PATHOPHYSIOLOY OF HEART FAILURE

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HEART FAILURE

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

Heart Failure

Categorized into one of two groups:

- HF with a depressed EF or HFrEF(commonly referred to as *systolic failure*) or
- HF with a preserved EF or HFpEF (EF greater than 50%) commonly referred to as *diastolic failure*
- Patients with a LV EF between 40 and 50% have been considered as having a borderline or mid-rangeEF. At the time of this writing, the epidemiology of these patients is unclear

Heart Failure:

- HEART DIVIDED INTO 2 PUMPING SYSTEMS- RIGHT AND LEFT VENTRICLES
- CARDIAC FUNCTIONING REQUIRES EACH VENTRICLE TO PUMP OUT EQUAL AMOUNTS OF BLOOD
- CONDITIONS THAT CAUSE HEART FAILURE MAY AFFECT ONE OR BOTH OF THE HEARTS PUMPING SYSTEMS

Causes of heart failure

Causes of heart failure

- **Main causes**

  Coronary artery disease (CAD), Hypertension Cardiomyopathy

- **Other causes**: VHD, Congenital heart disease, Alcohol and drugs, Arrhythmia and Pericardial disease, Hyperdynamic circulation (anaemia, thyrotoxicosis,haemocatosis,Paget's disease)

ETIOLOGY

- In industrialized countries, coronary artery disease (CAD) has become the predominant cause in men and women and is responsible for 60–75% of cases of HF

- Hypertension contributes to the development of HF in 75% of patients, including most patients with CAD

ETIOLOGY

- Both CAD and hypertension interact to augment the risk of HF, as does diabetes mellitus

ETIOLOGY

- Although the etiology of HF in patients with a preserved EF differs from that of patients with depressed EF, there is considerable overlap between the etiologies of these two conditions

Causes of heart failure

- Right ventricular systolic dysfunction (RVSD) may be secondary to chronic LVSD but can occur with primary and secondary pulmonary hypertension, right ventricular infarction

Depressed Ejection Fraction (<40%)	
Coronary artery disease	Nonischemic dilated cardiomyopathy
Myocardial infarction[a]	Familial/genetic disorders
Myocardial ischemia[a]	Infiltrative disorders[a]
Chronic pressure overload	Toxic/drug-induced damage
Hypertension[a]	Metabolic disorder[a]
Obstructive valvular disease[a]	Viral
Chronic volume overload	Chagas' disease
Regurgitant valvular disease	Disorders of rate and rhythm
Intracardiac (left-to-right) shunting	Chronic bradyarrhythmias
Extracardiac shunting	Chronic tachyarrhythmias
Preserved Ejection Fraction (>40–50%)	
Pathological hypertrophy	Restrictive cardiomyopathy
Primary (hypertrophic cardiomyopathies)	Infiltrative disorders (amyloidosis, sarcoidosis)
Secondary (hypertension)	Storage diseases (hemochromatosis)
Aging	Fibrosis
	Endomyocardial disorders
Pulmonary Heart Disease	
Cor pulmonale	
Pulmonary vascular disorders	
High-Output States	
Metabolic disorders	Excessive blood-flow requirements
Thyrotoxicosis	Systemic arteriovenous shunting
Nutritional disorders (beriberi)	Chronic anemia

PROGNOSIS

PROGNOSIS

- Despite recent advances in the management of HF, the development of symptomatic HF still carries a poor prognosis

- Community-based studies indicate that 30–40% of patients die within 1 year of diagnosis and 60– 70% die within 5 years, mainly from worsening HF or as a sudden event (probably because of a ventricular arrhythmia)

PROGNOSIS

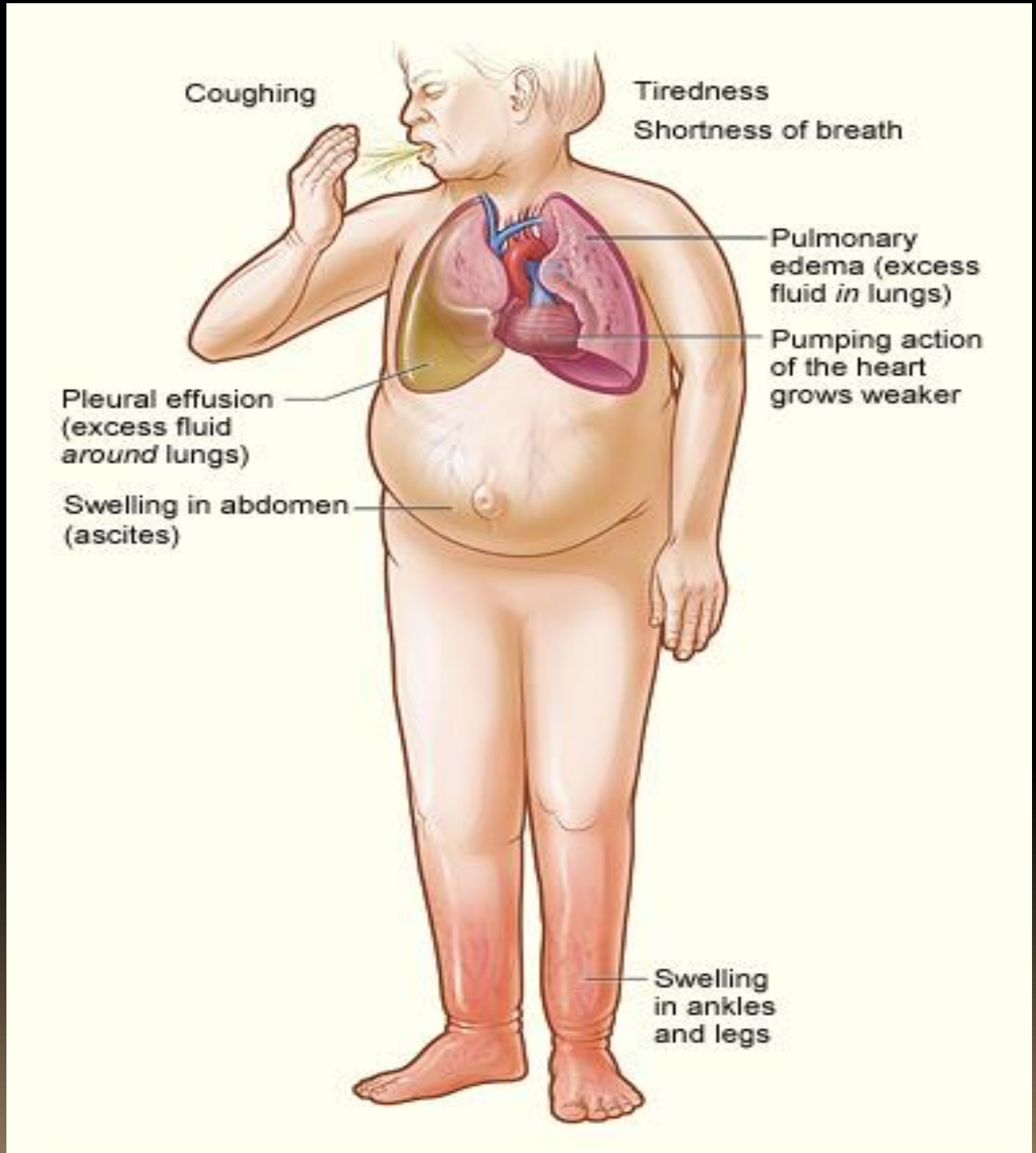
- Although it is difficult to predict prognosis in an individual, patients with symptoms at rest (New York Heart Association [NYHA class IV) have a 30–70% annual mortality rate, whereas patients with symptoms with moderate activity (NYHA class II) have an annual mortality rate of 5–10%

- Thus, functional status is an important predictor of patient outcome

New York Heart Association Classification

Functional Capacity	Objective Assessment
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Pathogenesis Of HF with Reduced EF


Coughing
Tiredness
Shortness of breath
Pulmonary edema (excess fluid *in* lungs)
Pumping action of the heart grows weaker
Pleural effusion (excess fluid *around* lungs)
Swelling in abdomen (ascites)
Swelling in ankles and legs

Pathogenesis:

- Progressive disorder that is initiated after an *index event* either damages the heart muscle, with a resultant loss of functioning cardiac myocytes, or alternatively disrupts the ability of the myocardium to generate force, thereby preventing the heart from contracting normally

Pathogenesis:

- This index event may have an abrupt onset, as in the case of a MI; it may have a gradual or insidious onset, as in the case of hemodynamic pressure or volume overloading; or it may be hereditary, as in the case of many of the genetic cardiomyopathies

Pathogenesis:

- Regardless of the nature of the inciting event, the feature that is common to each of these index events is that they all, in some manner, produce a decline in the pumping capacity of the heart

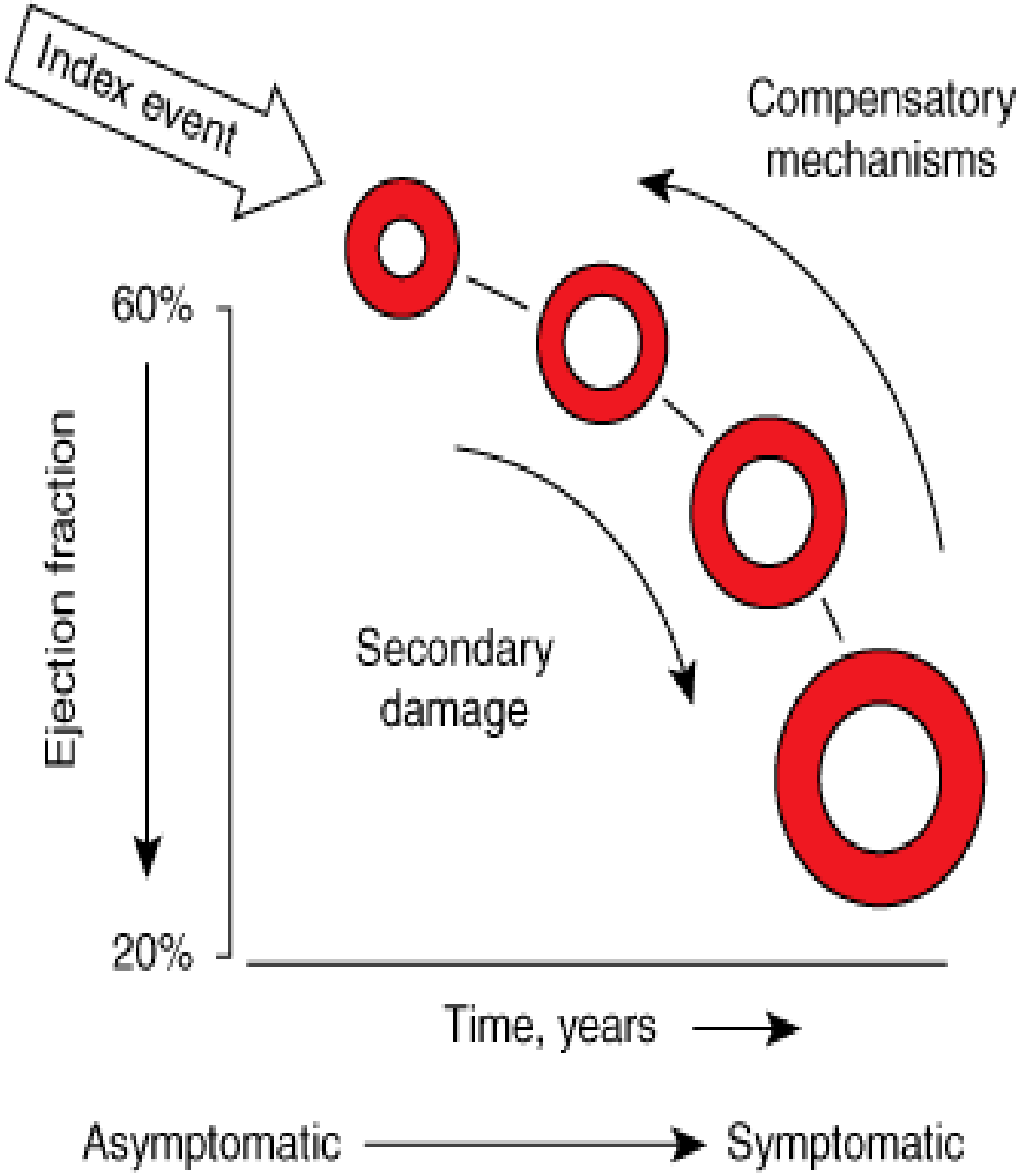
Pathogenesis:

- LV dysfunction is necessary, but not sufficient, for the development of the syndrome of HF

Pathogenesis:

- The decrease in cardiac output in heart failure activates a series of compensatory adaptations that are intended to maintain cardiovascular homeostasis

- Thus, patients may remain asymptomatic or minimally symptomatic for a period of years; however, at some point patients become overtly symptomatic, with a resultant striking increase in morbidity and mortality rates


Index event
Compensatory mechanisms
60%
Ejection fraction
Secondary damage
20%
Time, years
Asymptomatic
Symptomatic

Pathogenesis:

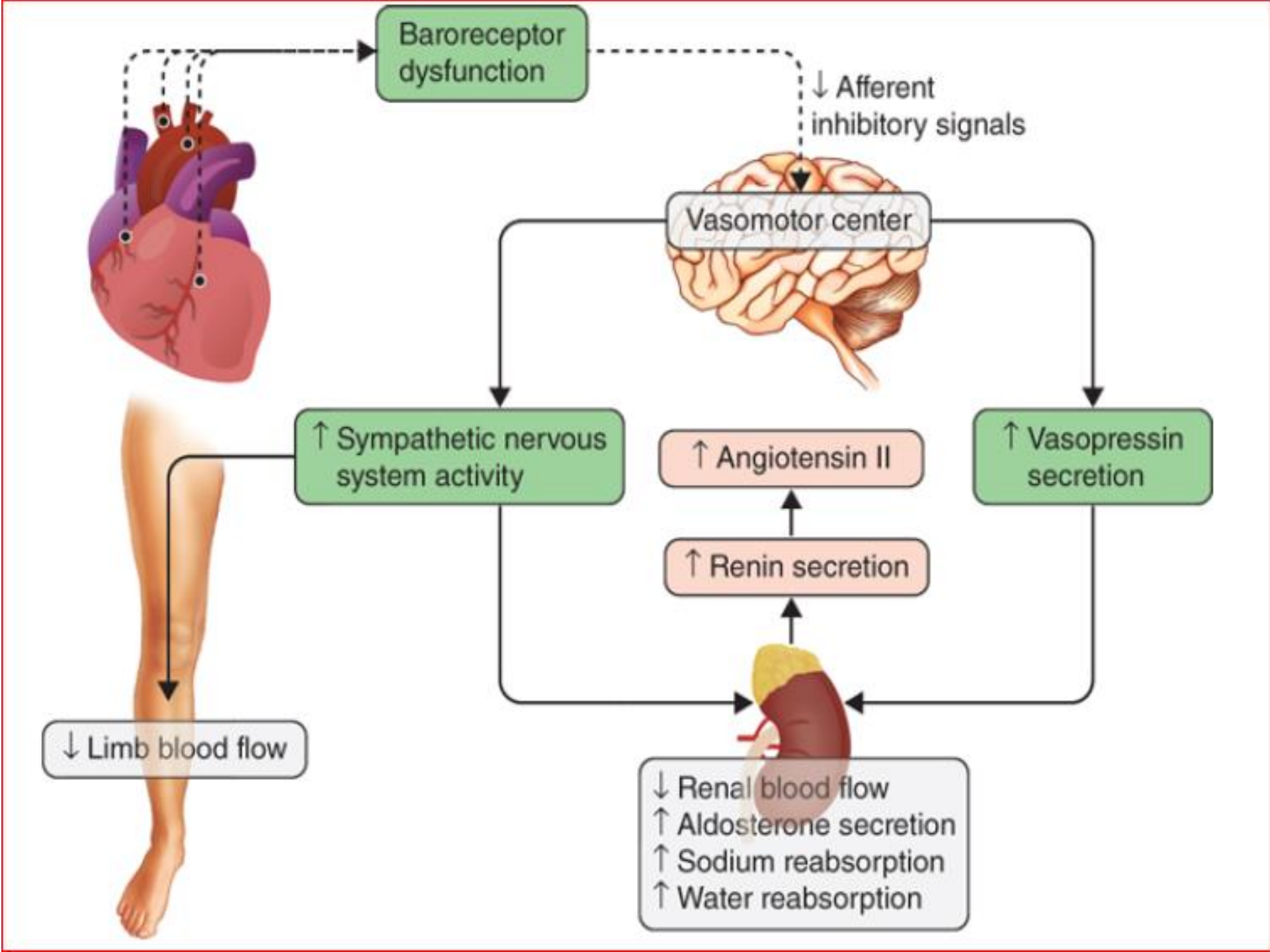
- The decreased cardiac output in heart failure (HF) patients results in an "unloading" of high-pressure baroreceptors in the LV, carotid sinus, and aortic arch

- This unloading of the peripheral baroreceptors leads to a loss of inhibitory parasympathetic tone to the central nervous system (CNS), with a resultant generalized increase in efferent sympathetic tone, and nonosmotic release of arginine vasopressin (AVP) from the pituitary

Pathogenesis:

- These afferent signals to the CNS also activate efferent sympathetic nervous system pathways that innervate the heart, kidney, peripheral vasculature, and skeletal muscles

- AVP (or antidiuretic hormone [ADH]) is a powerful vasoconstrictor that increases the permeability of the renal collecting ducts, leading to the reabsorption of free water


Baroreceptor dysfunction
↓ Afferent inhibitory signals
Vasomotor center
↑ Sympathetic nervous system activity
↑ Angiotensin II
↑ Vasopressin secretion
↑ Renin secretion
↓ Limb blood flow
↓ Renal blood flow
↑ Aldosterone secretion
↑ Sodium reabsorption
↑ Water reabsorption

Pathogenesis:

- **Activation of neurohormonal systems in heart failure:**
- Release of arginine vasopression (AVP) from the posterior pituitary
- Activate efferent sympathetic nervous system pathways ⟶

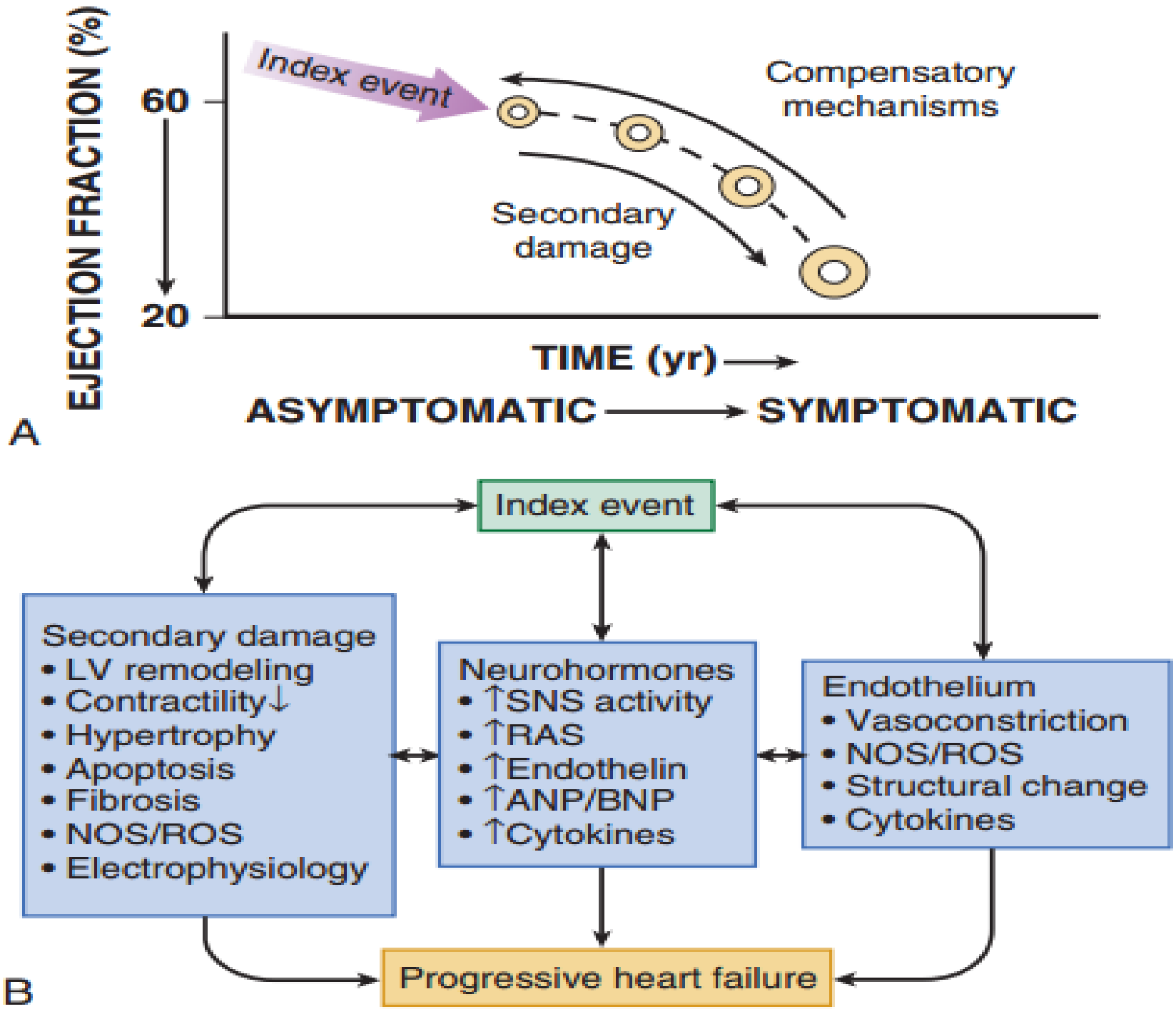
activation ⟶ renin-angiotensin-aldosterone system salt and water retention and leads to vasoconstriction of the peripheral vasculature, myocyte hypertrophy, myocyte cell death, and myocardial fibrosis

Neurohormonal Mechanisms

Neurohormonal Mechanisms

- Heart failure progresses as a result of the overexpression of biologically active molecules that are capable of exerting deleterious effects on the heart and circulation

- The portfolio of compensatory mechanisms that have been described thus far includes activation of the adrenergic nervous systemic system and the renin angiotensin system (RAS)


EJECTION FRACTION (%)
60
20
Index event
Compensatory mechanisms
Secondary damage
TIME (yr)
ASYMPTOMATIC
SYMPTOMATIC
A
Index event
Secondary damage
• LV remodeling
• Contractility↓
• Hypertrophy
• Apoptosis
• Fibrosis
• NOS/ROS
• Electrophysiology
Neurohormones
• ↑SNS activity
• ↑RAS
• ↑Endothelin
• ↑ANP/BNP
• ↑Cytokines
Endothelium
• Vasoconstriction
• NOS/ROS
• Structural change
• Cytokines
Progressive heart failure
B

Activation of the Sympathetic Nervous System

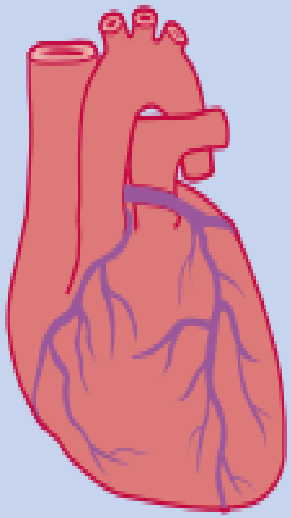
Activation of the Sympathetic Nervous System

- One of the most important adaptations is activation of the sympathetic (adrenergic) nervous system, which occurs early in the course of heart failure

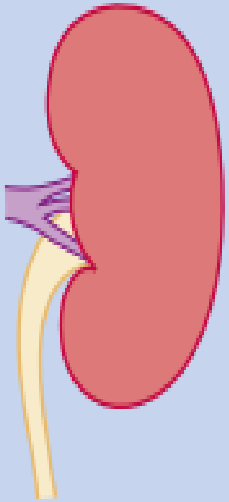
- In patients with advanced heart failure, the circulating levels of NE in resting patients are two to three times those found in normal subjects

- Withdrawal of parasympathetic nerve stimulation has been associated with decreased nitric oxide (NO) levels, increased inflammation, increased sympathetic activity and worsening LV remodeling

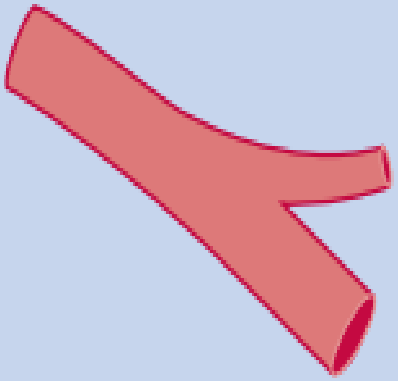
Sympathetic nervous system



↓β-AR responsiveness
Myocyte hypertrophy
Myocyte necrosis and apoptosis, fibrosis
↓Norepinephrine stores
↓Sympathetic innervation
Arrhythmias
Impaired diastolic, systolic function



↑Tubular reabsorption of Na^+
Activation of RAS
↑Renal vascular resistance
↓Response to natriuretic factors
↑Renin release



Neurogenic vacoconstriction
Vascular hypertrophy

Activation of the Renin- Angiotensin System

Activation of the Renin-Angiotensin System

- The presumptive mechanisms for RAS activation in heart failure include renal hypoperfusion, decreased filtered sodium reaching the macula densa in the distal tubule, and increased sympathetic stimulation of the kidney, leading to increased renin release from jutaglomerular apparatus

- Angiotensin II has several important actions that are critical to maintaining short-term circulatory homeostasis

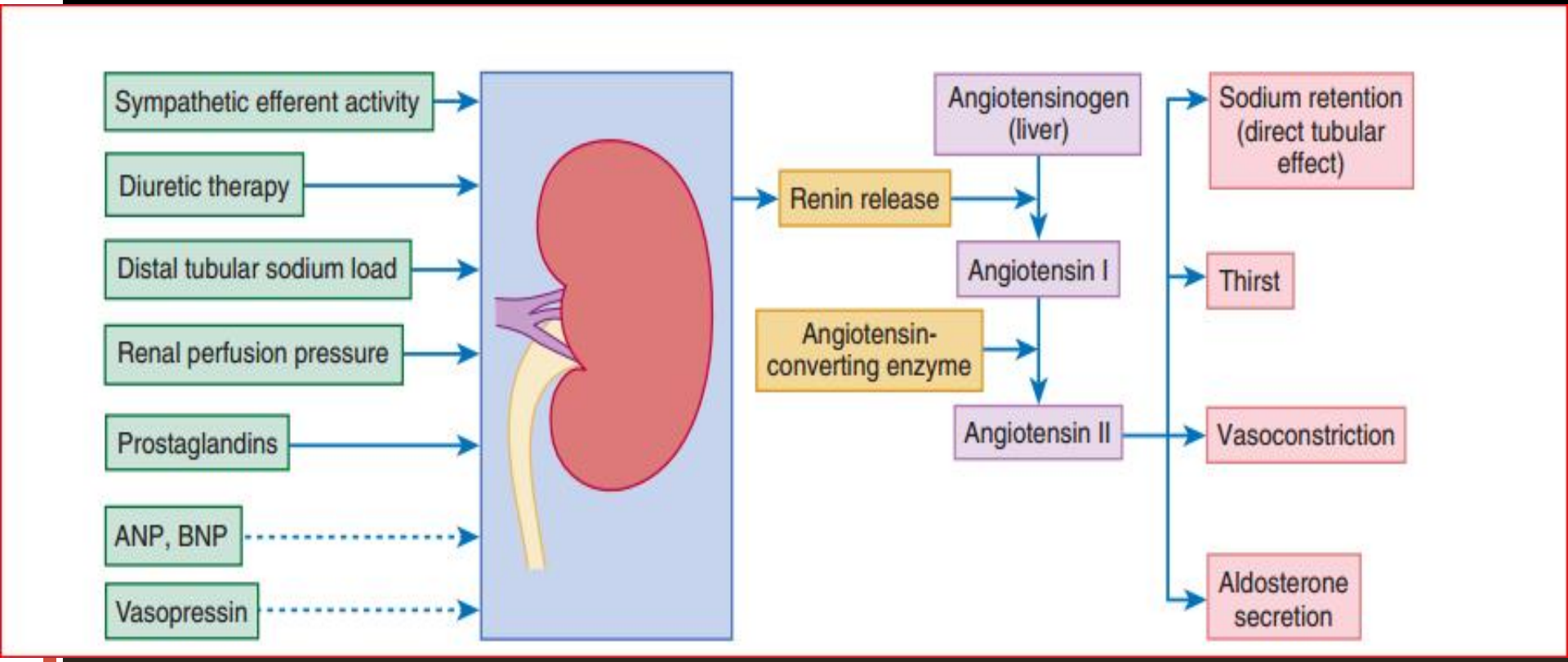
- The sustained expression of angiotensin II is maladaptive, however, leading to fibrosis of the heart, kidneys, and other organs

- Angiotensin II can also lead to worsening neurohormonal activation by enhancing the release of NE from sympathetic nerve endings, as well as stimulating the zona glomerulosa of the adrenal cortex to produce aldosterone

- The sustained expression of **aldosterone** may exert harmful effects by provoking hypertrophy and fibrosis within the vasculature and the myocardium, contributing to reduced vascular compliance and increased ventricular stiffness

- In addition, aldosterone provokes endothelial cell dysfunction, baroreceptor dysfunction, and inhibition of NE uptake, any or all of which may lead to worsening of heart failure

- The mechanism of action of aldosterone in the cardiovascular system appears to involve oxidative stress, with resultant inflammation in target tissue


Sympathetic efferent activity
Diuretic therapy
Distal tubular sodium load
Renal perfusion pressure
Prostaglandins
ANP, BNP
Vasopressin
Renin release
Angiotensinogen (liver)
Angiotensin I
Angiotensin-converting enzyme
Angiotensin II
Sodium retention (direct tubular effect)
Thirst
Vasoconstriction
Aldosterone secretion

Oxidative Stress

Oxidative Stress

- "Oxidative stress" occurs when the production of ROS exceeds the buffering capacity of antioxidant defense systems, leading to an excess of ROS within the cell

- Substantial evidence indicates that the level of oxidative stress is increased both systemically and in the myocardium of patients with heart failure

Oxidative Stress

- Oxidative stress in the heart may be due to reduced antioxidant capacity and/or increased production of ROS

- In cultured cardiac myocytes ROS stimulate myocyte hypertrophy, reexpression of fetal gene programs, and apoptosis

Oxidative Stress

- ROS also can modulate fibroblast proliferation and collagen synthesis, and can trigger increased matrix metalloproteinase (MMP) abundance and activation

- ROS also can affect the peripheral vasculature in heart failure by decreasing the bioavailability of NO

- These and other observations have led to the suggestion that strategies to reduce ROS may be of therapeutic value in patients with heart failure

Neurohormonal Alterations of Renal Function

Neurohormonal Alterations of Renal Function

- One of the signatures of advancing heart failure is increased salt and water retention by the kidneys

- Volume overload in heart failure probably is secondary to a functional derangement of renal physiology in response to several factors that have the potential to cause increased sodium reabsorption including:
  - Activation of the sympathetic nervous system
  - Activation of RAS
  - Reduced renal perfusion pressures
  - Blunting of renal responsiveness to natriuretic peptides

Natriuretic Peptides

Pathogenesis:

- Compensatory mechanisms:

- A family of countervailing vasodilatory molecules, including the atrial and brain natriuretic peptides (ANP and BNP), prostaglandins (PGE_2 and PGI_2), and nitric oxide (NO), that offset the excessive peripheral vascular vasoconstriction

Natriuretic Peptides

- Under physiologic conditions, ANP and BNP function as natriuretic hormones that are released in response to increases to atrial and or myocardial stretch, often secondary to excessive sodium intake

- Biomarkers :

- Normal concentration of natriuretic peptides in an untreated patient is extremely useful for excluding the diagnosis of HF

- A very low BNP or N-terminal pro-BNP may be helpful in excluding a cardiac cause of dyspnea

Biomarkers :

- In current clinical guidelines, natriuretic peptide testing in the diagnosis of acute dyspnea is currently the only class I indication for a biomarker test in heart failure

Left Ventricular Remodeling

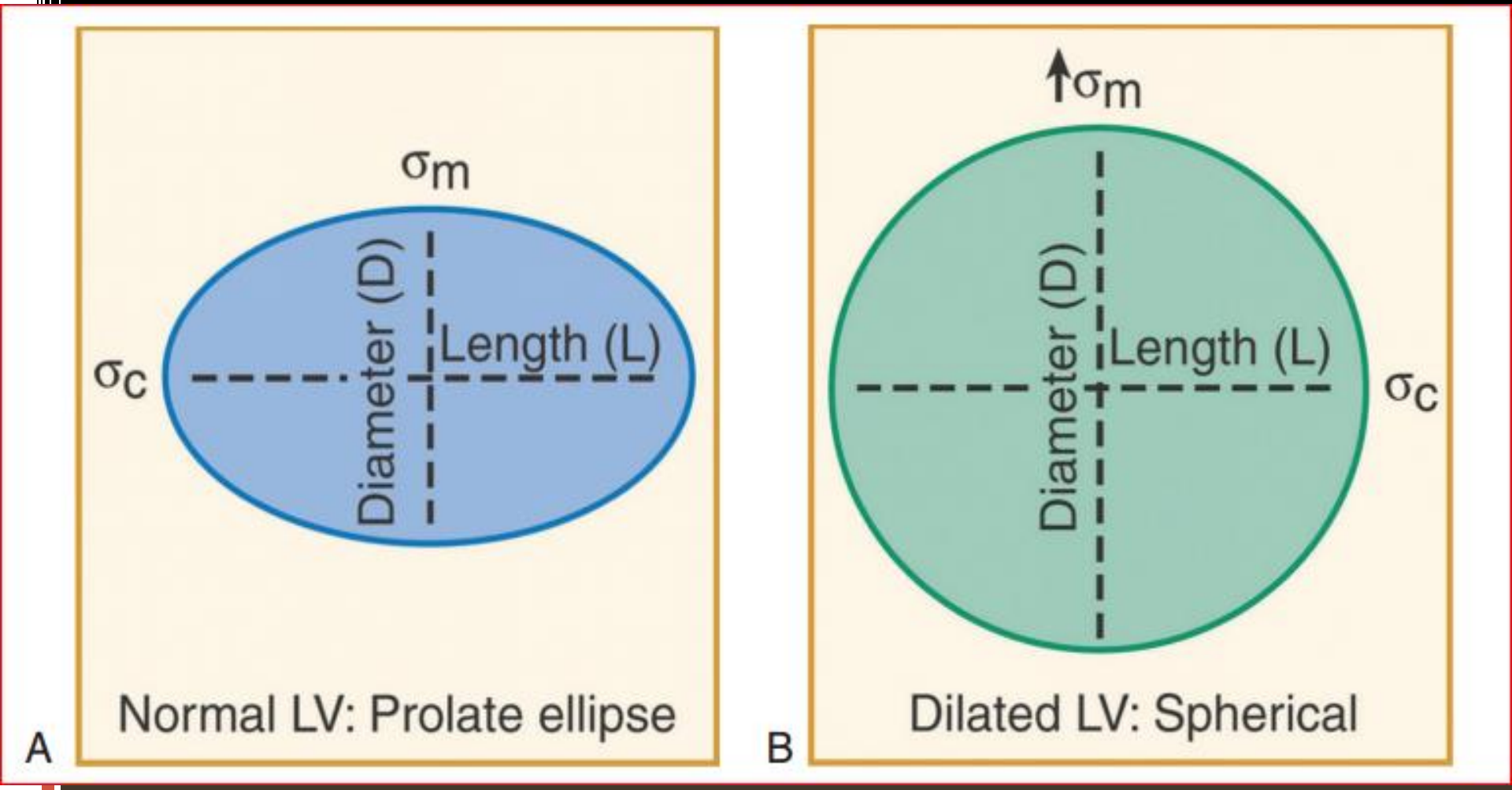
Pathogenesis:

- Activation of the renin-angiotensin-aldosterone (RAA) and adrenergic nervous systems, cytokine systems , lead to a series of adaptive changes within the myocardium, collectively referred to as ***LV remodeling***

Left Ventricular Remodeling

- Refers to the changes in LV mass, volume, shape, and composition of the heart that occur following cardiac injury and/or abnormal hemodynamic loading conditions

- Contribute independently to the progression of HF by virtue of the mechanical burdens that are engendered by the changes in the geometry of the remodeled LV, from a prolate ellipsoid of revolution to a more spherical shape → increase in wall stress of the LV


σm
σc
Diameter (D)
Length (L)
Normal LV: Prolate ellipse
A
σm
Diameter (D)
Length (L)
σc
Dilated LV: Spherical
B

Left Ventricular Remodeling

- It has been suggested that the process of LV remodeling is directly related to future deterioration in LV performance and a less favorable clinical course in patients with heart failure

Overview of LV Remodeling

Alterations in Myocyte Biology

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

Myocardial Changes

Myocyte loss
- Necrosis
- Apoptosis
- Autophagy

Alterations in extracellular matrix
- Matrix degradation
- Myocardial fibrosis

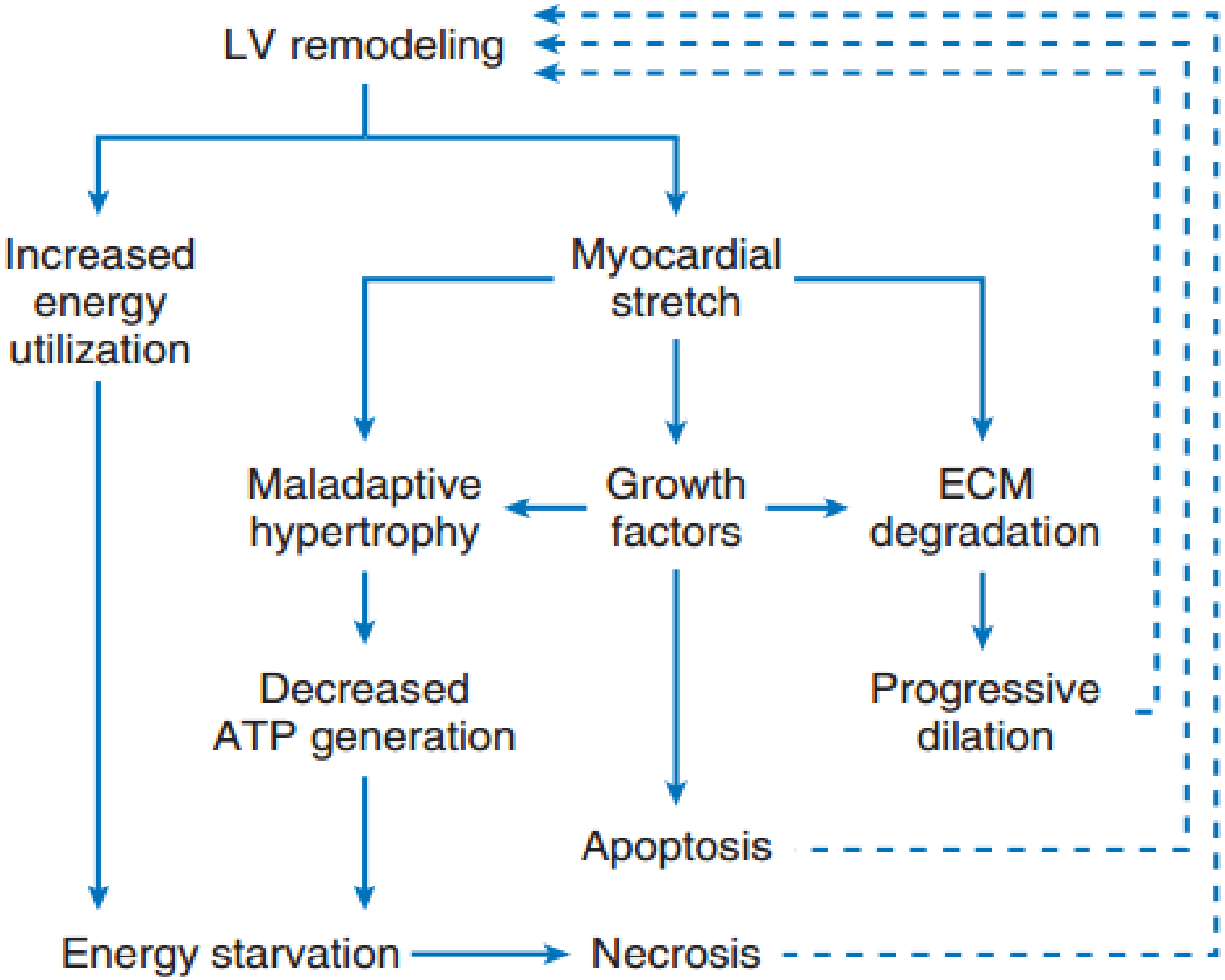
Alterations in Left Ventricular Chamber Geometry

Left ventricular (LV) dilation
Increased LV sphericity
LV wall thinning
Mitral valve incompetence

Mechanical Disadvantages Created by LV Remodeling

Increased wall stress (afterload)
Afterload mismatch
Episodic subendocardial hypoperfusion
Increased oxygen utilization
Functional mitral regurgitation
Worsening hemodynamic overloading
A stretch-induced activation of maladaptive signal transduction pathways
Stretch-induced activation of maladaptive gene programs

Self-amplifying nature of LV remodeling



Pathogenesis:

- Indeed, one of the goals of therapy for HF is to prevent and/or reverse LV remodeling

Reversibility of LV Remodeling

Reversibility of LV Remodeling

- Clinical studies have shown that medical and device therapies that reduce heart failure morbidity and mortality also lead to decreased LV volume and mass and restore a more normal elliptical shape to the ventricle

Reversibility of LV Remodeling

- The term reverse remodeling, as it is currently used, describes the biologic process of reversal of the cellular, myocardial, and anatomic abnormalities seen in the remodeled ventricle

Reversibility of LV Remodeling

- Whose hearts have undergone reverse remodeling may experience one of two potential outcomes:
  - Freedom from future heart failure events (myocardial recovery)
  - Recurrence of heart failure events(myocardial remission)

Reversibility of LV Remodeling

- Based on the disparate clinical outcomes of reverse remodeling, it has been suggested that the term myocardial recovery should be used to describe the normalization of the molecular, cellular, myocardial, and LV geometric changes that are associated with freedom from future heart failure events

Reversibility of LV Remodeling

- Whereas the term myocardial remission should be used to refer to the normalization of the molecular, cellular, myocardial, and LV geometric changes that provoke cardiac remodeling that are insufficient to prevent the recurrence of heart failure in the face of normal and/or perturbed hemodynamic loading conditions

Reversibility of LV Remodeling

- It is possible that myocardial remission represents reversal of the heart failure phenotype superimposed upon hearts that have sustained irreversible damage, whereas myocardial recovery represents reversal of the heart failure phenotype superimposed upon hearts that have not sustained irreversible damage

Heart Failure with a Preserved EF

Pathogenesis:

- In contrast to our understanding of the pathogenesis of HF with a depressed EF, our understanding of the mechanisms that contribute to the development of HF with a preserved EF is still evolving

- Although diastolic dysfunction was thought to be the only mechanism responsible for the development of HF with a preserved EF, community-based studies suggest that additional extracardiac mechanisms may be important, such as increased vascular stiffness and impaired renal function

Pathogenesis:

- Diastolic Dysfunction:

- Myocardial relaxation is an ATP-dependent process

- Reductions in ATP concentration, as occurs in ischemia, may interfere with these processes and lead to slowed myocardial relaxation

Pathogenesis:

- Diastolic Dysfunction:
- If LV filling is delayed because LV compliance is reduced (e.g.from hypertrophy or fibrosis), LV filling pressures will similarly remain elevated at end diastole

- Elevated LV end-diastolic filling pressures result in increases in PCWP, which can contribute to the dyspnea experienced by patients with diastolic dysfunction

CLINICAL SYNDROMES OF HEART FAILURE

- **HFpEF** is a syndrome consisting of symptoms and signs of heart failure with preserved left ventricular ejection fraction above **>50%** and abnormal left ventricular relaxation assessed by echocardiography

HF with preserved EF

- The prevalence of **HFpEF** increases dramatically with age and is much more common in women than in men at any age

- **HFpEF** is more common in elderly hypertensive patients but may occur with primary cardiomyopathies (hypertrophic, restrictive, infiltrative)


Thank you...