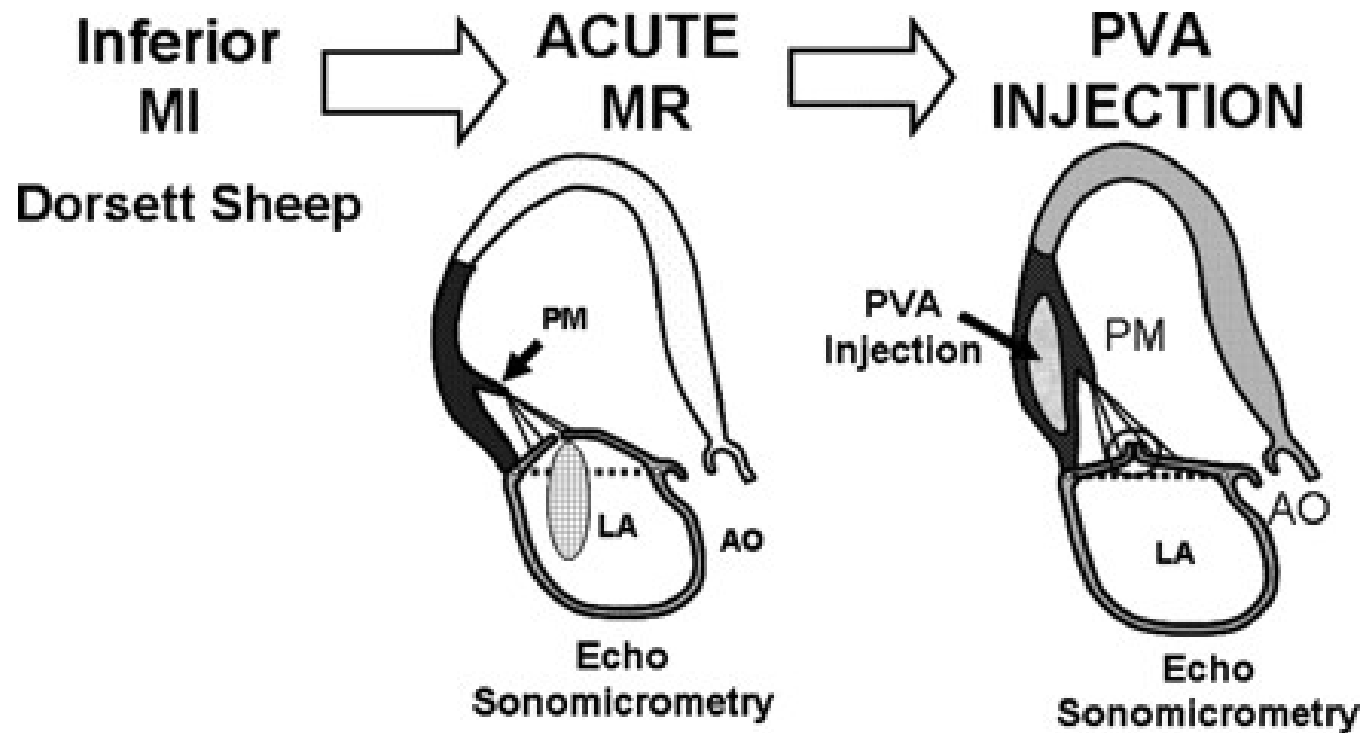


# Tissue engineering of all Heart





# A Novel Approach for Reducing Ischemic Mitral Regurgitation by Injection of a Polymer to Reverse Remodeling and Reposition Displaced Papillary Muscles



*Hung & Levine. Circulation. 2008;118:S263-S269*

# **Sleeping Student: Take home message**



# Overview of the pathophysiology of myocardial remodeling

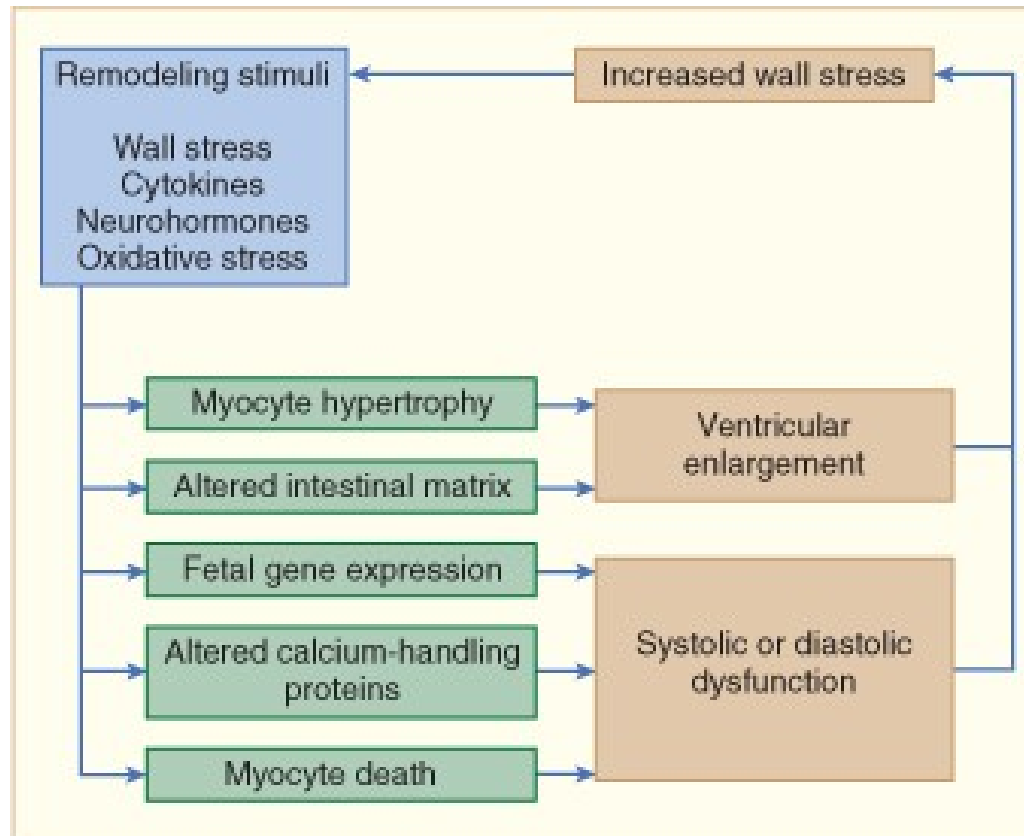


Figure 21-10

Copyright 2005 by Elsevier Science

# שאלה

מדידה שלו בדם 6 שעות מהסמנים מנבאת פרוגנוזה  
לאחר אוטם שריר הלב  
(ברנוולד פרק 22)

1. טרופונין T
2. טרופונין I
3. נטרירורטיק פפטיד (ANP)
4. קולגן

# שאלה

מתן מעכבי ACE לרמודלינג של הלב יעכב הכל

למעט (סמן תשובה לא נכונה)

- Beta-adrenergic desensitization** 1.
- Fetal gene expression** 2.
- Myocyte necrosis** 3.
- MMP activation** 4.
- E-C coupling** 5.

# שאלה

• מיוציטים עלולים למות מכל הנ"ל למעט (תשובה לא נכונה):

1. נקרודיס
2. אפופטודיס
3. אטופאגי
4. אטרופי