"Cardiomyopathies" 🫀

Definition

Cardiomyopathies are cardiac diseases caused by intrinsic dysfunction of the myocardium (heart muscle), leading to impaired cardiac performance.

📌 *Literal meaning:* "Heart muscle diseases"

What is INCLUDED and EXCLUDED?

✔ Included

- Diseases primarily affecting the myocardium
- May be primary or secondary

❌ Excluded (important for exams!)

Myocardial dysfunction due to:

- Coronary artery disease
- Hypertension
- Valvular heart disease
- Congenital heart disease

Types of Cardiomyopathies

1. Based on Etiology

🔹 Primary cardiomyopathies → Disease confined mainly to the myocardium

🔹 Secondary cardiomyopathies → Cardiac involvement as part of a systemic disorder

Examples of conditions causing cardiomyopathy:

- Inflammatory: *Myocarditis*
- Immunologic: *Sarcoidosis*
- Metabolic: *Hemochromatosis*
- Neuromuscular: *Muscular dystrophies*
- Genetic: Disorders of myocardial fibers 🧬

📌 Idiopathic cardiomyopathy

- Cause unknown
- Many previously "idiopathic" cases are now known to be due to genetic defects in:

- Cardiac energy metabolism
- Structural proteins
- Contractile proteins

Clinical-Pathologic Classification 📚

For diagnosis and management, cardiomyopathies are classically divided into three major patterns:

Major Types

1. Dilated cardiomyopathy (DCM)
   → *Most common* (~90% cases)
   → Includes Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)
2. Hypertrophic cardiomyopathy (HCM)
3. Restrictive cardiomyopathy
   → *Least common*

📌 Exam tip:

- Clinical features may overlap

- Each type can be idiopathic or secondary to a known cause

DILATED CARDIOMYOPATHY (DCM) 🩸

Definition

Dilated cardiomyopathy is characterized by:

- Progressive dilation of cardiac chambers
- Systolic dysfunction (↓ contractility)
- Usually accompanied by myocardial hypertrophy

📌 *Key idea:*
➡ Regardless of cause, final clinicopathologic pattern is similar

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Pathogenesis of Dilated Cardiomyopathy ⚠️

At the time of diagnosis, DCM has usually progressed to end-stage heart disease, characterized by:

- Poor myocardial contractility
- Heart failure
- Lack of specific distinguishing pathological features

Initiating Factors

The myocardial damage may begin due to:

Inherited abnormalities OR environmental exposures → Progressive myocyte injury → Impaired force generation → Ventricular dilation → Systolic heart failure 🫀

Genetic Causes of DCM 🧬

📊 Contribution:

- 20–50% of DCM cases are hereditary

Inheritance Pattern

- Mostly Autosomal dominant
- Some X-linked forms

Key Molecular Mechanism

🔻 Loss-of-function mutations affecting:

- Cytoskeletal proteins
- Proteins linking sarcomere ↔ cytoskeleton

Important Mutated Genes

- β-myosin heavy chain
- α-myosin heavy chain
- Cardiac troponin T
- Titin ⭐ (MOST COMMON)

📌 Why titin matters?

- Titin is essential for sarcomeric force generation
- Its mutation → weak contraction → chamber dilation

Important Exam Concept ⚠️

📌 *Same genes, different disease!*

Loss-of-function mutation → Dilated cardiomyopathy

Gain-of-function mutation (same sarcomeric genes) → Hypertrophic cardiomyopathy

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X-Linked Dilated Cardiomyopathy

Most commonly due to:

- Dystrophin gene mutation

🔹 Dystrophin function:

- Anchors intracellular cytoskeleton → To extracellular matrix (ECM)

Loss of dystrophin → Sarcolemmal instability → Myocyte injury → Progressive dilation

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Other Genetic Associations

- Desmin mutation → Principal intermediate filament in cardiac myocytes

- Lamin A and C mutations → Nuclear envelope proteins

📌 Clinical correlation (exam favorite):
Since myocytes and conduction fibers share a developmental origin:

- Inherited DCM may show → Congenital conduction abnormalities ⚡

Infectious Causes (Viral Myocarditis → DCM) 🦠

Earlier studies identified:

- Adenovirus
- Enterovirus

More recent studies show higher association with:

- Parvovirus B19
- Human herpesvirus-6 (HHV-6)

📌 Important exam concept:

Even in late-stage DCM, viral nucleic acid "footprints" (especially *Coxsackievirus B* and other enteroviruses) may still be detected in myocardium.

Pathogenetic Sequence (High-Yield Flowchart)

Viral infection of myocardium → Acute infectious myocarditis → Myocyte injury & necrosis → Incomplete healing / immune-mediated damage → Progressive ventricular dilation → Dilated cardiomyopathy 🫀

📌 Clinical correlation:

- Serial endomyocardial biopsies have shown progression of myocarditis to DCM
- Absence of inflammation in end-stage heart does NOT exclude viral etiology
- Detection of viral RNA or high antiviral antibody titers

  → Suggests "missed" early myocarditis

Alcohol & Other Toxic Exposures 🍺

- Chronic alcohol abuse is strongly associated with DCM
- Alcohol & metabolites (acetaldehyde) have:
    - Direct toxic effects on myocytes

Additional contributing mechanism:

- Chronic alcoholism
  → Thiamine (Vitamin B1) deficiency
  → Element of beriberi heart disease

Other Cardiotoxic Agents

- Cobalt
- Doxorubicin (chemotherapeutic drug) ⭐ *very important*

📌 Exam pearl:
Doxorubicin causes dose-dependent, irreversible cardiomyopathy

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Peripartum Cardiomyopathy 🤰❤️‍🩹

Occurs:

- Late in pregnancy
- Or weeks to months postpartum

Proposed Contributing Factors

- Pregnancy-associated hypertension
- Volume overload
- Nutritional deficiency
- Metabolic derangements (e.g., gestational diabetes)
- Impaired angiogenic signaling

📌 Key feature:

- ~50% of patients recover spontaneously with return of normal cardiac function

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Iron Overload (Hemochromatosis) 🩸

Sources:

- Hereditary hemochromatosis
- Repeated blood transfusions (chronic anemia)

Mechanism of Injury

Iron accumulation → Interference with metal-dependent enzymes → Iron-mediated reactive oxygen species (ROS) production → Myocyte injury & fibrosis → DCM (most common manifestation)

📌 Note:
Although iron overload can cause restrictive cardiomyopathy, DCM is more common

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Clinical Features of Dilated Cardiomyopathy 📋

Fundamental Defect

➡ Ineffective myocardial contraction (systolic dysfunction)

Key Functional Findings

- Ejection fraction < 25%
  (Normal: 50–65%)

Common Complications

- Secondary mitral regurgitation
- Arrhythmias
- Mural thrombus formation
  → Systemic embolization ⚠️

Typical Patient Profile

- Age: 20–50 years
- Presentation: Slowly progressive congestive heart failure

Symptoms

- Dyspnea
- Easy fatigability
- Poor exercise tolerance

Prognosis & Treatment

- Median survival (to death or transplant): 4–6 years
- Common causes of death:
  - Progressive heart failure
  - Arrhythmias

Definitive Treatment

- Cardiac transplantation ⭐

Supportive / bridging therapy:

- Long-term ventricular assist devices (VADs)
- In some patients:
  - Mechanical support
    → Durable regression of cardiac dysfunction

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) ⚡🫀

Overview

- Autosomal dominant disorder
- Affects right ventricle
- Causes:
    - Right-sided heart failure
    - Serious rhythm disturbances
    - Sudden cardiac death

📊 Epidemiology

- Prevalence: 1 in 2000 – 1 in 5000
- Responsible for:
    - ~10% of sudden deaths in athletes 🏃‍♂️⚠️

Pathogenesis

Mutations in:

- Desmosomal junction proteins at intercalated discs
    - e.g., Plakoglobin
- Proteins interacting with desmosomes
    - e.g., Desmin

Mechanism (Flowchart)

Desmosomal protein mutation → Weak intercellular adhesion → Myocyte detachment during stress/exercise → Myocyte death → Fatty ± fibrous replacement → Arrhythmias & RV failure ⚡

Morphology

- Severely thinned right ventricular wall
- Replacement of myocardium by:
  - Fat
  - Lesser amounts of fibrosis

📌 Exercise increases risk due to enhanced mechanical stress

Morphology of Dilated Cardiomyopathy 🔬

Gross Morphology

- Heart:
  - Enlarged (2–3× normal weight)
  - Flabby
- Dilation of all chambers
- Ventricular wall thickness:
  - May be ↓, normal, or ↑ (due to dilation + hypertrophy)

📌 Common finding:

- Mural thrombi → source of thromboembolism

🚫 By definition absent:

- Valvular disease
- Coronary artery disease
- Other causes of secondary dilation

Microscopic (Histologic) Features

- Nonspecific changes
- Myocytes show:

    - Hypertrophy
    - Enlarged nuclei
    - Attenuation & stretching
- Interstitial & endocardial fibrosis
- Scattered replacement fibrosis

📌 Replacement fibrosis may represent:

- Prior ischemic necrosis (hypoperfusion)
- "Footprints" of previous myocarditis

Special Feature: Iron Overload DCM

- Marked intramyocardial hemosiderin deposition
- Demonstrated by:
    - Prussian blue stain 🔵

HYPERTROPHIC CARDIOMYOPATHY (HCM) 🫀⚡

Definition

Hypertrophic cardiomyopathy is characterized by:

- Marked myocardial hypertrophy
- Defective diastolic filling
- Ventricular outflow tract obstruction in ~⅓ of cases

📌 Key contrast with DCM (exam favorite):

- HCM: Thick, heavy, hypercontractile heart
- DCM: Dilated, flabby, poorly contractile heart

Functional Abnormality 🔄

- Systolic function: Usually normal or increased
- Primary problem: Diastolic dysfunction

Why diastolic dysfunction?

Hypertrophied myocardium → Impaired relaxation → ↓ Ventricular filling during diastole → ↓ Cardiac output

📌 Important clinical differentiation:

HCM must be distinguished from:

- Restrictive cardiomyopathy (e.g., amyloidosis)
- Causes of secondary hypertrophy:
  - Aortic stenosis
  - Hypertension

Pathogenesis of HCM 🧬

Genetic Basis

- Autosomal dominant inheritance
- Variable expressivity

Over 400 mutations identified in 9 genes

Unifying Molecular Mechanism

All mutations are:

- Missense
- Gain-of-function
- Affect sarcomeric proteins

Pathogenetic Sequence (Flowchart)

Gain-of-function sarcomeric mutation → ↑ Myofilament contractility → ↑ Energy consumption → Myocyte hypercontractility → Net negative energy balance → Myocyte hypertrophy & disarray ⚠️

Most Commonly Mutated Genes

Protein	Frequency
β-myosin heavy chain	Most common
Myosin-binding protein C	Common
Troponin T	Common

📌 These 3 genes account for 70–80% of HCM cases

Important Comparison with DCM ⚠️

Some genes (e.g., β-myosin) are mutated in both HCM and DCM:

- HCM: Gain-of-function mutation
- DCM: Loss-of-function mutation

➡ Same gene, opposite functional outcome = different cardiomyopathy

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Morphology of HCM 🔬

Gross Morphology

- Massive myocardial hypertrophy
- No ventricular dilation

Patterns of Hypertrophy

- Asymmetric septal hypertrophy – 90% cases ⭐
- Concentric hypertrophy – 10%

📌 Characteristic ventricular cavity shape:

- On longitudinal section:
  - LV cavity becomes compressed
  - Appears "banana-shaped" 🍌 (classic exam description)

Left Ventricular Outflow Tract (LVOT) Obstruction

During systole:

- Anterior mitral leaflet moves toward septum (Systolic Anterior Motion - *SAM*)

Mechanism (Flowchart)

Septal hypertrophy → Narrowed LV outflow tract → Systolic anterior motion of mitral valve → Mitral leaflet contacts septum → LVOT obstruction → Harsh (crescendo-decrescendo) systolic murmur ⚡

📌 Results in:

- Plaque formation in LVOT
- Thickening of mitral leaflet

Microscopic (Histologic) Features ⭐

Classic triad of HCM:

1. Myocyte hypertrophy
2. Haphazard myocyte (fiber) disarray 🧩
3. Interstitial fibrosis

📌 *Myofiber disarray is highly characteristic and frequently tested*

Clinical Features of HCM 🩺

Age of Presentation

- Can occur at any age
- Most commonly manifests during:
    - Post-pubertal growth spurt

Pathophysiology-Based Symptoms

Impaired relaxation + LVOT obstruction
→ ↓ Effective cardiac output
→ ↑ Pulmonary venous pressure

Resulting Symptoms

- Exertional dyspnea
- Harsh systolic ejection murmur

Myocardial Ischemia Without CAD ⚠️

Massive hypertrophy → ↑ Oxygen demand → ↓ Intramural coronary flow → Angina, even with normal coronaries

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Major Complications 🚨

- Atrial fibrillation → Mural thrombus → Embolism

- Ventricular fibrillation → Sudden cardiac death
- Infective endocarditis (mitral valve)
- Congestive heart failure

Sudden Cardiac Death ⚡

- HCM is a leading cause of sudden death in young athletes
- Accounts for:
  - ~⅓ of sudden cardiac deaths in athletes <35 years

📌 Exam pearl:
Young athlete + collapse during exertion → Think HCM first

Management (Conceptual – Exam Relevant) 💊

- Medical therapy:
  - Improves ventricular relaxation

- Interventional options for LVOT obstruction:
  - Surgical septal myectomy
  - Alcohol septal ablation
    (controlled therapeutic infarction)

RESTRICTIVE CARDIOMYOPATHY 🫀📉

Definition

Restrictive cardiomyopathy is characterized by:

- Decreased ventricular compliance
- Impaired ventricular filling during diastole

📌 *Simply put:*

➡ The ventricular wall becomes stiff, not weak.

Basic Functional Defect 🔄

Normal systolic contraction

- Impaired relaxation → ↓ Diastolic filling → ↓ Cardiac output → Signs of heart failure ⚠️

📌 Key distinction:

- Systolic function is often normal or near-normal

- Primary problem: Diastolic dysfunction

Etiology

Restrictive cardiomyopathy may be:

1. Idiopathic
    - No identifiable cause
2. Secondary to myocardial diseases
    - Radiation-induced fibrosis
    - Amyloidosis
    - Sarcoidosis
    - Inborn errors of metabolism
        - Mucopolysaccharidoses
        - Sphingolipidoses

Important Types of Restrictive Cardiomyopathy ⭐

1. Cardiac Amyloidosis 🧬⚠️

Pathogenesis

Deposition of extracellular proteins → Formation of insoluble β-pleated sheets → Myocardial stiffening → Restrictive physiology

Clinical Settings

- Part of systemic amyloidosis
  - e.g., *Multiple myeloma*
- Isolated cardiac amyloidosis

Transthyretin (ATTR) Amyloidosis 🧠🩺

- Due to deposition of:
  - Normal or mutant transthyretin
- Transthyretin:
  - Synthesized in liver
  - Transports thyroxine & retinol

📌 Epidemiology:

- ~4% of African Americans carry a transthyretin mutation
- Increases risk of cardiac amyloidosis >4-fold

AL Amyloidosis – Extra Damage

Immunoglobulin light chains:

- Deposit as amyloid
- Are directly cardiotoxic

➡ Contribute further to myocardial dysfunction

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2. Endomyocardial Fibrosis 🌍❤️‍🩹

Epidemiology

- Predominantly affects:
  - Children & young adults
  - Africa & tropical regions
- Most common restrictive cardiomyopathy worldwide

Pathologic Features

- Diffuse fibrosis of:
  - Ventricular endocardium
  - Subendocardium
- Frequent involvement of:
  - Tricuspid valve
  - Mitral valve

Functional Consequences (Flowchart)

Endocardial fibrosis → ↓ Ventricular volume → ↓ Compliance → Restrictive physiology → Diastolic heart failure ⚠️

Etiologic Associations

- Nutritional deficiencies
- Chronic inflammation
- Helminthic infections 🪱

3. Loeffler Endomyocarditis 🧪⚠️

Key Features

- Endocardial fibrosis
- Large mural thrombi
- No geographic or racial predilection

Characteristic Association

- Peripheral hypereosinophilia
- Eosinophilic tissue infiltration

Pathogenesis

Hypereosinophilia → Eosinophil infiltration of myocardium → Release of granule contents (especially major basic protein) → Endocardial & myocardial necrosis → Fibrosis + mural thrombus formation →

Thrombus organization → Restrictive cardiomyopathy

📌 Major basic protein = key toxic mediator

Morphology of Restrictive Cardiomyopathy 🔬

Gross Morphology

- Ventricles:
  - Normal size or mildly enlarged
  - No dilation
  - Firm myocardium
- Atria:
  - Bilaterally dilated ⭐
  - Due to:
    - Impaired ventricular filling
    - Chronic pressure overload

Microscopic Features

- Variable interstitial fibrosis
- Gross appearance may be similar across causes

📌 Diagnostic tip:

- Endomyocardial biopsy often reveals:
  - Amyloid deposition
  - Endomyocardial fibrosis
  - Other specific etiologies

COMPARISON TABLE: CARDIOMYOPATHIES 📊

Feature	Dilated (DCM)	Hypertrophic (HCM)	Restrictive
LV Ejection Fraction	<40%	50–80%	25–50%
Primary Defect	Systolic dysfunction	Diastolic dysfunction	Diastolic dysfunction
Ventricular Size	Dilated	Small / normal	Normal
Ventricular Wall	Thin or hypertrophied	Markedly thickened	Rigid / stiff
Atria	Normal or mildly dilated	Mild dilation	Marked dilation ⭐

Common Causes	Genetic, alcohol, myocarditis, doxorubicin	Genetic (sarcomeric)	Amyloidosis, radiation
Mimickers	IHD, valve disease, HTN	HTN, aortic stenosis	Constrictive pericarditis

📌 Normal EF: ~50–65%

Exam Pearls – One Look Revision 🧠

- DCM = weak pump
- HCM = tight ventricle + obstruction
- Restrictive = stiff ventricle
- Biatrial dilation → think restrictive
- Young athlete sudden death → think HCM
- Endomyocardial biopsy helpful in restrictive CM

-> The End <-