Myocardial Genetics Introduction

Ralph Knöll
Professor & Chair

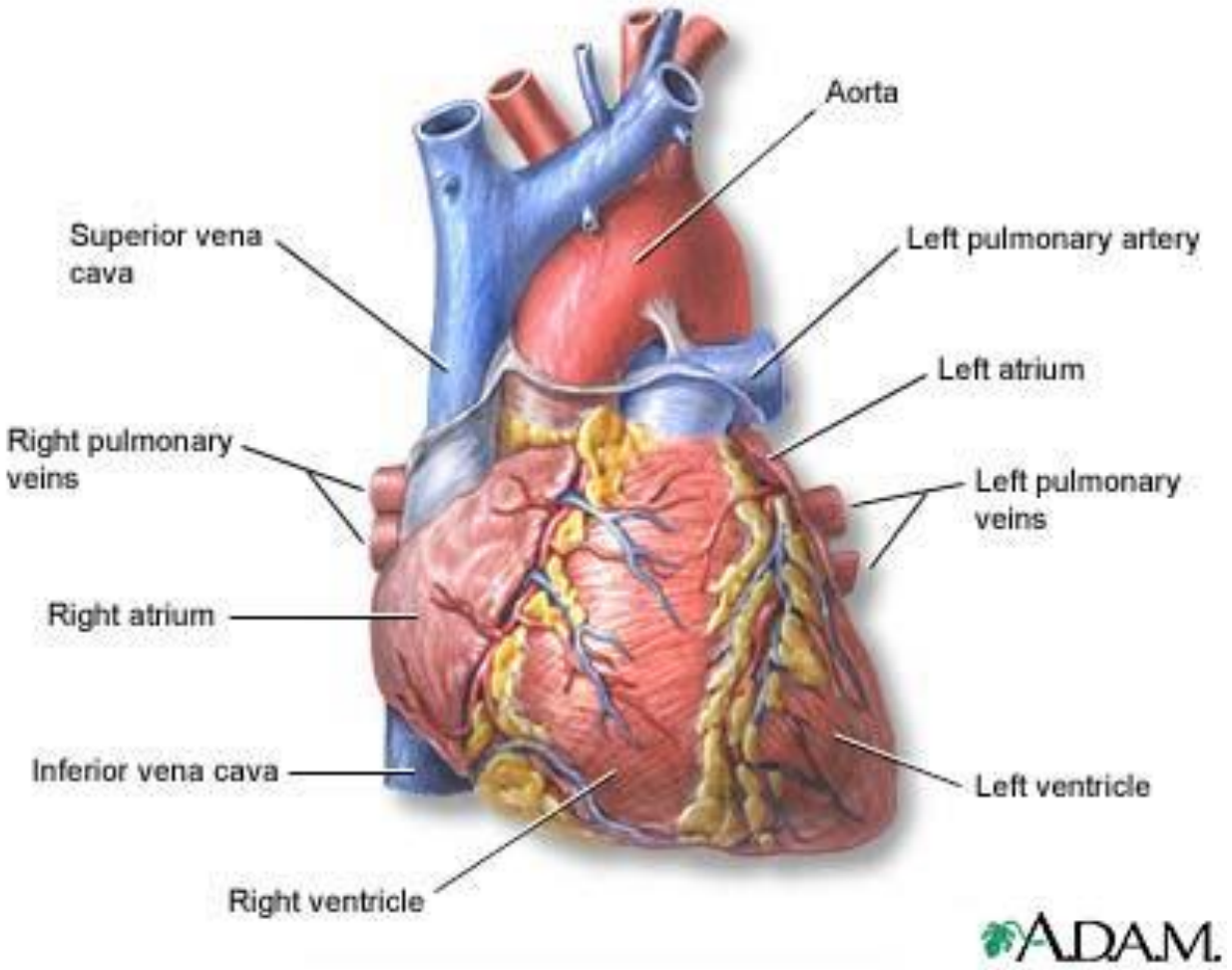
Lecture 1

Literature

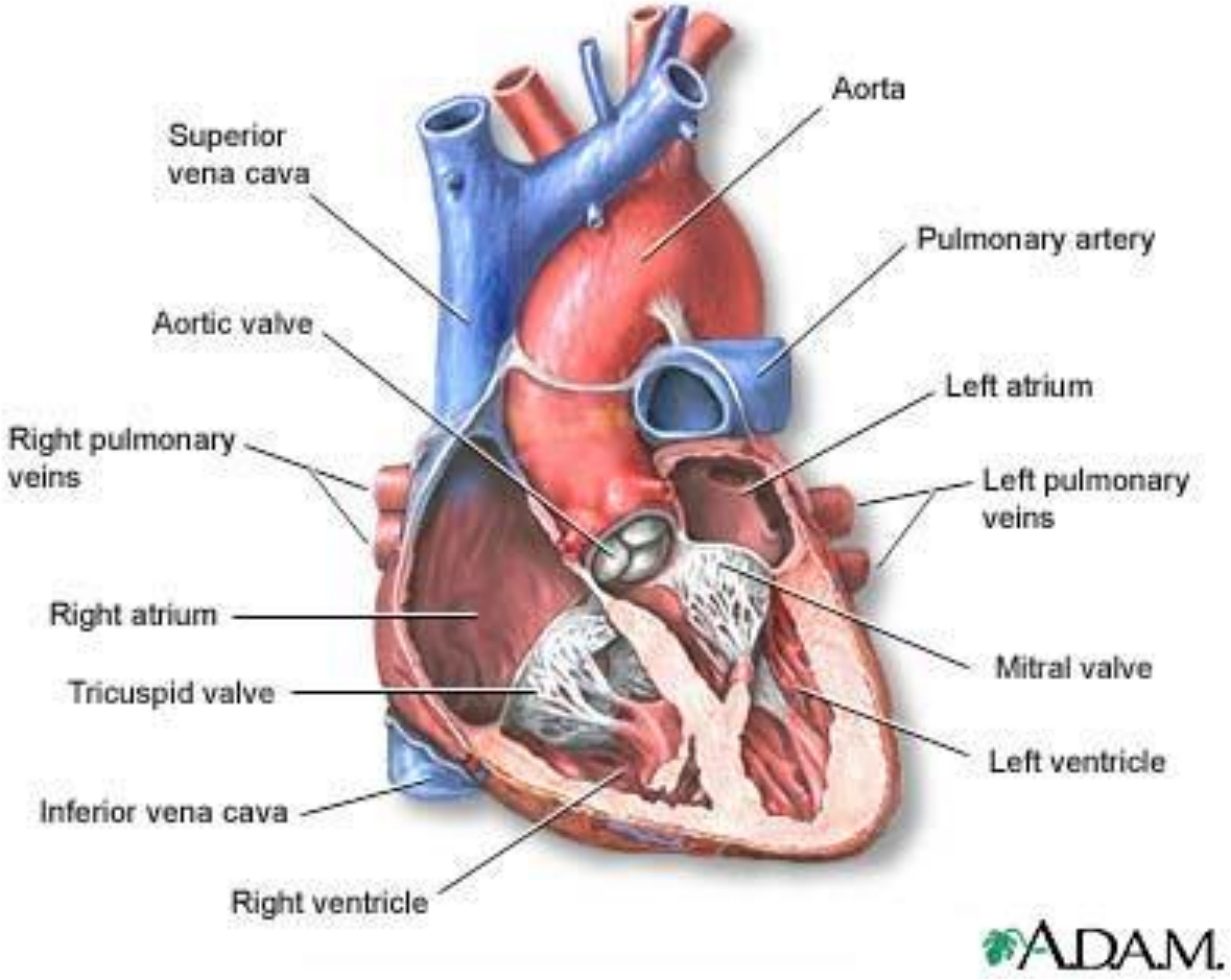
- J. Levick: An introduction to Cardiovascular Physiology
- E. Braunwald: Heart Disease
- **Kenneth R. Chien: Molecular Basis of Cardiovascular Disease**
- Harrison‘s Principles of Internal Medicine

- Internet: Pubmed
- www.ncbi.nlm.nih.gov/disease
- www.cvphysiology.com

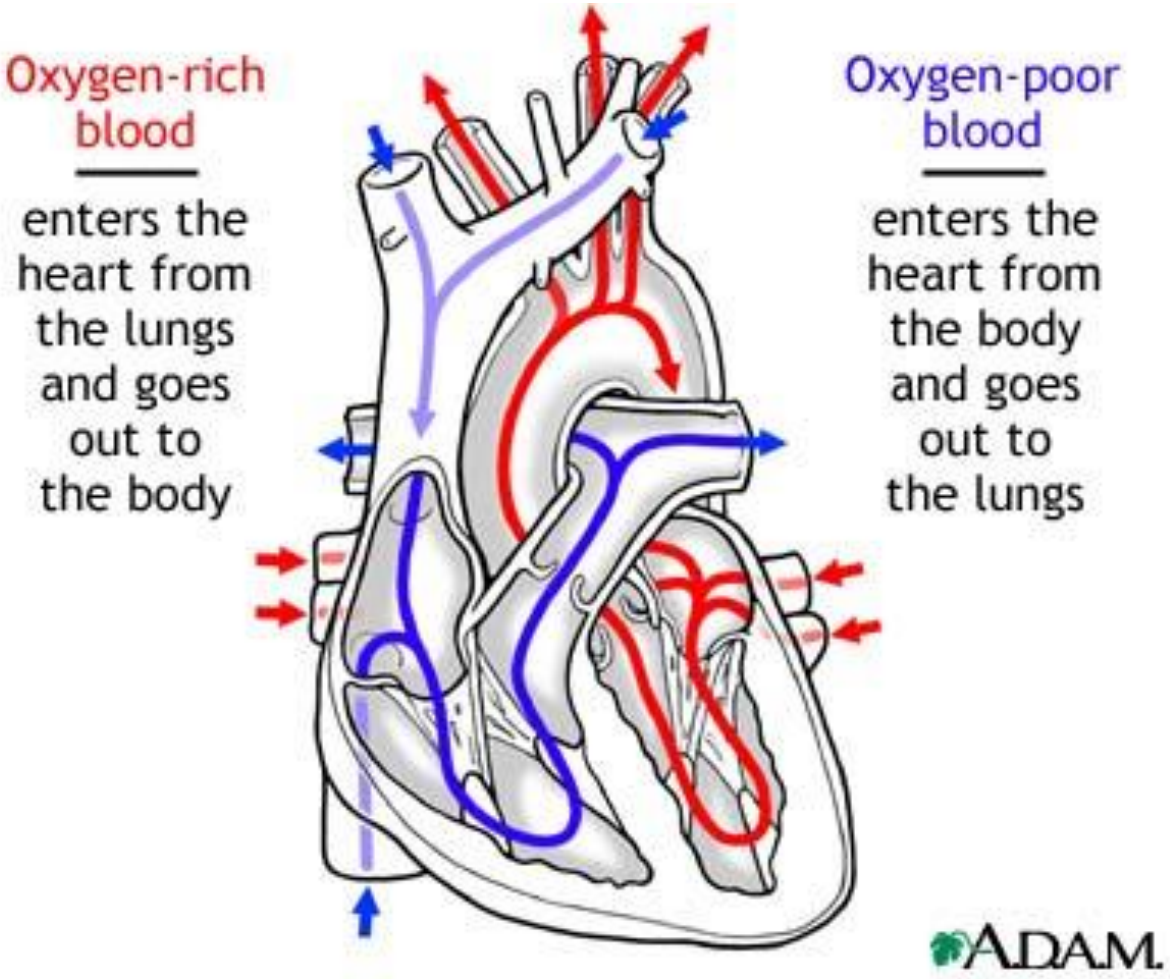
The Heart


Aorta
Superior vena cava
Left pulmonary artery
Left atrium
Right pulmonary veins
Left pulmonary veins
Right atrium
Inferior vena cava
Left ventricle
Right ventricle
A.D.A.M.

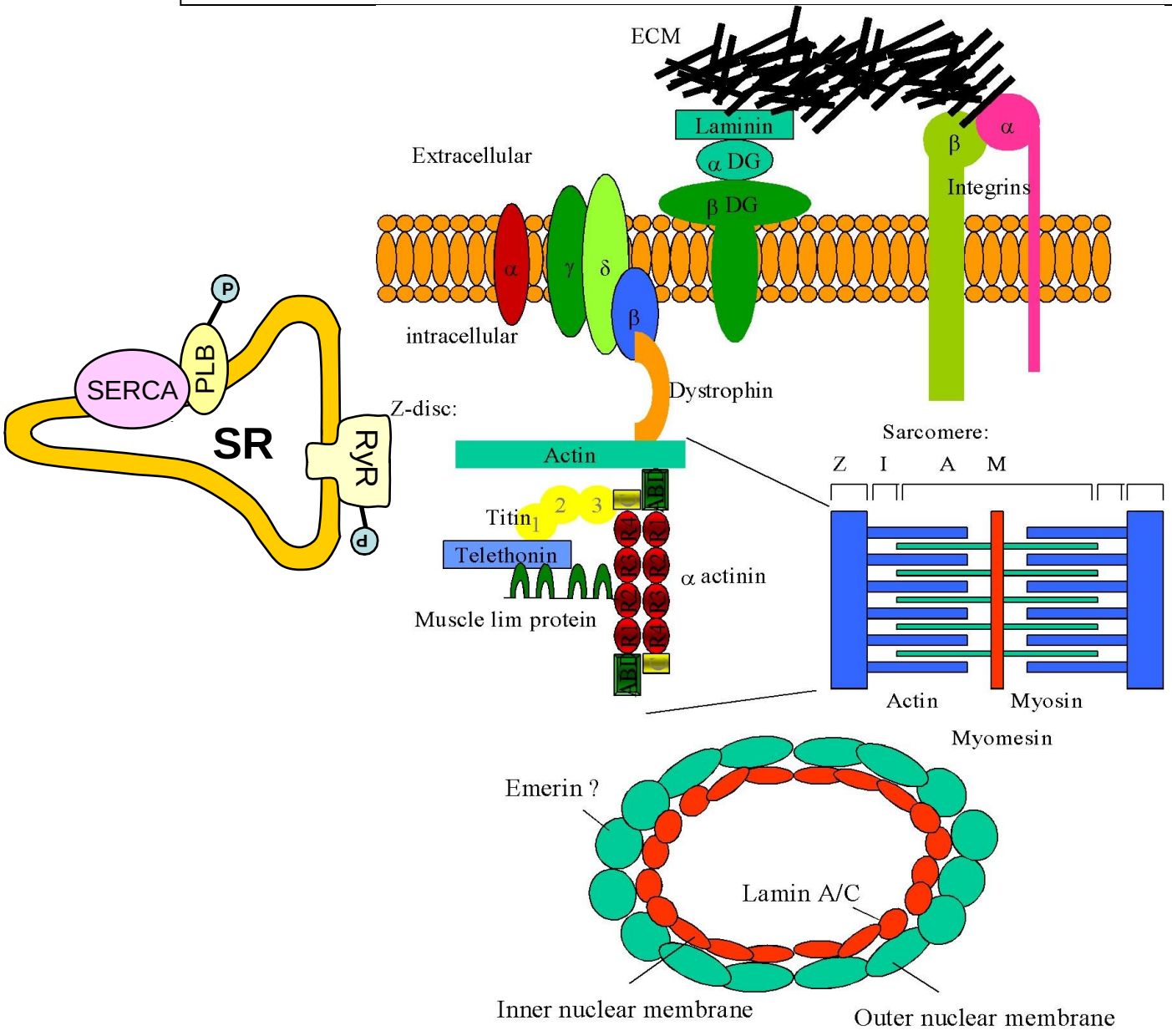
The Heart


Aorta
Superior vena cava
Pulmonary artery
Aortic valve
Left atrium
Right pulmonary veins
Left pulmonary veins
Right atrium
Mitral valve
Tricuspid valve
Left ventricle
Inferior vena cava
Right ventricle
A.D.A.M.

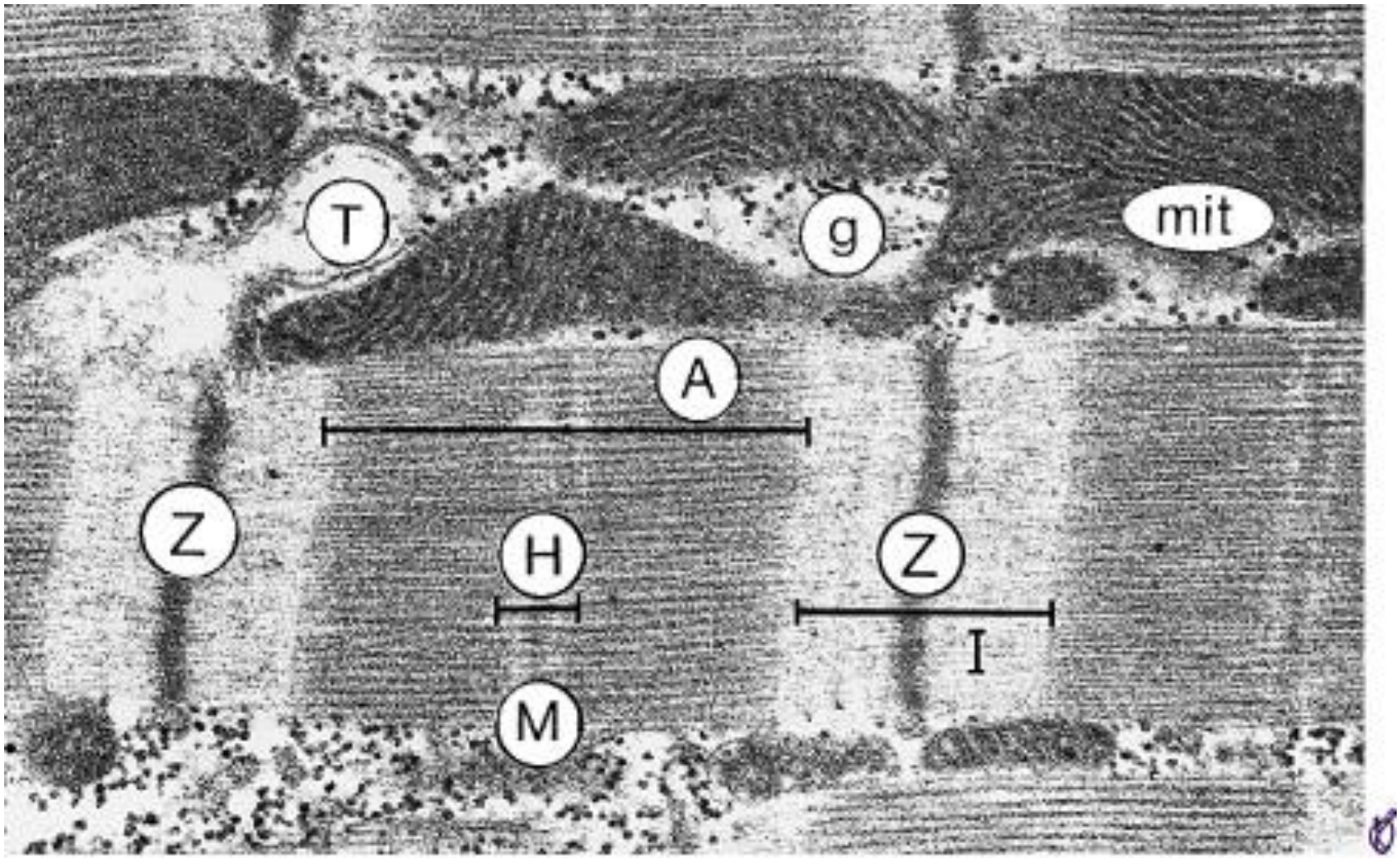
The Heart


Oxygen-rich blood
enters the heart from the lungs and goes out to the body
Oxygen-poor blood
enters the heart from the body and goes out to the lungs
A.D.A.M.

Overview – Cardiomyocyte



The sarcomere



Braunwald: Heart Disease

Heart Failure-Definition

- Definition: A complication of HEART DISEASES. Defective cardiac filling and/or impaired contraction and emptying, resulting in the heart's inability to pump a sufficient amount of blood to meet the needs of the body tissues or to be able to do so only with an elevated filling pressure. (from Braunwald, Heart Disease, 5th ed)
- Heart Failure is a syndrome caused by a variety of different causes (“etiologies”).

Epidemiology

- **70% of all heart failures are due to coronary heart disease**
- **Cardiomyopathies (particularly dilated cardiomyopathies)**
- **Hypertensive Heart Disease**
- **Congenital Heart Disease**
- **Heart Valve Disease**
- **Arrhythmias**

Epidemiology

- **About 1-2% of the population is affected by heart failure**
- **Men much more than females (because of 3 X higher incidence of coronary heart failure in men)**
- **Western developed societies become "older" and as a consequence the importance of heart failure increases**

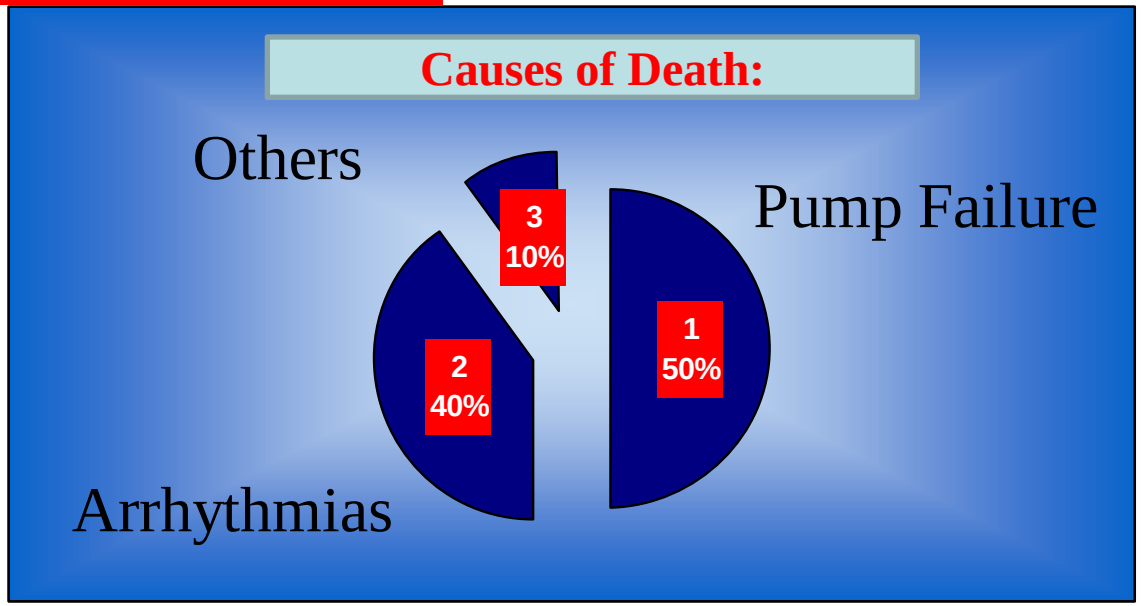
New York Heart Association (NYHA) – An Important Classification

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Prognosis

State:	1 Year Mortality:
NYHA I	5% (SOLVD – Study)
NYHA II	10-20%
	5 Year Mortality (all studies):
NYHA II-IV	>50%

Others: problems associated with changes in blood flow for example (Thrombus? Apoplex?)



Causes 1

- Loss of myocardium (Myocardial Infarction)
- Pressure overload (arterial hypertonus - *Cor Hypertensivum,* Aortic Stenosis)
- Volumeoverload (Aortic insufficience, Shunts, Vitia)
- Primary diseases of the heart muscle (dilatated cardiomyopathy, myocarditis)
- Restrictive diseases of the heart (inhibit filling of the ventricles)
- Arrhythmias (Brady-Tachycardias)

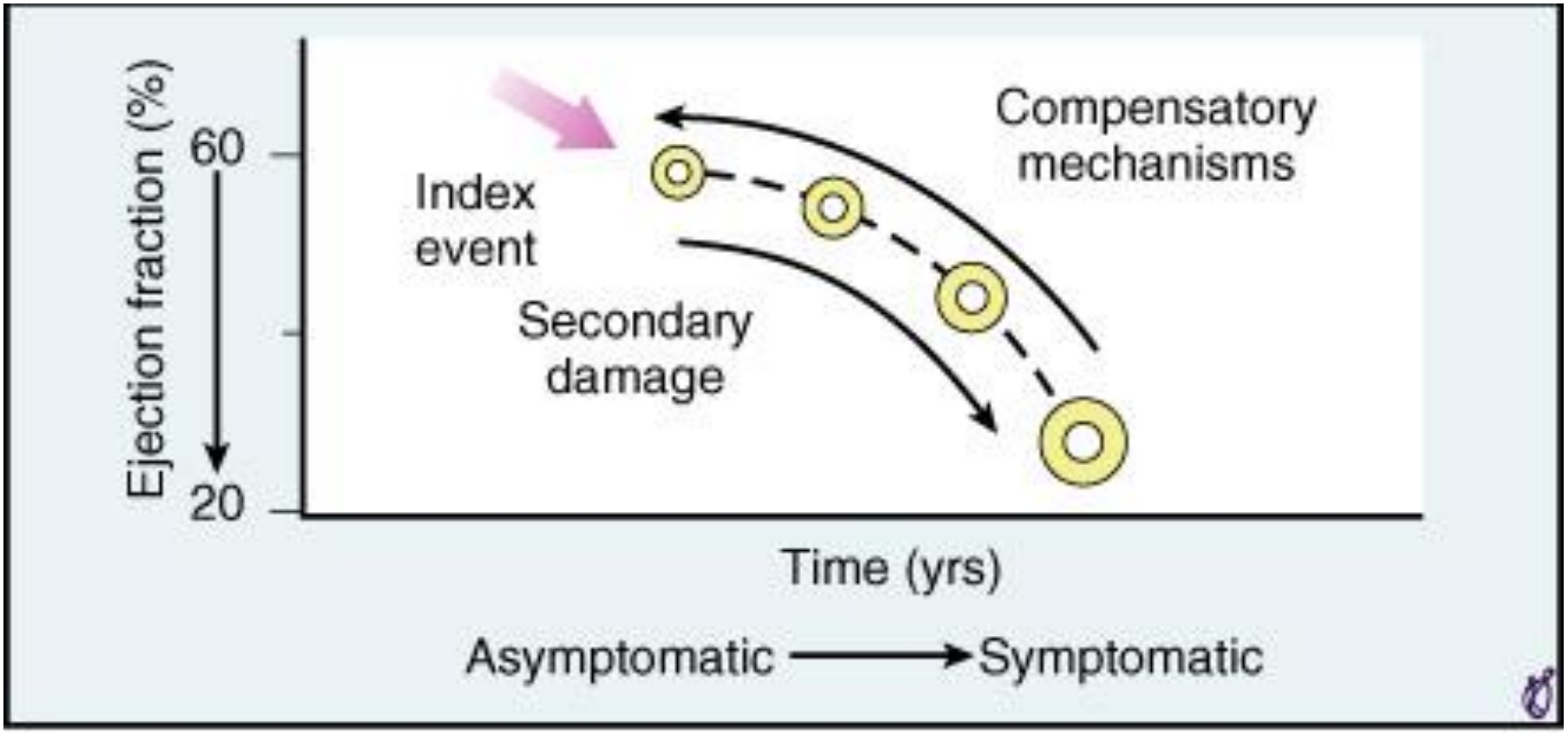
Causes 2

- Congenital heart disease
- Valve diseases
- „Cor pulmonale“ (primary disease of the lung affecting secundarily the heart)
- Diseases of the pericardium
- Cardiac tumors (rare)
- Cardiac manifestations of systemic diseases (i. e. Lupus Erythematodes)
- Traumata (i. e. consequences of car accidents)

TABLE 20–2 Definitions of Terms Used to Describe Systolic and Diastolic Function

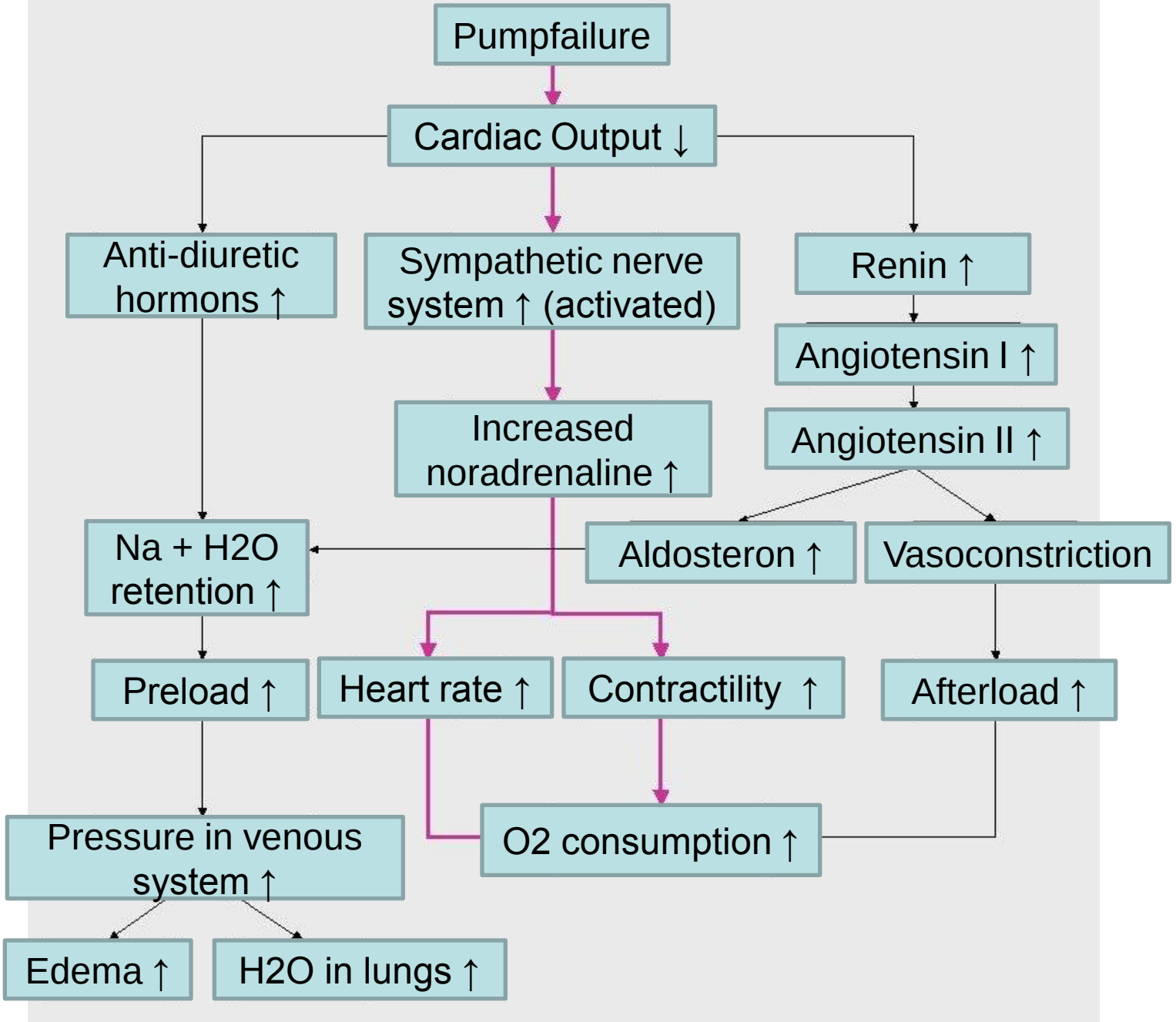
Term	Definition
Preload	Distending force of the ventricular wall, which is highest at end-diastole and is responsible for sarcomere length at the beginning of systolic contraction
Afterload	Resisting force of the ventricular wall during systolic ejection, which is necessary to overcome peripheral vascular resistance or impedance; measures of afterload are peak-systolic, mean-systolic, or end-systolic wall stress
Contractility	Intrinsic ability of the myocardium to generate force at a certain rate and time (controlled for loading conditions)
Cardiac output	Stroke volume multiplied by heart rate
Stroke work	Mean systolic blood pressure multiplied by stroke volume
Stroke force	Stroke work per ejection time
Stress	Force per area
Wall stress	Pressure multiplied by radius, divided by wall thickness × 2
Compliance or distensibility	Change in volume per change in pressure (dV/dP)
Elastance	Slope of the end-systolic pressure-volume relation
Elasticity	Property of a material to restore its initial length or geometry after distending force has been removed
Strain	Length change in percent of initial length; two definitions are used: LaGrangian strain $e = (l - l_o)l_o$ and natural strain $e = \ln(l/lo)$
Stiffness	Pressure per volume change (dP/dV). *Ventricular stiffness* is a measure for changes of the ventricle as a whole; *myocardial stiffness* is a measure for changes of the myocardium itself. Ventricular properties are characterized by instantaneous pressure-volume relations, whereas myocardial properties are best described by stress-strain relations.
Creep	Time-dependent lengthening of a material in the presence of a constant force
Stress relaxation	Time-dependent decrease of stress in the presence of a constant length
Viscoelasticity	Resistance of a material to length changes (strain) or the velocity of length changes (strain rate)

Heart Failure – Schematic Diagram – Dynamic Process, not constant

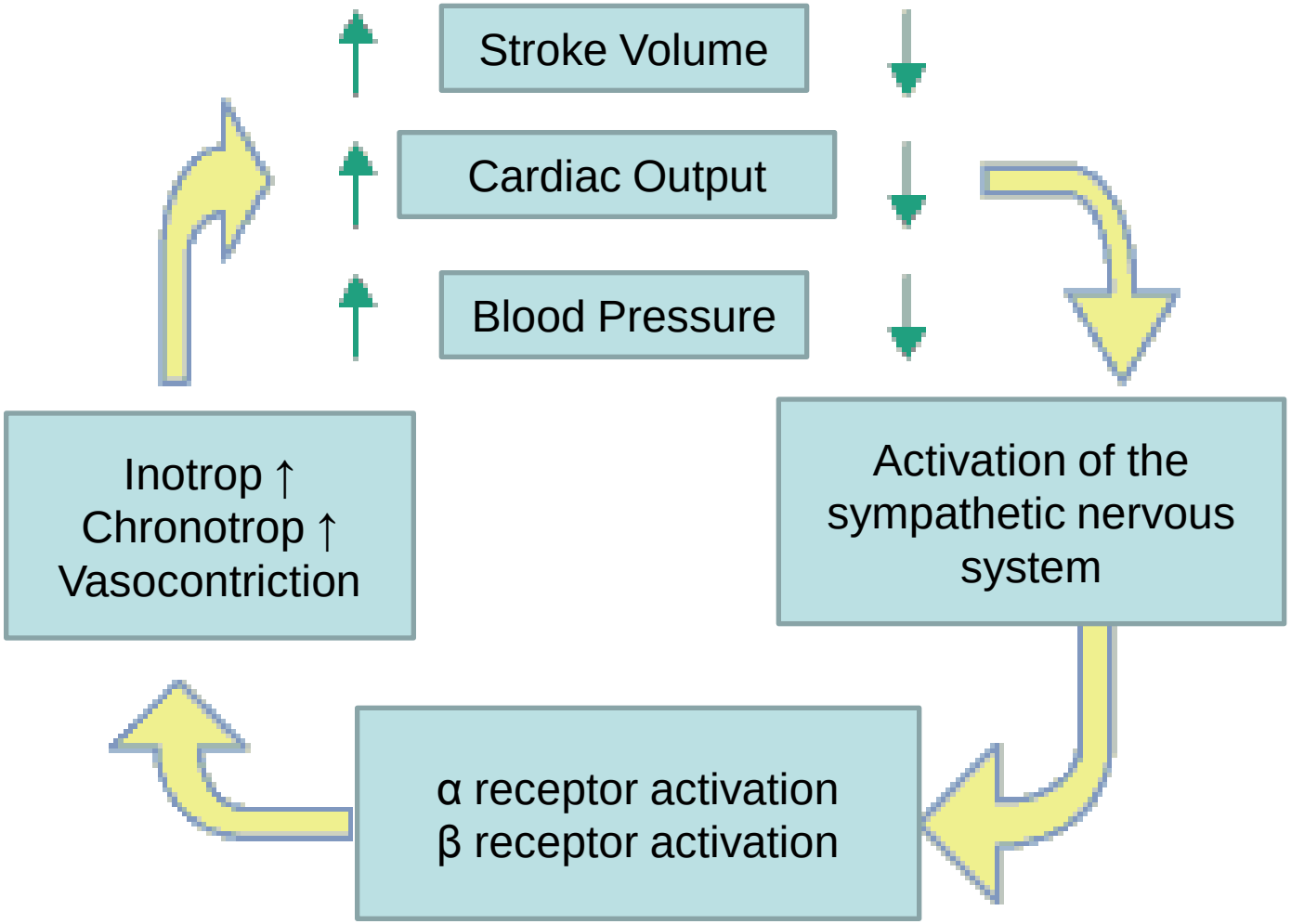


Braunwald: Heart Disease

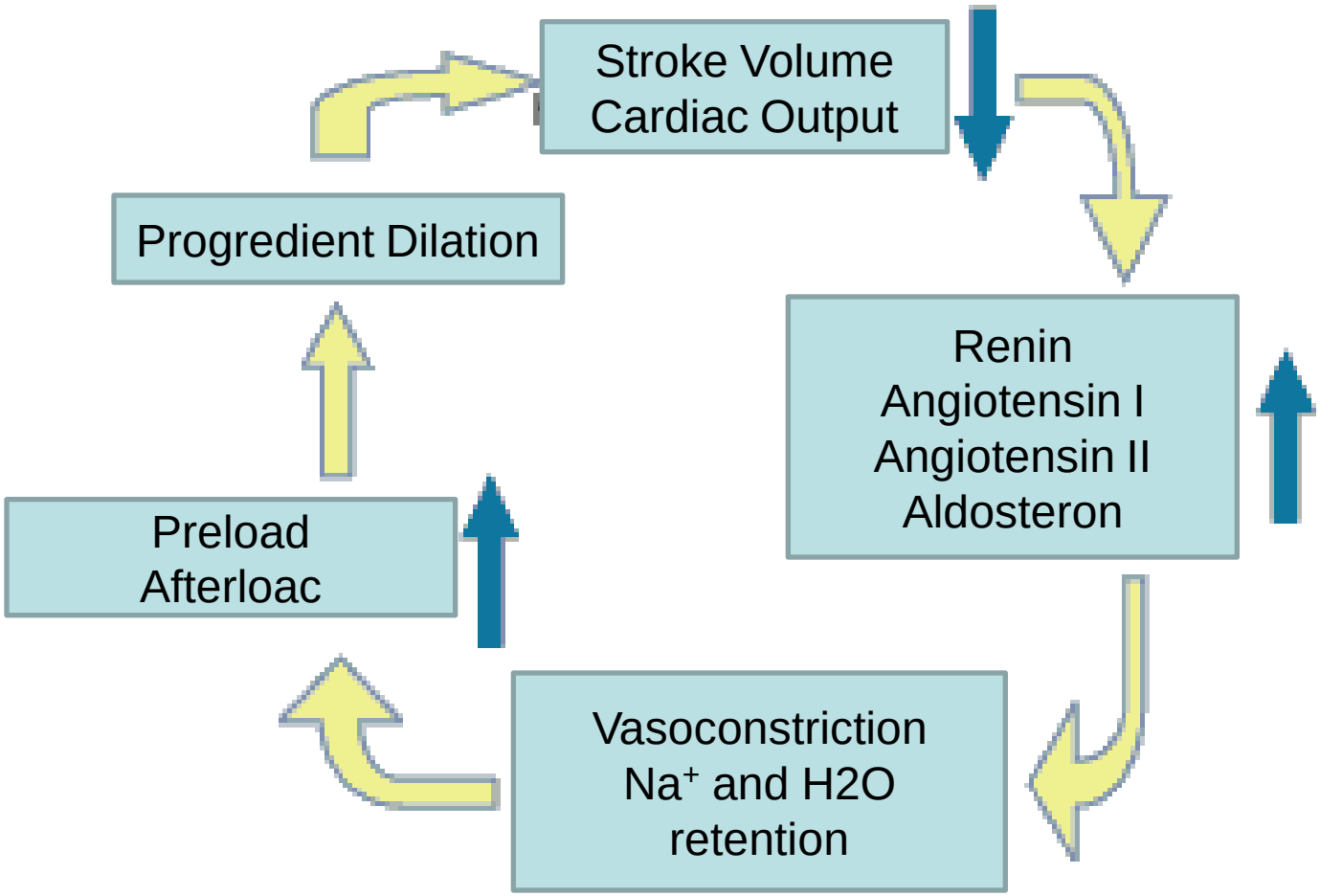
Compensatory Mechanisms



Heart Failure:
Circulus vitiosus – vicious cycle



Heart Failure:
Circulus vitiosus – vicious cycle



Cardiac and Vascular Changes Accompanying Heart Failure

Cardiac

Decreased stroke volume & cardiac output
Increased end-diastolic pressure
Ventricular dilation and / or hypertrophy
Impaired filling (diastolic dysfunction)
Reduced ejection fraction (systolic dysfunction)

Vascular

Increased systemic vascular resistance
Decreased aterial pressure
Impaired arterial pressure
Impaired organ perfusion
Decreased venous compliance
Increased venous pressure
Increased blood volume

Compensatory Mechanisms During Heart Failure

Cardiac
Frank-Starling mechanism
Ventricular dilation or hypertrophy
Tachycardia

Autonomic Nerves
Increased sympathetic adrenergic activity
Reduced vagal activity to heart

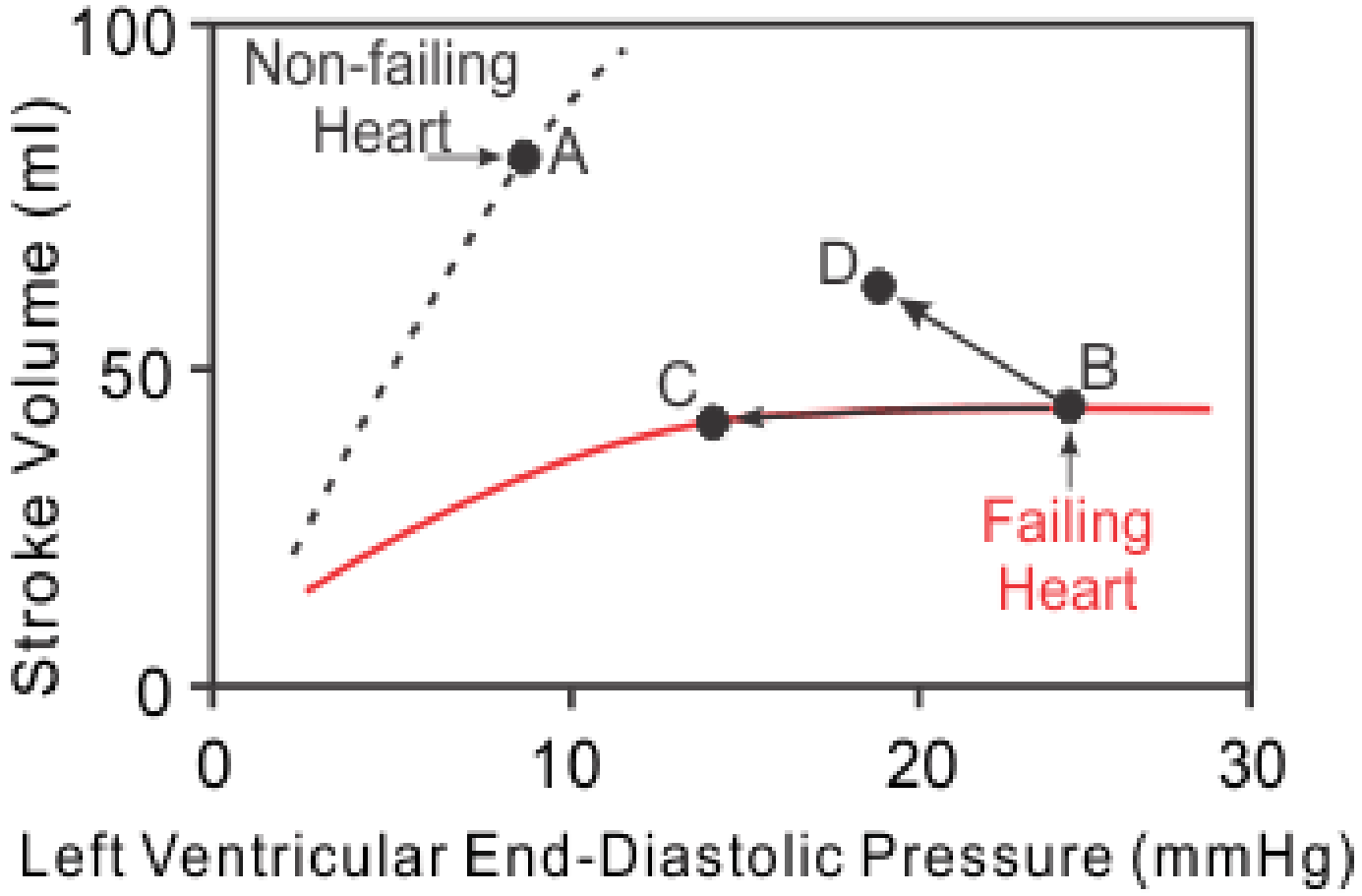
Hormones
Renin-angiotensin-aldosterone system
Vasopressin (antidiuretic hormone)
Circulating catecholamines
Natriuretic peptide

Time dependent effects:
1. Short term
2. Long term

Changes of the cardiac phenotype

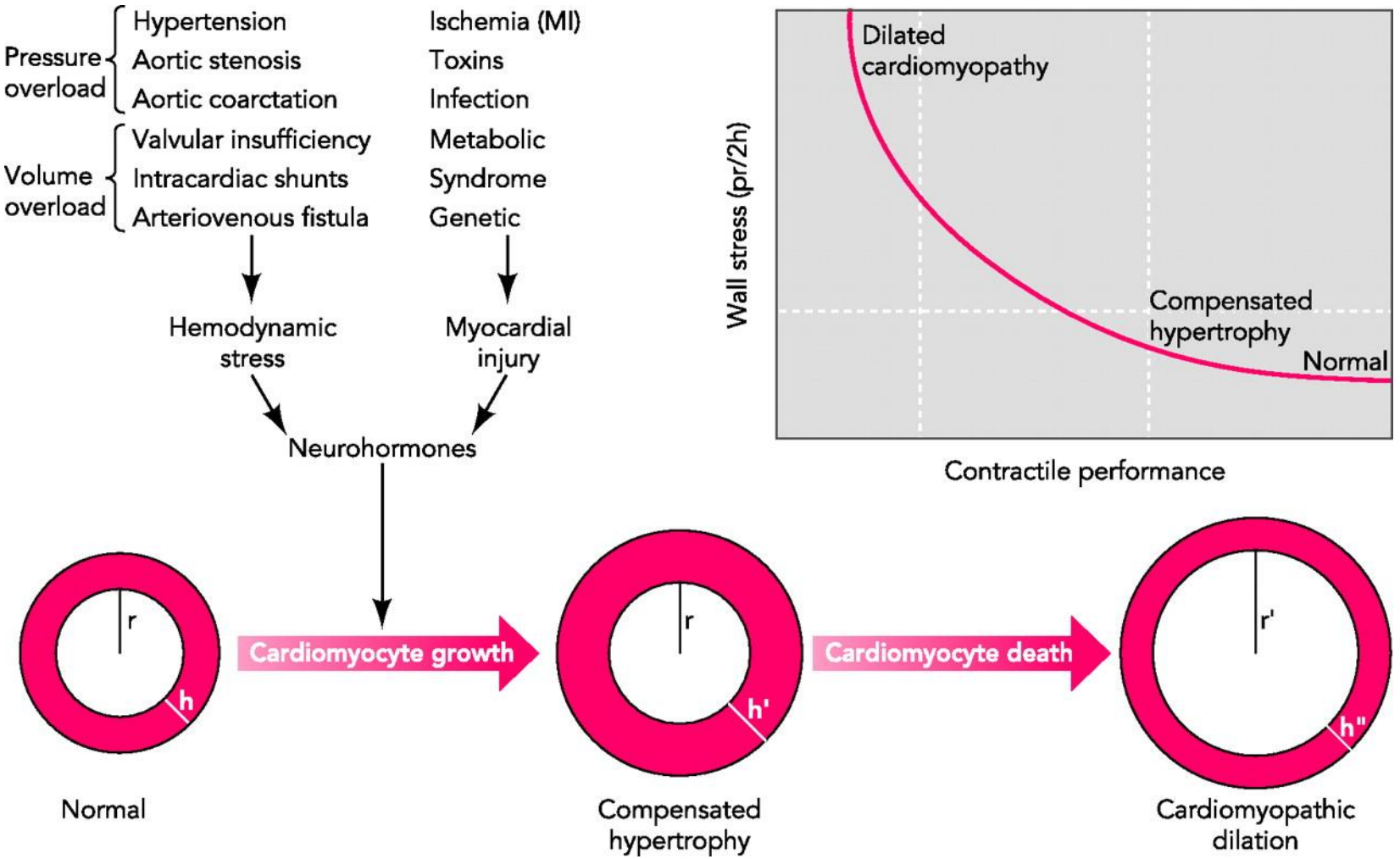
- Changes in cell structure / function (sarcomeres in series or in parallel)
- Extracellular Matrix (Fibrosis)
- Membrane receptors: $\beta 1$ Receptor down regulation
- Ion channels
- contractile proteins (α MHC down, β MHC up)
- Calcium metabolism (SERCA down)
- atrial natriuretic peptide (ANP) and BNP (brain natriuretic peptide) induced
- Energy metabolism (“fatty acid metabolism increased”)
- In general: “fetal pattern of gene expression”

Hemodynamics



A = operating point for non-failing heart
B = operating point for failing heart
C = effects of a diuretic or venodilator
D = effects of mixed vasodilator or inotropic drug

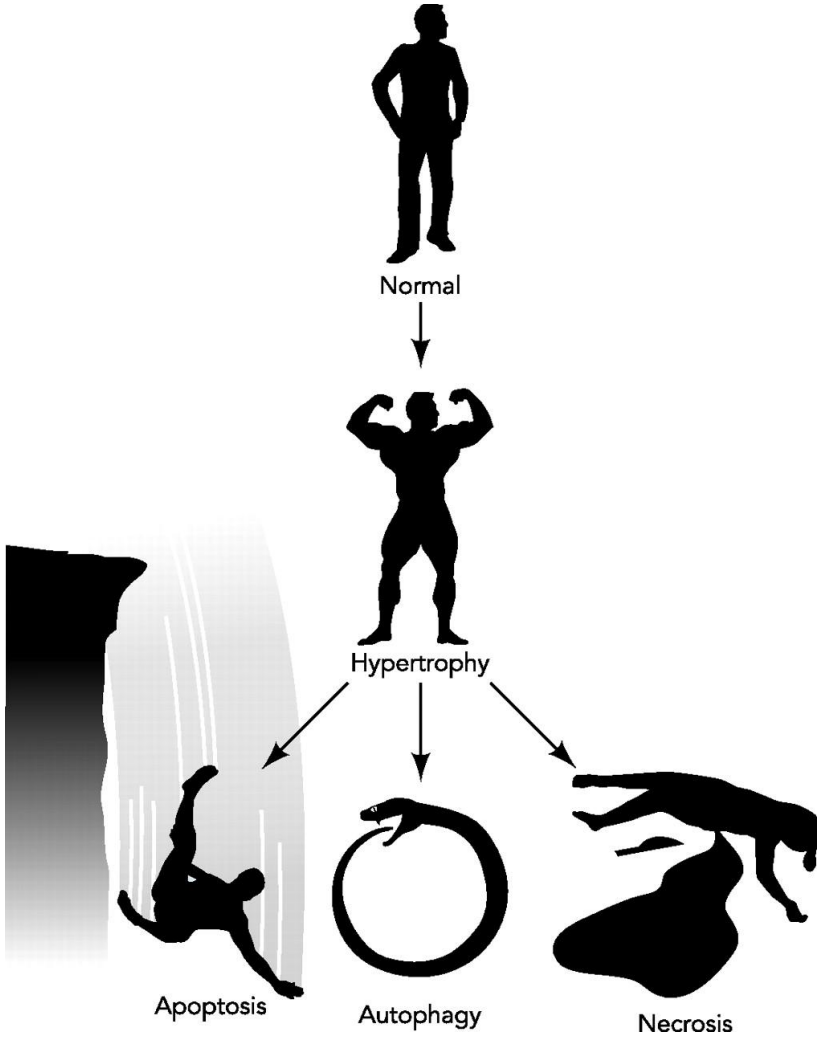
Development and progression of decompensated chamber hypertrophy



Diwan A , Dorn G W Physiology 2007;22:56-64

Physiology

Modes of cell death in hypertrophy



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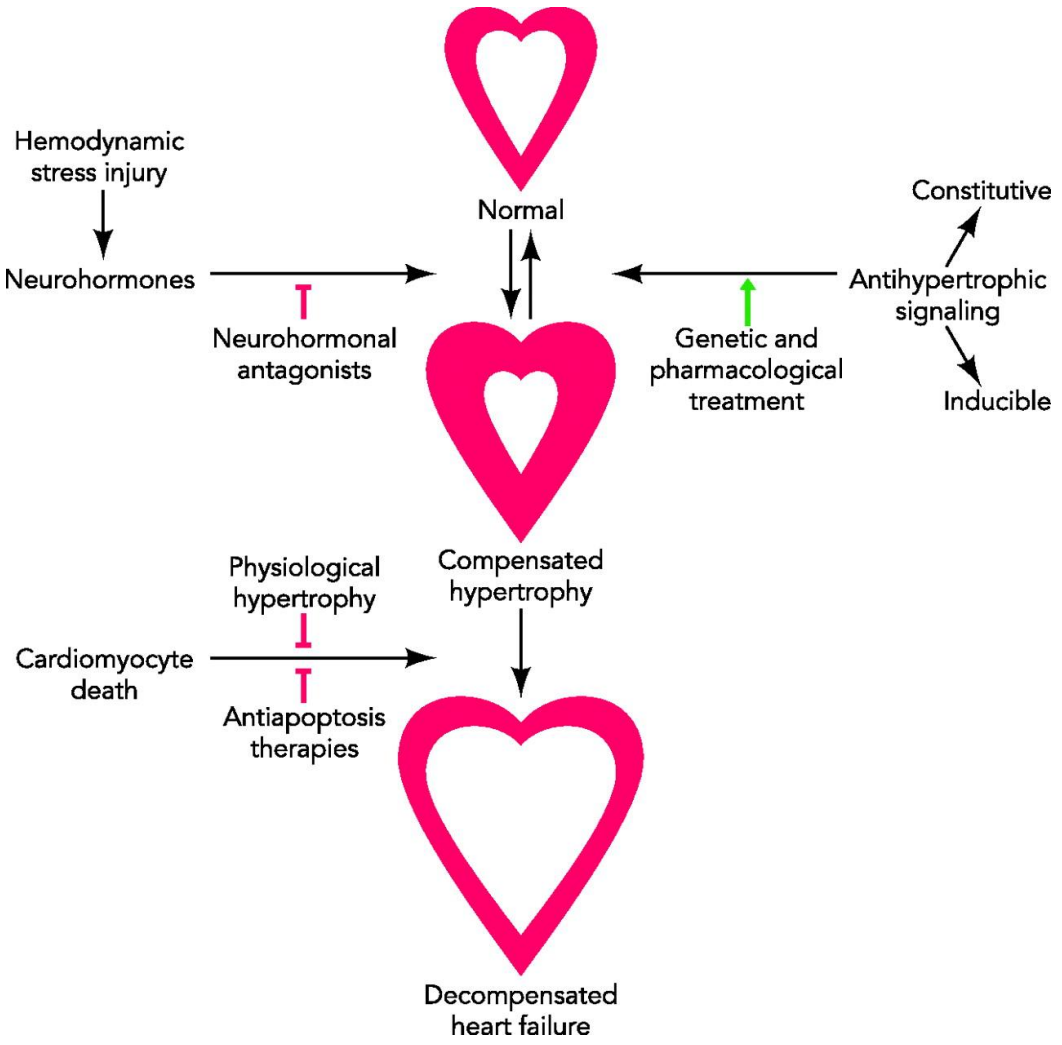
Therapeutic strategies to prevent decompensated heart failure



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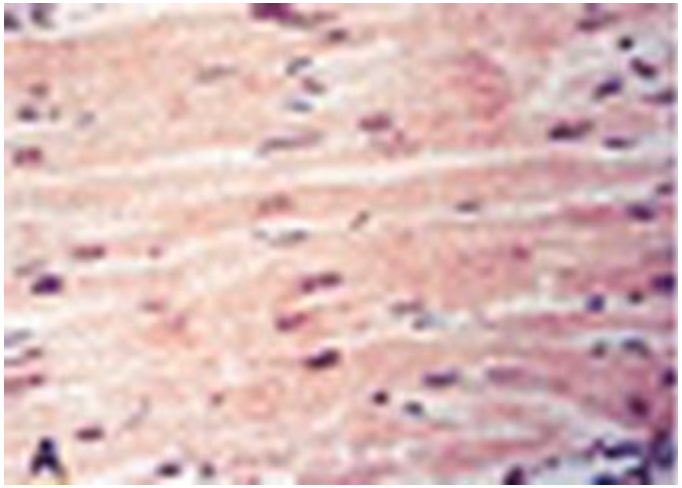
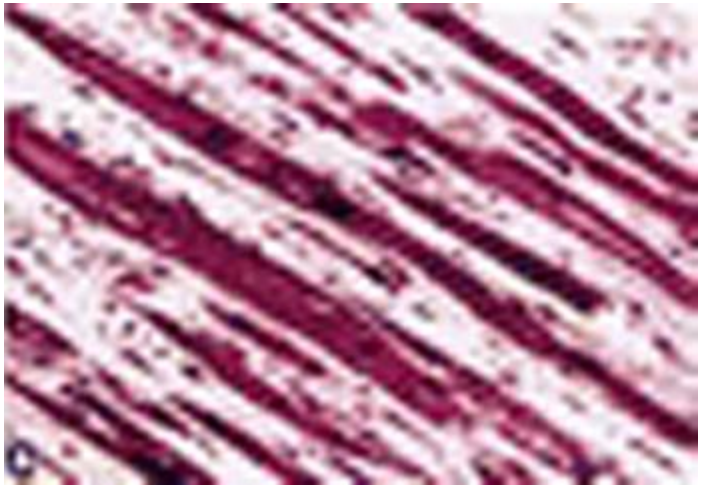
Heart Failure - Histology

H&E



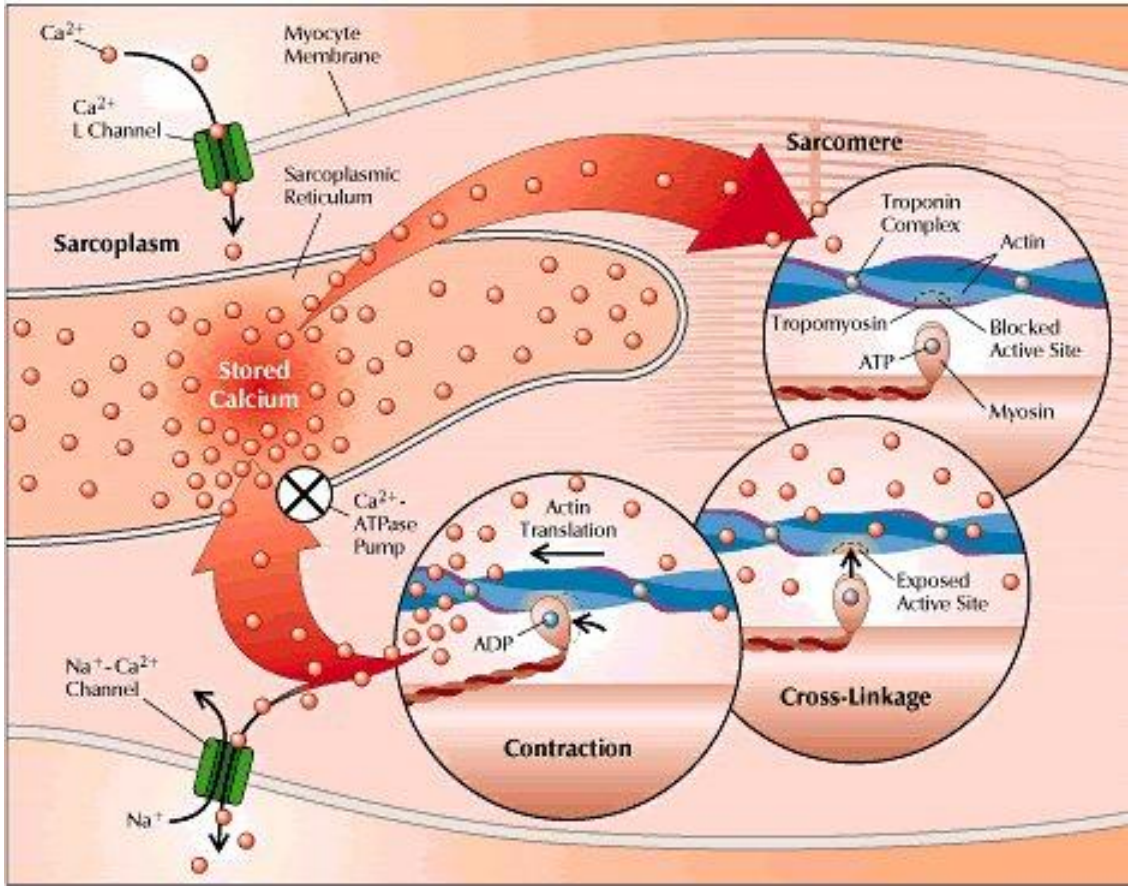
Normal (no or close to no interstial fibrosis; elongated, symmetric Myocytes)

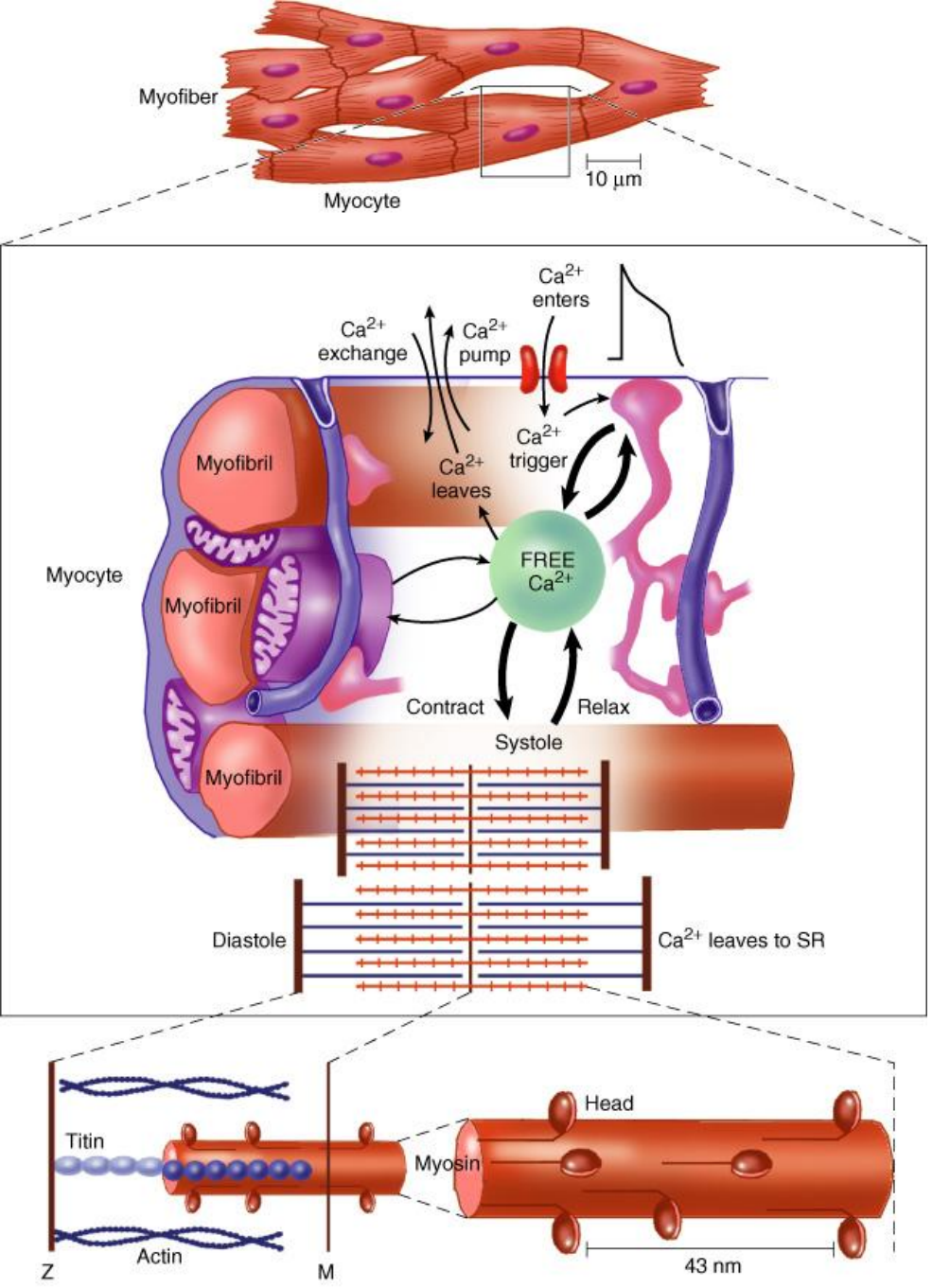
H&E



DCM (red: no Disarray, Hyper-trophic and degenerated myocytes, pink: interstitial fibrosis)

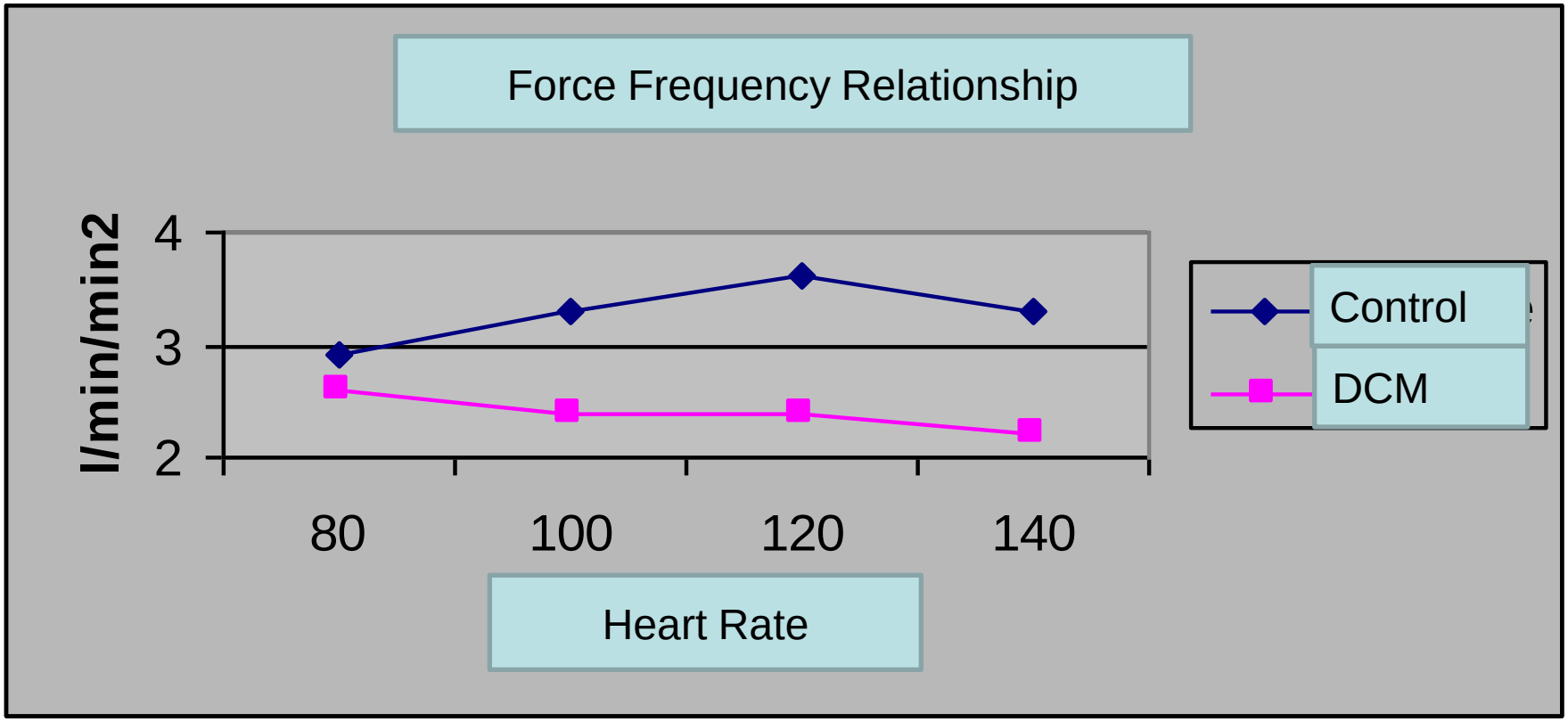
Sarcoplasmic Reticulum ATPase (SERCA)





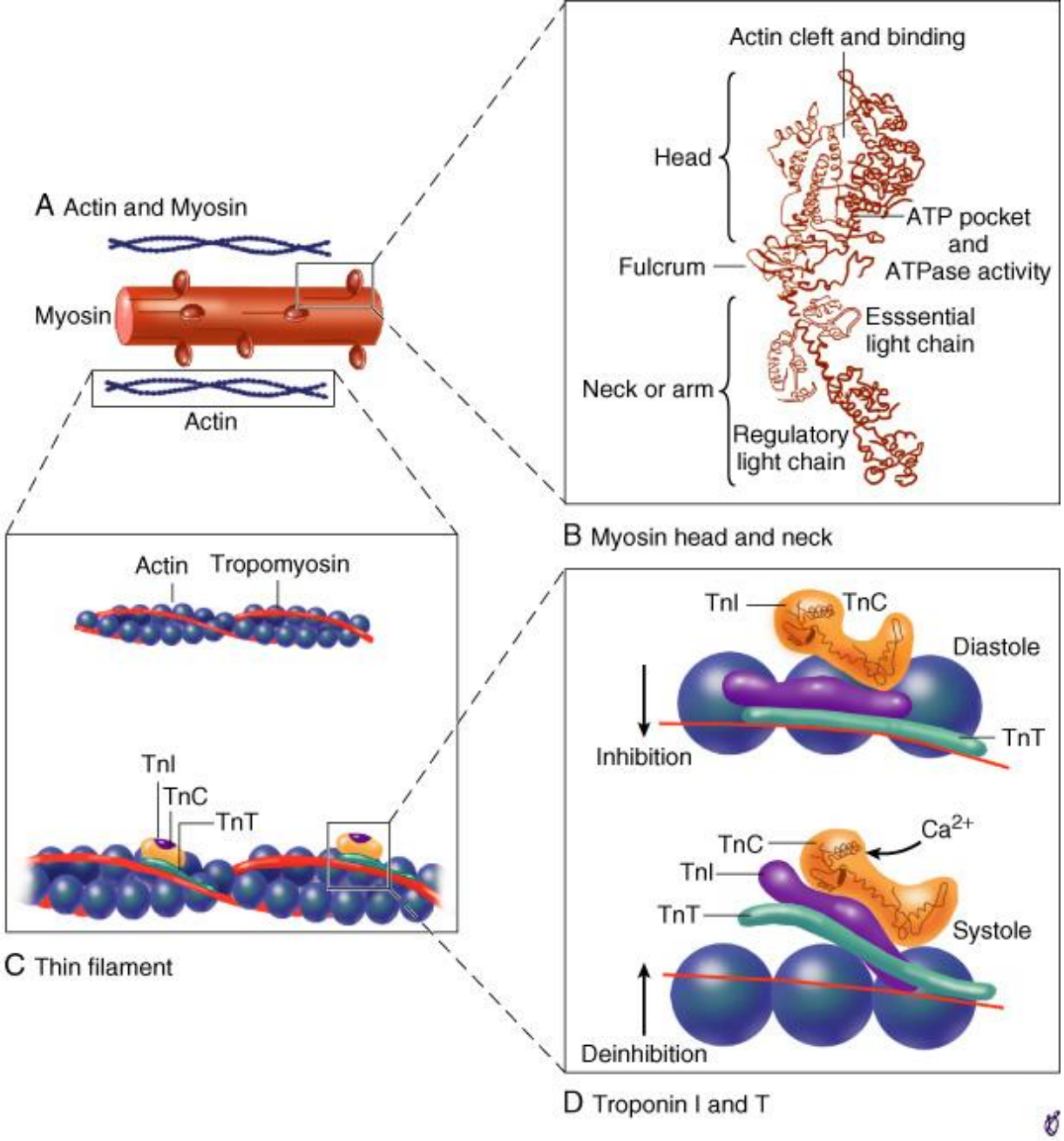
Electro-mechanical coupling

Heart Failure



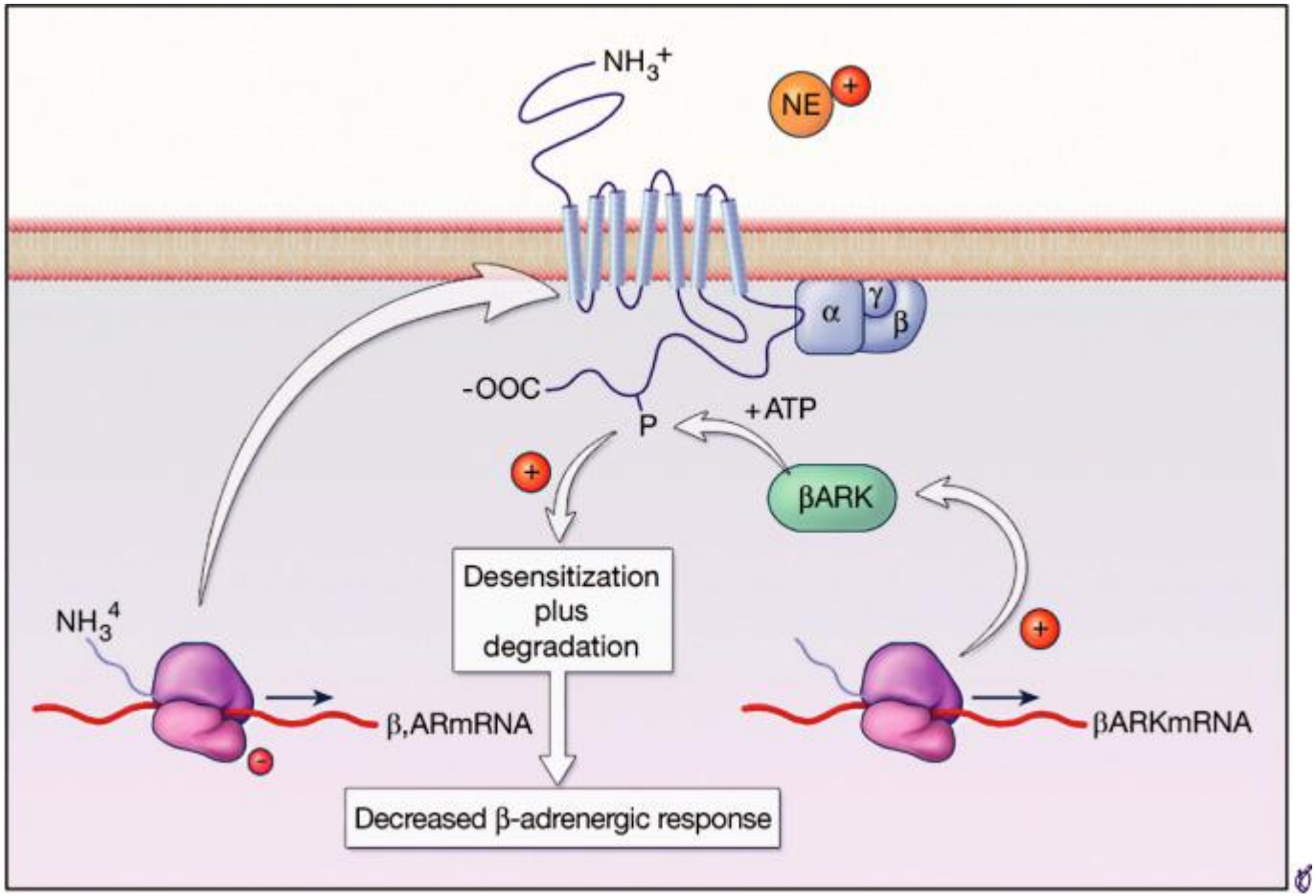
Physiology: increased frequency is associated with an increase in contractility (Frequence inotropism, “Treppe” (=stair case))

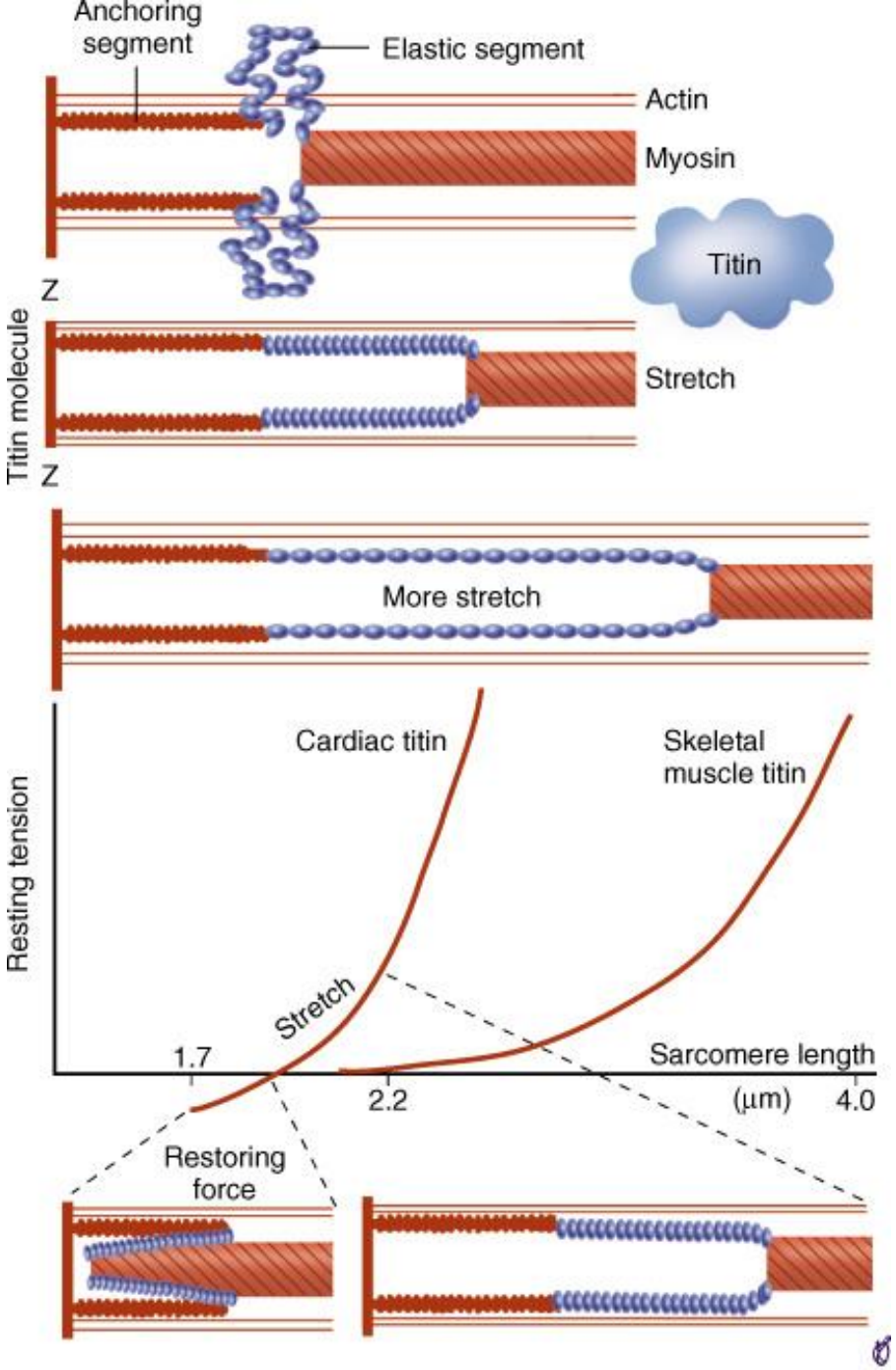
Heart Failure: increased frequency is not able to increase contractility



Acto-myosin Interaction

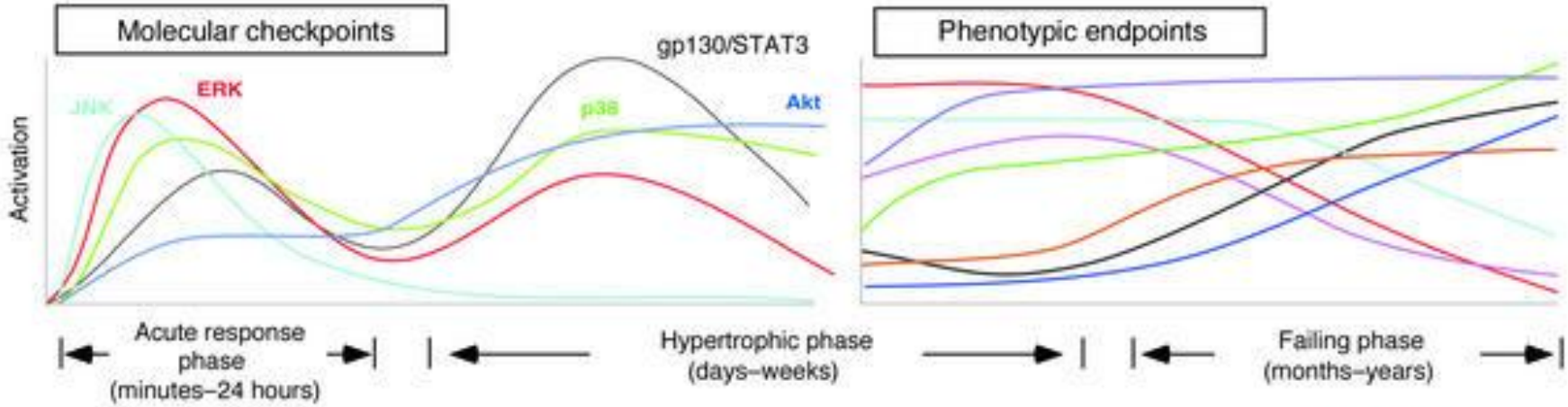
β-receptor downregulation, upregulation of βARK (desensitizes β-receptor signalling)





Titin

Heart Failure – Gene Expression



Gene expression profiles

(Acute phase)

Upregulation

c-fos
c-jun
junB
egr-1
nur77
BNP
SOCS3

(Hypertrophic-failing phase)

Upregulation

Secreted proteins
ANF, Lipocortin I, ET-1
HB-EGF, TGF-β1, BNP
Osteoblast-specific factor 2
Cytoskeletal proteins
αMHC, βMHC
MLC1a/v, MLC2a
MLC2v, Tropomyosin
Troponin C, Myomesin
Smooth muscle α–actin
Skeletal α–actin
α–cardiac actin
FHL1 (HCM), Sarcosin
Desmin, Gelsolin,
Extracellular matrix
Fibulin, Fibronectin
Laminin, Collagen
Others
Heat shock 70 kDa proteins 1, 6, 8
Quaking protein, CARP

Metabolism/translation
Ubiquitin, Pyruvate dehydrogenase α
NADH ubiquinone oxidoreductase
Creatin kinase, Myoglobin
Phosphorylase kinase catalytic subunit
Superoxide dismutase 2
Aldose reductase, EF-1a, EF-2, IF-4AII
28S, 60S ribosomal L3
Ion-channels/carriers
Na^+/Ca^{2+} exchanger, Kv1.4
Voltage-dependent anion channel-1
Signaling
Gsα, βARK, Adenylyl cyclase VII
A-kinase, C-kinase inhibitor-1, ILK
Rap1B, SOCS3, Id-1, GATA-4
SP1/3, PGD/D2 synthase

Downregulation

Cytoskeletal proteins
FHL1 (failing heart)
Nonsarcomeric MLC2
Ion-channels/carriers
L-type Ca^{2+} channel
SERCA2
Phospholambam
Kv4.2, 4.3
Kv1.5
KChIP2
Signaling
type-A like Ephrin receptor
Others
α1-Antichymotrypsin
αB-Crystallin
Plasminogen activator inhibitor-1
TIM17

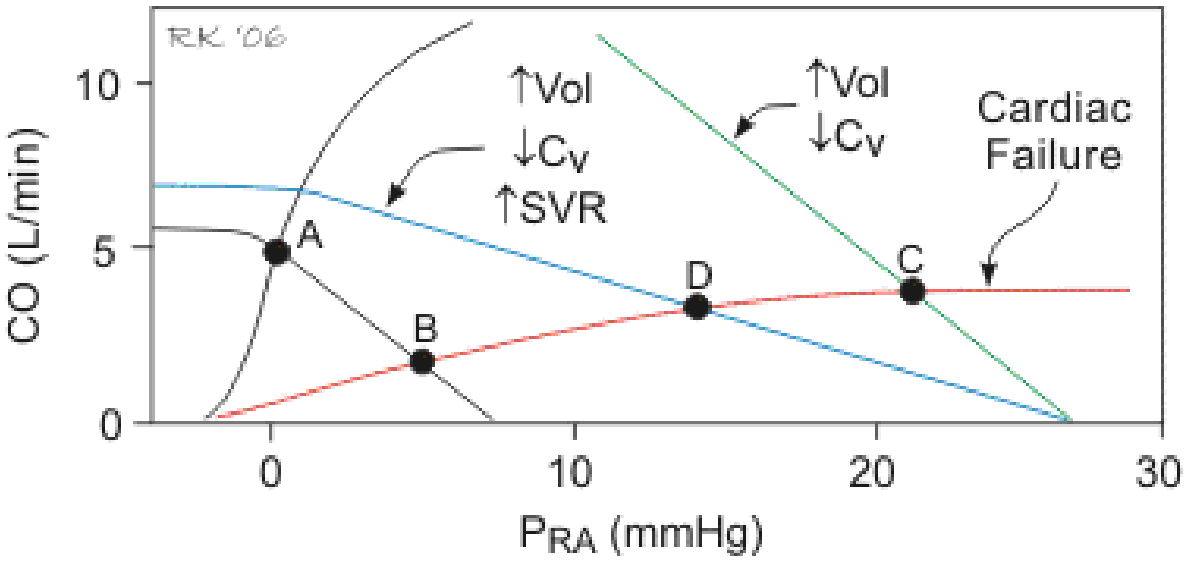
Contractility
Chamber size
Wall thickness
Left ventricular end diastolic pressure
Left ventricular end systolic pressure
Arrhythmia (e.g., AF, VT, AVB)
Myocyte dropout Replacement fibrosis
Embryonic gene program

Cultural Importance

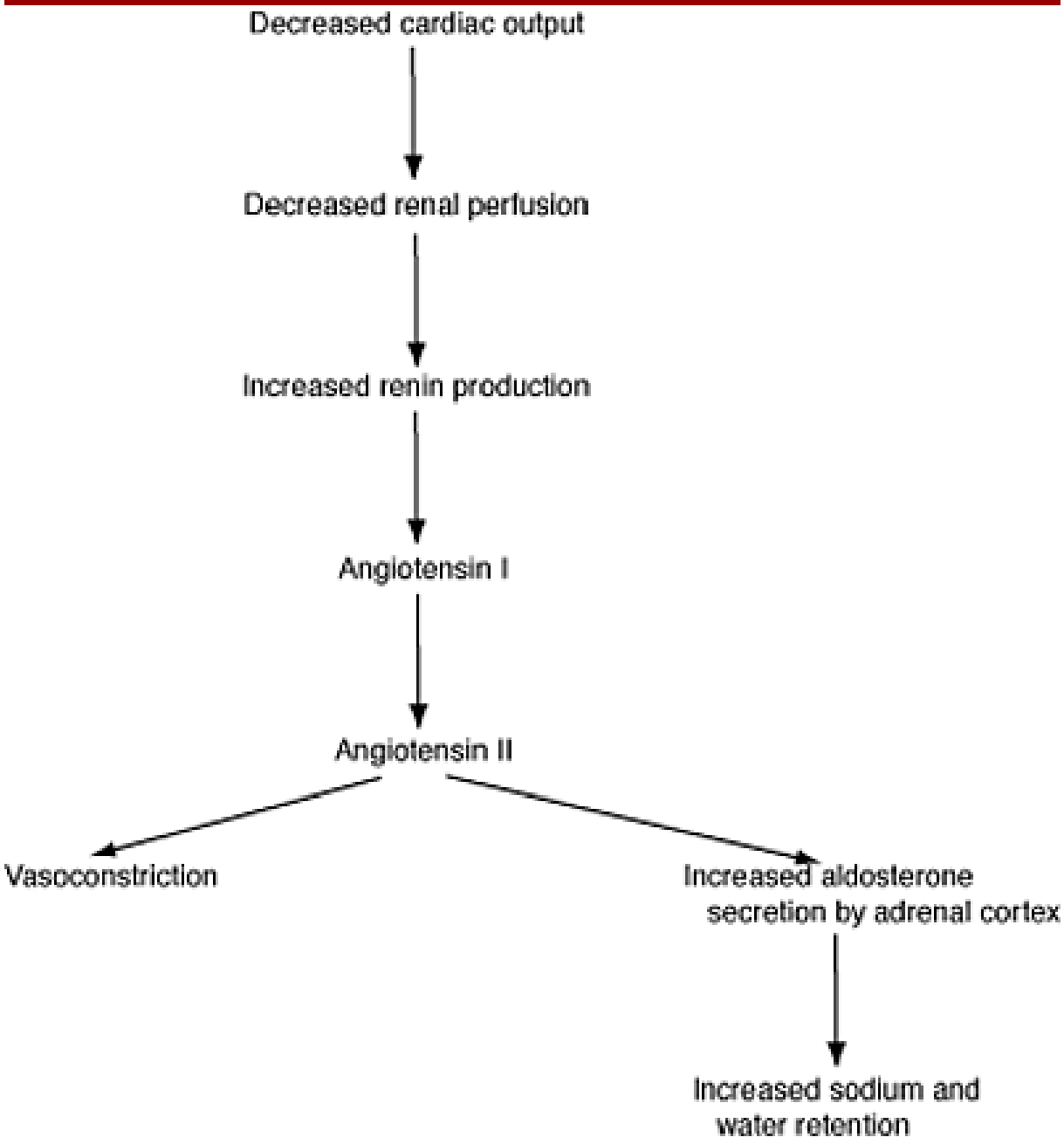
Ebers Papyrus (1600 v. Chr., 18,6 m long, 30 cm width)

“Wenn Du einen Mann findest
mit Herzbeschwerden, mit Schmerzen in seinen Armen,
auf der Seite seines Herzens,
dann ist der Tod nahe.”
(Vermutlich erste Beschreibung
eines Herzinfarktes in der Weltliteratur)

Thank you very much for your attention!



Changes in cardiac output (CO) and right atrial pressure (P_{RA}) in response to cardiac failure and compensatory increases in blood volume (Vol) and systemic vascular resistance (SVR), and decreased venous compliance (C_V). A, normal operating point; B, decreased cardiac performance; C, compensatory increase in Vol and decrease in C_V; and D, increased SVR coupled with increased Vol and reduced C_V.


Decreased cardiac output
Decreased renal perfusion
Increased renin production
Angiotensin I
Angiotensin II
Vasoconstriction
Increased aldosterone secretion by adrenal cortex
Increased sodium and water retention