שינויים מולקולאריים ומבניים באי ספיקת לב
אפשרויות לטיפול עתידני

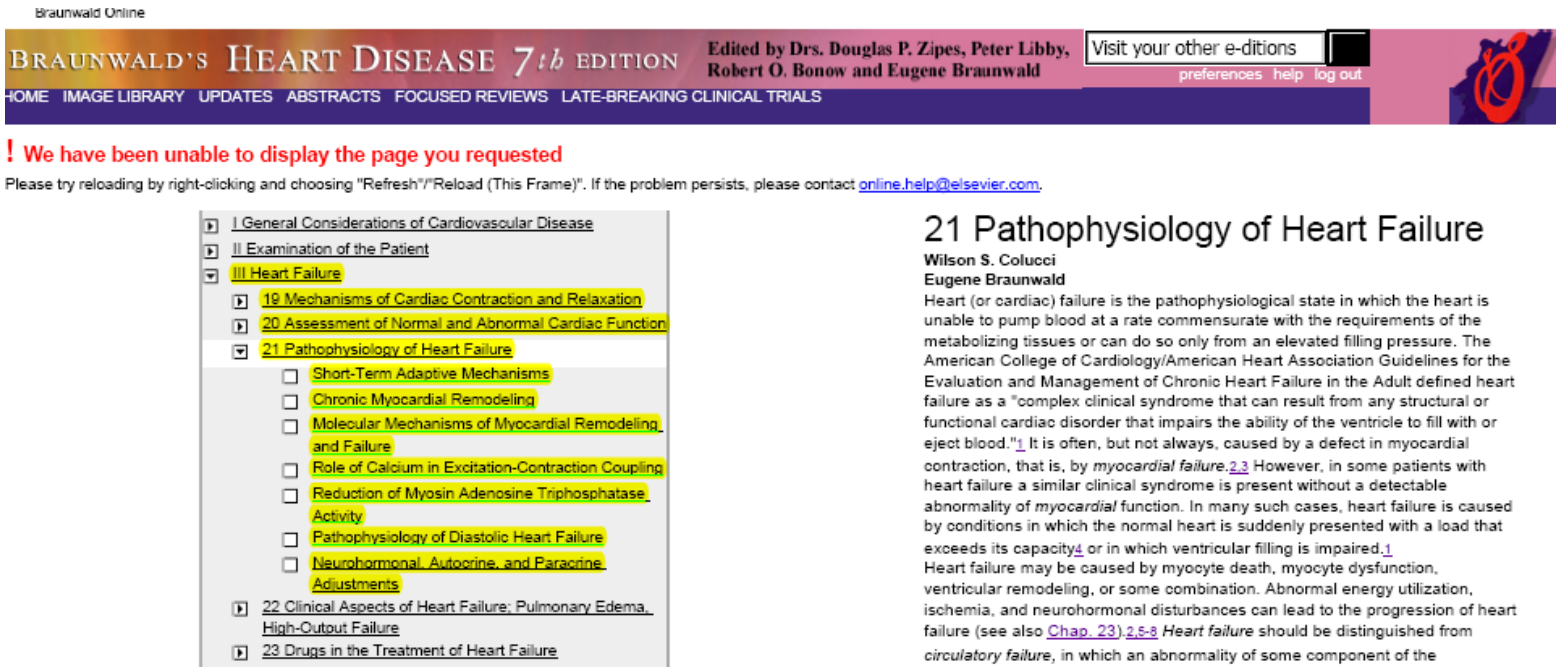
פרופ יהונתן ליאור

Braunwald's Heart Disease 8th Edition

Chapter 21 Mechanisms of Cardiac Contraction and Relaxation

Chapter 22 Pathophysiology of Heart failure

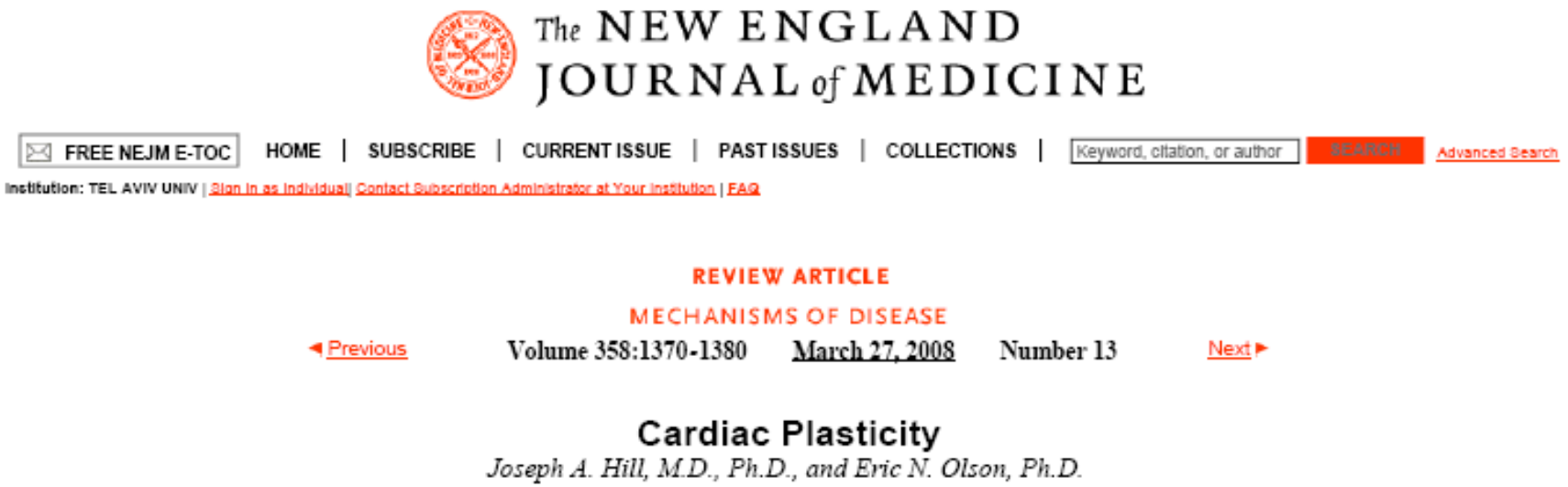
Chapter 29 Emerging therapies



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



שאלה

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

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

שאלה

מתן מעכבי ACE לרמודלינג של הלב יעכב הכל

למעט (סמן תשובה לא נכונה)

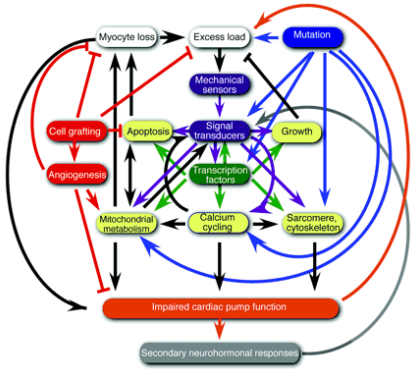
1. **Beta-adrenergic desensitization**
2. **Fetal gene expression**
3. **Myocyte necrosis**
4. **MMP activation**
5. **E-C coupling**

שאלה

- מיוציטים עלולים למות מכל הנ"ל למעט (תשובה לא נכונה):
  1. נקרוזיס
  2. אפופטוזיס
  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

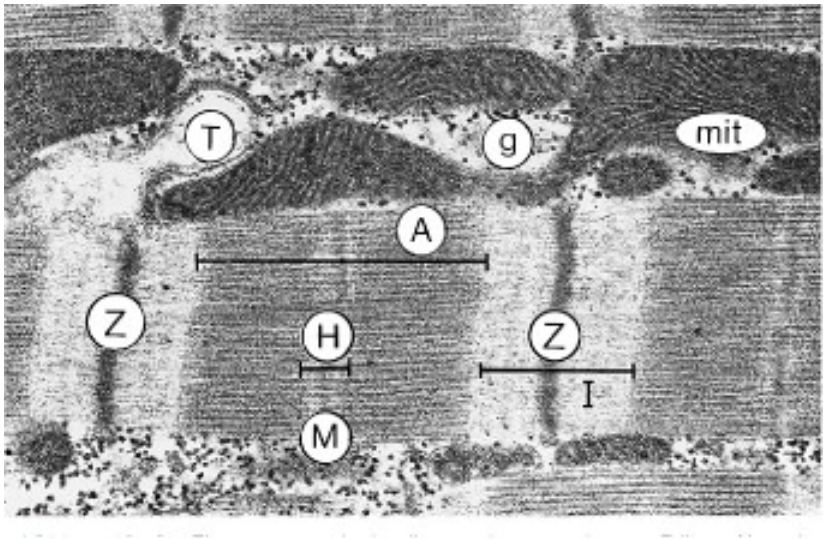
TABLE 1. Myocytes and Nonmyocytes in the Myocardium

Group	By Cell No.	By Cell Volume	By Cell Mass
Cardiomyocyte	25%[18]	≈75%[18]	...
	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

The Sarcomere



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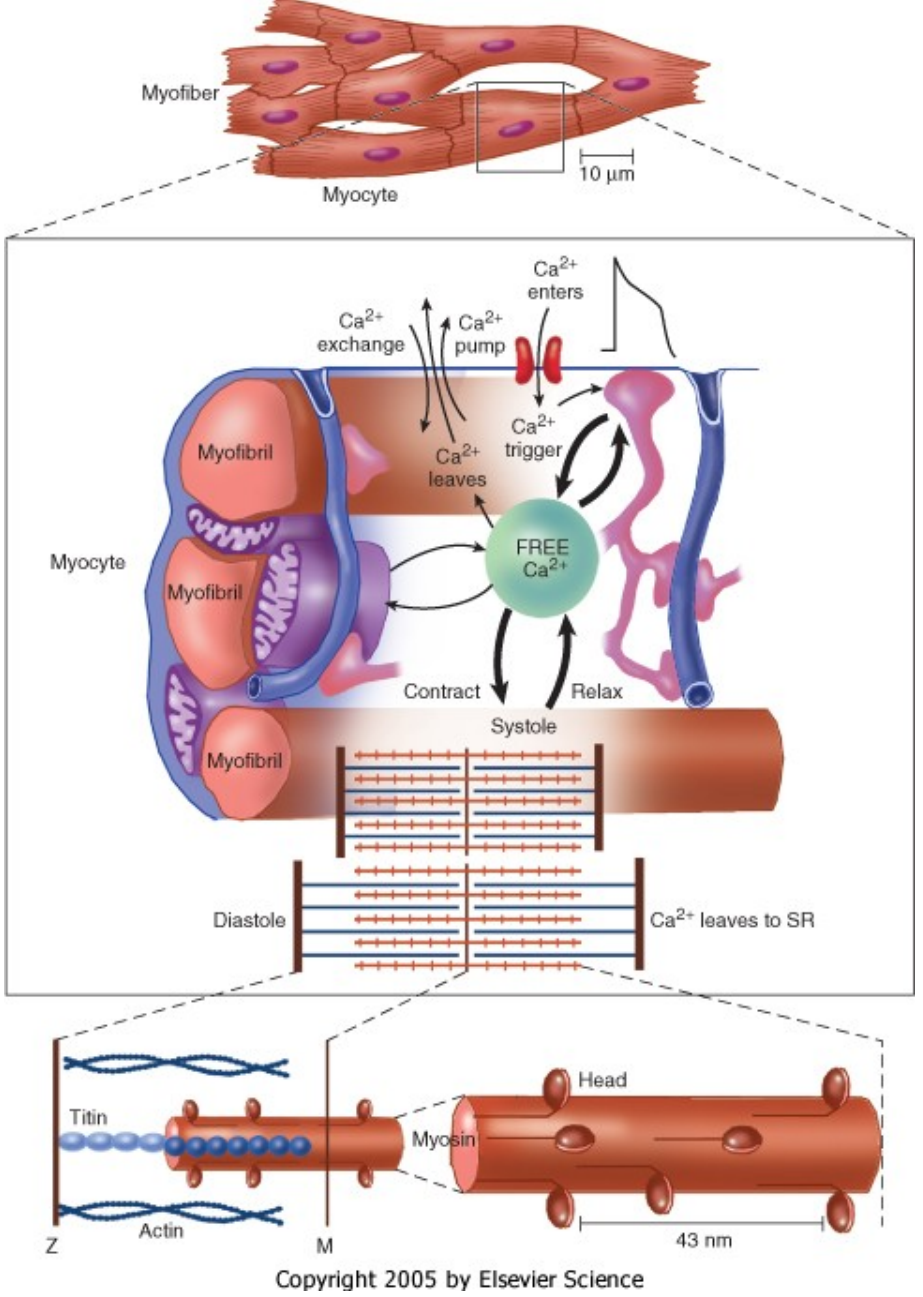

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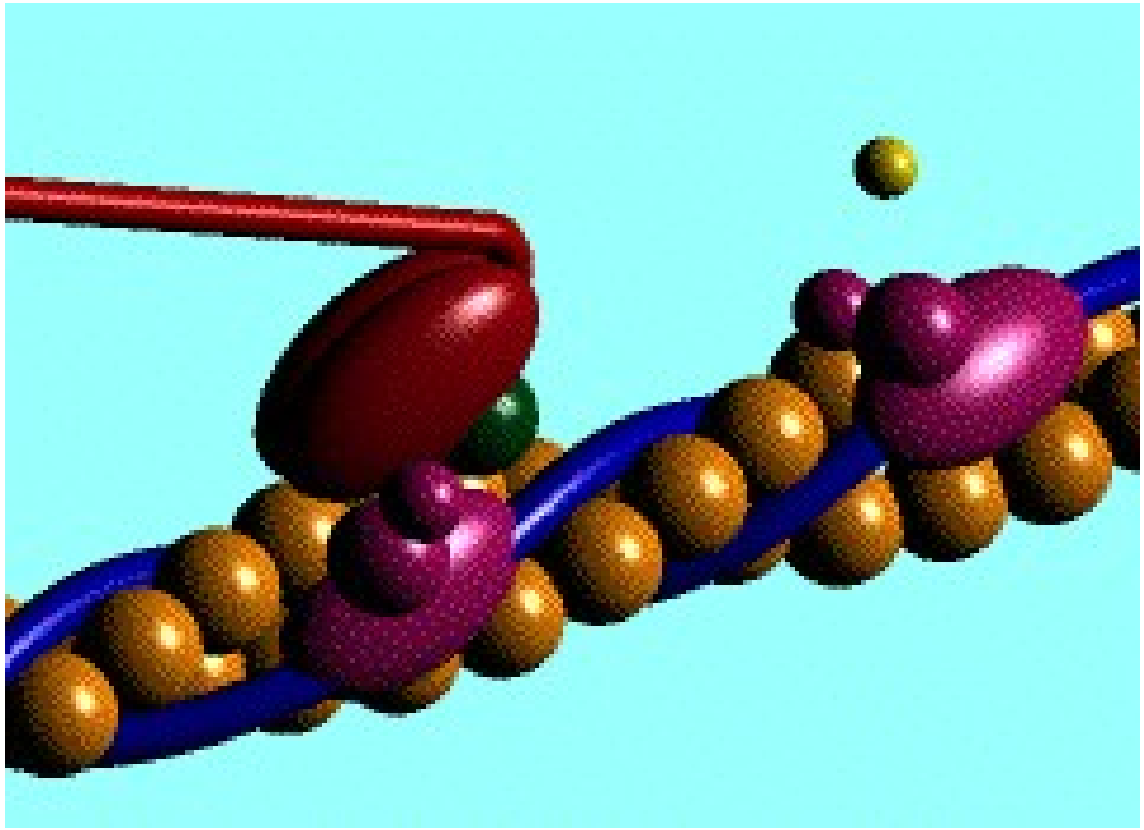
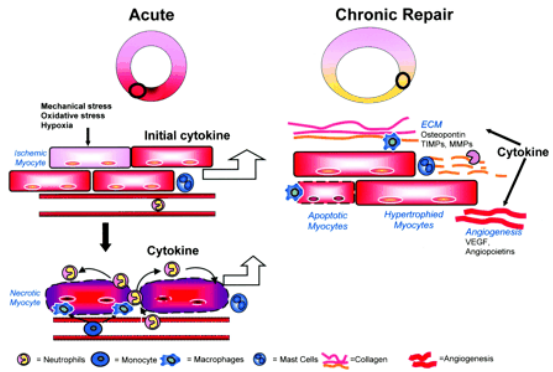
Figure 19-1 Braunwald 2005



Cardiac Damage and Repair



Prof. Jonathan Leor, I

Myocyte Cell Death

- Necrosis
- Apoptosis
- Autophagy

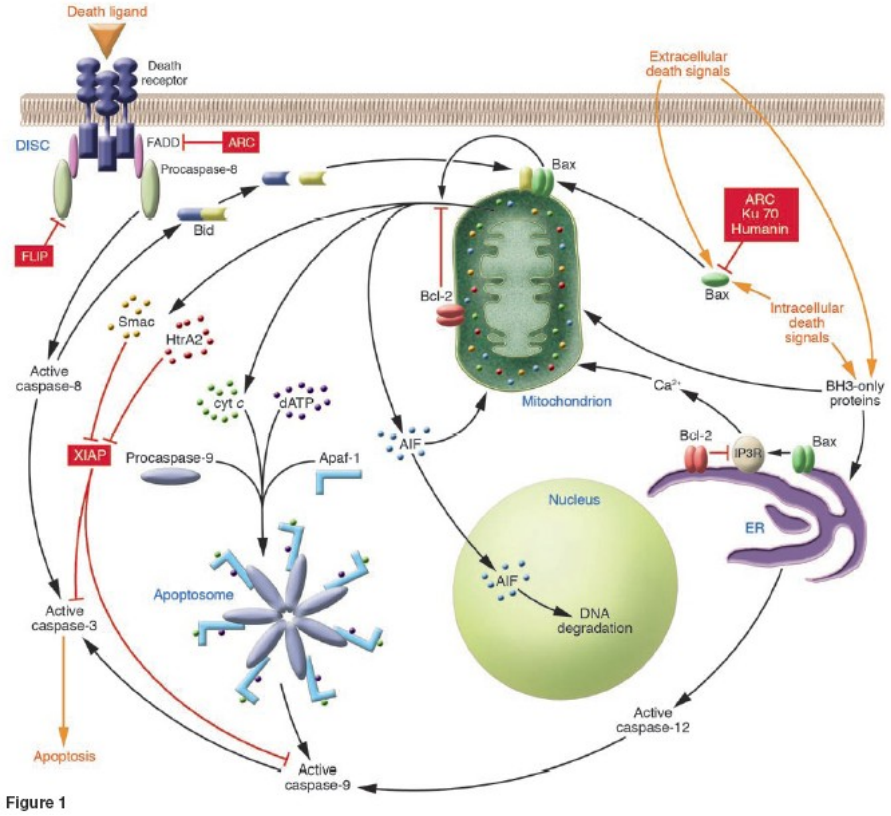
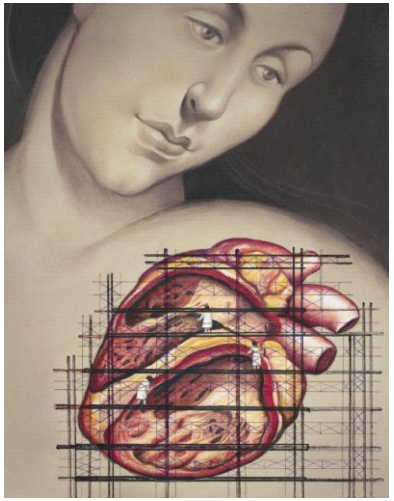


Figure 1

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

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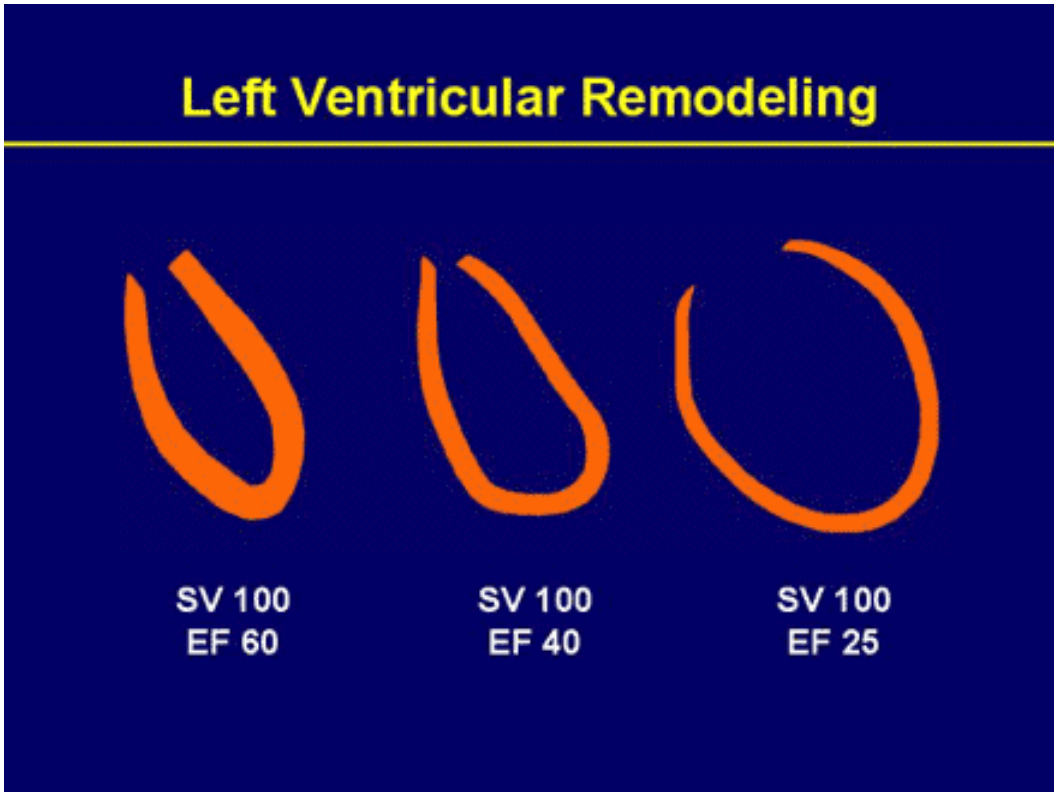

Left Ventricular Remodeling
SV 100
EF 60
SV 100
EF 40
SV 100
EF 25

Pathogenesis of heart failure

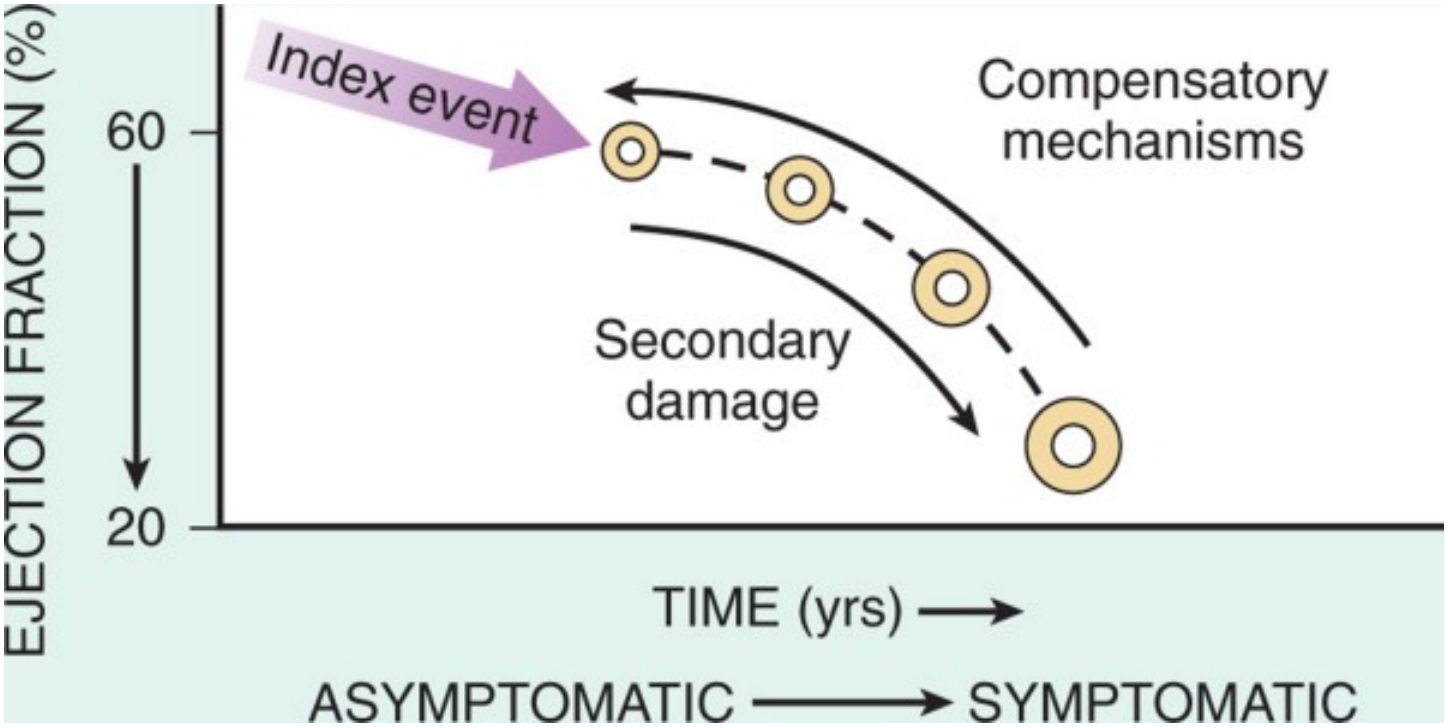
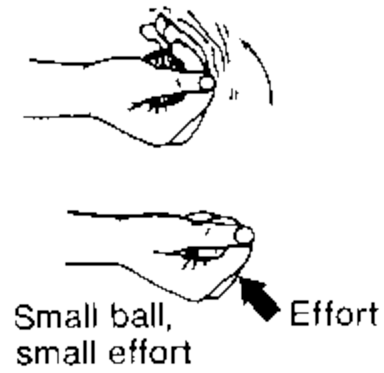
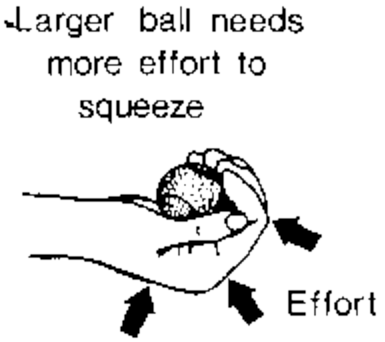
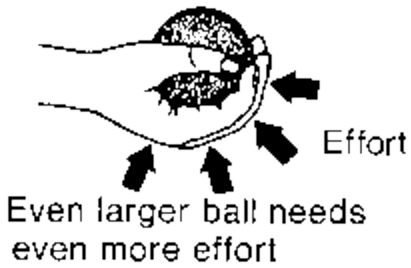


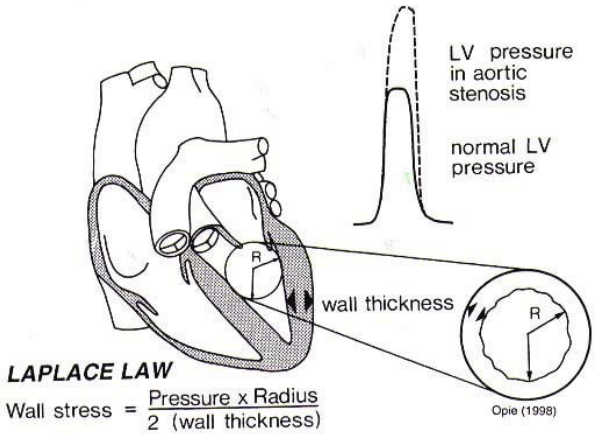
FIGURE 22-1

LV Dilatation

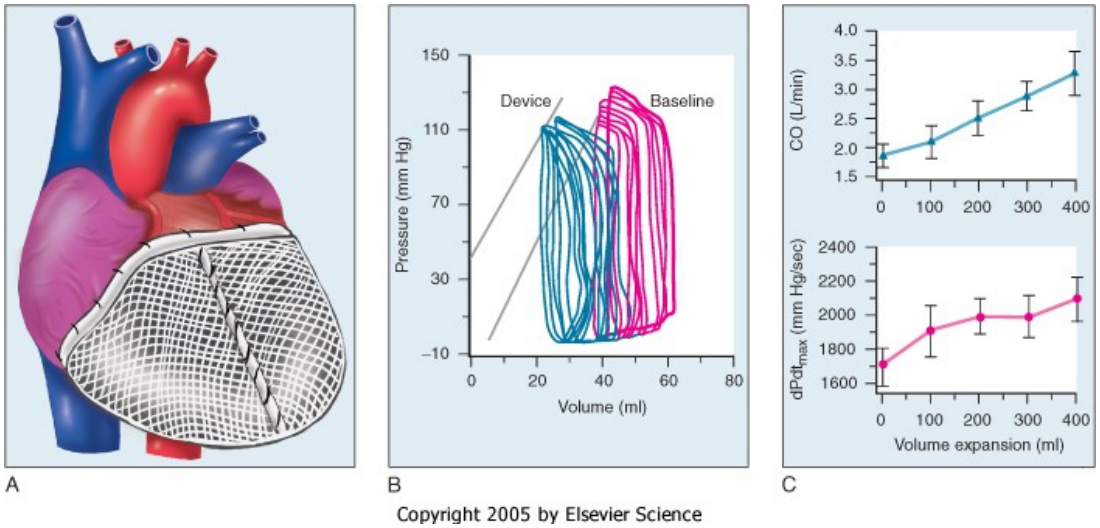








Cardiac Support Device



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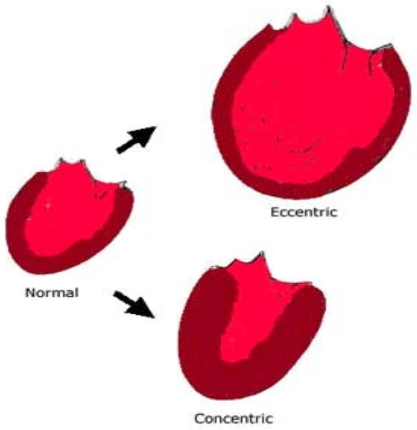

Figure 20-1

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

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Overview of the pathophysiology of myocardial remodeling

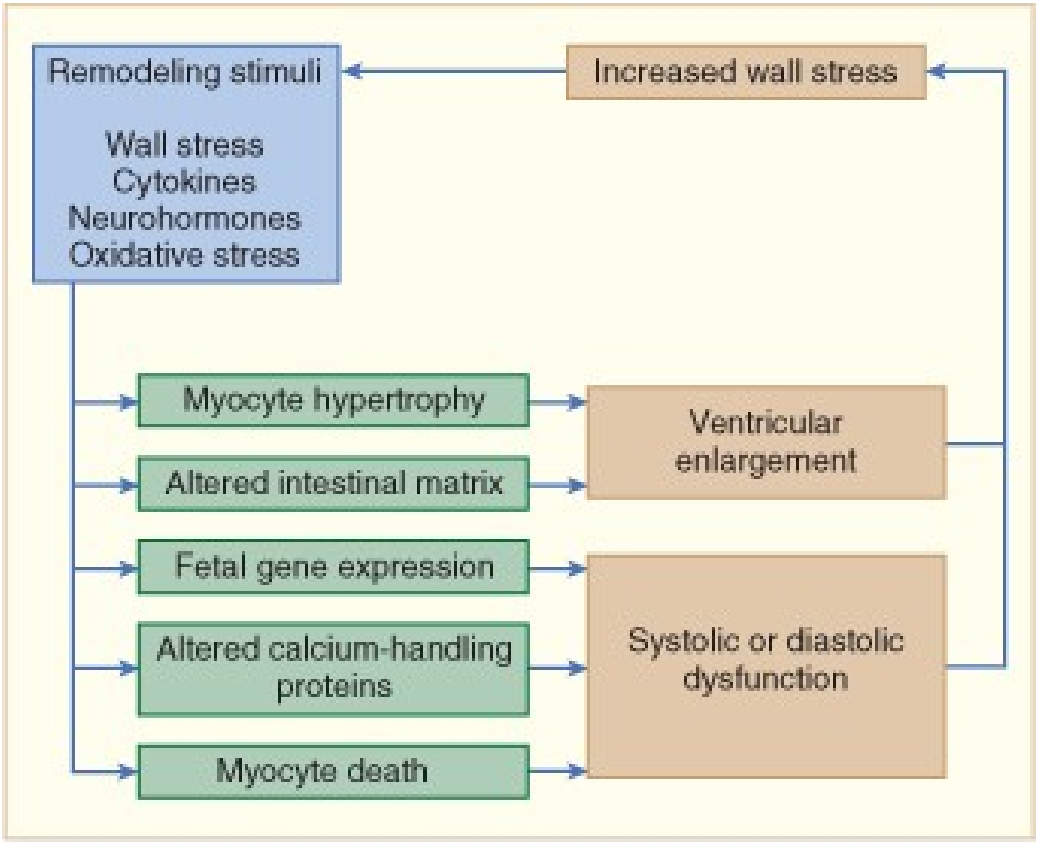

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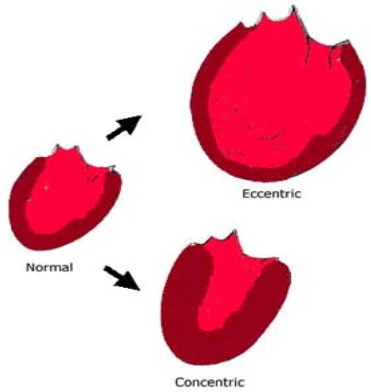
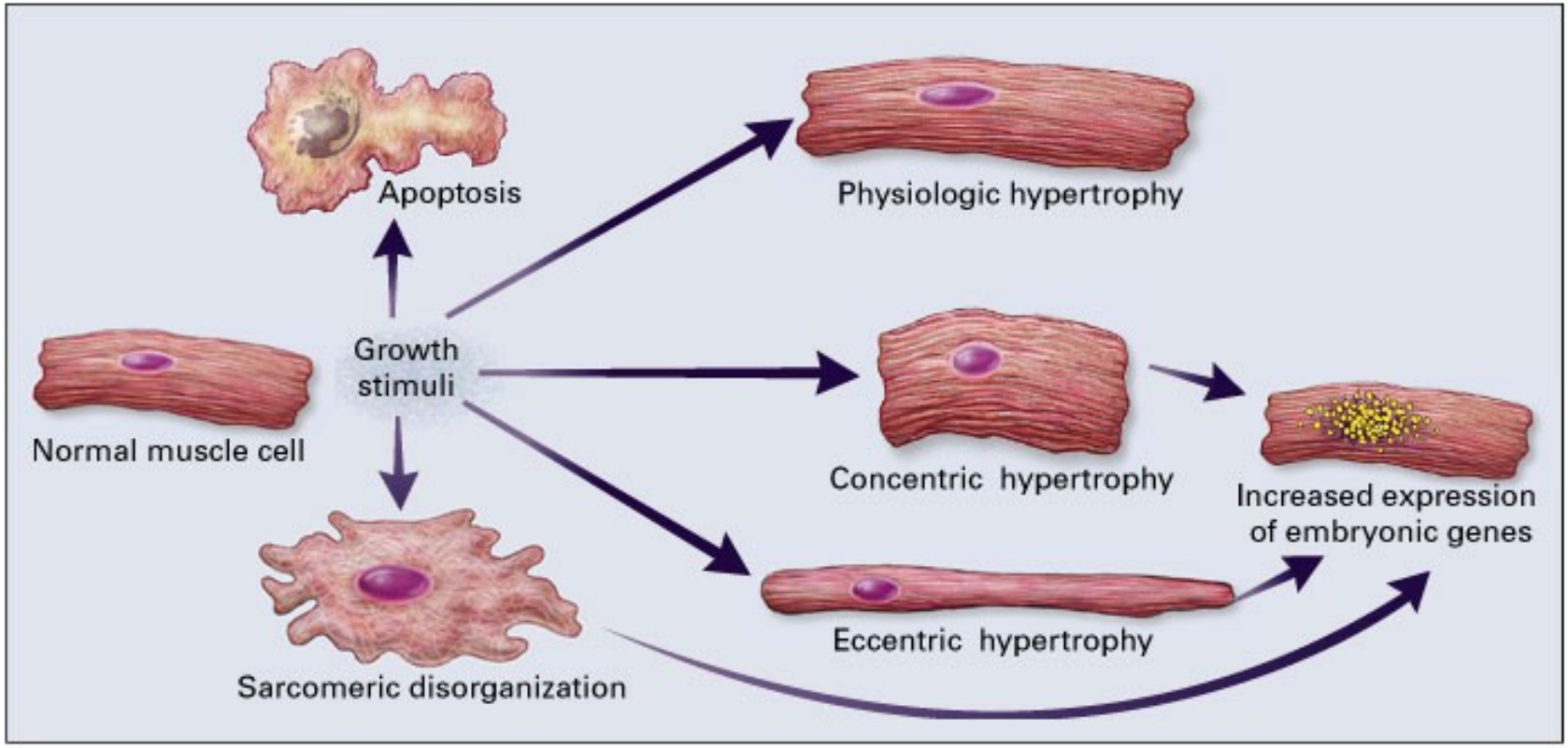
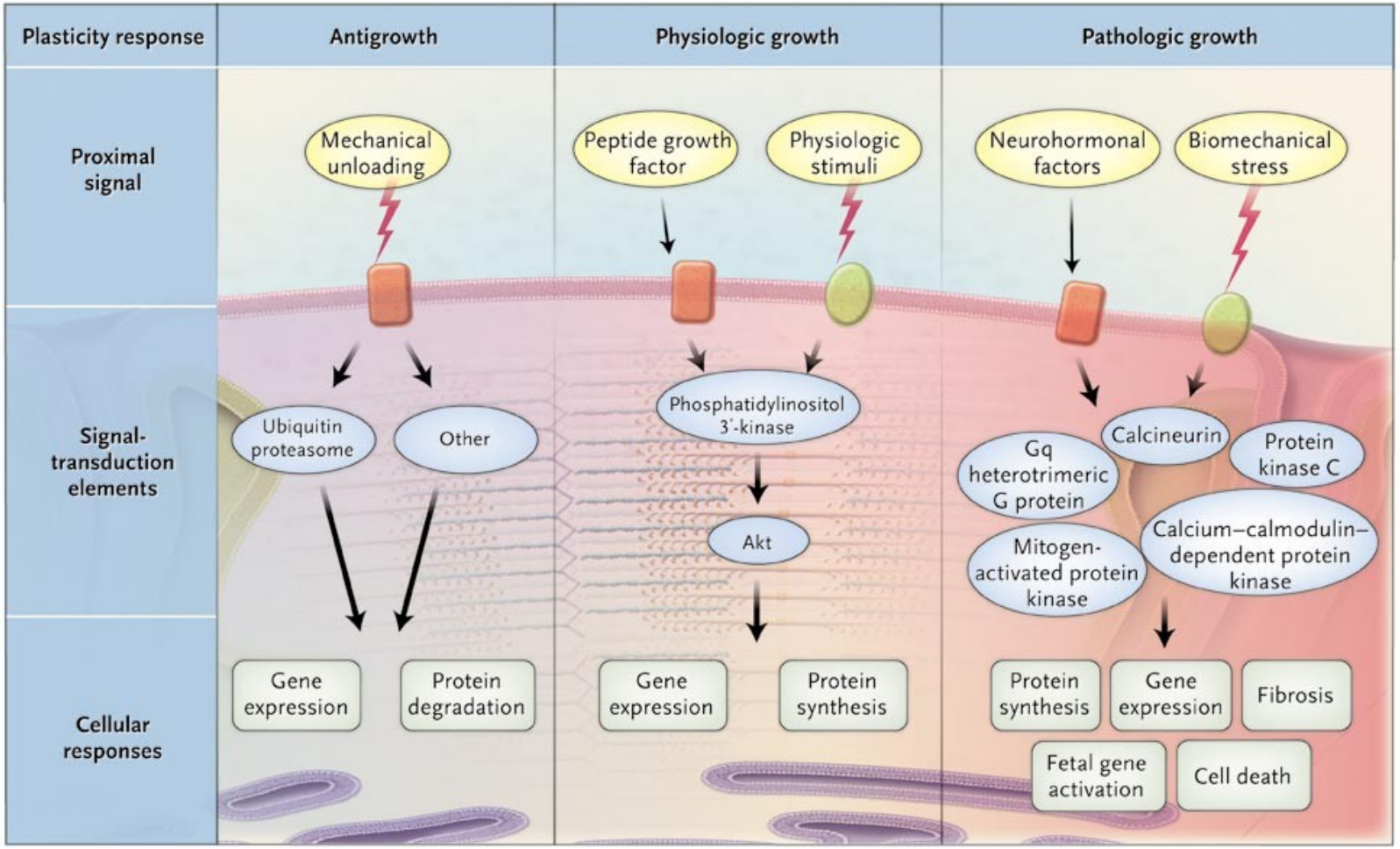
Figure 21-10

Cellular Hypertrophy



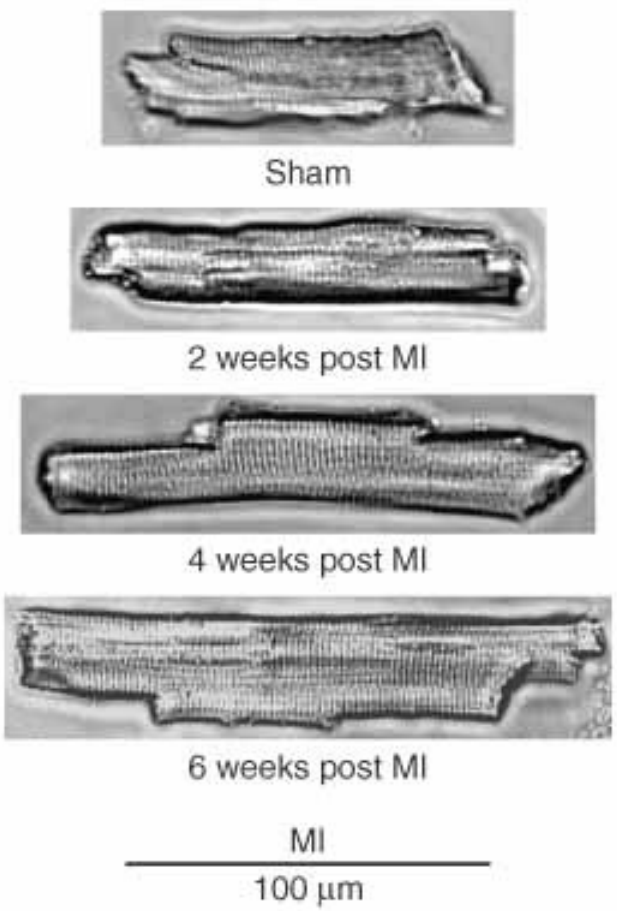


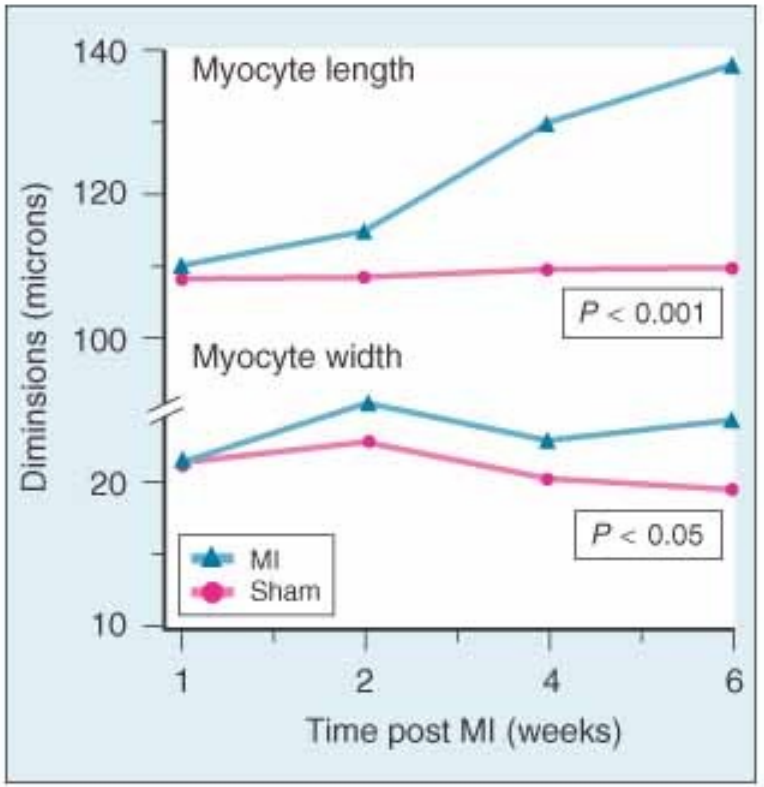
Extracellular Signals Triggering Intracellular Events in the Cardiac Myocyte



Hill and Olson 358 (13): 1370, Figure 4 March 27, 2008

Cardiac myocyte remodeling
Increased myocyte length and width





cardiac hypertrophy

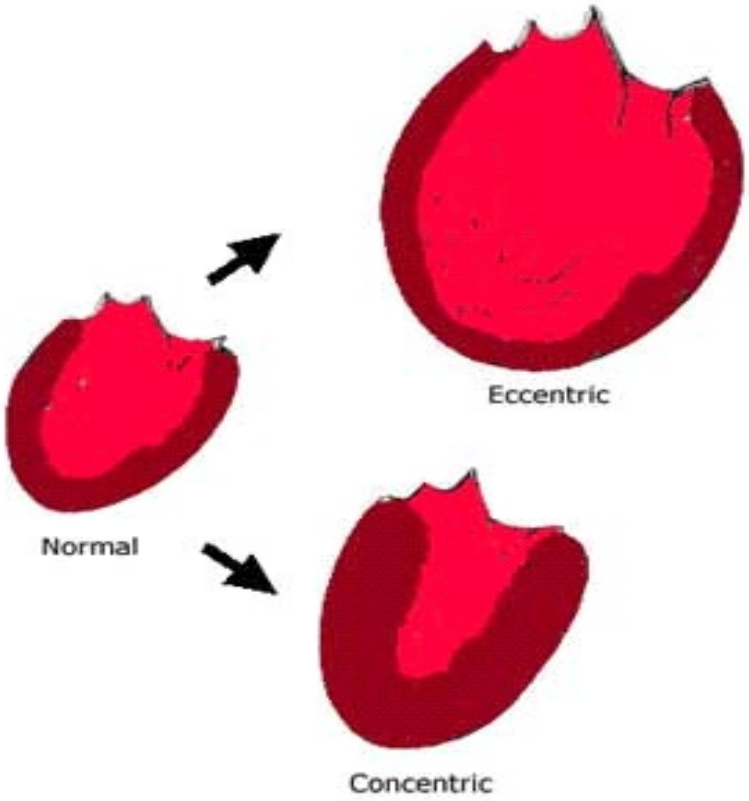
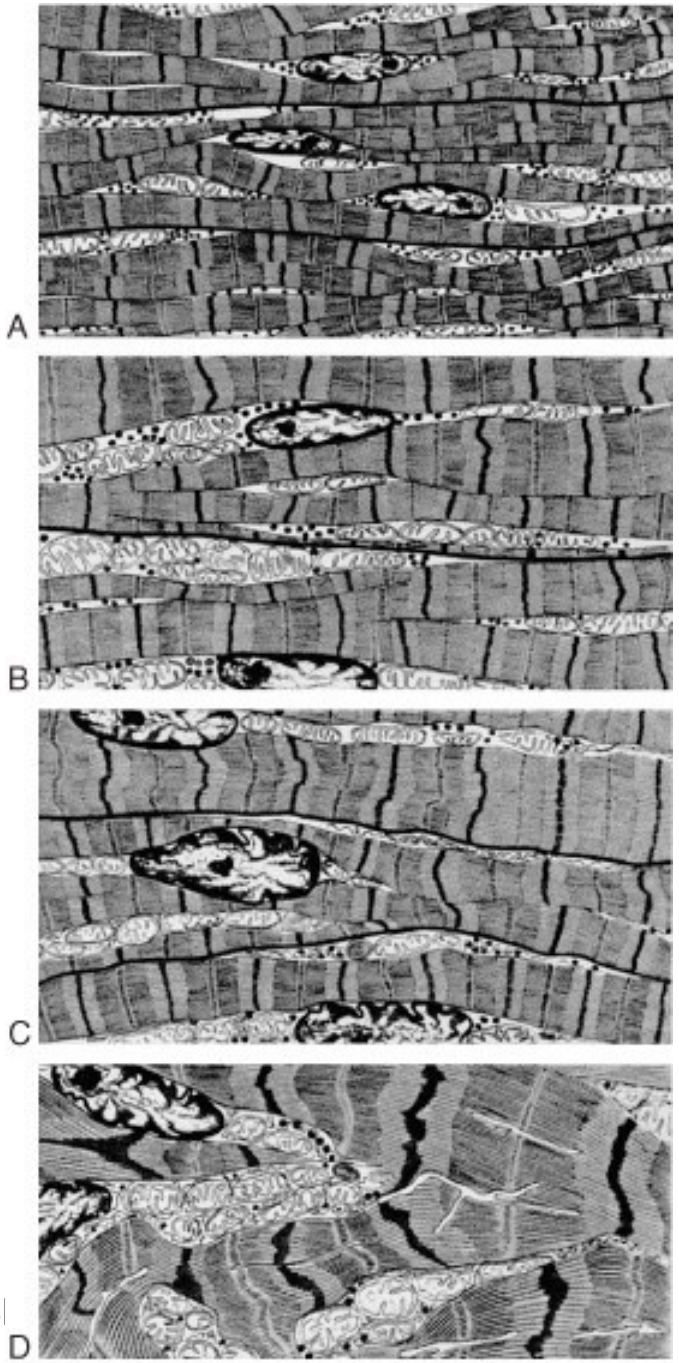


Figure 21-8



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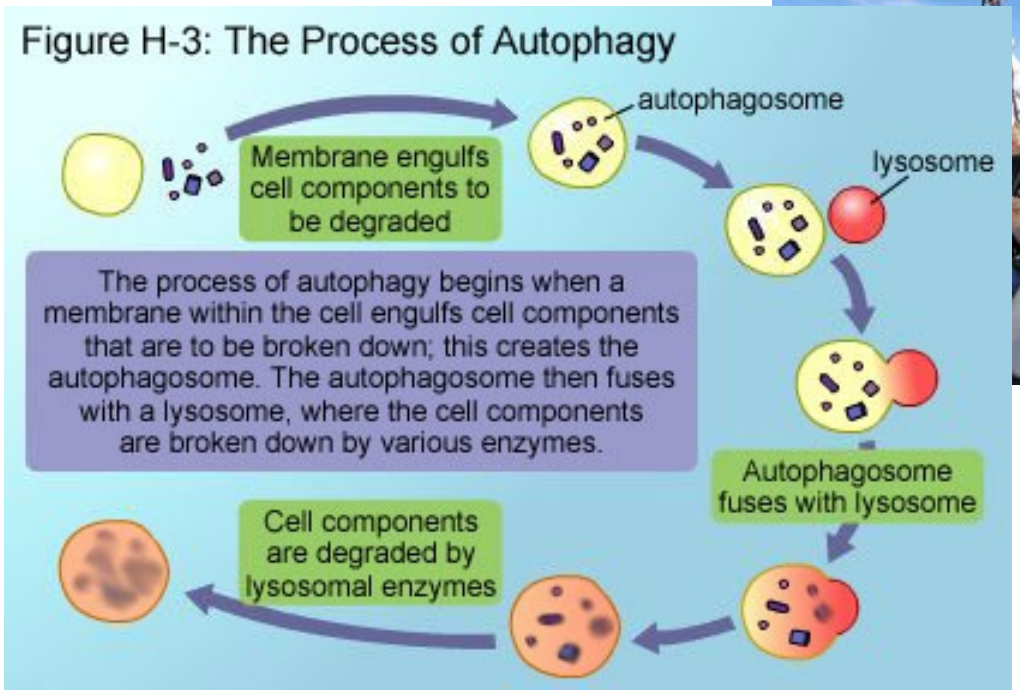
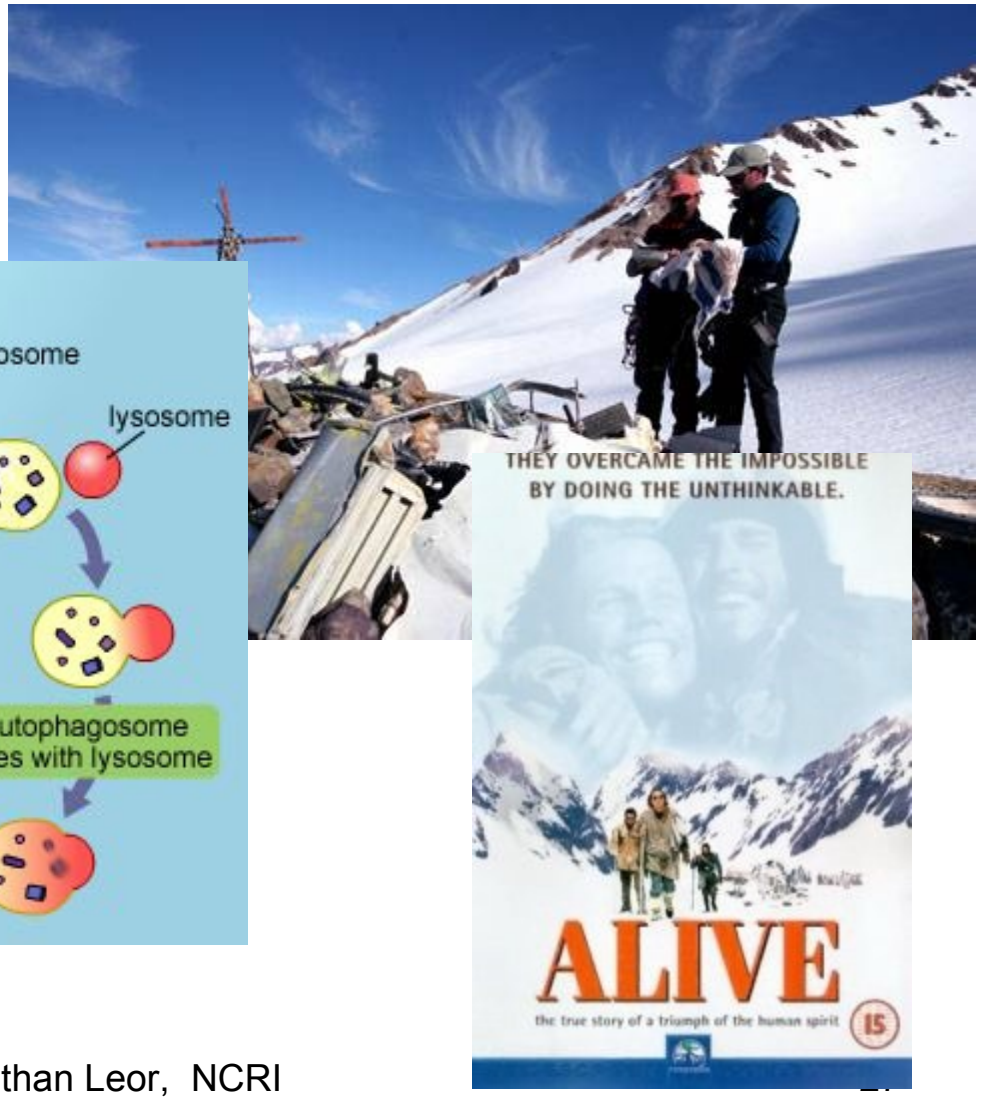
Autophagy





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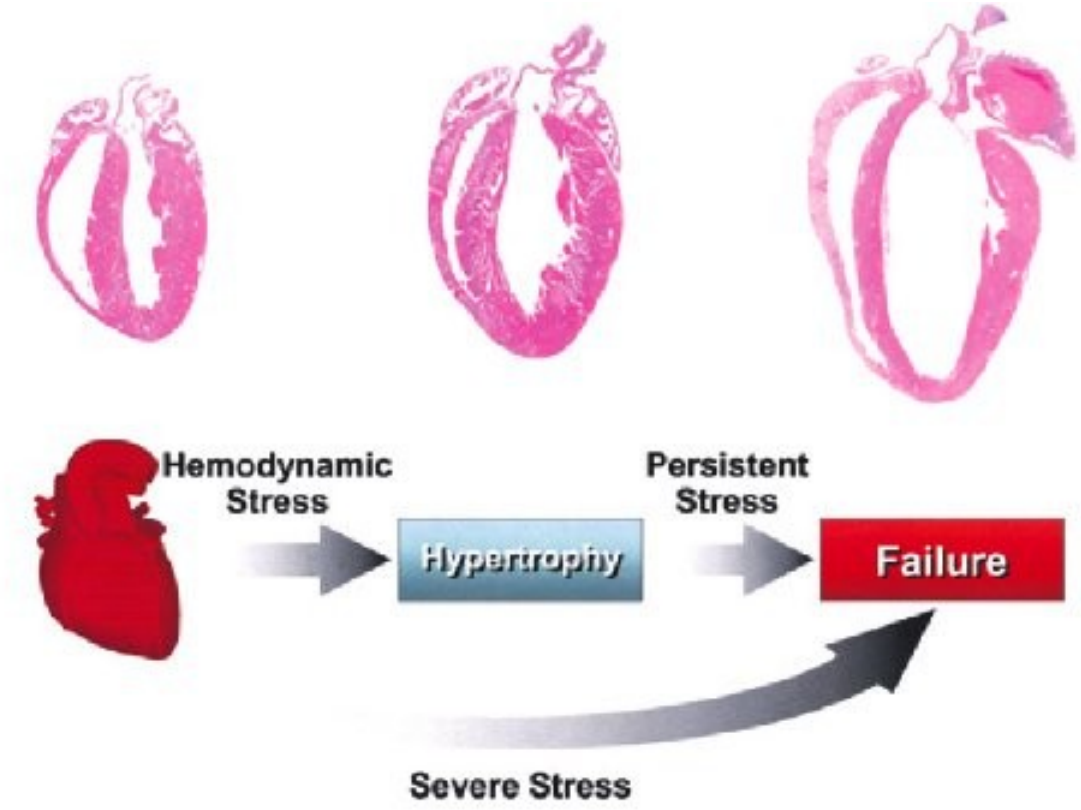
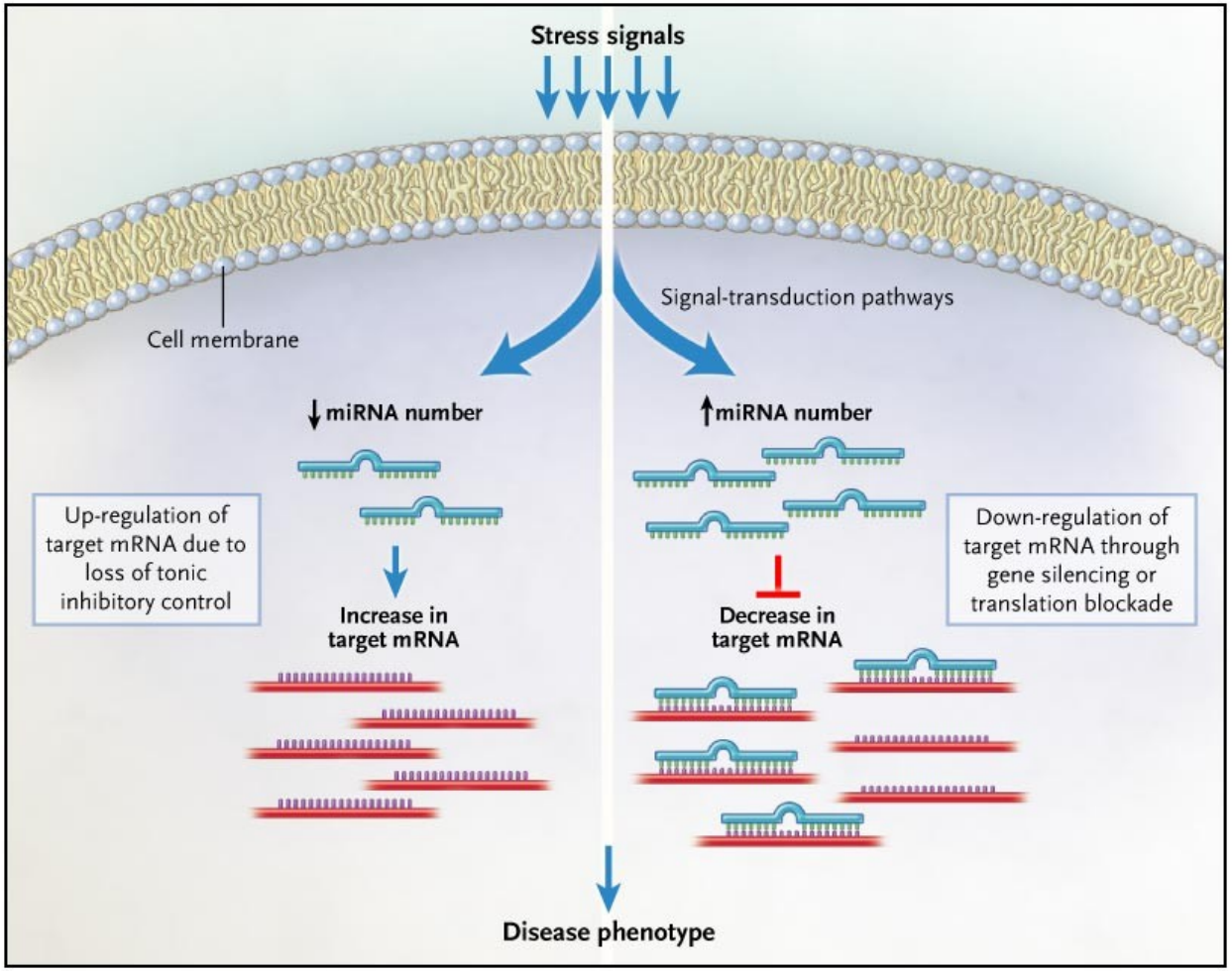
Small RNAs in a big heart

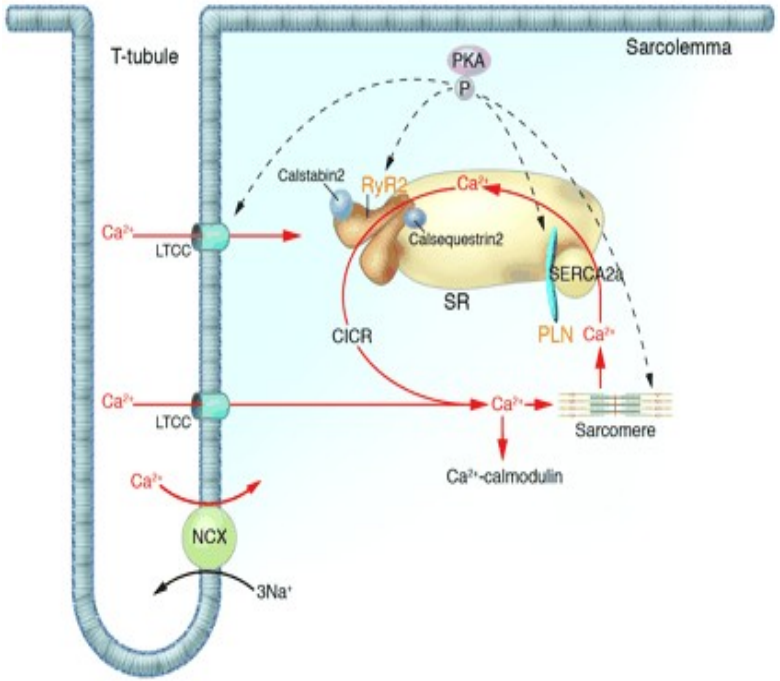


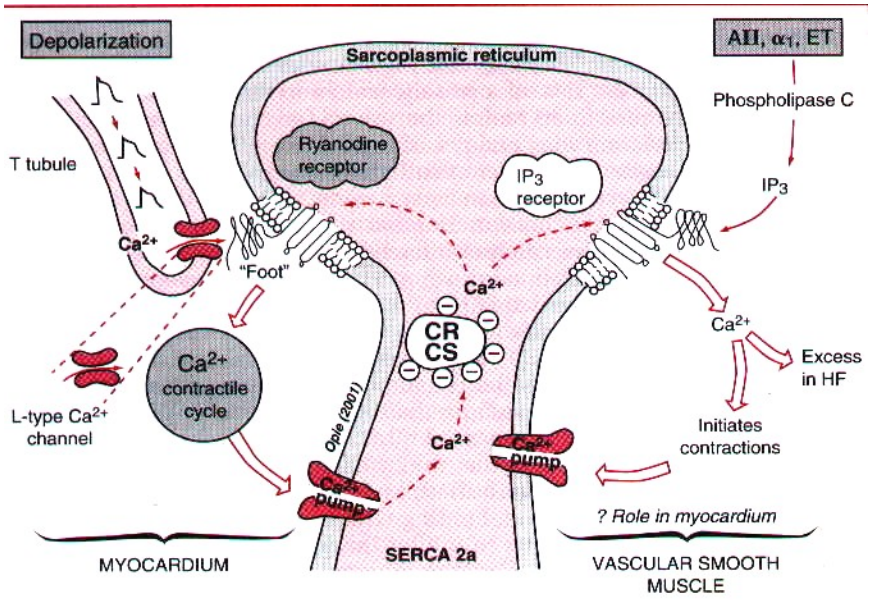
MicroRNAs as Mediators



Mann D. N Engl J Med 2007;356:2644-2645

Human mutations affecting Ca2+ cycling proteins





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

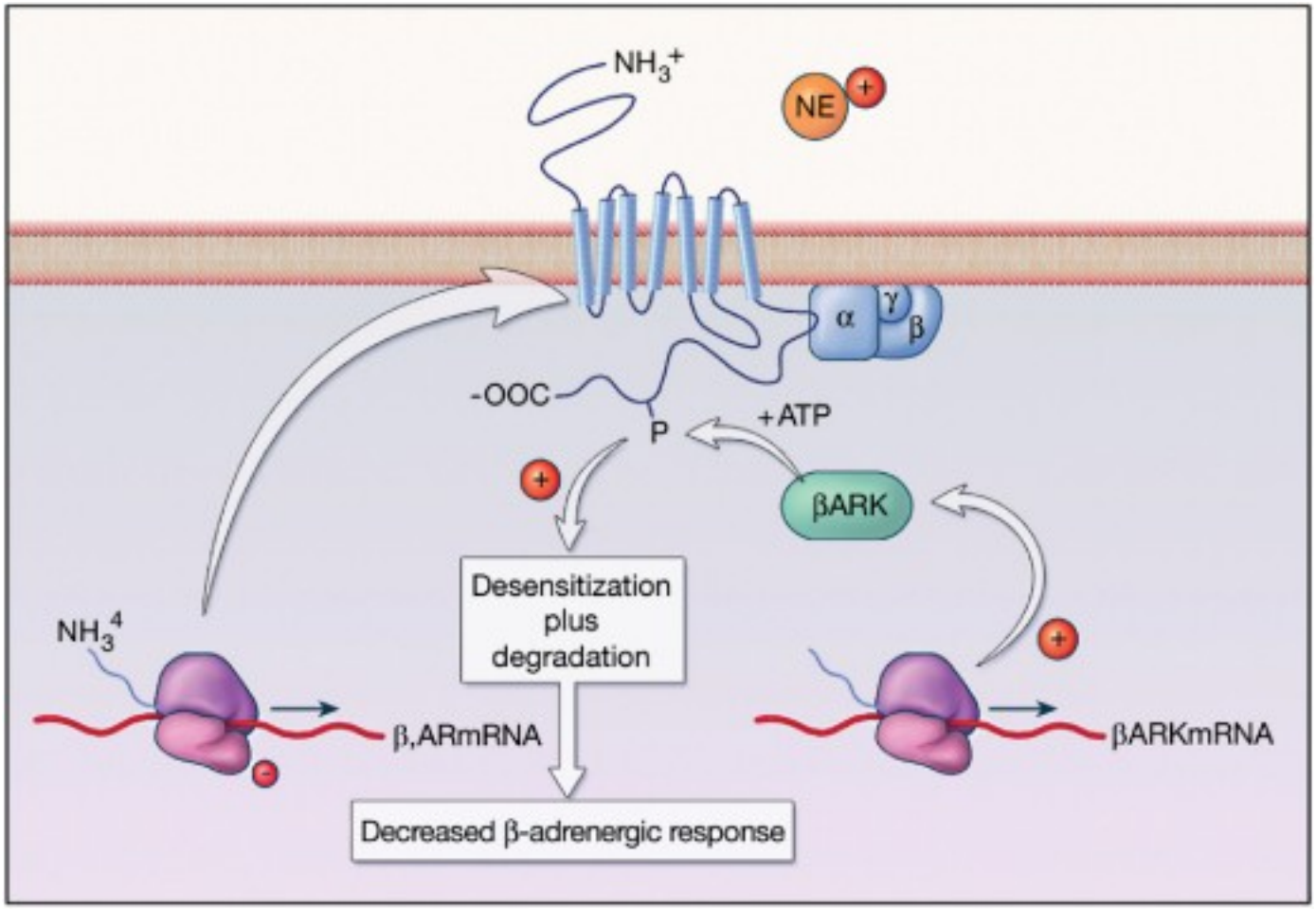
Braunwald p 453

Calcium Hemostasis in Failing Human Myocardium

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

From Braunwald pp

Alterations in beta-adrenergic pathways in the failing heart



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Braunwald Table 29-5

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

Target	Function
Beta-adrenergic receptor kinase inhibitor (βARKct)	Inhibits phosphorylation of β-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_1 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 Infl ammatory Mediators on Left Ventricular Remodeling.

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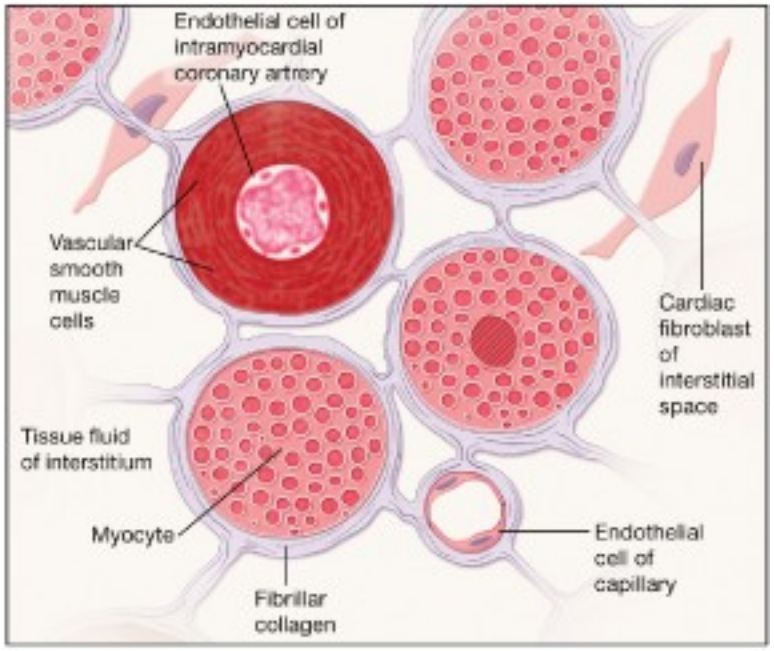
Braunwald Table 29-6

Effect of Gene Polymorphisms on the Pharmacological Treatment of Heart Failure


THE
MATRIX
Believe the unbelievable.

Extra Cellular Matrix



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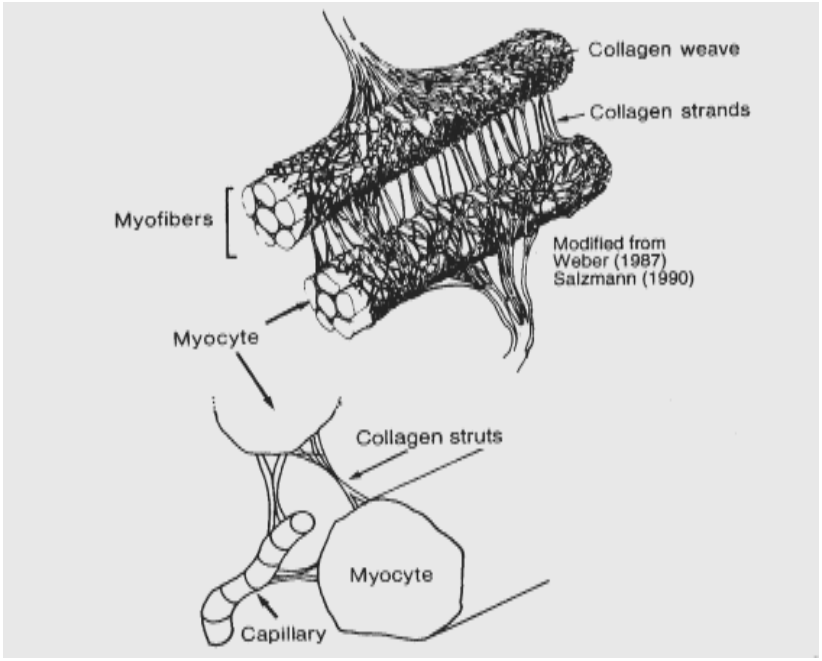
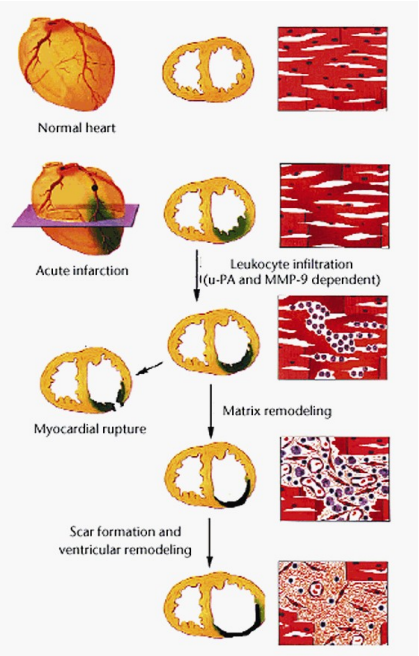
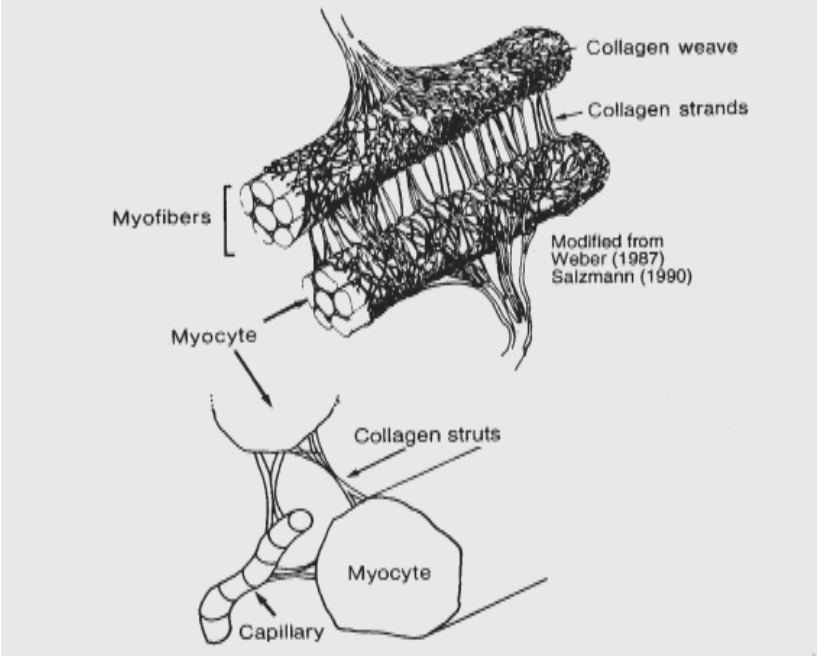


MMP activity site





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

The regulation of extracellular matrix degradation

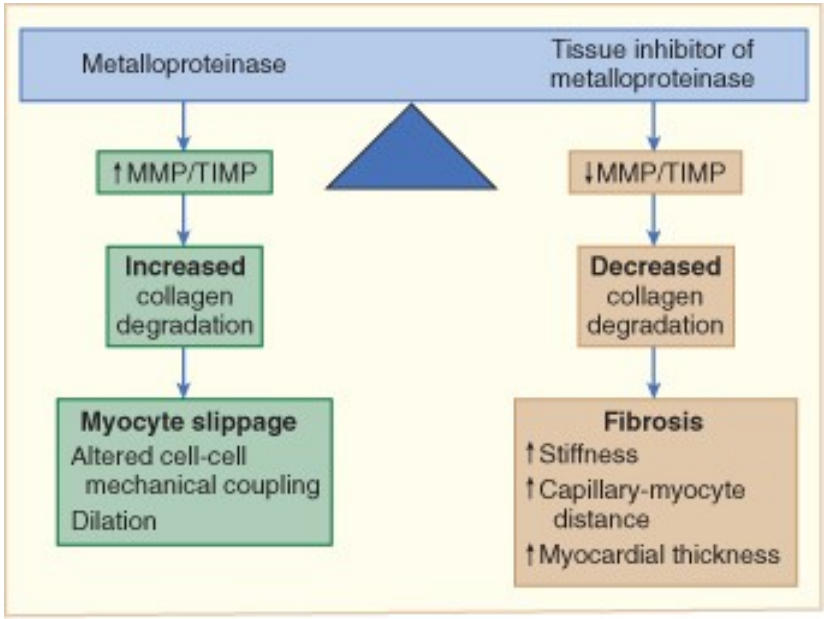


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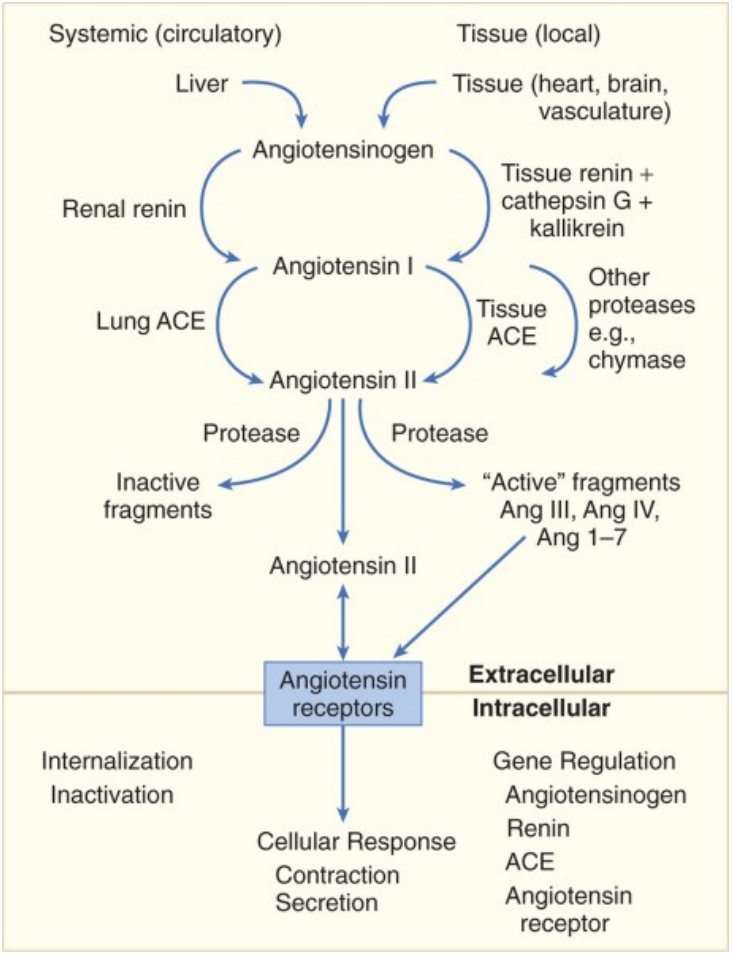
Figure 21-18

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)

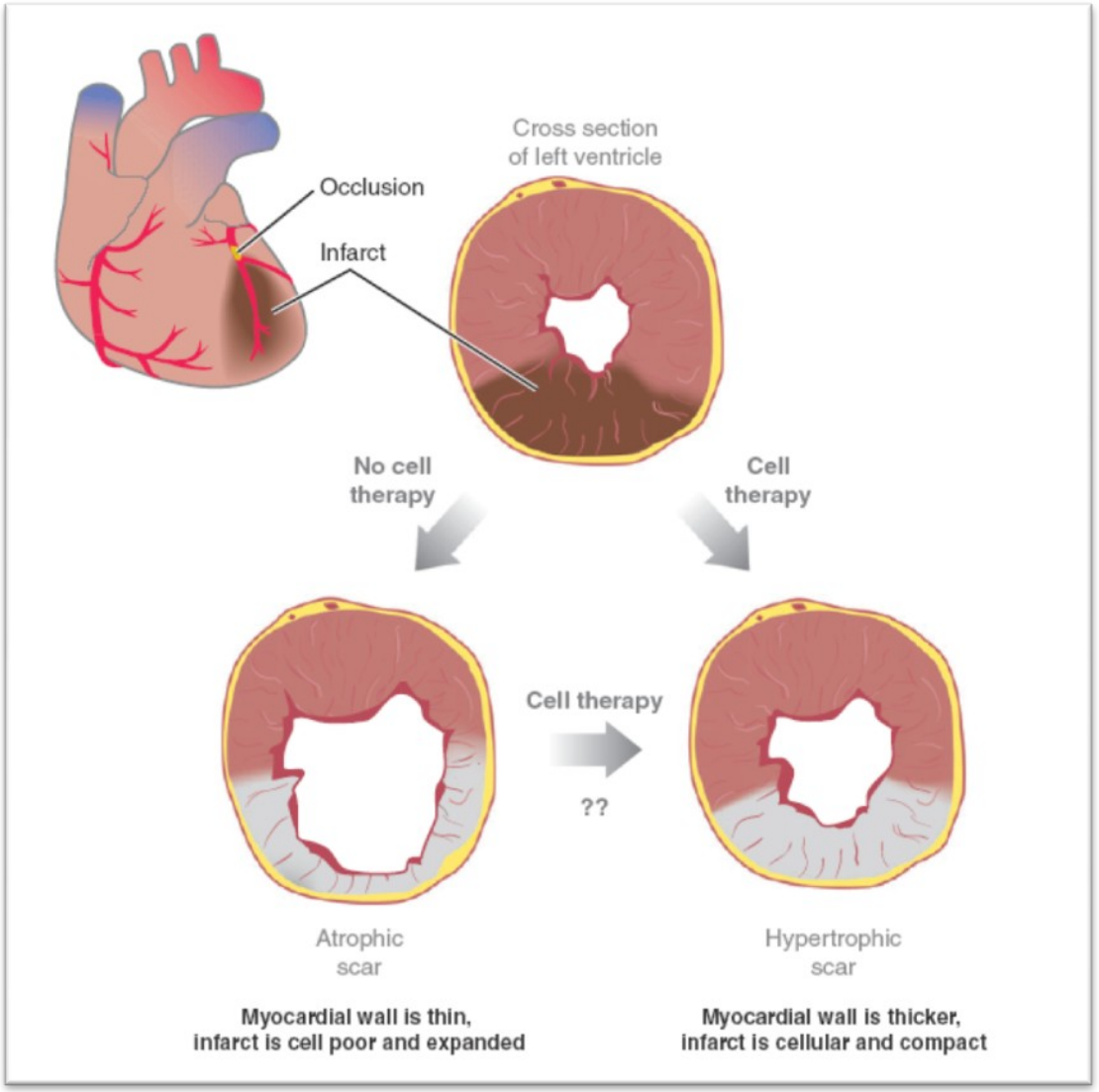
1. Continued expansion of infarct zone
2. Dilation and reshaping of the left ventricle
3. Myocyte hypertrophy
4. Ongoing myocyte loss
5. Excessive accumulation of collagen in the cardiac interstitium

Table 22-5

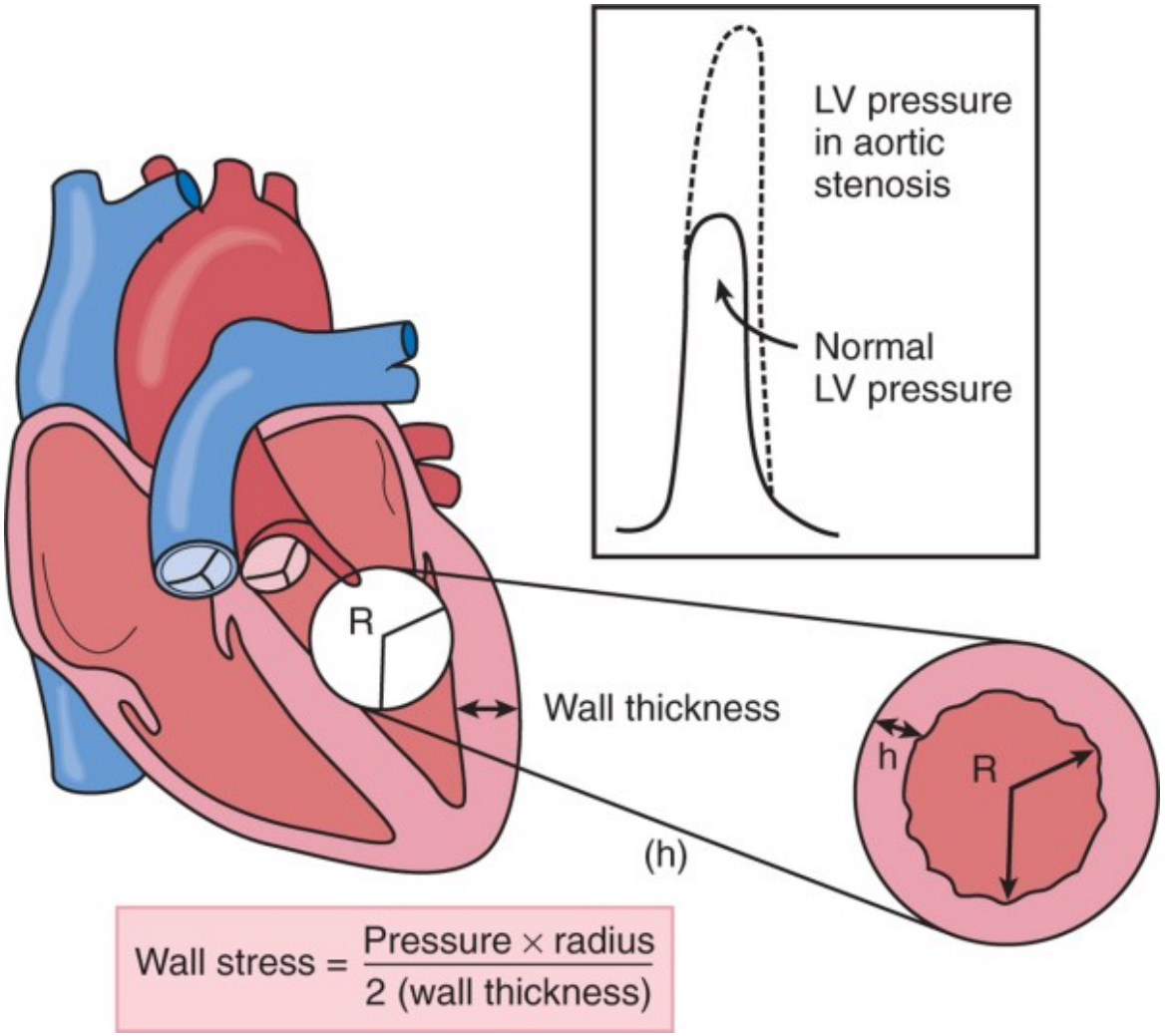
TABLE 22-5 -- Cellular and Molecular Determinants of Myocardial Recovery

	ACE Inhibitor	Beta Blocker	LVAD	CSD
Myocyte Defects				
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
Myocardial Defects				
Myocyte necrosis	Decreased	Decreased	Decreased	ND
Myocyte apoptosis	Decreased	Decreased	Decreased	Decreased
MMP activation	Decreased	Decreased	Decreased	Decreased
Fibrosis	Decreased	Decreased	Decreased	Decreased
LV Dilation	Stabilized	Decreased	Decreased	Decreased

Cell therapy for heart repair



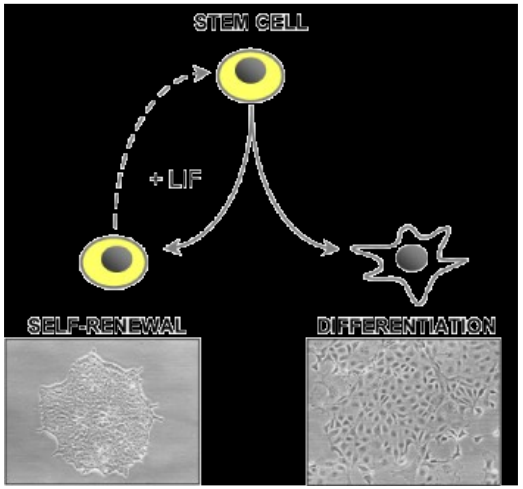
The rationale

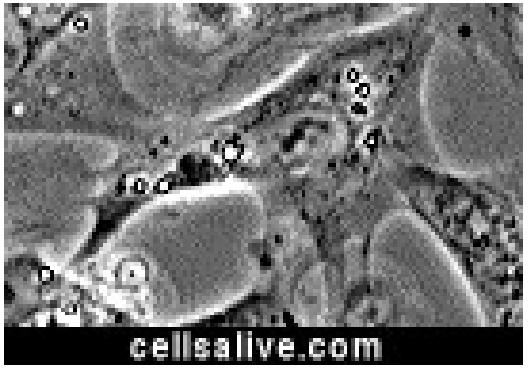


$$\text{Wall stress} = \frac{\text{Pressure} \times \text{radius}}{2\ (\text{wall thickness})}$$

Stem Cell

- Self renewal
- Give rise to specialized cells.





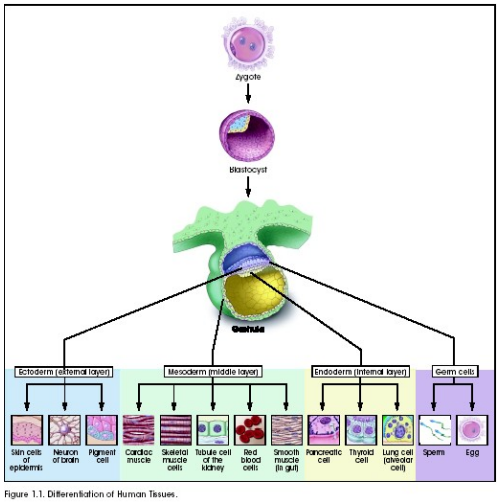
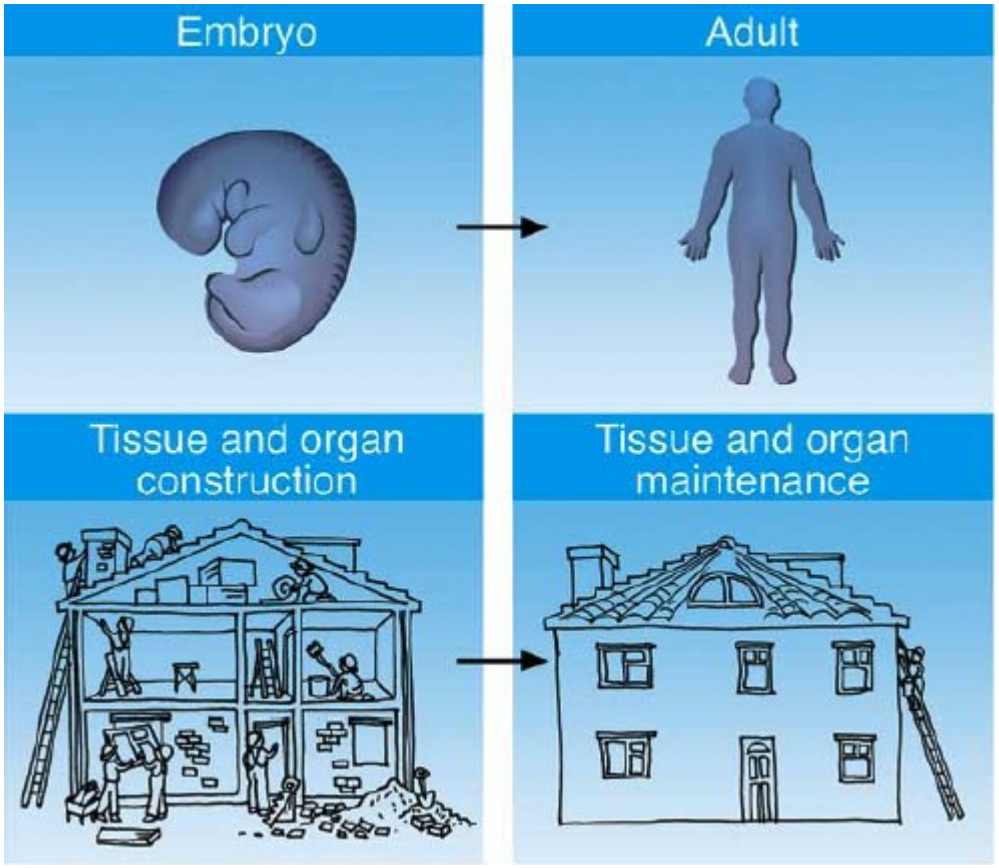


Figure 1.1. Differentiation of Human Tissues.

Embryonic and Adult Stem Cells



Myocardial repair

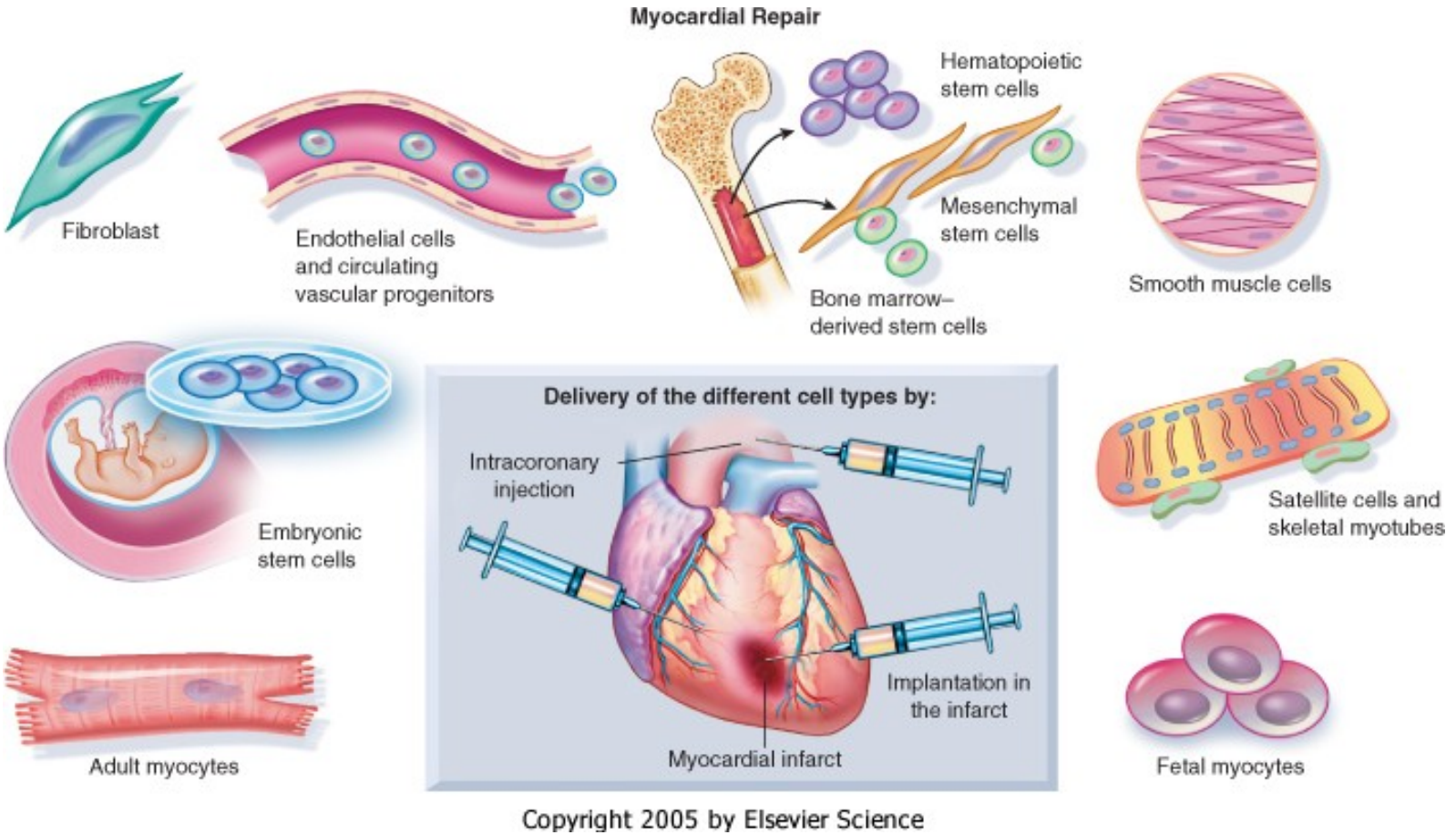


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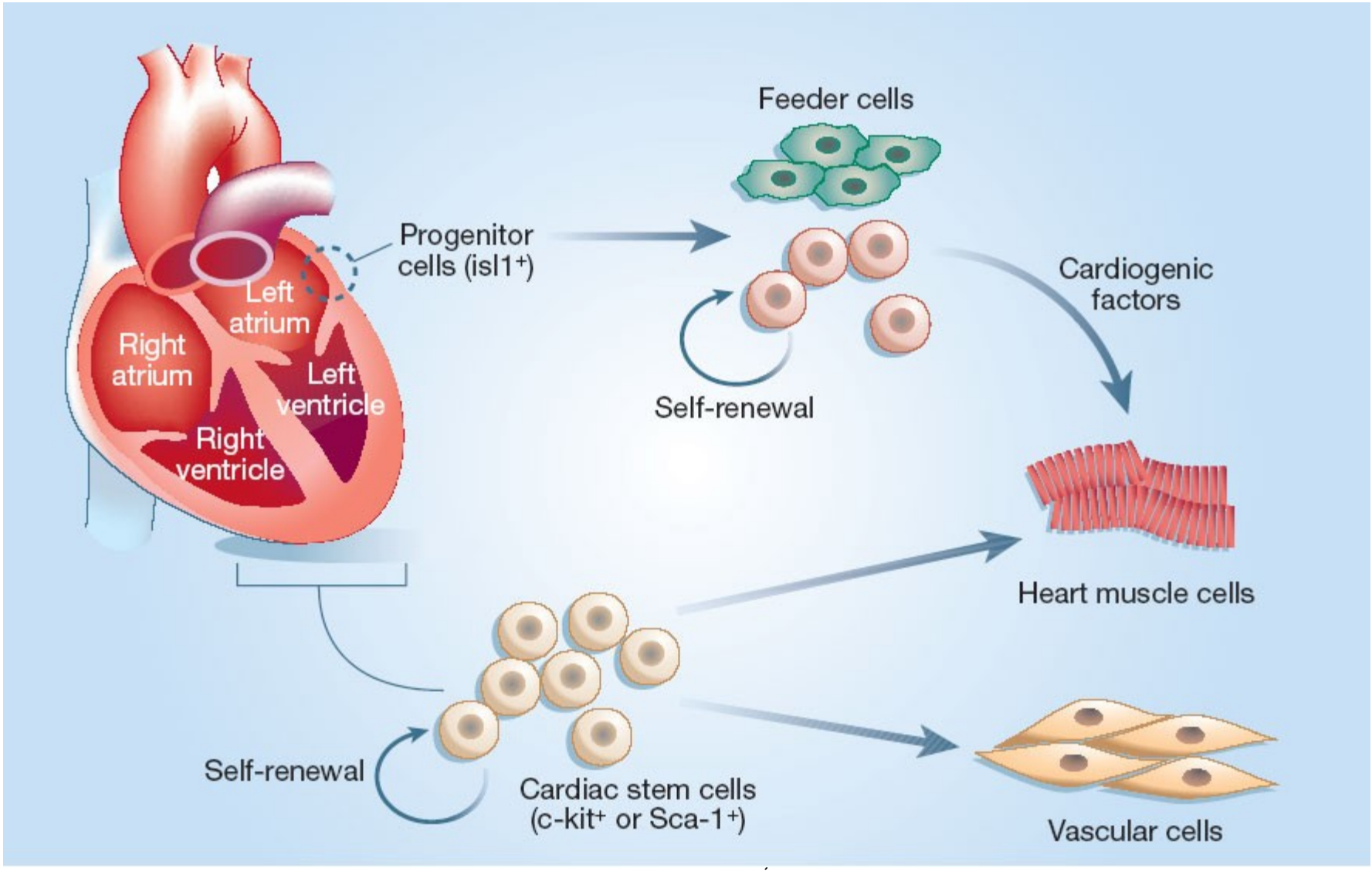
Figure 71-1

Cardiac Stem cells



Induced Pluripotent Stem cells iPS

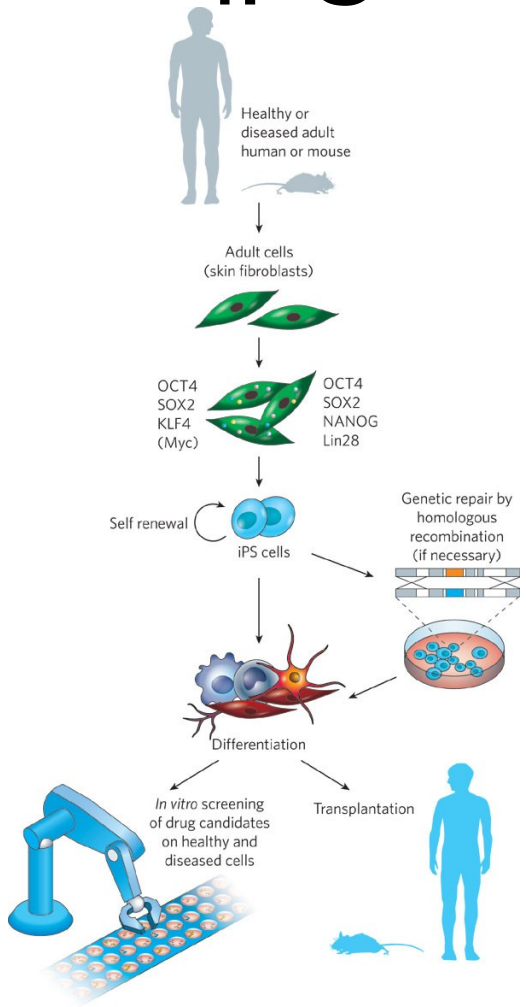
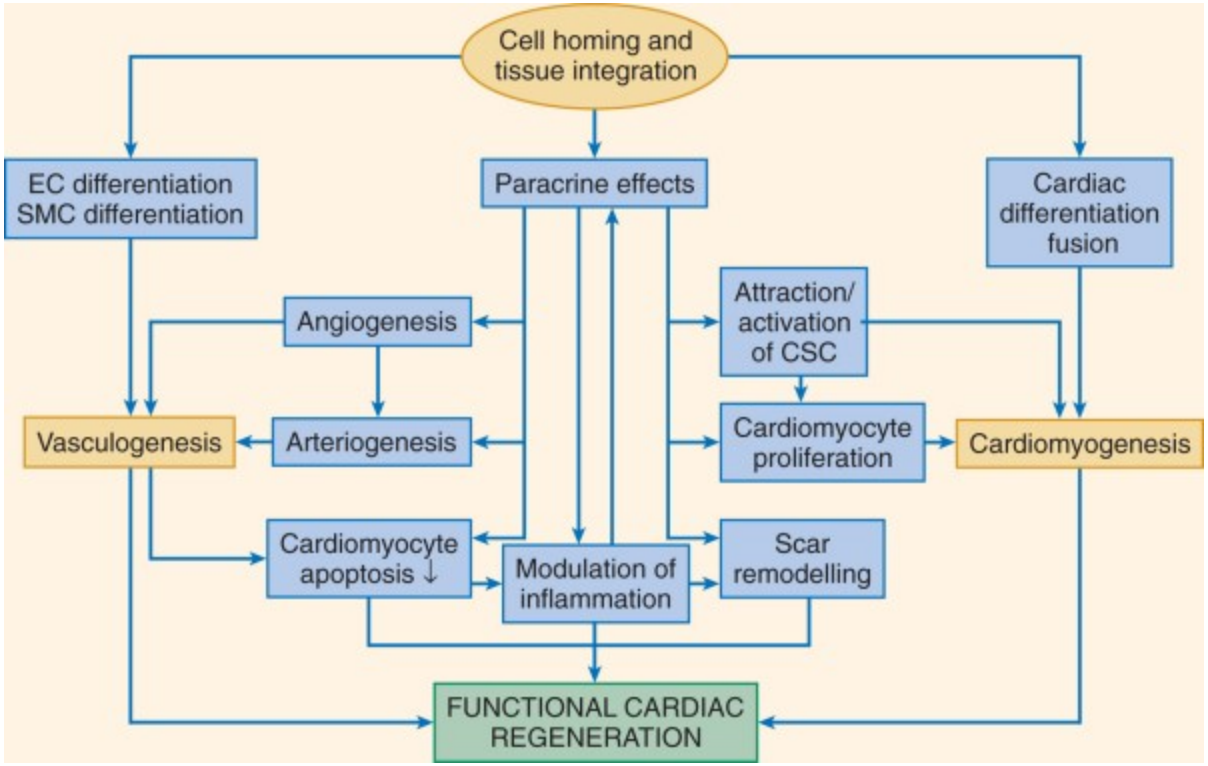
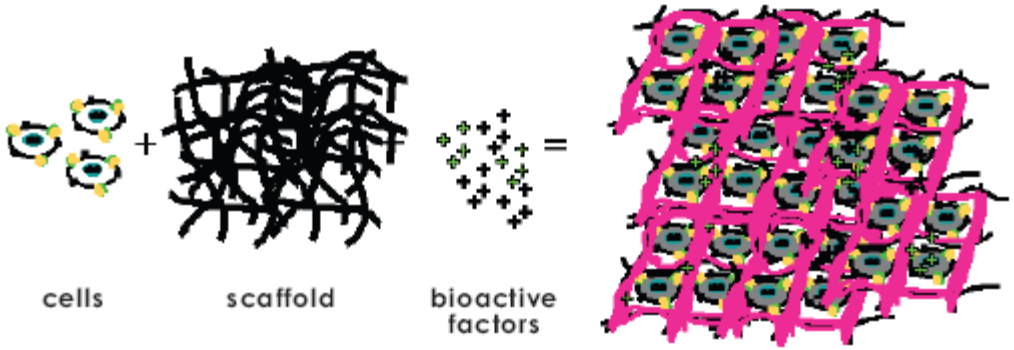
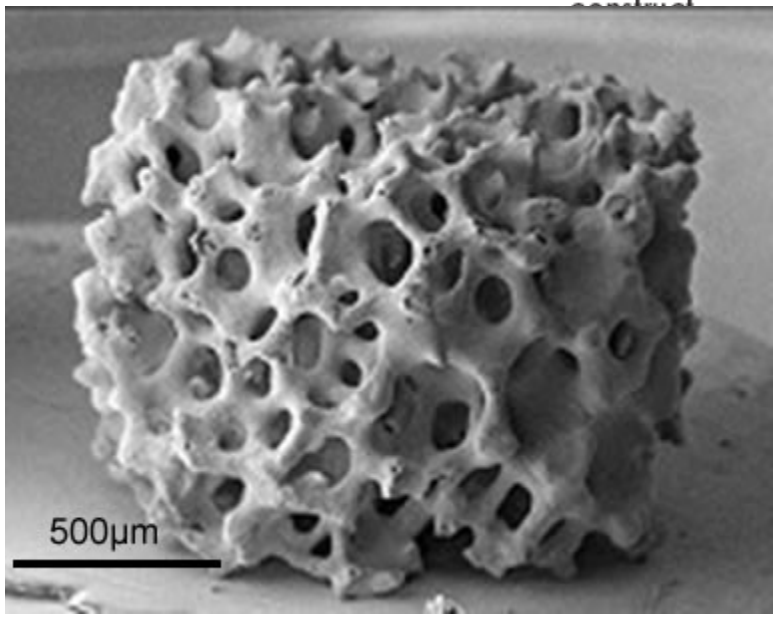


FIGURE 29-3 Proposed mechanisms of action of stem/progenitor cells in cardiovascular repair.

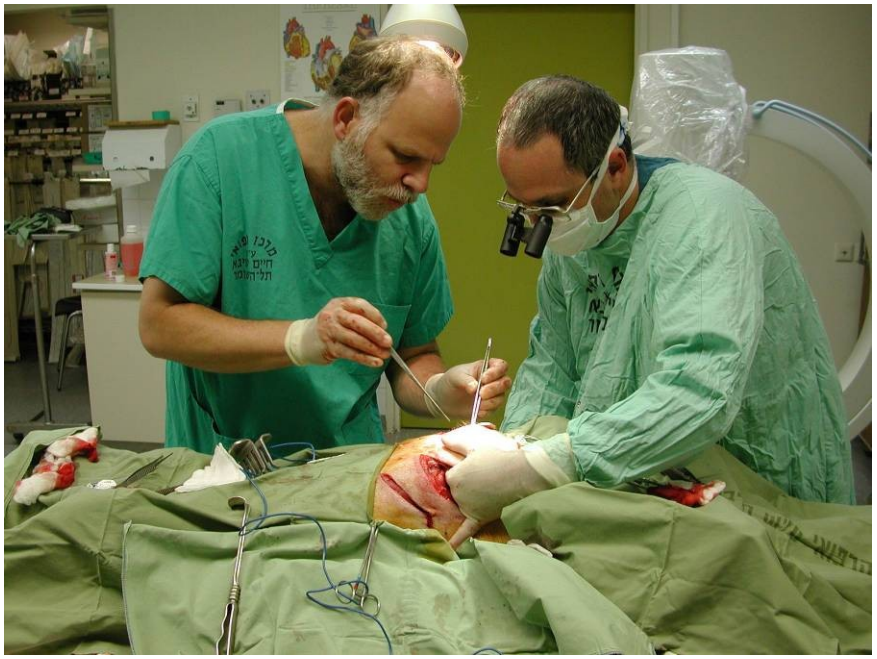


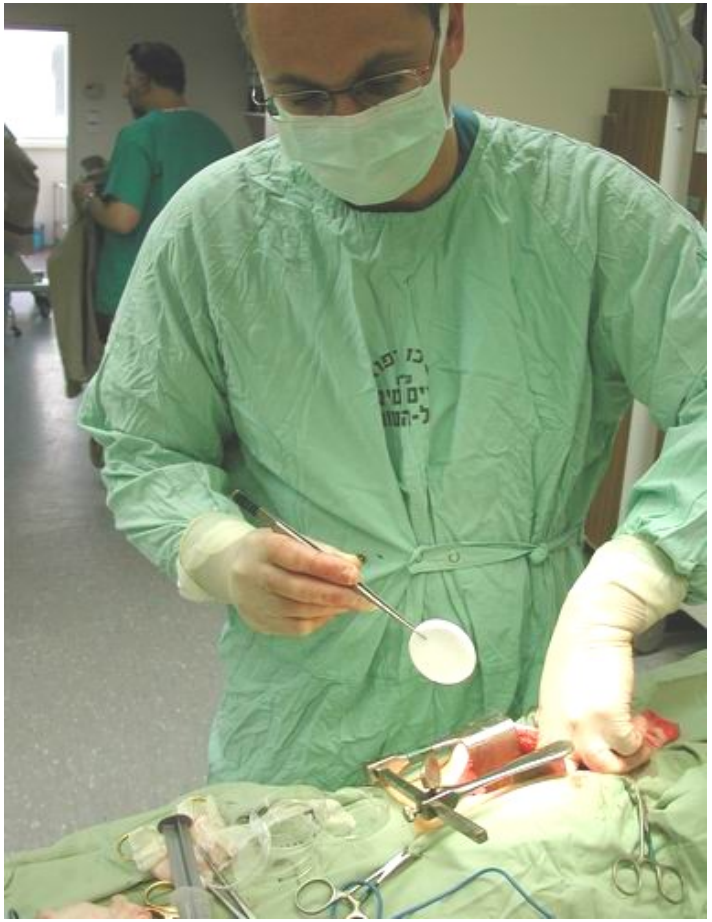
Cardiac Tissue Engineering





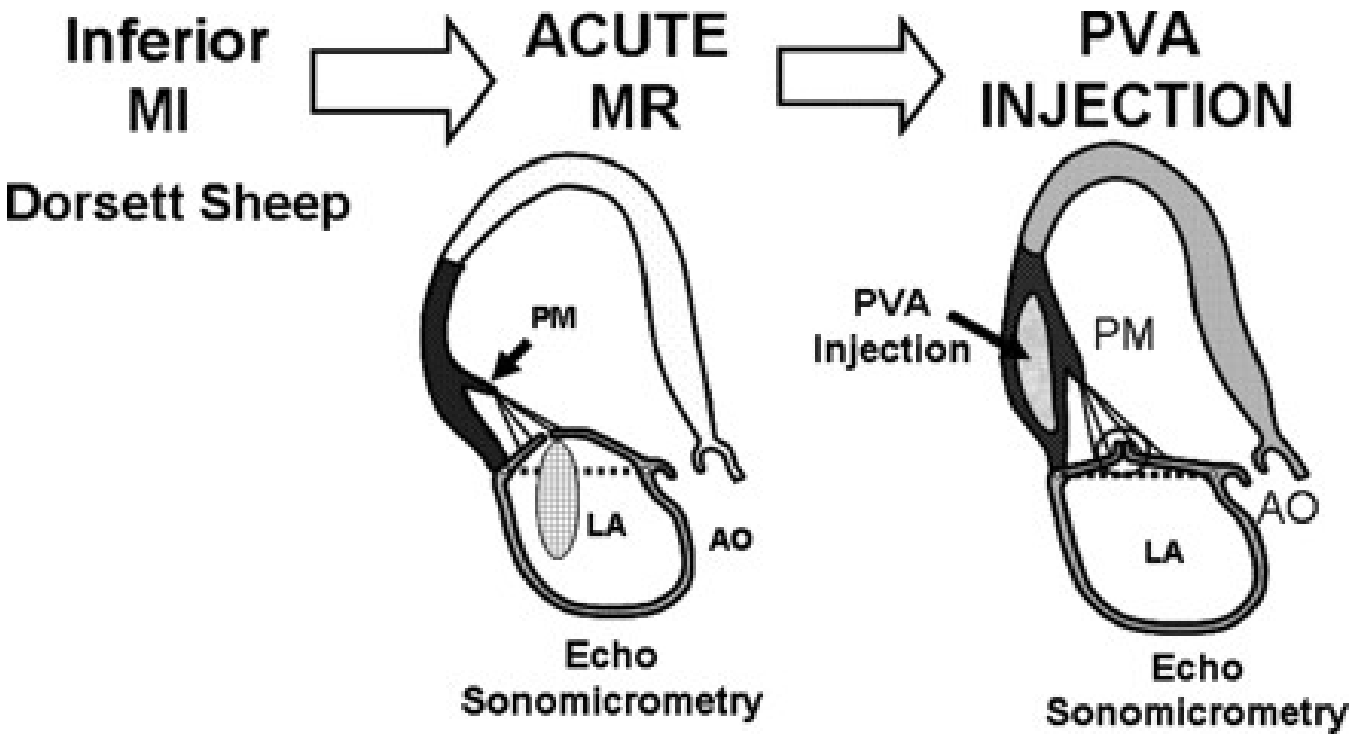
Cardiac tissue engineering in pig





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

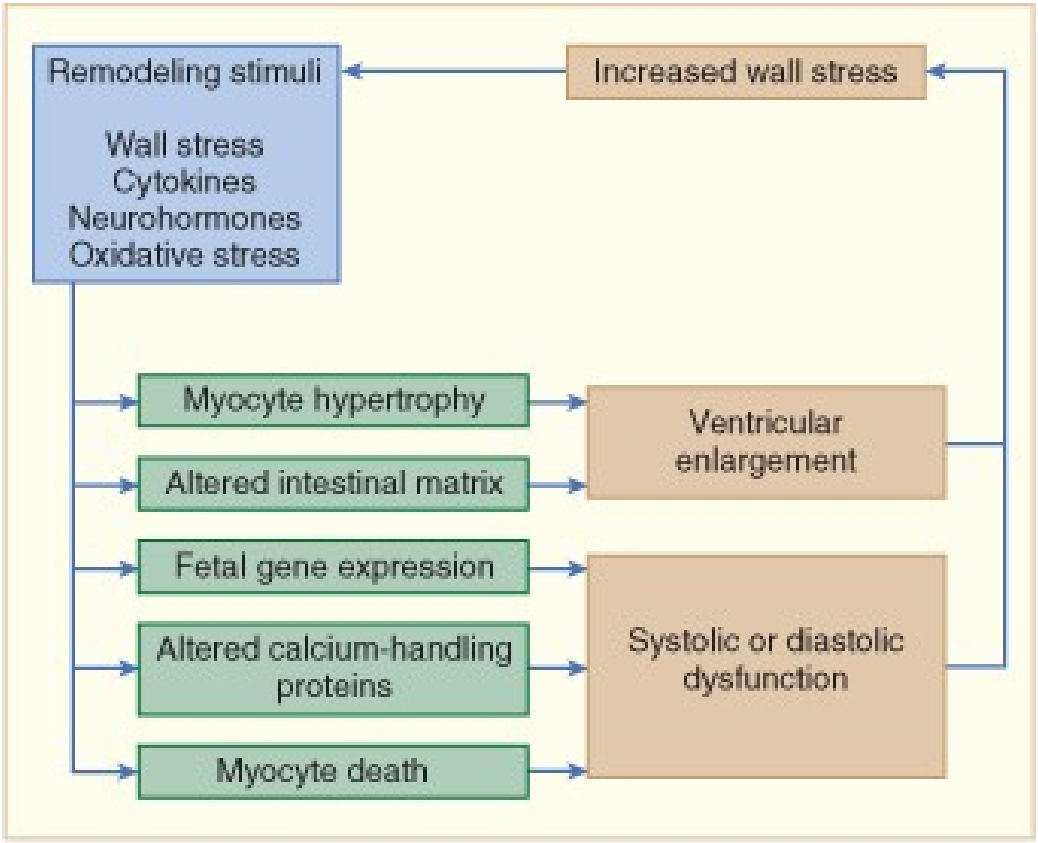


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Figure 21-10

שאלה

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

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

שאלה

מתן מעכבי ACE לרמודלינג של הלב יעכב הכל

למעט (סמן תשובה לא נכונה)

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

שאלה

- מיוציטים עלולים למות מכל הנ"ל למעט (תשובה לא נכונה):
  1. נקרוזיס
  2. אפופטוזיס
  3. אטופאגי
  4. אטרופי