

שינויים מולקולאריים ומבניים
באי ספיקת לב
אפשרויות לטיפול עתידי

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

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

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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."¹ It is often, but not always, caused by a defect in myocardial contraction, that is, by *myocardial failure*.^{2,3} 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 capacity⁴ or in which ventricular filling is impaired.¹ 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](#)).^{2,5-8} *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**



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Cardiac Plasticity

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

שאלה

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

1. טרופונין T
2. טרופונין I
3. נטרירורטיק פפטיד
4. קולגן

שאלה

מתן מעכבי ACE 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.

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.

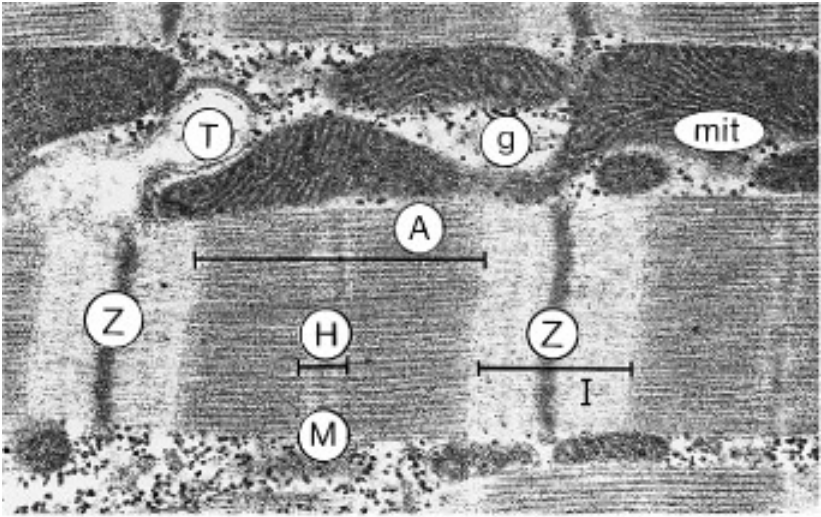
§Includes lumen (volume fraction).

†Mostly fibroblasts.

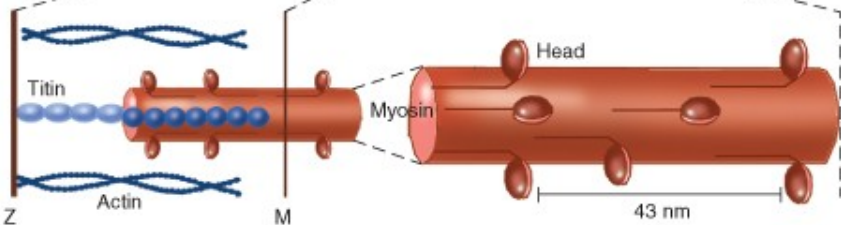
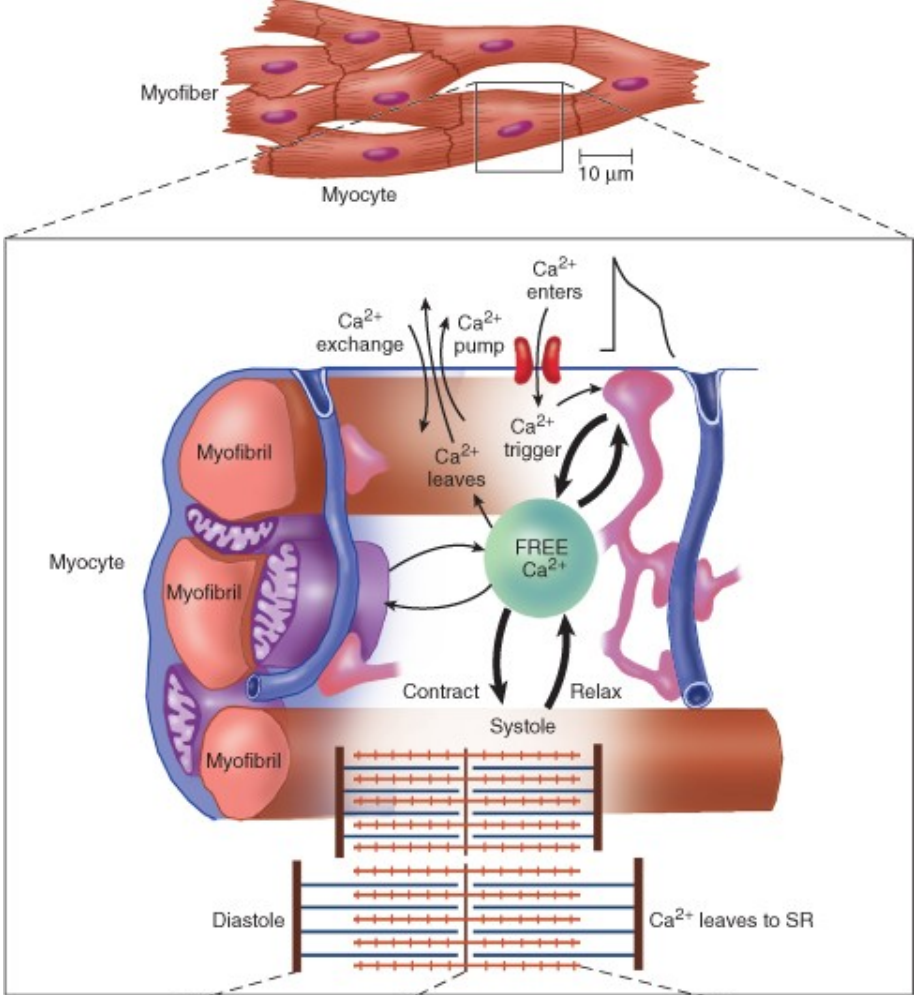
‡Fibroblasts as % of nonmyocyte fraction.

Jugdutt & al. Circulation 2003

The Sarcomere

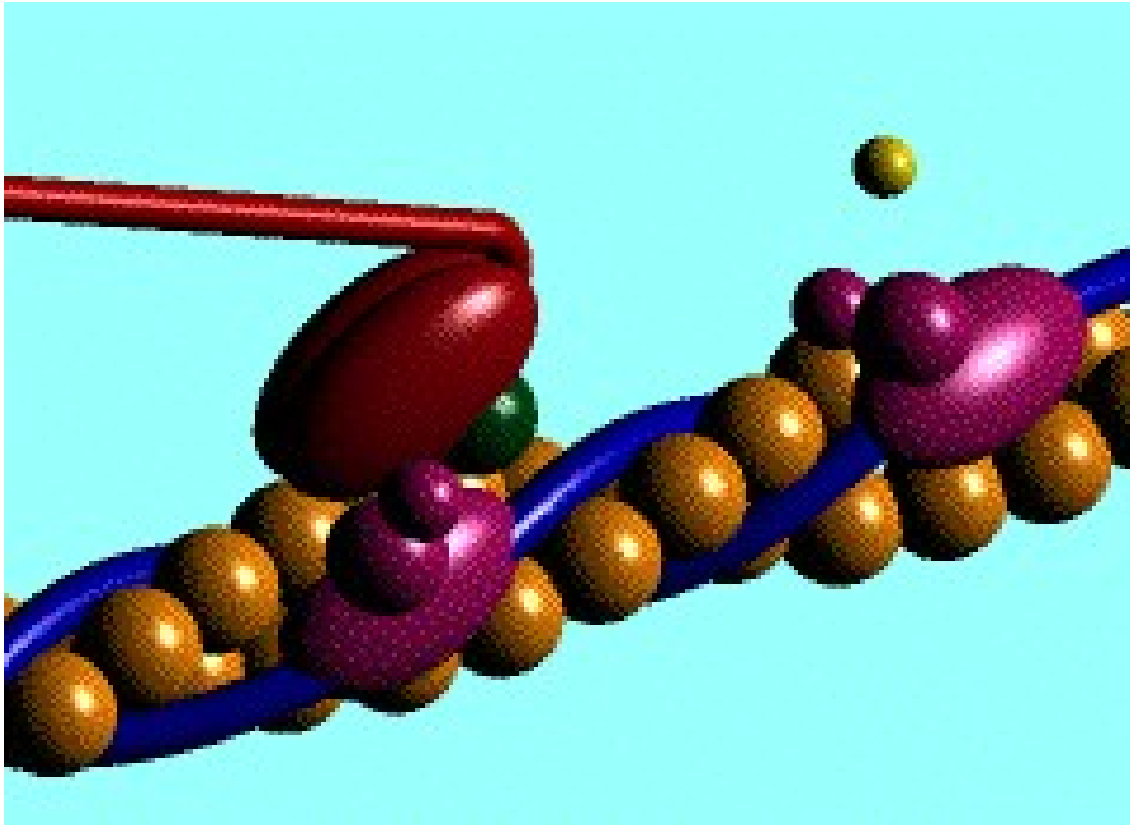


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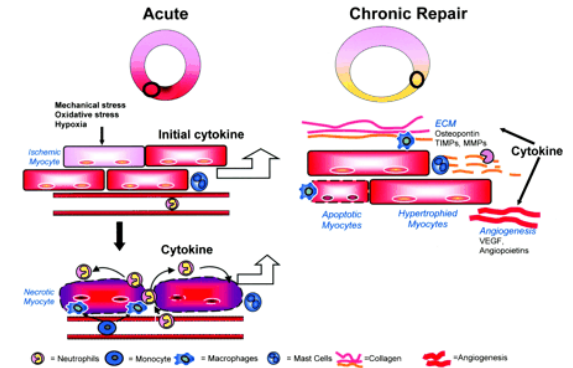


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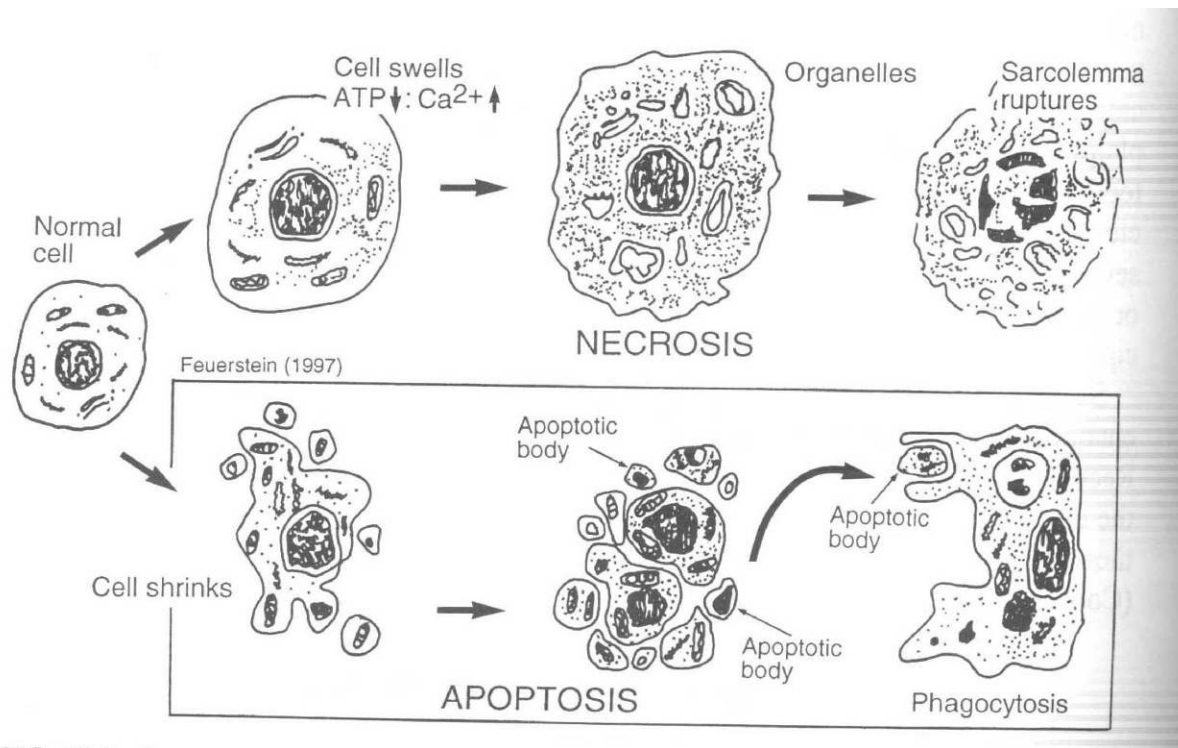
Figure 19-1 Braunwald 2005 Prof. Jonathan Leor, NCRI



Cardiac Damage and Repair



Apoptosis vs. Necrosis



Myocyte Cell Death

- Necrosis
- Apoptosis
- Autophagy

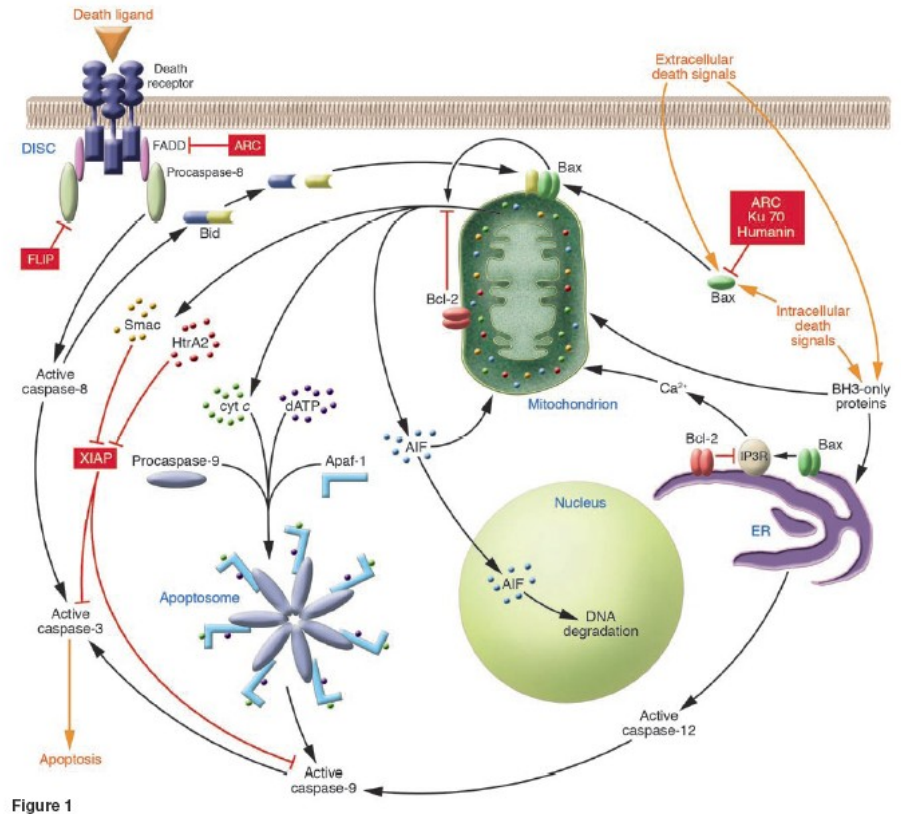


Figure 1

Healing Nomenclature

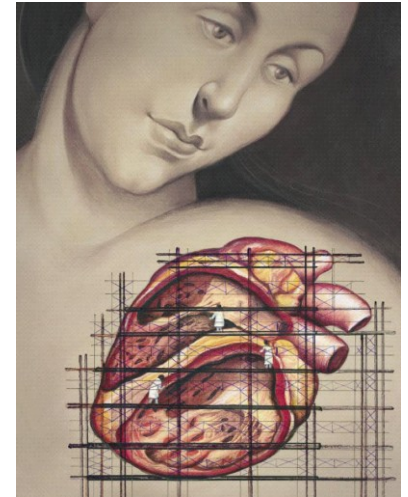
- **Regeneration**

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

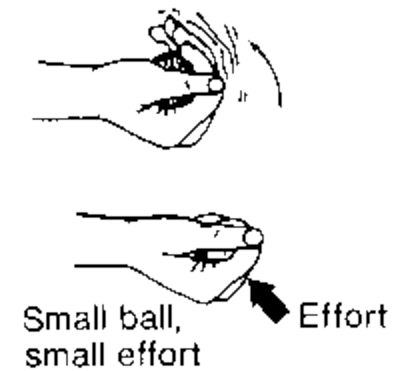


SV 100
EF 40

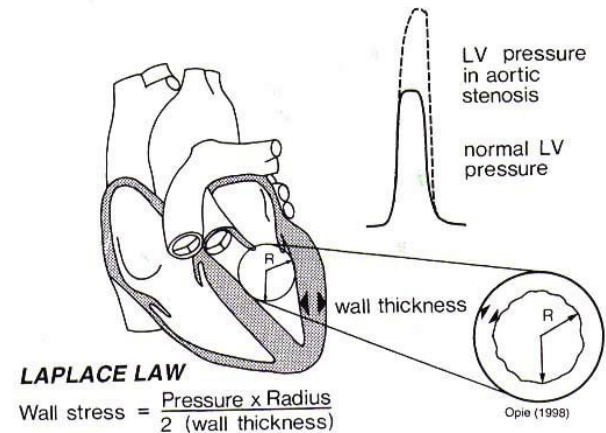
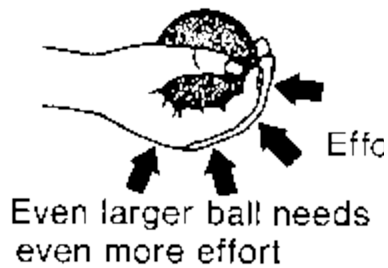


SV 100
EF 25

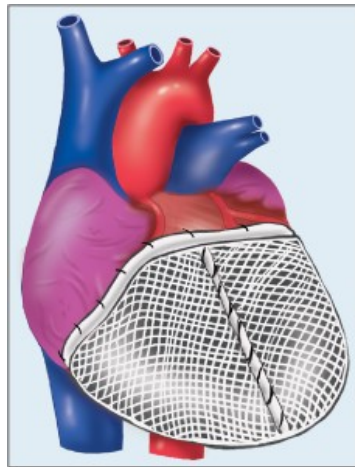
LV Dilatation



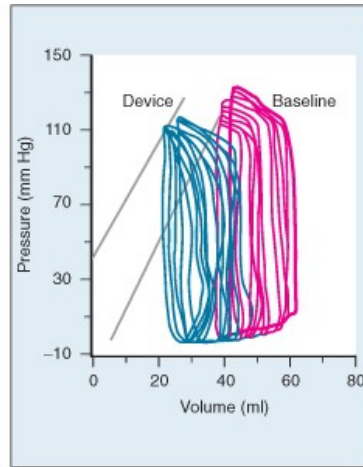
Larger ball needs more effort to squeeze



Cardiac Support Device

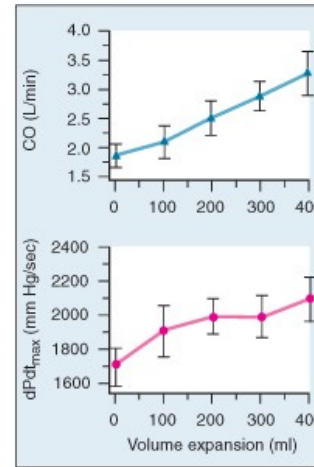


A



B

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C

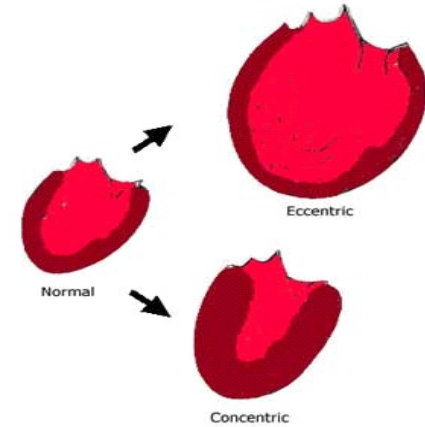


Figure 20-1



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

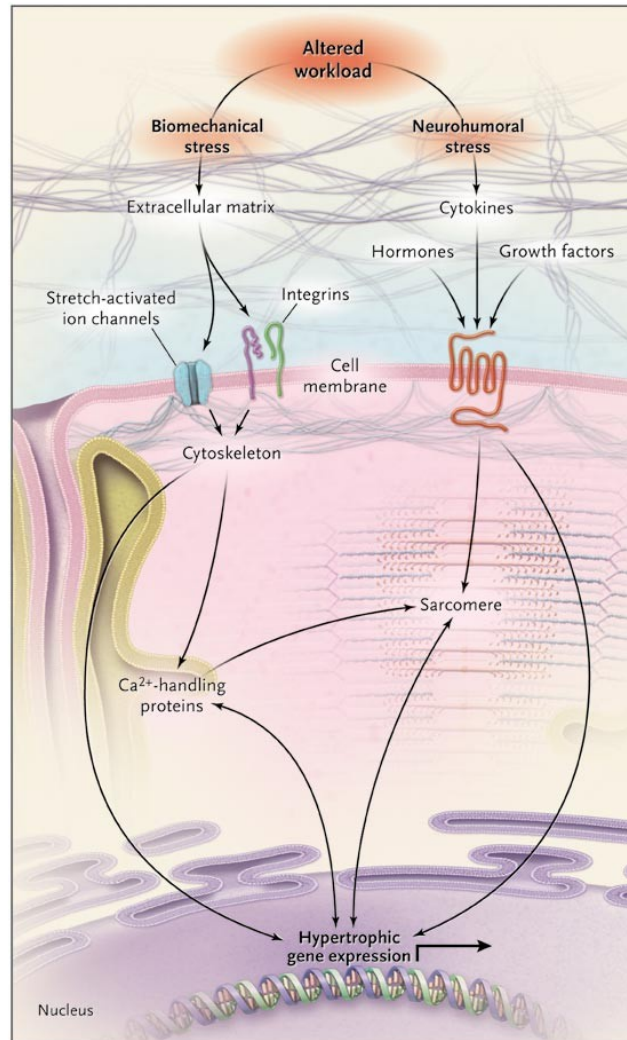
Alterations in Left Ventricular Chamber Geometry

LV dilation
Increased LV sphericity
LV wall thinning
Mitral valve incompetence



Cellular Events Triggered by Altered Workload.

A complex interplay of biomechanical and neurohumoral stress responses culminates in hypertrophic gene regulation and cell growth



Hill & Olson NEJM 2008

Pathogenesis of heart failure

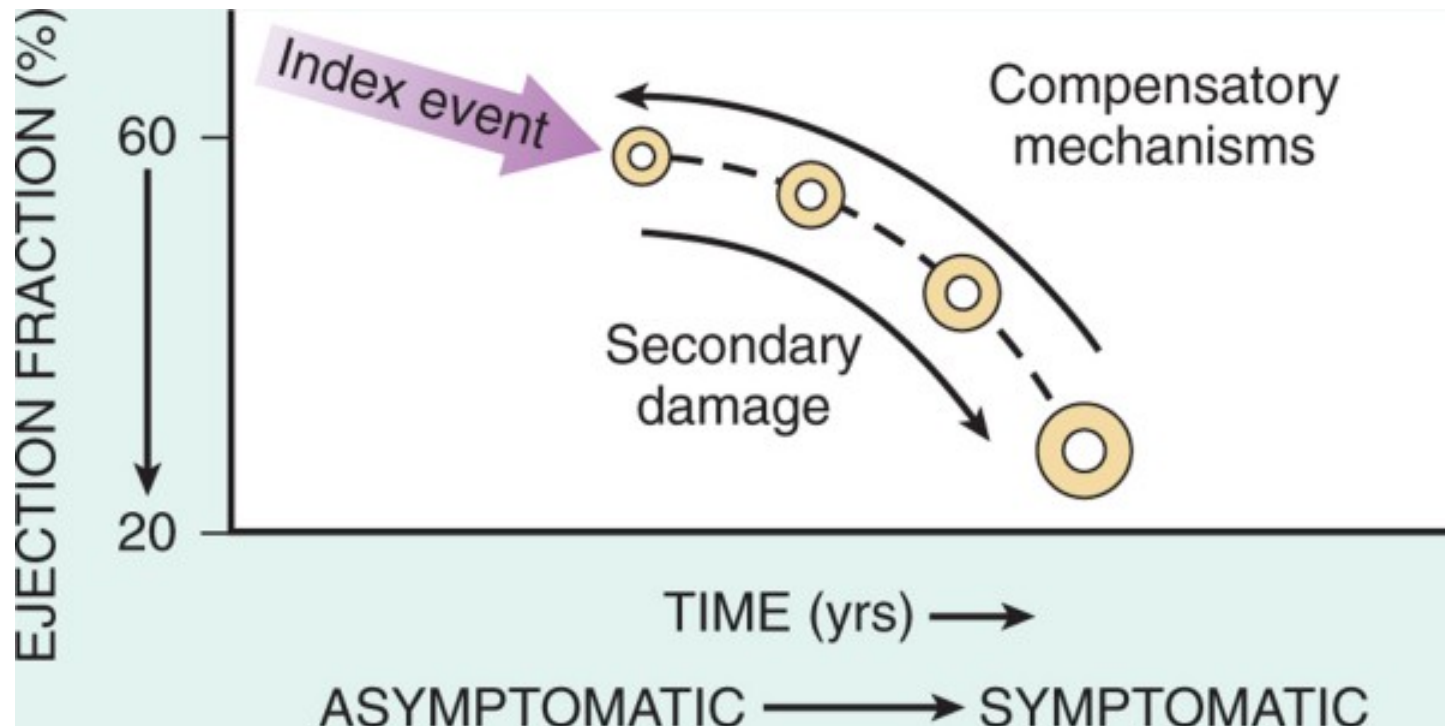


TABLE 22-1 -- Overview of Left Ventricular (LV) Remodel

<p>Alterations in Myocyte Biology</p> <ul style="list-style-type: none">Excitation contraction couplingMyosin heavy chain (fetal) gene expressionBeta-adrenergic desensitizationHypertrophyMyocytolysisCytoskeletal proteins
<p>Myocardial Changes</p> <ul style="list-style-type: none">Myocyte loss<ul style="list-style-type: none">NecrosisApoptosisAutophagy Alterations in extracellular matrix<ul style="list-style-type: none">Matrix degradationMyocardial fibrosis
<p>Alterations in Left Ventricular Chamber Geometry</p> <ul style="list-style-type: none">LV dilationIncreased LV sphericityLV wall thinningMitral valve incompetence

Overview of the pathophysiology of myocardial remodeling

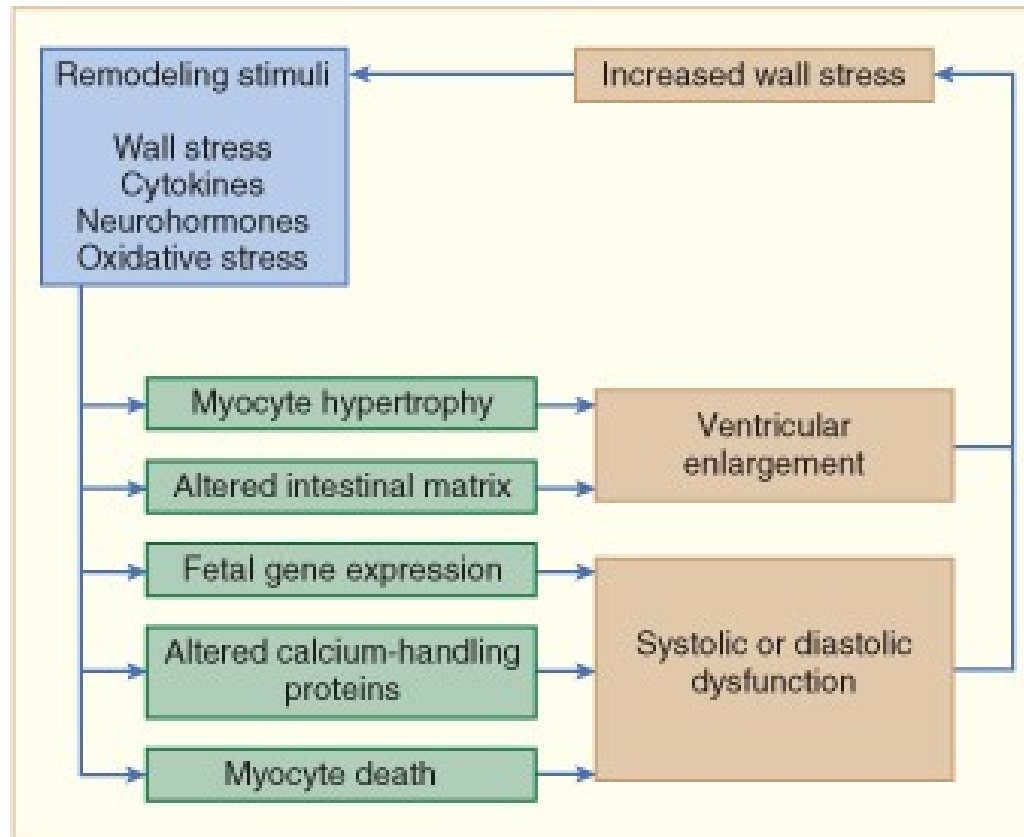
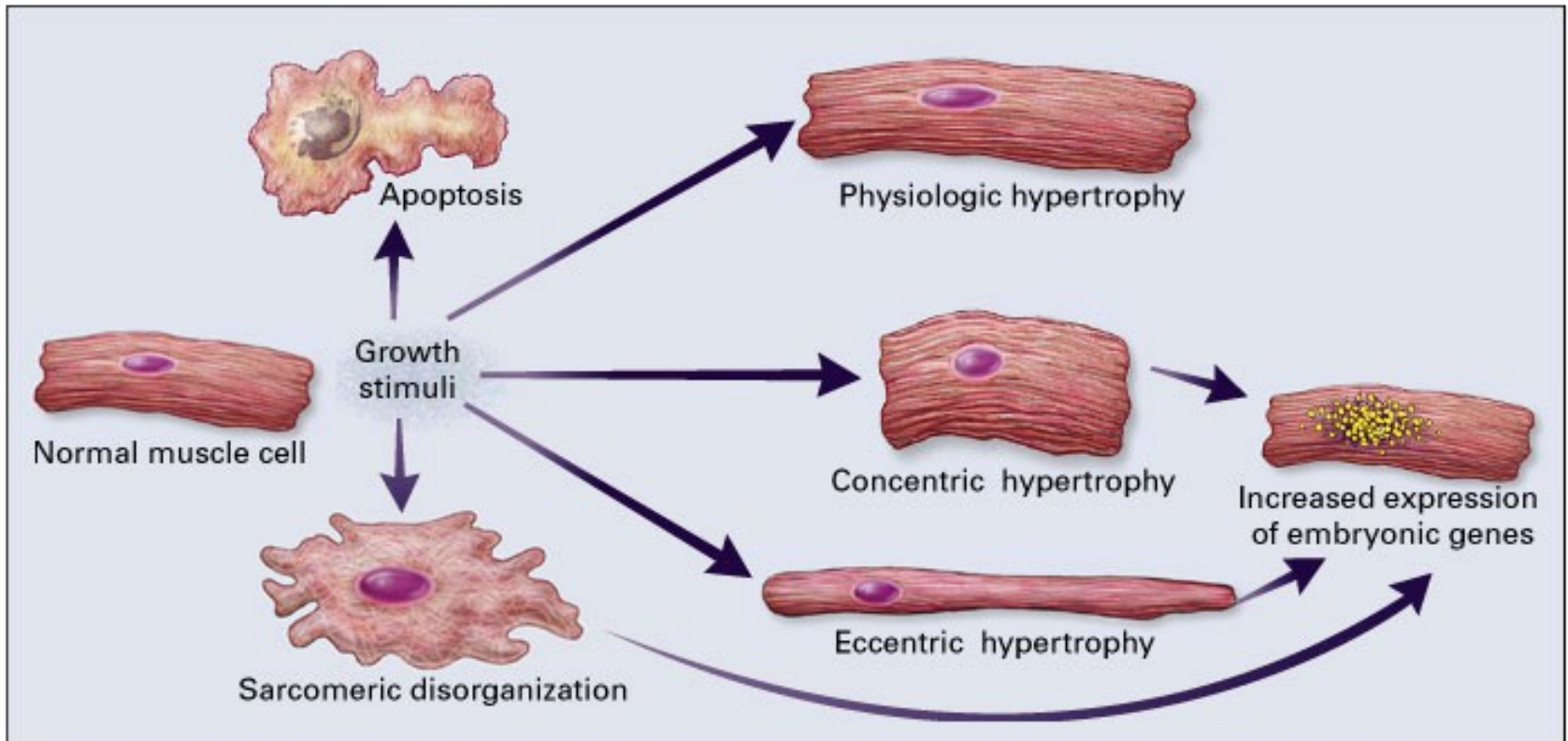
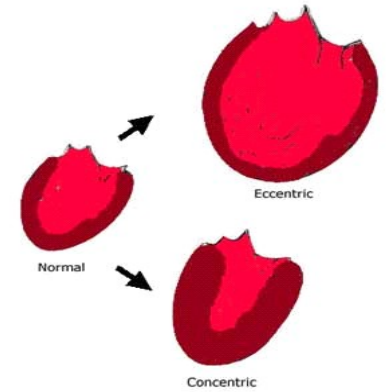


Figure 21-10

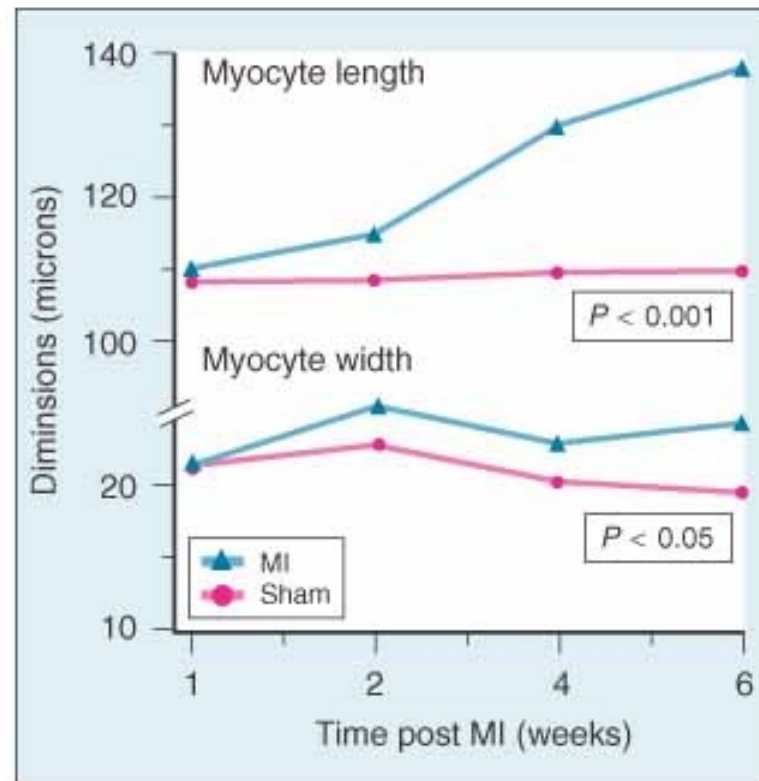
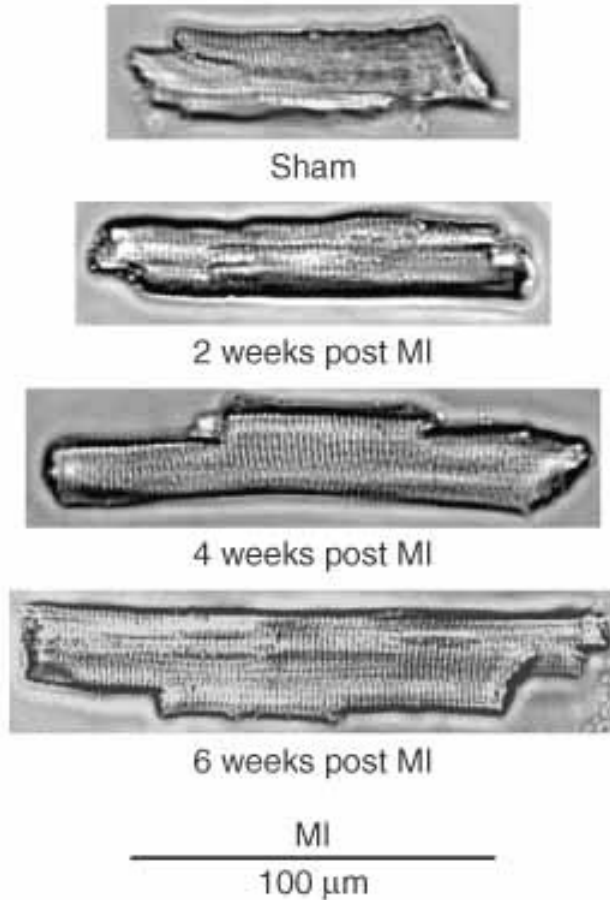
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Cellular Hypertrophy



Cardiac myocyte remodeling

Increased myocyte length and width



cardiac hypertrophy

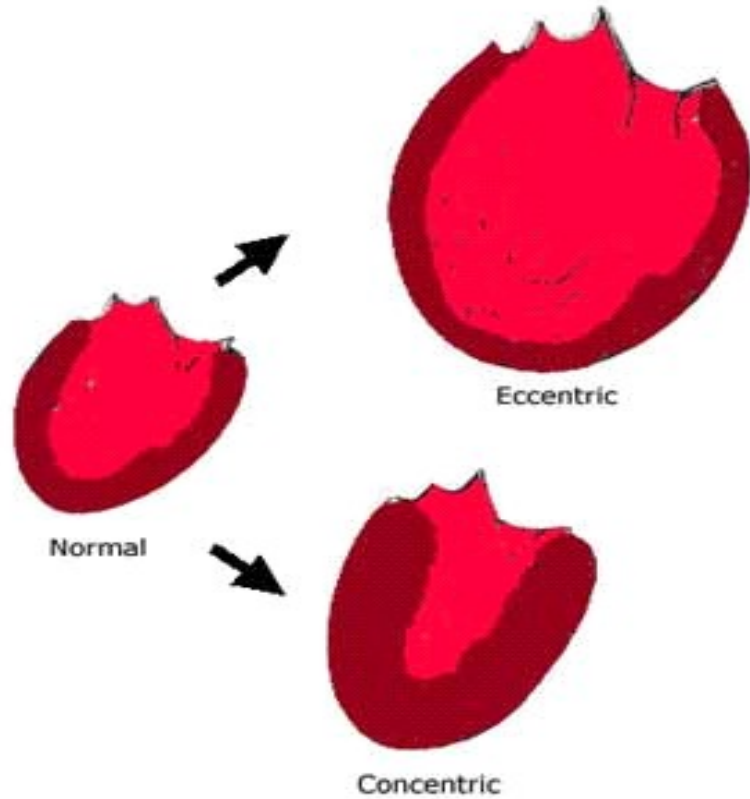
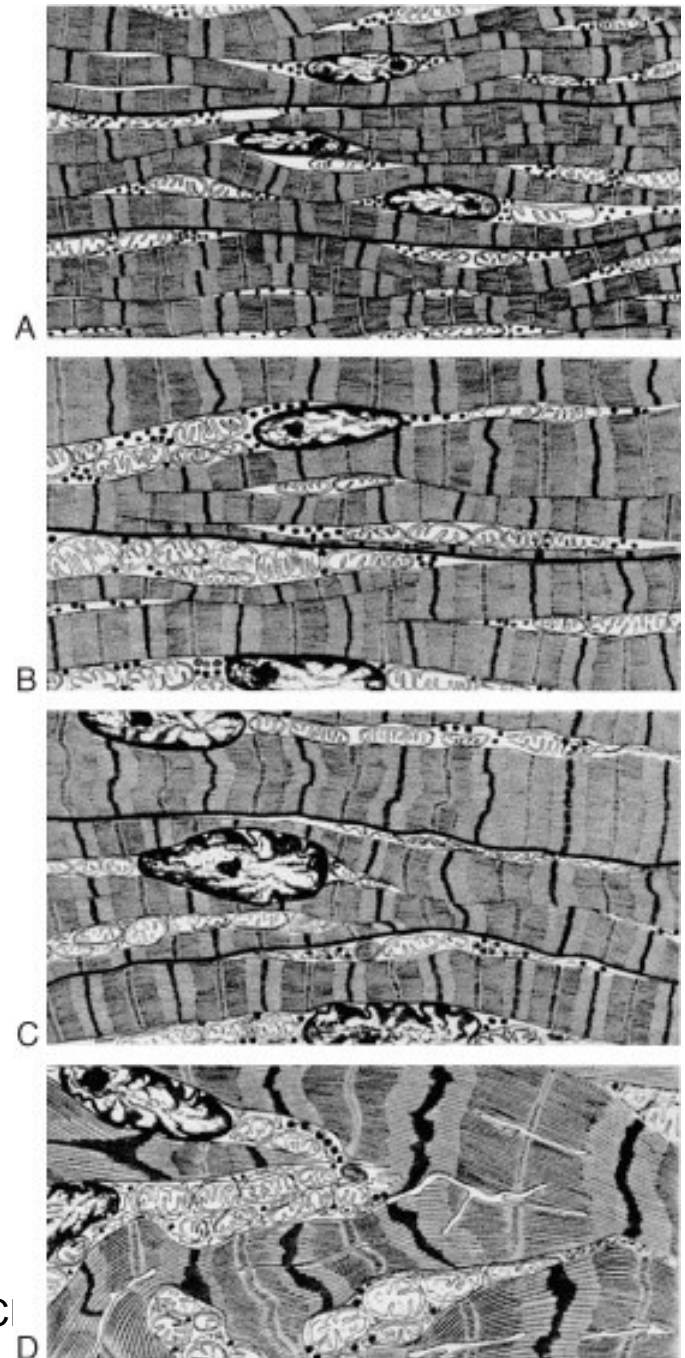


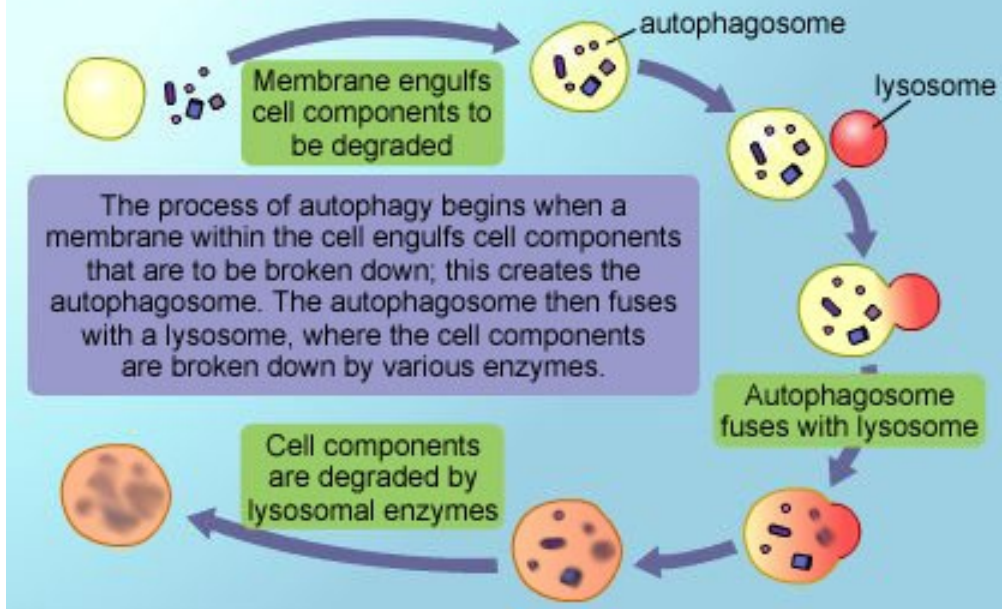
Figure 21-8

Prof. Jonathan Leor, NC



Autophagy

Figure H-3: The Process of Autophagy



Small RNAs in a big heart

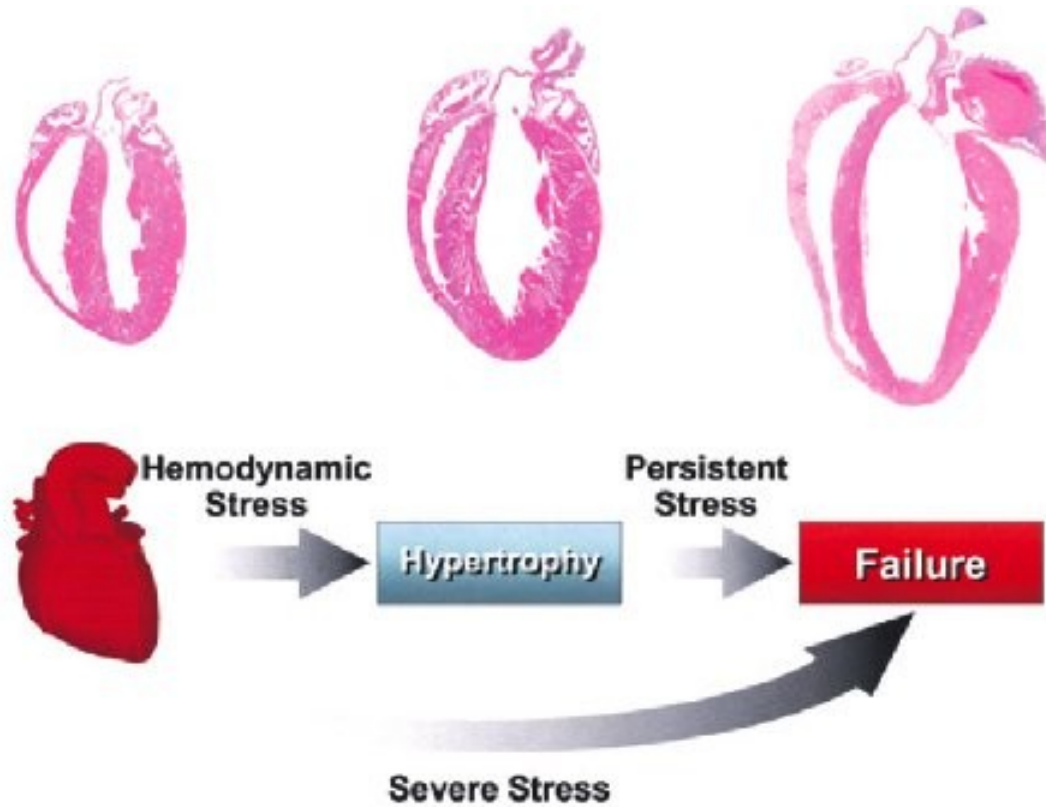
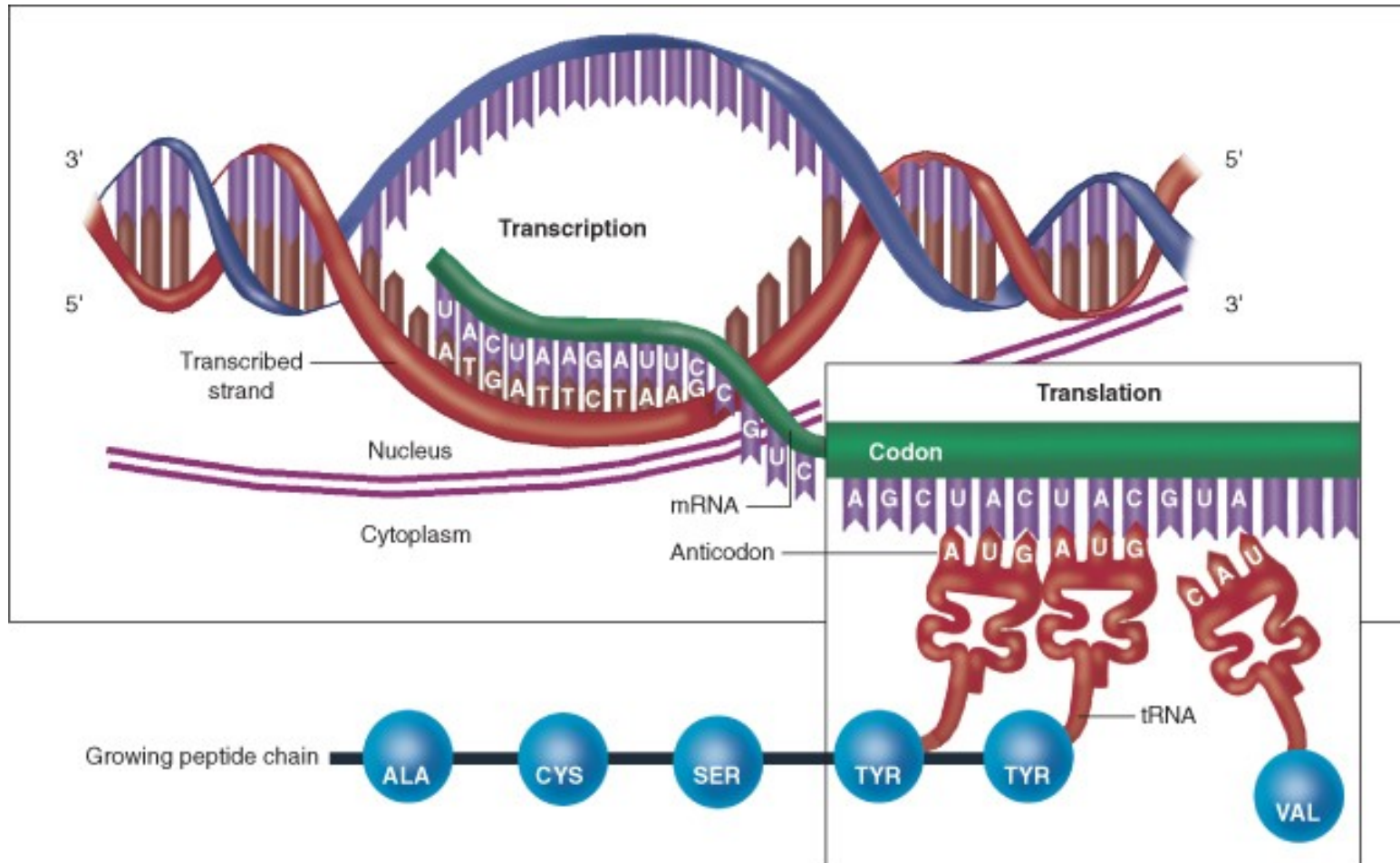
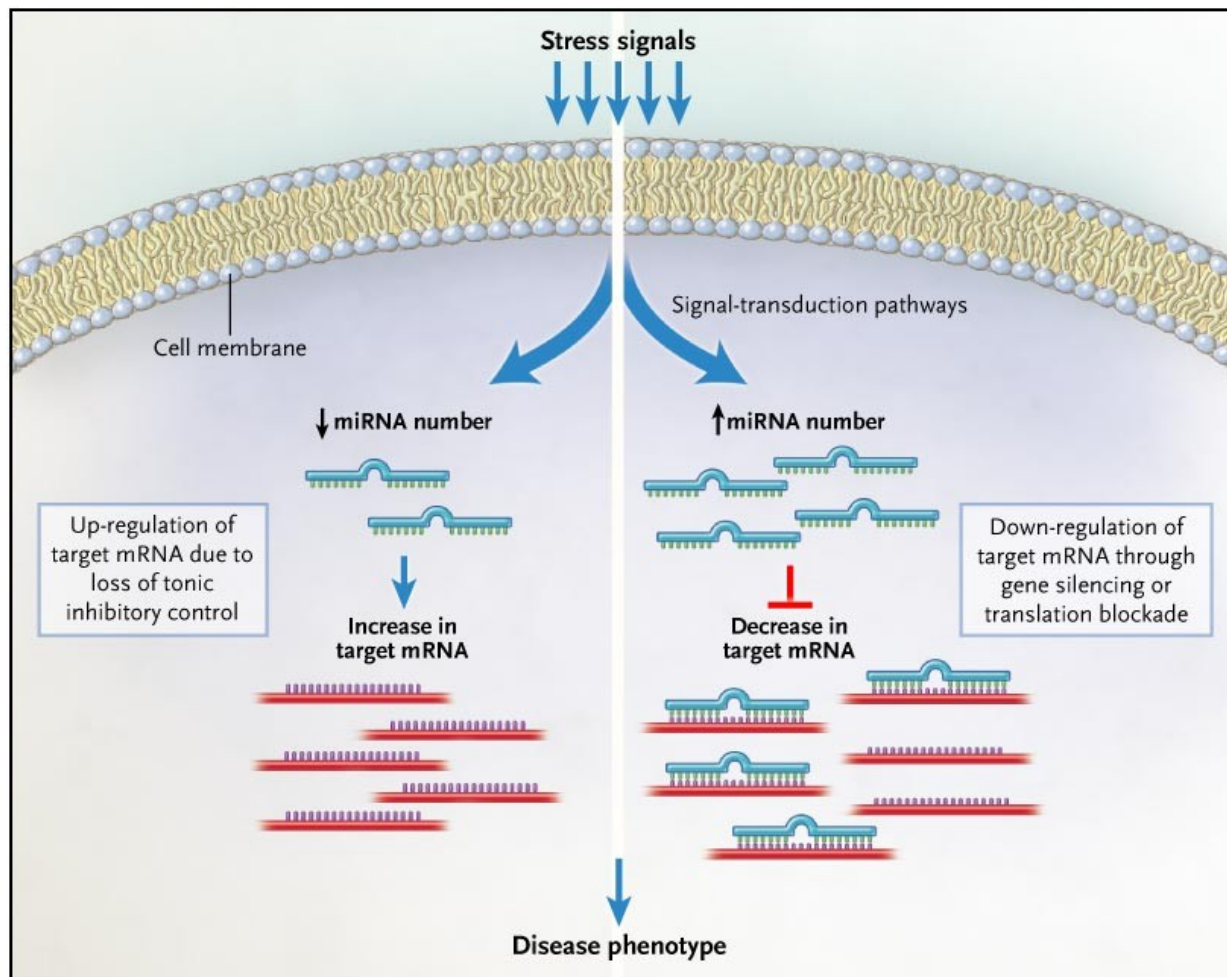


Figure 69-6 The flow of genetic information. Transcription in the nucleus creates a complementary ribonucleic acid copy from one of the DNA strands in the double helix. mRNA is transported into the cytoplasm, where it is translated into protein

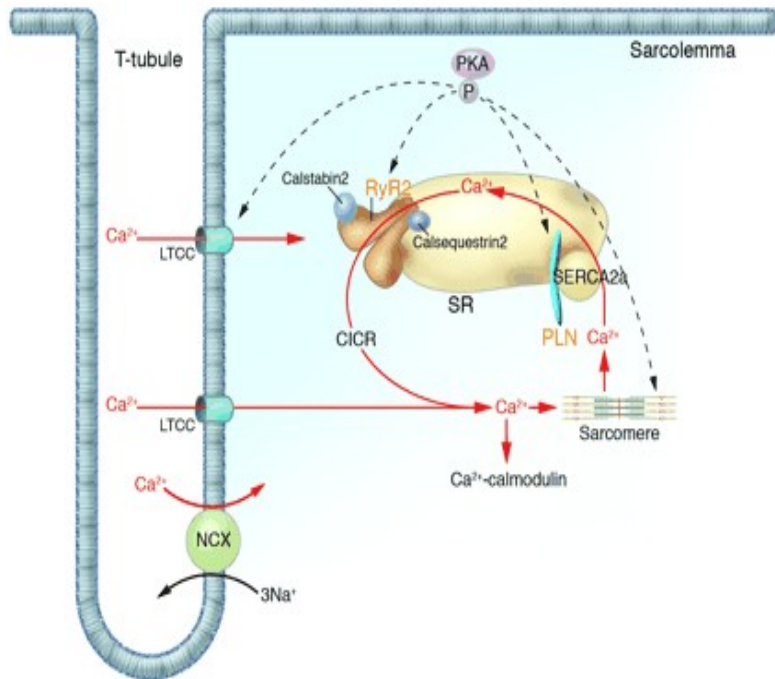


MicroRNAs as Mediators

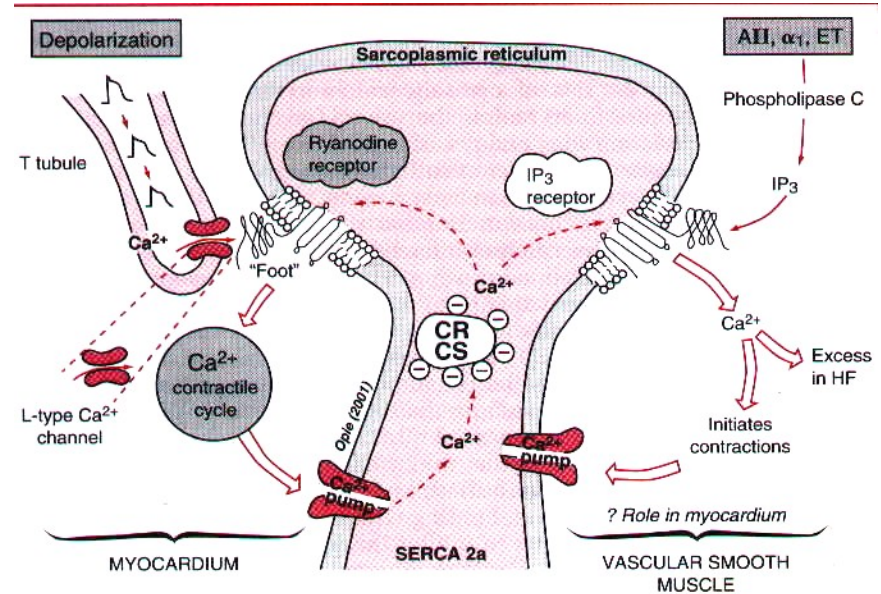
MicroRNAs as Mediators



Human mutations affecting Ca²⁺ 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

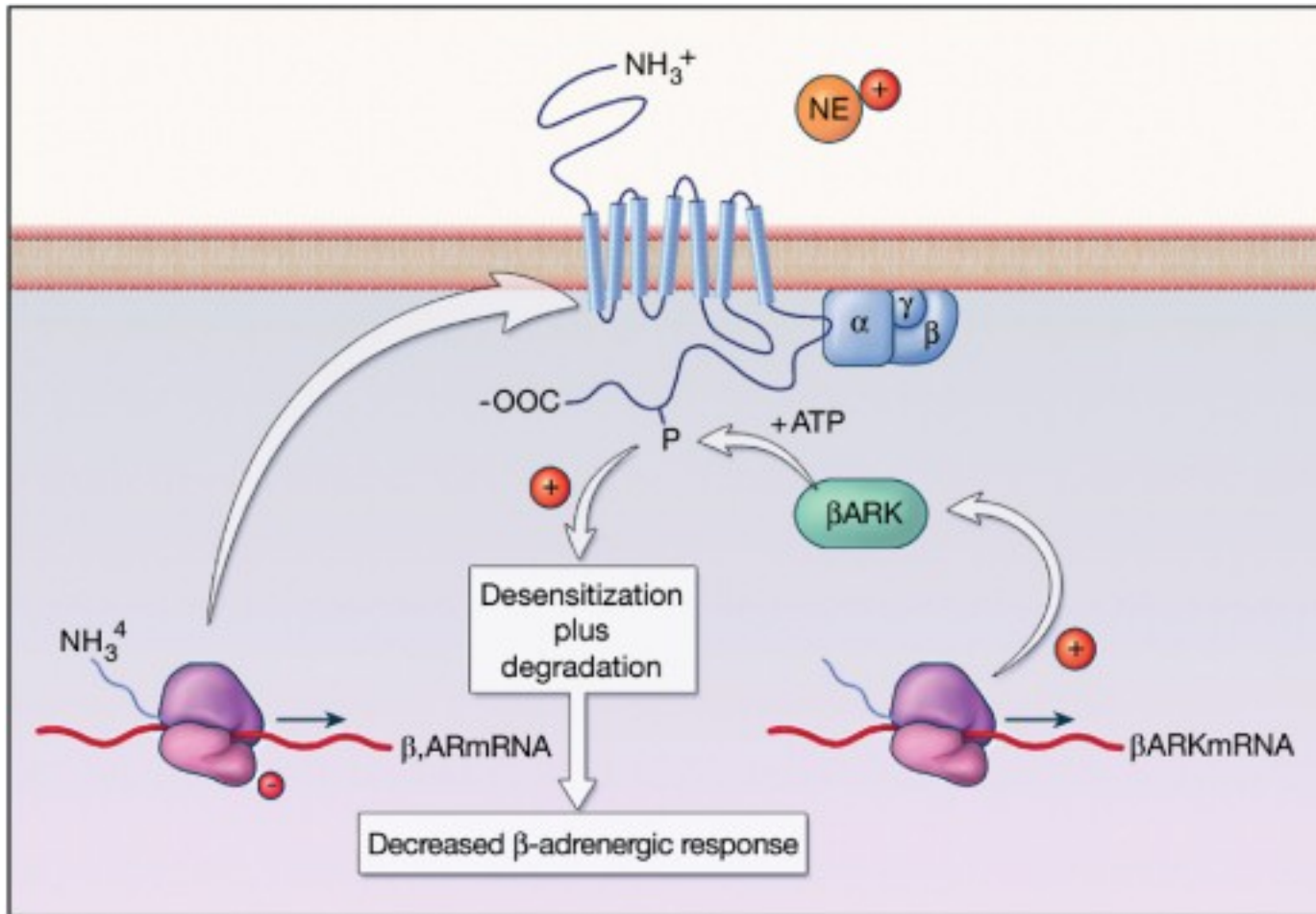


TABLE 22–4**Effects of Inflammatory Mediators on Left Ventricular Remodeling****Alterations in the Biology of the Myocyte**

- 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 AT₁ 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 29-5

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

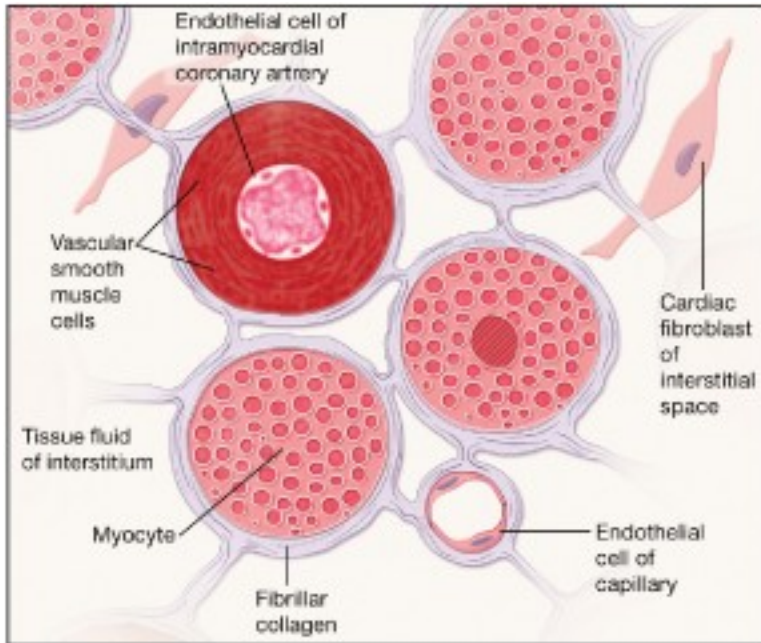
Target	Function
Beta-adrenergic receptor kinase inhibitor (β ARKct)	Inhibits phosphorylation of β -adrenergic receptor thus preventing its desensitization
Adenylyl cyclase (AC)	Synthesizes cAMP to activate PKA, which then phosphorylates substrates to regulate calcium handling
Sarcoplasmic reticulum Ca^{2+} 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

Braunwald Table 29-6

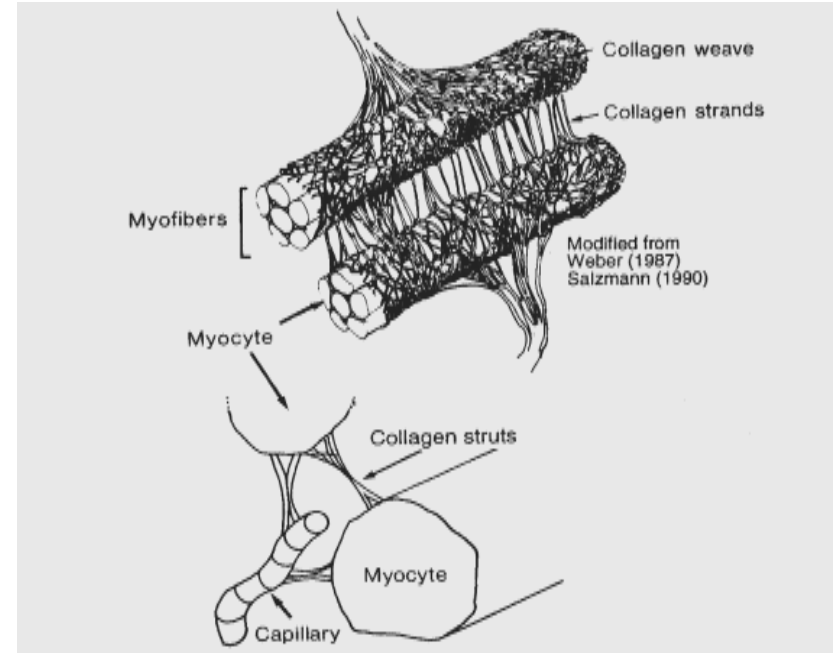
Effect of Gene Polymorphisms on the Pharmacological Treatment of Heart Failure



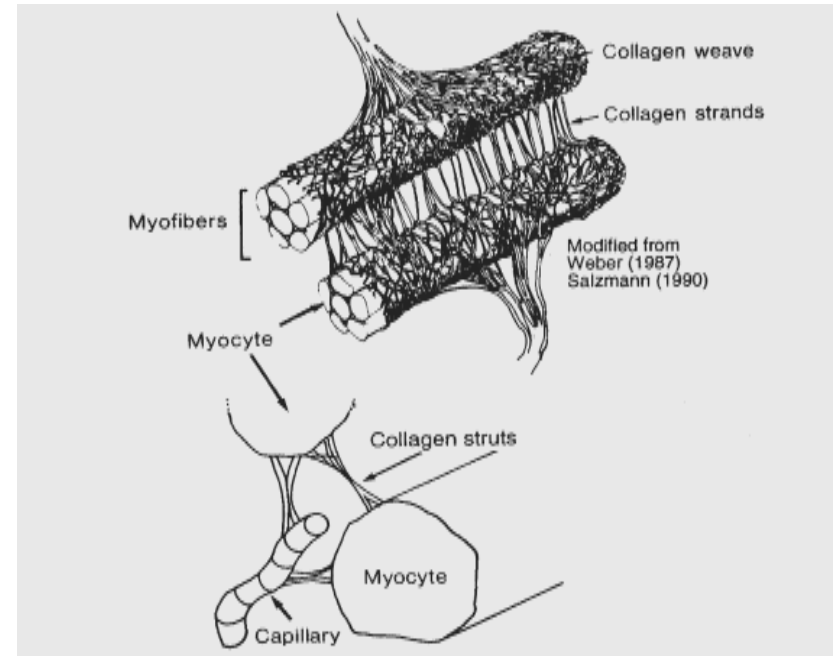
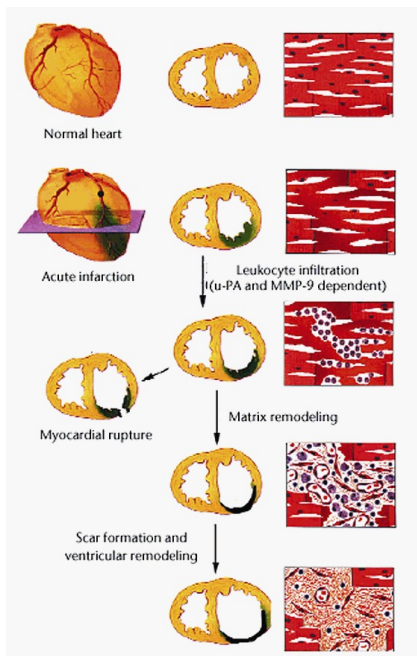
Extra Cellular Matrix



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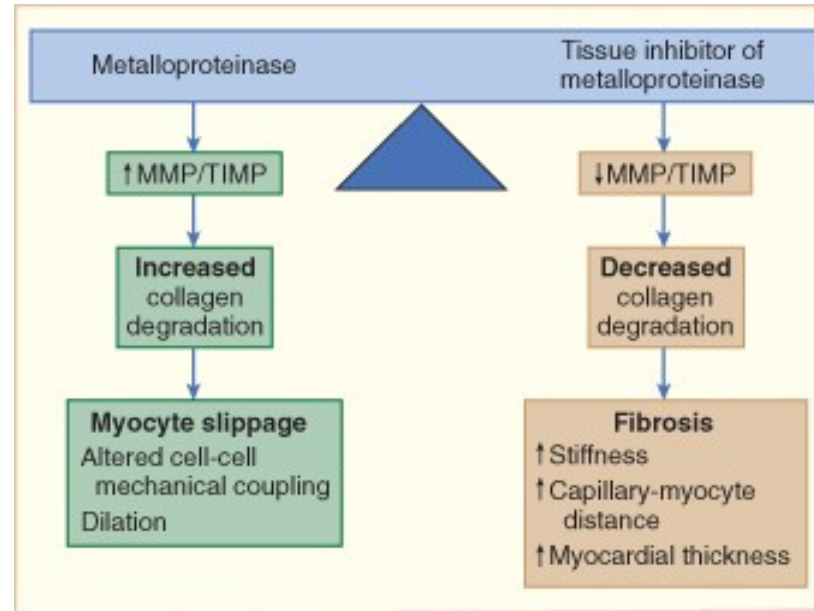


MMP activity site



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

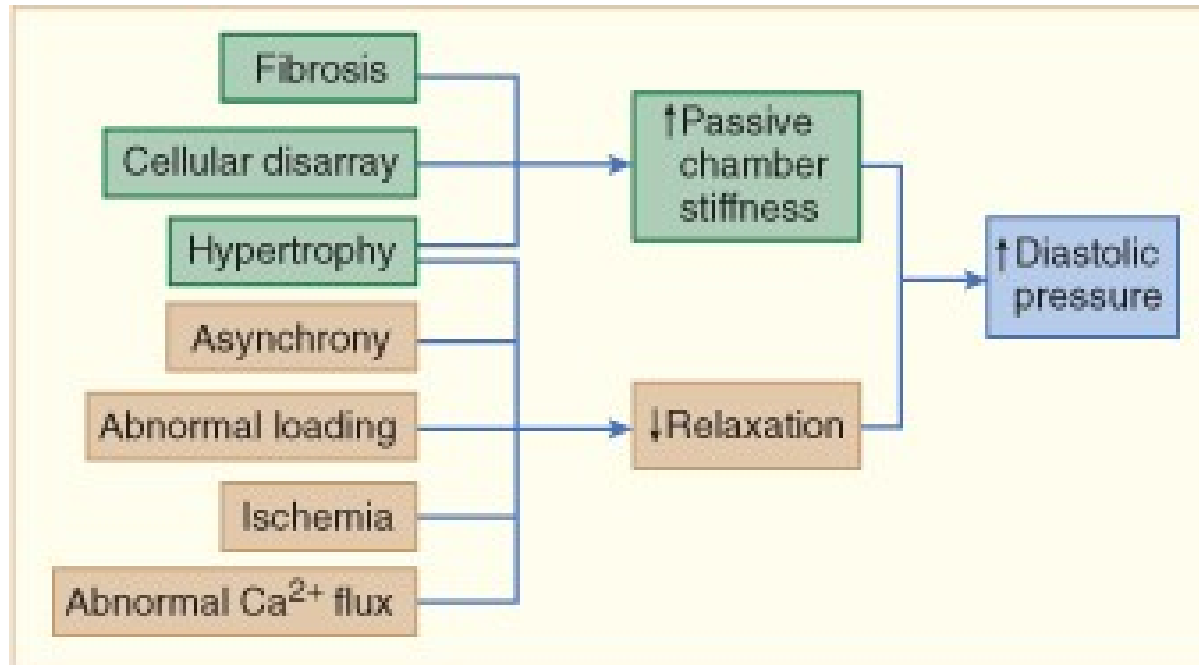
The regulation of extracellular matrix degradation



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Figure 21-18

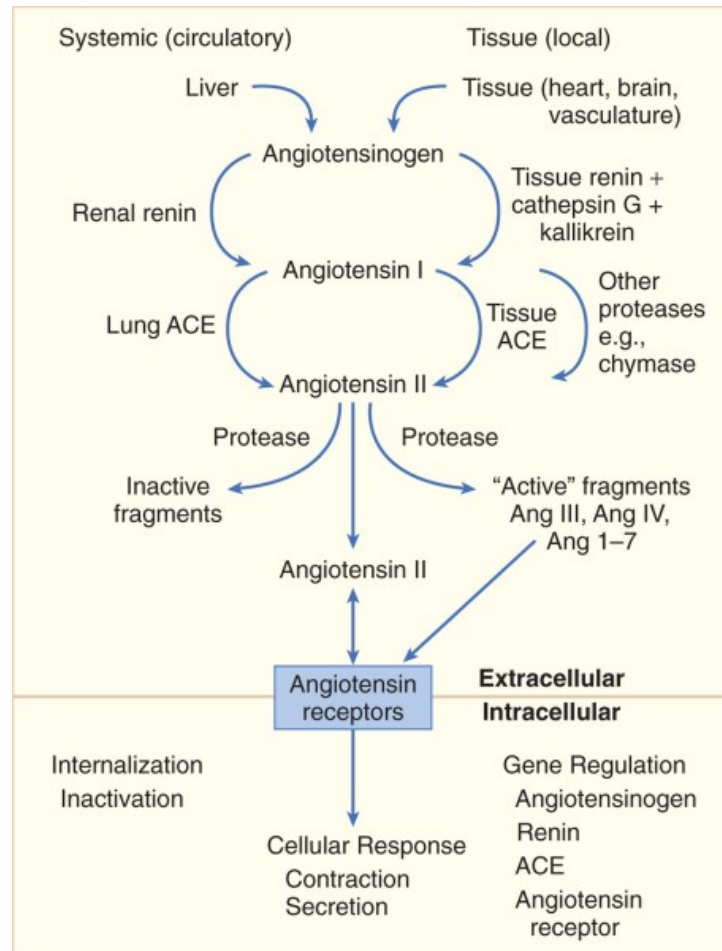
Factors responsible for diastolic dysfunction



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Figure 21-21

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)

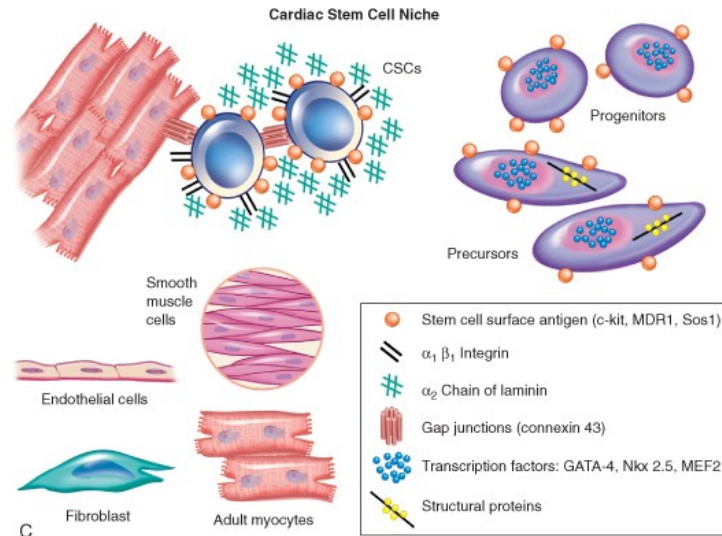
1. Continued expansion of infarct zone
2. Dilation and reshaping of the left ventricle
3. Myocyte hypertrophy
4. Ongoing myocyte loss
5. Excessive accumulation of collagen in the cardiac interstitium

Table 22-5

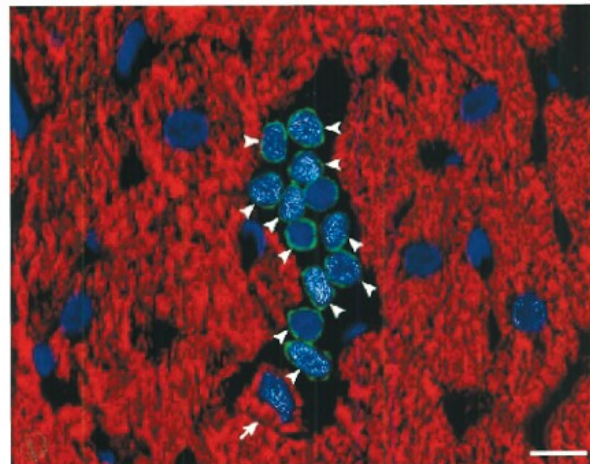
TABLE 22-5 -- Cellular and Molecular Determinants of Myocardial Recovery

	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

Myocardial regeneration and repair



C



D

Stem Cell

- Self renewal
- Give rise to specialized cells.

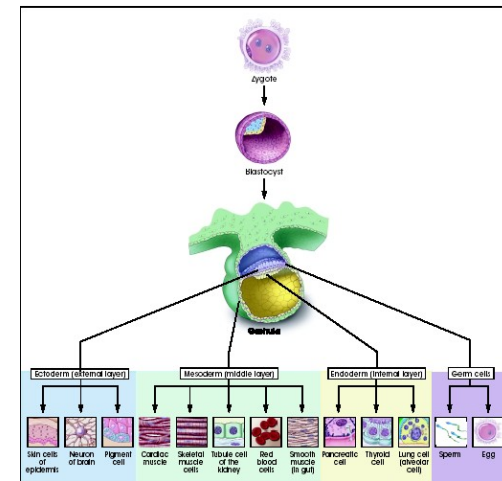
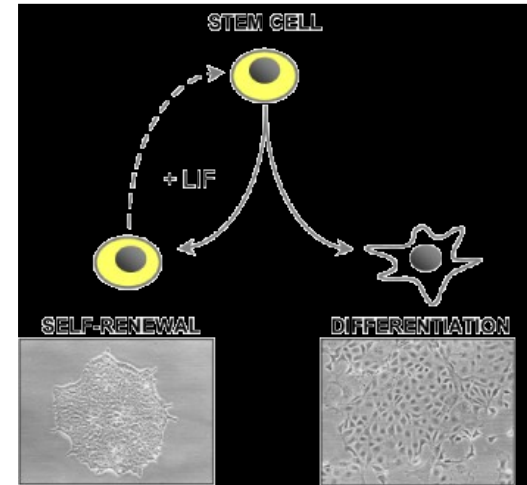
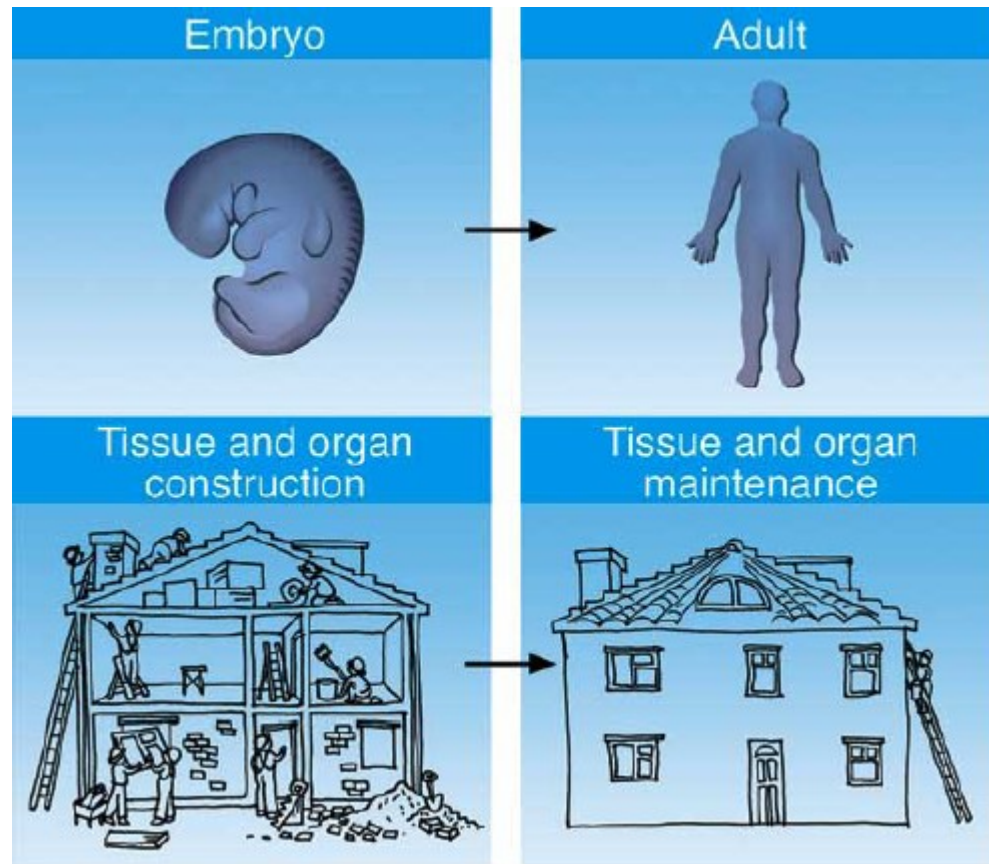
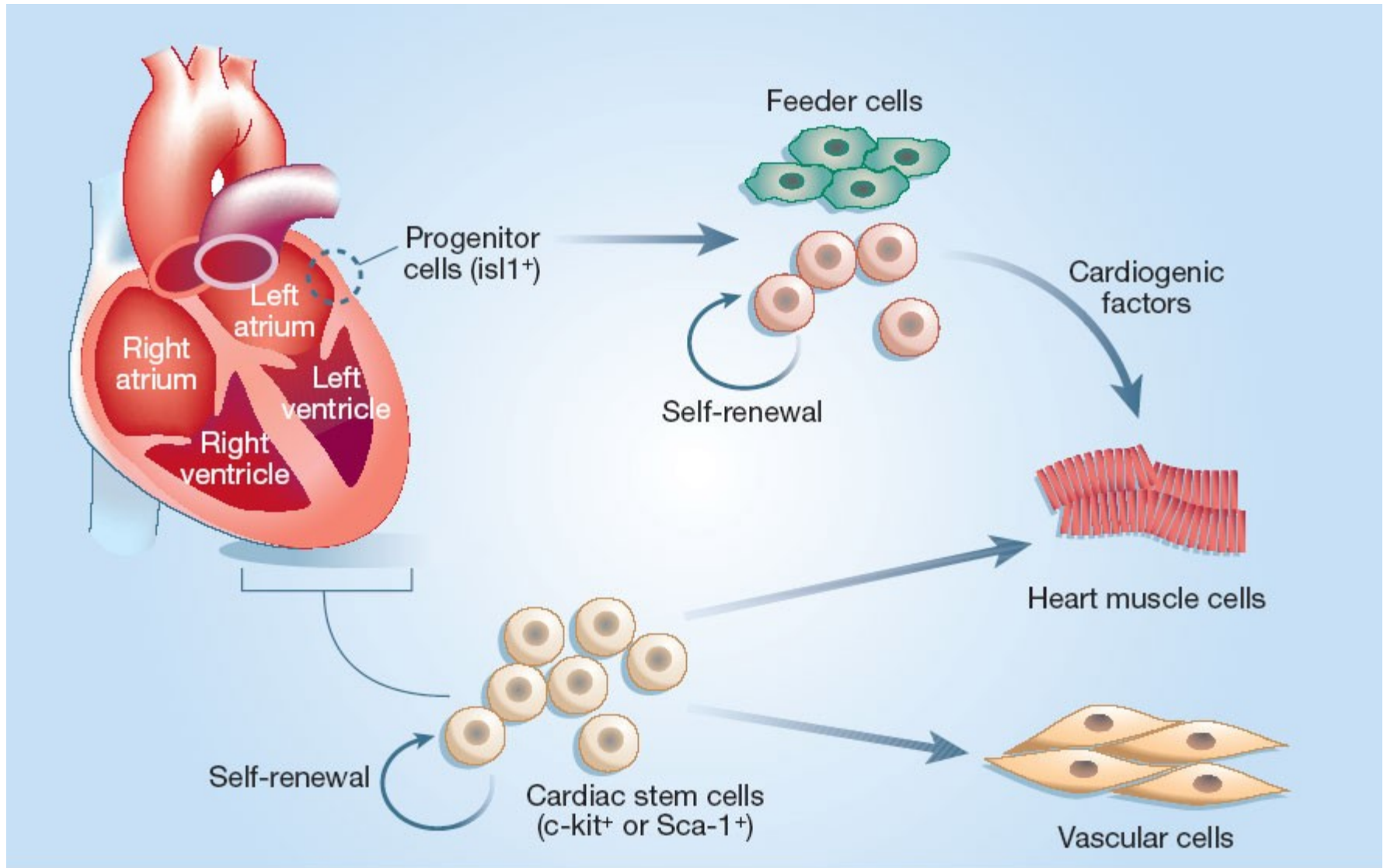


Figure 1.1. Differentiation of Human Tissues.

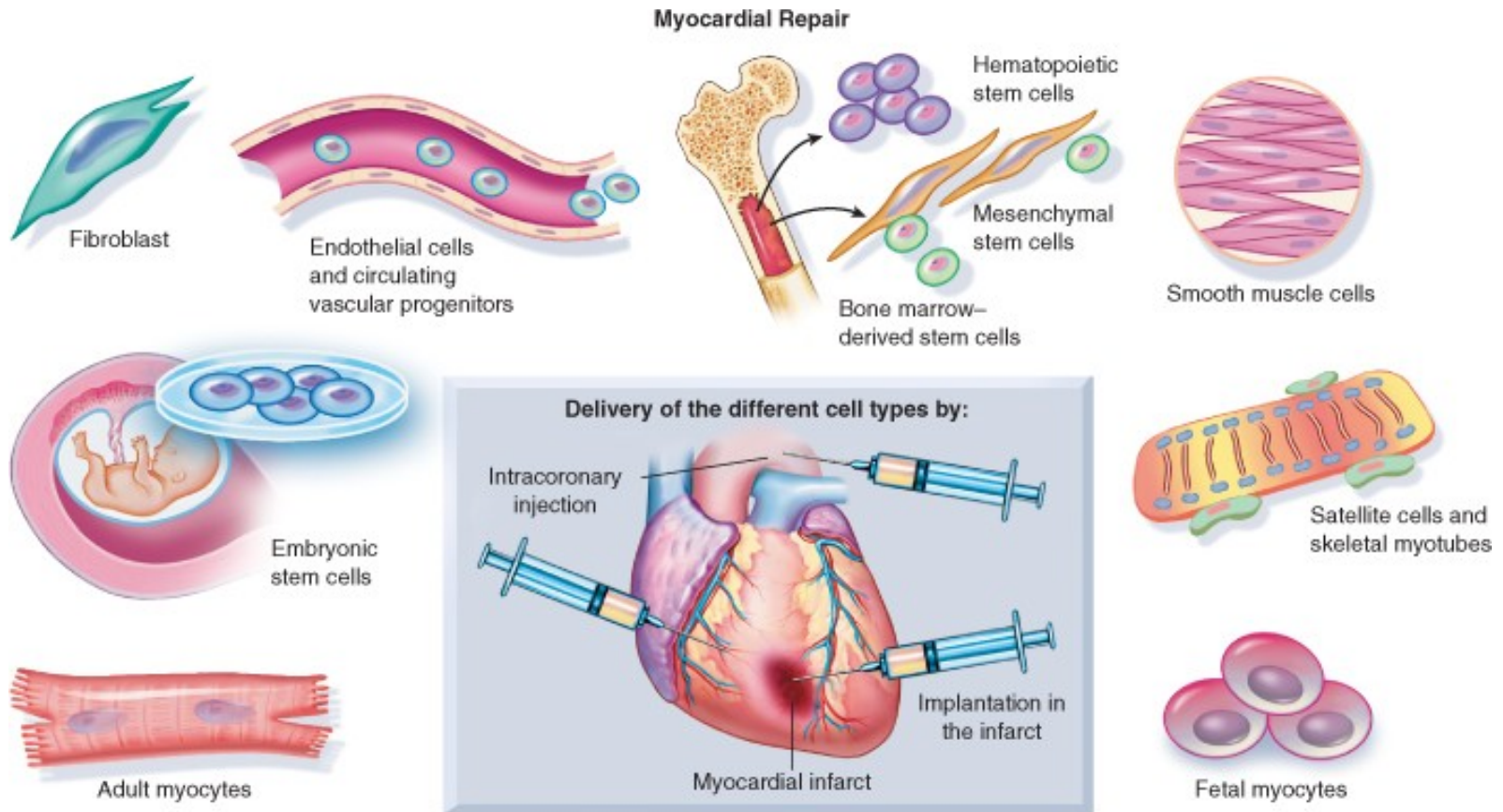
Embryonic and Adult Stem Cells



Cardiac Stem cells



Myocardial repair

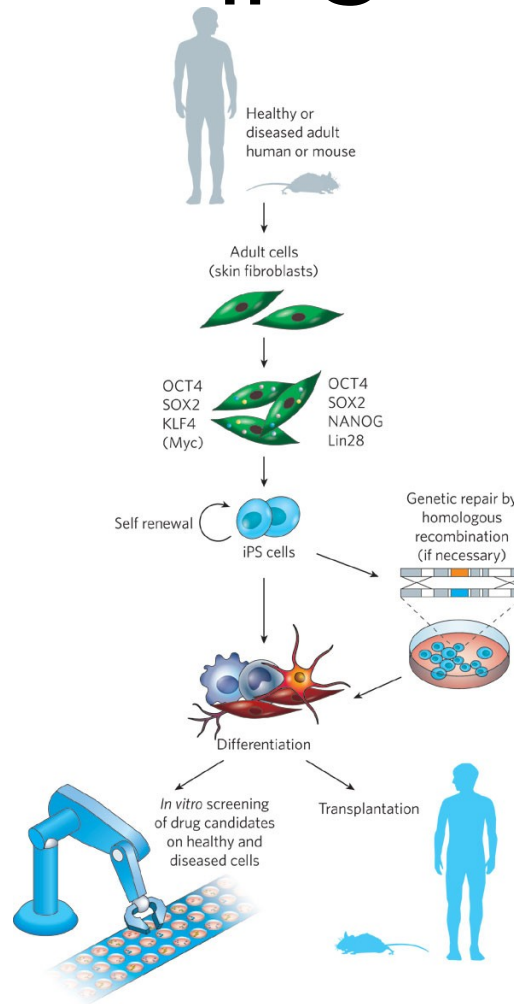


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Figure 71-1

Induced Pluripotent Stem cells

iPS



Possible mechanisms for successful cardiac regenerative therapy

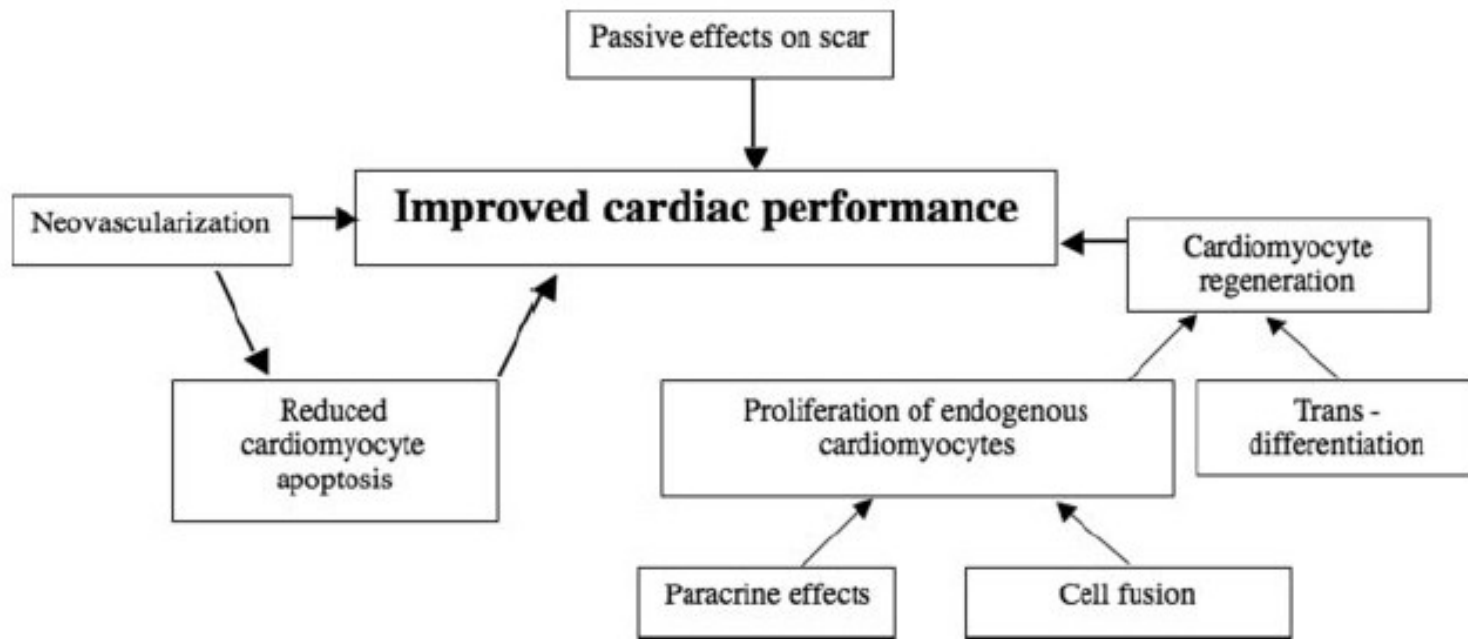
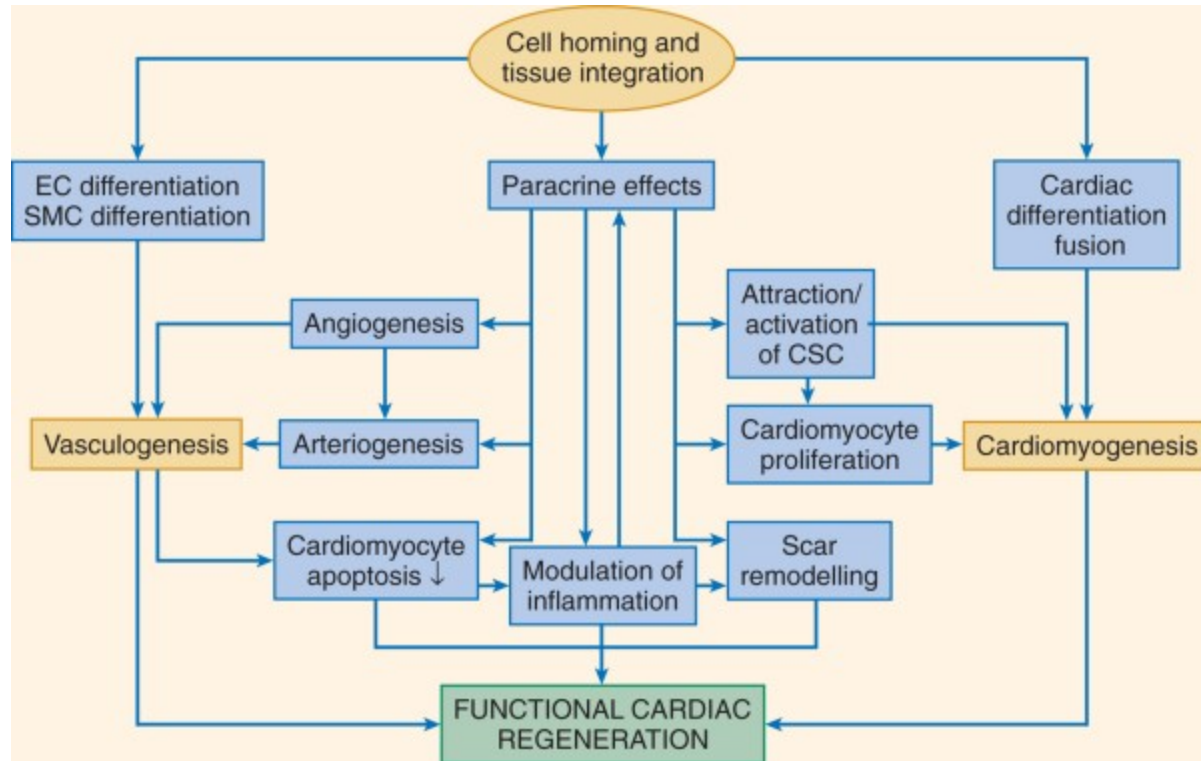


FIGURE 29-3 Proposed mechanisms of action of stem/progenitor cells in cardiovascular repair.



Future directions

Braunwald 2008

- **“.... future therapies will likely be focused on reversing and/or stabilizing the downstream biological consequences of neurohormonal activation, rather than on neurohormonal activation per se.”**

Sleeping Student: Take home message



Overview of the pathophysiology of myocardial remodeling

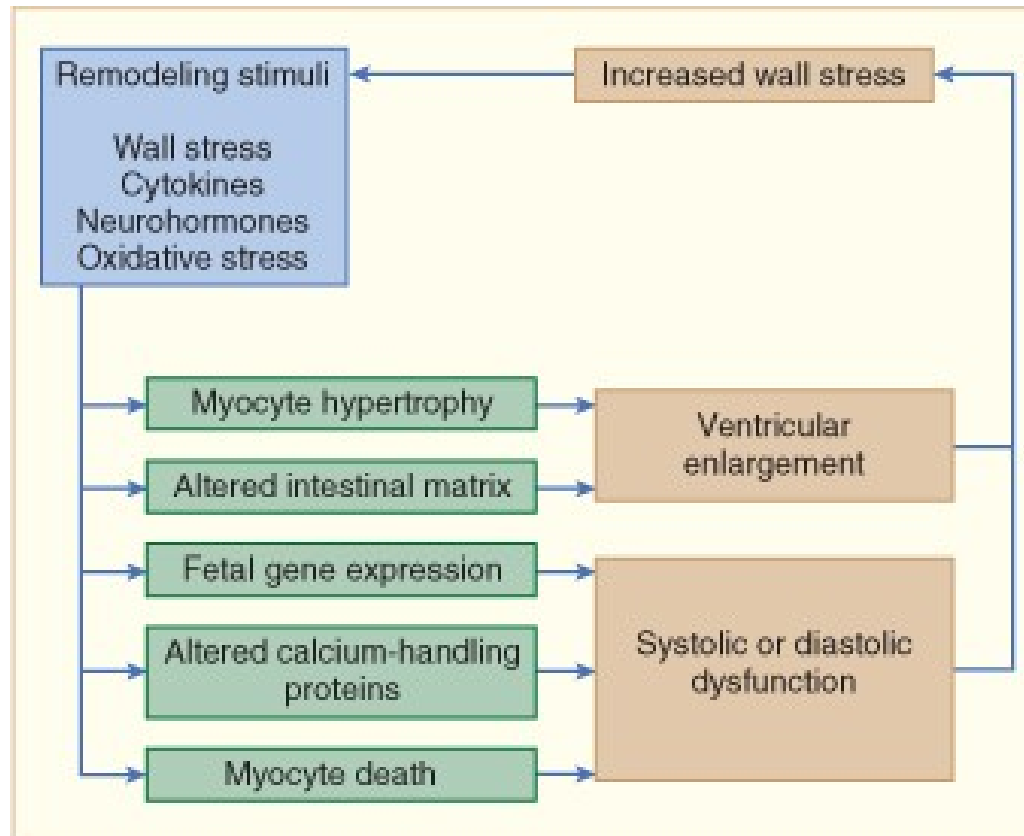


Figure 21-10

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