UNIT – 2 PATHOPHYSIOLOGY 🏥

POINTS TO BE COVERED IN THIS TOPIC

- ➤ CARDIOVASCULAR SYSTEM 💓
- ➤ RESPIRATORY SYSTEM 🫁
- ➤ RENAL SYSTEM 🫘

CARDIOVASCULAR SYSTEM 💓

The cardiovascular system consists of the heart and blood vessels that circulate blood throughout the body. Cardiovascular diseases are among the leading causes of morbidity and mortality worldwide, affecting millions of people across all age groups.

HYPERTENSION 📈

Definition Hypertension, commonly known as high blood pressure, is a chronic medical condition in which the arterial blood pressure is persistently elevated above normal levels. It is defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg.

Classification of Hypertension

Category	Systolic BP (mmHg)	Diastolic BP (mmHg)
Normal	<120	<80
Elevated	120-129	<80
Stage 1 Hypertension	130-139	80-89
Stage 2 Hypertension	≥140	≥90
Hypertensive Crisis	>180	>120

Types of Hypertension

PRIMARY (ESSENTIAL) HYPERTENSION

- Accounts for approximately 90-95% of all hypertensive cases
- No identifiable underlying cause
- Develops gradually over many years
- Associated with genetic factors, lifestyle, and environmental influences
- Multiple mechanisms contribute to its development including increased peripheral resistance

SECONDARY HYPERTENSION

- Accounts for 5-10% of hypertensive cases
- Has an identifiable underlying cause
- Often appears suddenly and causes higher blood pressure than primary hypertension
- Common causes include:
  - Renal diseases (chronic kidney disease, renovascular disease)

- Endocrine disorders (primary aldosteronism, pheochromocytoma, Cushing's syndrome)
- Sleep apnea
- Certain medications (NSAIDs, oral contraceptives, decongestants)

Pathophysiology The pathophysiology of hypertension involves multiple interconnected mechanisms that lead to sustained elevation of blood pressure. The fundamental equation governing blood pressure is: Blood Pressure = Cardiac Output × Peripheral Vascular Resistance.

Mechanisms Contributing to Hypertension:

Increased Cardiac Output

- Enhanced sympathetic nervous system activity
- Increased heart rate and stroke volume
- Elevated plasma volume due to sodium and water retention

Increased Peripheral Resistance

- Structural changes in resistance arteries (vascular remodeling)
- Functional vasoconstriction due to increased vascular tone
- Endothelial dysfunction leading to impaired vasodilation

Renin-Angiotensin-Aldosterone System (RAAS) Activation

- Increased renin release from juxtaglomerular cells
- Enhanced angiotensin II formation leading to vasoconstriction
- Aldosterone-mediated sodium and water retention

- Vascular and cardiac remodeling effects

Sympathetic Nervous System Hyperactivity

- Increased norepinephrine release
- Enhanced α1-adrenergic receptor-mediated vasoconstriction
- Increased β1-adrenergic receptor-mediated cardiac stimulation

Clinical Manifestations Hypertension is often called the "silent killer" because it typically presents no symptoms until complications develop. When symptoms occur, they may include:

- Headaches, particularly in the morning
- Dizziness and lightheadedness
- Shortness of breath
- Chest pain
- Visual disturbances
- Nosebleeds (in severe cases)

Complications Long-term uncontrolled hypertension leads to target organ damage:

- **Cardiovascular:** Coronary artery disease, heart failure, left ventricular hypertrophy
- **Cerebrovascular:** Stroke, transient ischemic attacks
- **Renal:** Chronic kidney disease, proteinuria
- **Retinal:** Hypertensive retinopathy, vision loss

CONGESTIVE HEART FAILURE 💔

Definition Congestive heart failure (CHF), also known as heart failure, is a complex clinical syndrome that occurs when the heart is unable to pump sufficient blood to meet the metabolic demands of the body or can do so only at elevated filling pressures.

Classification

Based on Ejection Fraction:

- **Heart Failure with Reduced Ejection Fraction (HFrEF):** EF ≤40%
- **Heart Failure with Preserved Ejection Fraction (HFpEF):** EF ≥50%
- **Heart Failure with Mildly Reduced Ejection Fraction (HFmrEF):** EF 41-49%

Based on Symptom Severity (NYHA Classification):

Class	Symptoms
Class I	No limitation of physical activity
Class II	Slight limitation of physical activity
Class III	Marked limitation of physical activity
Class IV	Unable to carry out any physical activity without discomfort

Pathophysiology Heart failure results from structural or functional cardiac abnormalities that impair ventricular filling or ejection of blood. The pathophysiology involves complex interactions between hemodynamic, neurohormonal, and cellular mechanisms.

Primary Mechanisms:

Systolic Dysfunction

- Impaired myocardial contractility
- Reduced stroke volume and cardiac output
- Common causes: ischemic heart disease, dilated cardiomyopathy, myocarditis

Diastolic Dysfunction

- Impaired ventricular relaxation and filling
- Elevated filling pressures despite normal ejection fraction
- Common causes: hypertensive heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy

Compensatory Mechanisms:

Frank-Starling Mechanism

- Increased preload leads to enhanced contractility
- Initially beneficial but becomes maladaptive over time
- Results in ventricular dilation and increased wall stress

Neurohormonal Activation

- **Sympathetic Nervous System:** Increased catecholamine release leading to increased heart rate, contractility, and vasoconstriction
- **Renin-Angiotensin-Aldosterone System:** Activation leads to vasoconstriction, sodium retention, and ventricular remodeling

- **Arginine Vasopressin:** Increased release causes water retention and vasoconstriction

Ventricular Remodeling

- Progressive changes in ventricular size, shape, and function
- Myocyte hypertrophy and apoptosis
- Increased collagen deposition and fibrosis
- Altered gene expression patterns

Clinical Manifestations

Left Heart Failure:

- Dyspnea (shortness of breath)
- Orthopnea (difficulty breathing when lying flat)
- Paroxysmal nocturnal dyspnea
- Fatigue and weakness
- Pulmonary edema

Right Heart Failure:

- Peripheral edema
- Jugular venous distension
- Hepatomegaly
- Ascites
- Weight gain

ISCHEMIC HEART DISEASE 💓

Ischemic heart disease (IHD) represents a spectrum of conditions caused by reduced blood flow to the myocardium, typically due to coronary artery disease. It encompasses various clinical presentations from stable angina to acute myocardial infarction.

ANGINA 😰

Definition Angina pectoris is a clinical syndrome characterized by chest pain or discomfort resulting from myocardial ischemia due to an imbalance between myocardial oxygen supply and demand.

Types of Angina

STABLE ANGINA

- Predictable chest pain triggered by physical exertion or emotional stress
- Pain typically lasts 2-5 minutes and is relieved by rest or nitroglycerin
- Results from fixed coronary artery stenosis (usually >70% luminal narrowing)
- Represents a chronic condition with relatively stable plaque

UNSTABLE ANGINA

- New onset angina, worsening of previously stable angina, or angina at rest
- Part of acute coronary syndrome spectrum
- Results from plaque rupture with partial coronary occlusion
- High risk for progression to myocardial infarction

VARIANT (PRINZMETAL'S) ANGINA

- Caused by coronary artery vasospasm
- Typically occurs at rest, often in early morning hours
- May occur in arteries with or without significant atherosclerosis
- Characterized by transient ST-segment elevation on ECG

Pathophysiology The fundamental mechanism underlying angina is myocardial ischemia resulting from an imbalance between myocardial oxygen supply and demand.

Factors Affecting Oxygen Supply:

- Coronary blood flow
- Oxygen-carrying capacity of blood
- Oxygen extraction by myocardium

Factors Affecting Oxygen Demand:

- Heart rate
- Myocardial contractility
- Ventricular wall tension (preload and afterload)

MYOCARDIAL INFARCTION

Definition Myocardial infarction (MI) is the irreversible necrosis of heart muscle secondary to prolonged ischemia, typically resulting from complete occlusion of a coronary artery.

Classification

Type 1 MI (Spontaneous):

- Primary coronary event (plaque rupture/erosion)
- Most common type (>90% of cases)

Type 2 MI (Secondary):

- Supply-demand mismatch without primary coronary event
- Causes: severe anemia, arrhythmias, hypotension, hypertensive crisis

Based on ECG Findings:

- **STEMI (ST-Elevation MI):** Complete coronary occlusion with ST elevation
- **NSTEMI (Non-ST-Elevation MI):** Partial occlusion without ST elevation

Pathophysiology Myocardial infarction typically results from atherothrombosis following rupture or erosion of an atherosclerotic plaque.

Sequence of Events:

1. **Plaque Rupture/Erosion:** Exposes thrombogenic material to circulating blood
2. **Platelet Activation:** Adhesion, activation, and aggregation at rupture site
3. **Coagulation Cascade:** Thrombin generation and fibrin formation
4. **Thrombus Formation:** Complete or partial coronary occlusion
5. **Myocardial Ischemia:** Reduced oxygen delivery to myocardium
6. **Cellular Death:** Irreversible myocyte necrosis if ischemia persists

Timeline of Myocardial Necrosis:

- **0-30 minutes:** Reversible ischemia
- **30 minutes-2 hours:** Beginning of irreversible injury
- **2-6 hours:** Wavefront phenomenon of necrosis
- **6-12 hours:** Completion of transmural necrosis

ATHEROSCLEROSIS AND ARTERIOSCLEROSIS

ATHEROSCLEROSIS

Definition Atherosclerosis is a specific type of arteriosclerosis characterized by the accumulation of lipids, inflammatory cells, and fibrous tissue in the arterial wall, leading to the formation of atherosclerotic plaques.

Pathogenesis (Response-to-Injury Hypothesis)

Endothelial Dysfunction:

- Initial step in atherosclerosis development
- Causes: hyperlipidemia, hypertension, smoking, diabetes
- Results in increased permeability and expression of adhesion molecules

Lipid Accumulation:

- LDL cholesterol enters arterial wall and undergoes oxidation
- Oxidized LDL is taken up by macrophages forming foam cells
- Accumulation of foam cells creates fatty streaks

Inflammatory Response:

- Recruitment of monocytes and T-lymphocytes
- Release of inflammatory mediators and growth factors
- Smooth muscle cell migration and proliferation

Plaque Formation:

- Development of fibrous cap covering lipid core
- Ongoing inflammation and matrix remodeling
- Calcification in advanced lesions

Plaque Rupture:

- Vulnerable plaques have thin fibrous caps and large lipid cores
- Rupture exposes thrombogenic material leading to thrombosis
- Results in acute coronary syndromes

ARTERIOSCLEROSIS

Definition Arteriosclerosis is a general term referring to thickening and hardening of arterial walls, encompassing several distinct pathological processes.

Types:

- **Atherosclerosis:** Lipid accumulation in intima
- **Arteriolosclerosis:** Smooth muscle cell proliferation in small arteries
- **Mönckeberg's Sclerosis:** Calcium deposits in media without luminal narrowing

RESPIRATORY SYSTEM 🫁

The respiratory system is responsible for gas exchange, delivering oxygen to tissues and removing carbon dioxide from the body. Respiratory diseases significantly impact quality of life and represent major causes of morbidity and mortality worldwide.

ASTHMA 🍸

Definition Asthma is a chronic inflammatory disorder of the airways characterized by variable airway obstruction, bronchial hyperresponsiveness, and underlying inflammation, leading to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing.

Classification

Based on Control:

- **Well-Controlled Asthma:** Minimal symptoms, infrequent rescue medication use
- **Partly Controlled Asthma:** Some symptoms present, occasional limitations
- **Uncontrolled Asthma:** Frequent symptoms, significant activity limitation

Based on Severity:

- **Intermittent:** Symptoms <2 days/week, nighttime awakenings ≤2 times/month

- **Mild Persistent:** Symptoms >2 days/week but <1 time/day
- **Moderate Persistent:** Daily symptoms, nighttime awakenings 3-4 times/month
- **Severe Persistent:** Continuous symptoms, frequent nighttime awakenings

Pathophysiology Asthma is a complex disease involving multiple cellular and molecular mechanisms that result in chronic airway inflammation and hyperresponsiveness.

Key Pathophysiological Features:

Airway Inflammation:

- Infiltration of inflammatory cells (eosinophils, neutrophils, T-lymphocytes, mast cells)
- Release of inflammatory mediators (histamine, leukotrienes, prostaglandins, cytokines)
- Increased vascular permeability and mucus secretion
- Airway wall edema and thickening

Bronchial Hyperresponsiveness:

- Exaggerated bronchoconstrictor response to various stimuli
- Altered smooth muscle sensitivity and reactivity
- Enhanced cholinergic responsiveness
- Reduced β2-adrenergic responsiveness

Airway Remodeling:

- Structural changes in chronic asthma
- Smooth muscle hyperplasia and hypertrophy
- Subepithelial fibrosis and basement membrane thickening
- Increased goblet cell number and mucus gland hyperplasia

Immunological Mechanisms:

Type 2 Inflammation (Allergic Asthma):

- Th2 cell-mediated immune response
- IgE-mediated mast cell degranulation
- Eosinophilic inflammation
- IL-4, IL-5, IL-13 cytokine production

Type 1 Inflammation (Non-Allergic Asthma):

- Th1/Th17 cell-mediated response
- Neutrophilic inflammation
- Often associated with viral infections
- IL-17, IFN-γ cytokine production

Clinical Manifestations The classic symptoms of asthma include:

- **Wheezing:** High-pitched whistling sound during breathing
- **Dyspnea:** Shortness of breath, particularly on exertion
- **Chest Tightness:** Feeling of constriction in the chest
- **Cough:** Often dry, may be worse at night or early morning
- **Exercise Intolerance:** Reduced ability to perform physical activities

Triggers Common asthma triggers include:

- Allergens (dust mites, pollens, animal dander, molds)
- Respiratory infections (viral, bacterial)
- Environmental irritants (smoke, pollution, strong odors)
- Weather changes (cold air, high humidity)
- Exercise
- Emotional stress
- Medications (aspirin, beta-blockers)

CHRONIC OBSTRUCTIVE AIRWAYS DISEASES

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Definition COPD is a preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases.

Components of COPD:

CHRONIC BRONCHITIS

- Clinical definition: Productive cough for at least 3 months in each of 2 consecutive years
- Characterized by mucus hypersecretion and airway inflammation
- Predominantly affects large and medium-sized airways

EMPHYSEMA

- Anatomical definition: Abnormal permanent enlargement of airspaces distal to terminal bronchioles
- Destruction of alveolar walls without obvious fibrosis
- Loss of elastic recoil and gas exchange surface area

COPD Severity Classification (GOLD)

Grade	Severity	FEV1/FVC	FEV1 % Predicted
GOLD 1	Mild	<70%	≥80%
GOLD 2	Moderate	<70%	50-79%
GOLD 3	Severe	<70%	30-49%
GOLD 4	Very Severe	<70%	<30%

Pathophysiology COPD results from complex interactions between environmental exposures and host factors leading to chronic inflammation, oxidative stress, and protease-antiprotease imbalance.

Key Pathophysiological Mechanisms:

Chronic Inflammation:

- Infiltration of neutrophils, macrophages, and CD8+ T-lymphocytes
- Release of inflammatory mediators (IL-8, TNF-α, LTB4)
- Persistent inflammatory response even after smoking cessation
- Systemic inflammation contributing to comorbidities

Oxidative Stress:

- Increased production of reactive oxygen species

- Reduced antioxidant capacity
- Oxidative damage to proteins, lipids, and DNA
- Amplification of inflammatory responses

Protease-Antiprotease Imbalance:

- Increased activity of proteolytic enzymes (neutrophil elastase, MMPs)
- Decreased activity of antiproteases (α1-antitrypsin, TIMP)
- Destruction of lung parenchyma and loss of alveolar attachments
- Emphysematous changes and loss of elastic recoil

Structural Changes:

Airways:

- Airway wall thickening and fibrosis
- Smooth muscle hypertrophy
- Mucus gland hyperplasia and goblet cell metaplasia
- Loss of small airways

Alveoli:

- Alveolar wall destruction
- Loss of capillary bed
- Reduced gas exchange surface area
- Impaired gas transfer

Clinical Manifestations COPD typically presents with progressive symptoms:

- **Chronic Cough:** Often the first symptom, may be intermittent initially
- **Sputum Production:** Usually occurs with cough, may be clear or purulent
- **Dyspnea:** Progressive breathlessness, initially on exertion, later at rest
- **Wheezing:** May be present, especially during exacerbations
- **Chest Tightness:** Feeling of constriction or heaviness in chest

COPD Exacerbations:

- Acute worsening of symptoms beyond normal day-to-day variation
- Usually triggered by respiratory infections or environmental exposures
- Characterized by increased dyspnea, cough, and sputum production
- May require change in medication or hospitalization

RENAL SYSTEM

The renal system plays crucial roles in maintaining fluid and electrolyte balance, acid-base homeostasis, blood pressure regulation, and waste elimination. Renal diseases significantly impact these vital functions and can progress to life-threatening complications.

ACUTE RENAL FAILURE

Definition Acute renal failure (ARF), also known as acute kidney injury (AKI), is characterized by a rapid decline in kidney function occurring over hours to days, resulting in accumulation of nitrogenous waste products and disturbances in fluid and electrolyte balance.

Classification (KDIGO Criteria)

Stage 1 (Mild):

- Serum creatinine increase ≥0.3 mg/dL or 1.5-1.9× baseline
- Urine output <0.5 mL/kg/hr for 6-12 hours

Stage 2 (Moderate):

- Serum creatinine 2.0-2.9× baseline
- Urine output <0.5 mL/kg/hr for ≥12 hours

Stage 3 (Severe):

- Serum creatinine ≥3.0× baseline or ≥4.0 mg/dL
- Urine output <0.3 mL/kg/hr for ≥24 hours or anuria for ≥12 hours

Etiology and Classification

PRE-RENAL AKI (60-70% of cases):

- Decreased renal blood flow with structurally normal kidneys
- **Causes:**
  - Volume depletion (hemorrhage, dehydration, diarrhea)
  - Cardiovascular causes (heart failure, shock)
  - Medications (NSAIDs, ACE inhibitors, diuretics)
  - Hepatorenal syndrome

INTRINSIC RENAL AKI (25-30% of cases):

- Direct kidney parenchymal damage

- **Acute Tubular Necrosis (ATN):** Most common intrinsic cause
  - Ischemic ATN: Prolonged hypoperfusion
  - Nephrotoxic ATN: Drugs, contrast agents, toxins
- **Acute Interstitial Nephritis:** Drugs, infections, autoimmune
- **Glomerulonephritis:** Rapidly progressive forms
- **Vascular causes:** Thrombotic microangiopathy, vasculitis

POST-RENAL AKI (5-10% of cases):

- Obstruction of urinary flow
- **Causes:**
  - Ureteral obstruction (stones, tumors, fibrosis)
  - Bladder outlet obstruction (BPH, neurogenic bladder)
  - Urethral obstruction (strictures, blood clots)

Pathophysiology

Pre-Renal AKI:

- Reduced effective circulating volume
- Activation of compensatory mechanisms (RAAS, sympathetic nervous system)
- Renal vasoconstriction and decreased GFR
- Preserved tubular function initially
- Reversible if underlying cause corrected promptly

Intrinsic Renal AKI (ATN Focus):

Initiation Phase:

- Direct cellular injury or ischemia-reperfusion injury
- ATP depletion and cellular energy failure
- Loss of cell polarity and cytoskeletal disruption
- Increased vascular permeability and inflammation

Maintenance Phase:

- Continued cellular injury and death
- Tubular obstruction by cellular debris and casts
- Persistent reduction in GFR
- Oliguria or anuria may develop

Recovery Phase:

- Restoration of cellular integrity and function
- Removal of tubular obstruction
- Gradual improvement in GFR
- Polyuria may occur initially

Clinical Manifestations AKI often presents with nonspecific symptoms:

- **Oliguria:** Urine output <400 mL/24 hours (not always present)
- **Fluid Retention:** Edema, weight gain, hypertension
- **Uremic Symptoms:** Nausea, vomiting, altered mental status
- **Electrolyte Abnormalities:** Hyperkalemia, hyperphosphatemia, metabolic acidosis

- **Cardiovascular:** Arrhythmias, pericarditis (in severe cases)

CHRONIC RENAL FAILURE 📉

Definition Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function present for more than 3 months, with implications for health. It is characterized by progressive and irreversible loss of nephron function.

CKD Staging (KDIGO)

Stage	Description	GFR ($mL/min/1.73m^2$)	Clinical Features
1	Normal/High with kidney damage	≥90	Structural abnormalities
2	Mild decrease with kidney damage	60-89	Minimal symptoms
3a	Mild-moderate decrease	45-59	Early complications
3b	Moderate-severe decrease	30-44	Multiple complications
4	Severe decrease	15-29	Preparation for RRT
5	Kidney failure	<15	RRT required

Etiology Leading causes of CKD vary by geographic region and population:

Primary Kidney Diseases:

- Diabetic nephropathy (leading cause worldwide)
- Hypertensive nephrosclerosis

- Glomerulonephritis (various types)
- Polycystic kidney disease
- Interstitial nephritis

Secondary Kidney Diseases:

- Systemic lupus erythematosus
- Vasculitis
- Multiple myeloma
- Amyloidosis

Pathophysiology CKD progression involves multiple interconnected mechanisms leading to progressive nephron loss and functional decline.

Initial Injury and Adaptation:

- Primary insult causes nephron loss
- Remaining nephrons undergo compensatory hyperfiltration
- Initially maintains near-normal GFR
- Adaptive changes become maladaptive over time

Progressive Mechanisms:

Hemodynamic Factors:

- Glomerular hypertension and hyperfiltration
- Increased single-nephron GFR
- Enhanced protein filtration
- Progressive glomerulosclerosis

Non-Hemodynamic Factors:

- Tubular toxicity from filtered proteins
- Activation of complement cascade
- Inflammatory cell infiltration
- Cytokine and growth factor release

Common Final Pathway:

- Regardless of initial cause, CKD follows similar progression
- Chronic tubulointerstitial inflammation
- Progressive fibrosis and scarring
- Vascular changes and ischemia
- Accelerated nephron loss

Complications of CKD

Mineral and Bone Disorders:

- Secondary hyperparathyroidism
- Bone pain and fractures
- Vascular calcification
- Phosphate retention and vitamin D deficiency

Cardiovascular Disease:

- Leading cause of mortality in CKD
- Accelerated atherosclerosis
- Left ventricular hypertrophy

- Arrhythmias and sudden cardiac death

Anemia:

- Erythropoietin deficiency
- Iron deficiency
- Chronic inflammation
- Reduced red blood cell lifespan

Electrolyte and Acid-Base Disorders:

- Hyperkalemia
- Metabolic acidosis
- Sodium and water retention
- Hyperphosphatemia and hypocalcemia

Clinical Manifestations CKD is often asymptomatic in early stages. Symptoms typically appear when GFR falls below 30 mL/min/1.73m^2:

Early Stages (1-3):

- Often asymptomatic
- Detected by routine laboratory testing
- Proteinuria or hematuria may be present
- Hypertension development

Advanced Stages (4-5):

- **Uremic Symptoms:** Fatigue, weakness, nausea, loss of appetite
- **Fluid Retention:** Edema, shortness of breath

- **Neurological:** Confusion, seizures, peripheral neuropathy
- **Cardiovascular:** Chest pain, arrhythmias
- **Bone Disease:** Bone pain, muscle weakness
- **Skin Changes:** Pruritus, pigmentation changes

End-Stage Complications:

- Pericarditis
- Bleeding disorders
- Immune dysfunction
- Growth retardation (in children)
- Infertility and sexual dysfunction

CONCLUSION 📚

This comprehensive overview of cardiovascular, respiratory, and renal pathophysiology provides fundamental knowledge essential for understanding disease mechanisms, clinical presentations, and therapeutic approaches. The integration of these systems and their pathological processes forms the basis for evidence-based medical practice and patient care optimization.

Understanding these pathophysiological concepts enables healthcare professionals to:

- Recognize early disease manifestations
- Implement appropriate diagnostic strategies

- Develop targeted therapeutic interventions
- Monitor disease progression effectively
- Prevent complications through proactive management

The complexity of these disease processes highlights the importance of multidisciplinary approaches in modern healthcare, emphasizing prevention, early detection, and comprehensive management strategies for optimal patient outcomes.