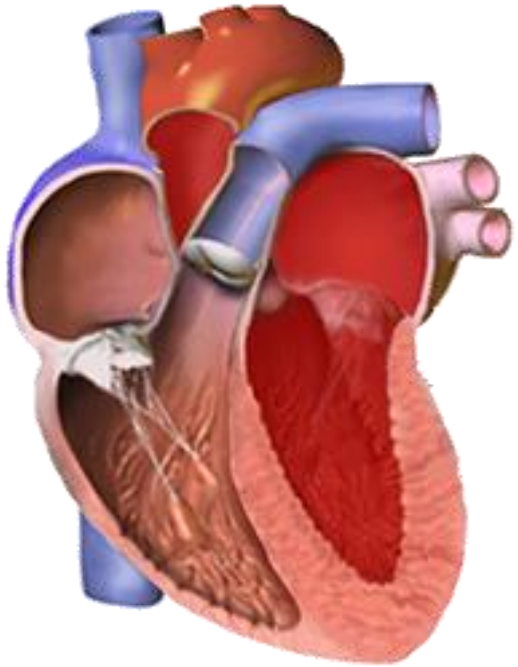
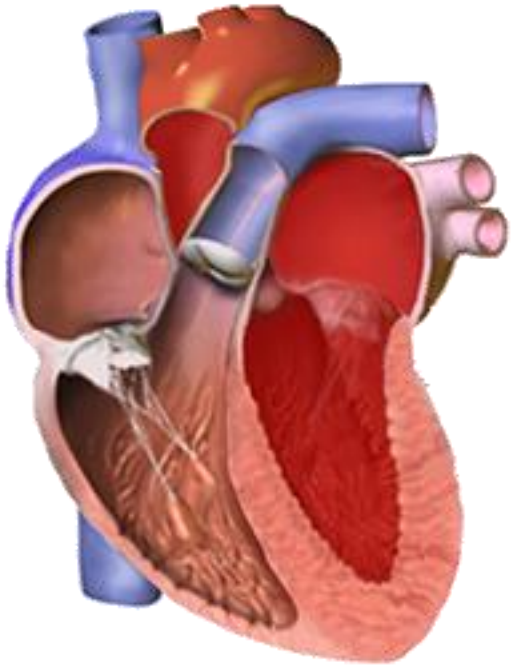


Pathophysiology of cardiomyopathies



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VL

Pathophysiology of cardiomyopathies

Goals:

- Distinguish DCM, HCM, RCM, ARVC (+ LVNC as a phenotype).
- Explain systolic vs diastolic dysfunction (HFrEF vs HFpEF).
- Link mechanism → typical findings (ECG/ECHO/MRI) and clinical consequences.
- Understand why cardiomyopathies lead to arrhythmias and sudden death.

Definition and classification (phenotype ≠ cause)

- Diseases of the myocardium with mechanical/electrical dysfunction, often genetic, often with remodeling and fibrosis. Classification by phenotype:
  - **DCM (dilated cardiomyopathy) → systolic heart failure**
  - **HCM (hypertrophic) → diastolic dysfunction ± LVOT obstruction**
  - **RCM (restrictive) → stiff walls, high filling pressures**
  - **ARVC (arrhythmogenic right ventricular) → arrhythmias + RV failure**
  - **LVNC (left ventricular non-compaction) → a trabeculated phenotype with variable dysfunction**
- Common denominator: energy impairment, Ca^{2+} dysregulation, neurohumoral activation, microvascular dysfunction, fibrosis.

Terminology

DCM = dilatation + systolic dysfunction
HCM = hypertrophy + diastolic dysfunction ± LVOT obstruction
RCM = stiffness + high filling pressures
ARVC = RV fibrofatty remodeling + VT

Common pathophysiological pillars

- Energetics/mitochondria: ATP deficit, oxidative stress.
- Ca^{2+} dysregulation: weaker contraction + slower relaxation.
- Neurohumoral activation (SNS/RAAS): short-term compensation, long-term remodeling.
- Microvascular dysfunction: relative ischemia, especially in hypertrophy/inflammation.
- Fibrosis: interstitial (stiffness) and replacement (arrhythmogenic substrate).

Basic mechanisms

A. Hemodynamics

- **Systolic dysfunction:** ↓ contractility → ↑ ESV, ↓ SV, activation of RAAS/SNS → remodeling
- **Diastolic dysfunction:** impaired relaxation + ↑ stiffness (fibrosis, hypertrophy, deposits) → ↑ LVEDP →

  left atrial dilation → pulmonary venous hypertension → dyspnea

B. Myocardial remodeling

- **Concentric hypertrophy** (pressure overload, some forms of HCM) vs.

  eccentric hypertrophy/dilatation (volume overload, DCM)
- **Fibrosis:**
  - **Interstitial** (diffuse, diastolic stiffness)
  - **Replacement** (after injury; arrhythmogenic substrate)

C. Electrical instability (why arrhythmias?)

- **"Triad" of arrhythmogenesis:**
  1. **Substrate:** fibrosis/scars, myocyte disorganization, fibro-fatty replacement (ARVC)
  2. **Trigger:** extrasystoles, ischemia, electrolyte disturbances
  3. **Modulator:** SNS, inflammation, drugs, channelopathies

Systolic vs diastolic dysfunction

Systolic (HFrEF)

- ↓ contractility → ↑ ESV, ↓ SV (the ventricle cannot eject effectively—EF and cardiac output fall)
- Activation of SNS/RAAS → remodeling
- Often congestion + low output
- Typical of DCM

Diastolic (HFpEF)

- Impaired relaxation + ↑ stiffness
- EF may be normal, but filling pressures are high:

  ↑ LVEDP → ↑ LA pressure/dilatation
- Pulmonary venous HTN → dyspnea
- Typical of HCM/RCM

➢ *This distinction is key: DCM typically leads to systolic dysfunction, whereas HCM and RCM primarily lead to diastolic dysfunction*.

Pressure–volume relationships (PV)

- Systolic dysfunction: contractility falls, shift of the end-systolic curve → ↑ ESV, ↓ SV.
- Diastolic stiffness: steeper diastolic P–V curve → a small ↑ in volume = a large ↑ in pressure.
- Clinical consequence: high filling pressures = dyspnea and congestion even with normal EF.
- Tachycardia shortens diastole → worsening symptoms in HCM/RCM.

➢ *This is the mechanism of dyspnea in HCM and RCM: filling pressures are high even when EF may be normal.*

Practical takeaway:

EF by itself does not exclude heart failure. Filling pressures and compliance are decisive.

Remodeling and Laplace’s principle

- **Remodeling is the heart’s adaptation to chronic load—initially compensation, later maladaptation.**
- Eccentric hypertrophy/dilatation: typically volume overload or ↓ contractility (DCM).
- Concentric hypertrophy: pressure overload or genetic phenotypes (HCM).
- Laplace explains progression: dilatation → ↑ radius → ↑ wall stress → ↑ energy demand and O_2 requirement → further deterioration.

Why cardiomyopathies are arrhythmogenic

- Arrhythmias do not arise randomly. They require a substrate, a trigger, and a modulator.
- **Substrate = structural heterogeneity: fibrosis/scars, myocyte disarray*, fibrofatty remodeling (ARVC).**
- **Trigger: extrasystoles, ischemia, electrolyte disturbances, or inflammation.**
- **Modulator: sympathetic tone, drugs, hormones, stress.**
- The combination explains the risk of VT/VF and sudden death (especially in HCM, ARVC).

*Loss of the normal, parallel arrangement of cardiac muscle cells; instead they are arranged in disorganized, perpendicular or oblique “star-like” patterns, often with increased connective tissue. It is the characteristic histologic feature of HCM; it can also be seen in HTN and AS (aortic stenosis).

Clinical implication:

We assess arrhythmic risk based on the substrate (fibrosis, scars), not only on EF.

DCM: definition and typical causes

- Definition: dilatation of the ventricle(s) + systolic dysfunction.
- Etiology is heterogeneous: genetic defects of the sarcomere/cytoskeleton, post-myocarditis injury, toxic influences (alcohol, some drugs), peripartum state, tachycardia-induced cardiomyopathy.
- Pathophysiologic core: ↓ contractility → compensatory dilatation → subsequent maladaptive remodeling.

DCM: cellular mechanisms

- **At the cellular level, DCM often combines impaired calcium cycling with an energy deficit.**
- Ca^{2+} handling → impaired contraction and relaxation:
  - When reuptake of calcium into the sarcoplasmic reticulum is reduced, contraction is weaker and relaxation is slower.
- Mitochondrial dysfunction and oxidative stress → damage myocytes and promote apoptosis:
  - Mitochondria/ROS: energy deficit, myocyte injury.
- Apoptosis/necrosis + extracellular matrix remodeling.
- Inflammation (in myocarditis): may persist and sustain injury and fibrosis/remodeling.

DCM: neurohumoral activation and progression

- Reduced cardiac output → activation of SNS/RAAS: maintenance of perfusion and pressure.
- Short term: maintenance of pressure and perfusion.
- Long term: ↑ afterload, Na and water/fluid retention, fibrosis, arrhythmias.
- Clinically: congestion + low output; progression unless these mechanisms are interrupted.

➢ *The result is lower mechanical efficiency, higher filling pressures, and higher arrhythmic risk.*

DCM: functional mitral regurgitation and thromboembolism

- LV dilatation → dilatation of the mitral annulus + leaflet tethering (papillary muscle geometry changes) → functional MR.
- MR adds volume overload → further dilatation (accelerated dilatation) and congestion.
- Blood stasis in dilated chambers + low EF/AF → intracavitary thrombi → embolization.

Mini-case: post-myocarditis DCM

- 45-year-old man, viral illness 3 weeks ago, now dyspnea.
- EF 25%, troponin mildly ↑, MRI: edema + subepicardial late gadolinium enhancement.
- Question: describe the pathophysiological pathway from trigger to phenotype.

Take-home message

Inflammatory injury of myocytes → reduced contractility → neurohumoral activation → remodeling → dilatation + HFrEF.

DCM – Summary

Pathophysiology – core

- **Primary causes:** dysfunction of the contractile apparatus / cytoskeleton / mitochondria, or myocardial injury
  (e.g., myocarditis, toxins).
- **Mechanisms:**
  - ↓ contractility → compensatory dilatation (Frank–Starling mechanism) → later **worsening of mechanical efficiency**
  - **Laplace's law:** dilatation → ↑ wall stress → ↑ O_2 demand → disease progression
  - **Functional mitral regurgitation** (annular dilatation, leaflet tethering) → volume overload → further dilatation

Micro-level

- **Ca^{2+} handling abnormalities** (SERCA/ryanodine receptors), oxidative stress, apoptosis, mitochondrial dysfunction
- **Neurohumoral activation** (SNS/RAAS): short-term maintenance of perfusion, long-term damage (fibrosis, arrhythmias)

Clinical correlates

- **HFrEF phenotype:** fatigue, dyspnea, edema
- **Risks:** malignant ventricular arrhythmias, thromboembolism (intracavitary thrombi)

HCM: definition and three main pathophysiological problems

- Unexplained hypertrophy (often asymmetric) + myocyte disarray* + interstitial fibrosis.
- Triad: (1) diastolic dysfunction, (2) microvascular ischemia, (3) ± LVOT obstruction.
- Common consequences: dyspnea, angina, syncope, arrhythmias.

**Loss of the normal, parallel arrangement of cardiac muscle cells; instead they are arranged in disorganized, perpendicular or oblique "star-like" patterns, often with increased connective tissue. It is the characteristic histologic feature of HCM; it can also be seen in HTN and AS (aortic stenosis).*

HCM: diastolic dysfunction → dyspnea

- A hypertrophied myocardium is stiffer and relaxes more slowly (to reach the required diastolic volume, a higher diastolic pressure is needed).
- ↑ LVEDP → ↑ LA pressure → LA dilatation → pulmonary venous hypertension → dyspnea.
- Tachycardia shortens diastole → marked worsening of exertional dyspnea.

HCM: microvascular ischemia (angina without stenoses)

- Angina-like symptoms can occur even with normal epicardial coronary arteries (a microvascular mechanism).
- Hypertrophy → ↑ O_2 demand + relatively lower capillary density (capillary density is relatively insufficient and intramural vessels are more compressed).
- Compression of intramural vessels in systole + impaired vasodilation.
- The result is relative ischemia → promotes fibrosis and arrhythmias.

HCM: LVOT obstruction and SAM (dynamic obstruction)

- In obstructive HCM, the obstruction is dynamic. During systole, the mitral leaflet moves anteriorly toward the septum – SAM.
- SAM = systolic anterior motion of the mitral leaflet toward the septum.
- If the septum is hypertrophied, narrowing of the outflow tract and a pressure gradient develop.
- The gradient increases with: ↓ preload, ↓ afterload, ↑ contractility.
- Obstruction is worsened by: dehydration, vasodilation, sudden standing, tachycardia.
- Obstruction is improved by: slowing HR (prolonging diastole), maintaining preload.

HCM: maneuvers

- Valsalva / standing: ↓ preload (venous return) → smaller ventricle, ↑ obstruction → ↑ murmur.
- Squatting: ↑ preload (venous return) + ↑ afterload → ↓ obstruction → ↓ murmur.
- Purpose: to demonstrate the dynamic nature of LVOT obstruction.

Question for the audience

“What does the Valsalva maneuver do to the murmur in obstructive HCM, and why?”

HCM: maneuvers

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- Purpose: to demonstrate the dynamic nature of LVOT obstruction.

Question for the audience

"What does the Valsalva maneuver do to the murmur in obstructive HCM, and why?"

Valsalva reduces venous return (preload), the ventricle becomes smaller, obstruction worsens, and the murmur becomes louder.

In contrast, squatting increases venous return and afterload, obstruction decreases, and the murmur becomes softer.

HCM: arrhythmias, atrial fibrillation, and sudden death

- Ventricular arrhythmias: disarray + fibrosis + ischemia → re-entry.
- LA dilatation → atrial fibrillation; worsens filling of a stiff ventricle.
- Arrhythmic risk is determined by the substrate (fibrosis), not only by symptoms.

- In HCM, arrhythmic risk results from the combination of disarray, fibrosis, and ischemia.
- Ventricular tachyarrhythmias arise by a re-entry mechanism at the borders of fibrosis.
- The left atrium dilates under chronically elevated filling pressures, which promotes atrial fibrillation.
- Atrial fibrillation can markedly worsen symptoms because, with a stiff ventricle, the atrial contribution to filling is substantial.

Mini-case: HCM with exertional syncope

- 19-year-old athlete, exertional syncope.
- Systolic murmur: becomes louder with standing and Valsalva.
- Mechanism: dynamic LVOT obstruction that worsens when preload falls and may contribute to syncope ± an arrhythmic trigger.

HCM – Summary

Pathophysiology – core

- **Hypertrophy**, often **asymmetric** (septal), **myocyte disorganization (disarray)**, and **interstitial fibrosis**.
- **Main problems:**
  1. **Diastolic dysfunction** (increased stiffness + impaired relaxation)
  2. **Microvascular ischemia** (disproportionate hypertrophy relative to capillary density)
  3. **± LVOT obstruction (dynamic):** septal hypertrophy + systolic anterior motion (SAM) of the mitral valve
     → gradient increases with ↓ preload / ↓ afterload / ↑ contractility

Hemodynamic "triggers" of obstruction

- **Why it is risky:** dehydration, vasodilation, nitrates, sudden standing, tachycardia
- **Why these help:** beta-blockers (↓ HR, ↑ diastole), increased preload, avoidance of vasodilation in obstructive forms

Arrhythmias in HCM

- **Fibrosis + disarray → re-entry; ischemia → triggers**
- **Left atrial dilation → atrial fibrillation** (worsens LV filling)

RCM: definition and the hemodynamic core

- Primarily a “filling problem”: a steep diastolic pressure–volume curve (a small increase in volume causes a large increase in pressure).
- EF can remain relatively preserved for a long time, but filling pressures are high.
- Clinically, congestion predominates, with secondary pulmonary hypertension and right-sided symptoms.

RCM: causes and electrical consequences

- Mechanisms of RCM include infiltration or deposition, or diffuse fibrosis.
  - Infiltrative/deposit forms: amyloid, hemochromatosis, sarcoidosis.
- In amyloidosis, material is deposited in the interstitium and the myocardium becomes stiff.
- In sarcoidosis, granulomas and scars form, often also within the conduction system.
- In hemochromatosis, iron deposition damages mitochondria and electrical stability.
- Fibrotic forms: post-radiation, endomyocardial fibrosis (rare).
- Therefore, RCM often leads to congestion, as well as conduction disorders and arrhythmias (infiltration of the conduction system, scars).

RCM vs constrictive pericarditis

- In practice, it is important to distinguish myocardial restriction from pericardial constriction, because the therapeutic consequence is fundamental.
- RCM: the problem is in the myocardium (infiltration/fibrosis).
- Constrictive pericarditis: the problem is in the pericardium (a rigid “shell”).
- Hemodynamics: constriction shows more pronounced respiratory ventricular interdependence.
- Consequence: the therapeutic approach differs substantially—therefore it must be distinguished deliberately.

RCM – Summary

Pathophysiology – core

- Primary **“filling problem”**: **rapidly rising filling pressures with only a small increase in volume**
- **Causes (phenotypes):**
  - **Infiltrative / storage:** amyloidosis, hemochromatosis, sarcoidosis
  - **Fibrotic:** endomyocardial fibrosis, post-radiation

Hemodynamics

- **Near-normal ejection fraction for a long time**, but **marked congestion**, high **LA/RA pressures**
- **Secondary pulmonary hypertension** is common

Clinical correlates

- **Predominant signs of right-sided heart failure:** hepatomegaly, ascites
- **Arrhythmias and conduction disorders** (especially with infiltrative disease)

Restrictive cardiomyopathy (RCM)

- The rarest form of heart muscle disease.
- Characterized by increased stiffness of the ventricular walls and reduced compliance → severe diastolic dysfunction (impaired filling) with preserved systolic function, followed by atrial enlargement and development of chronic heart failure.
- Causes: infiltrative diseases (amyloidosis, hemochromatosis, sarcoidosis), idiopathic (unknown cause), genetic, or post-radiation states.

Restrictive cardiomyopathy (RCM)

- Diagnosis: Echocardiography is the cornerstone; it shows reduced ventricular compliance, normal wall thickness (or mild thickening) and enlarged atria (ECG – low QRS voltage / iron, proteins, molecules = “electrical insulators”).
- Symptoms: The main symptoms are dyspnea (shortness of breath), fatigue, leg edema, and reduced exercise tolerance.
- Treatment: Focuses on treating heart failure (diuretics) and treating the underlying cause.

RCM and ECG

Restrictive cardiomyopathy (RCM) – ECG

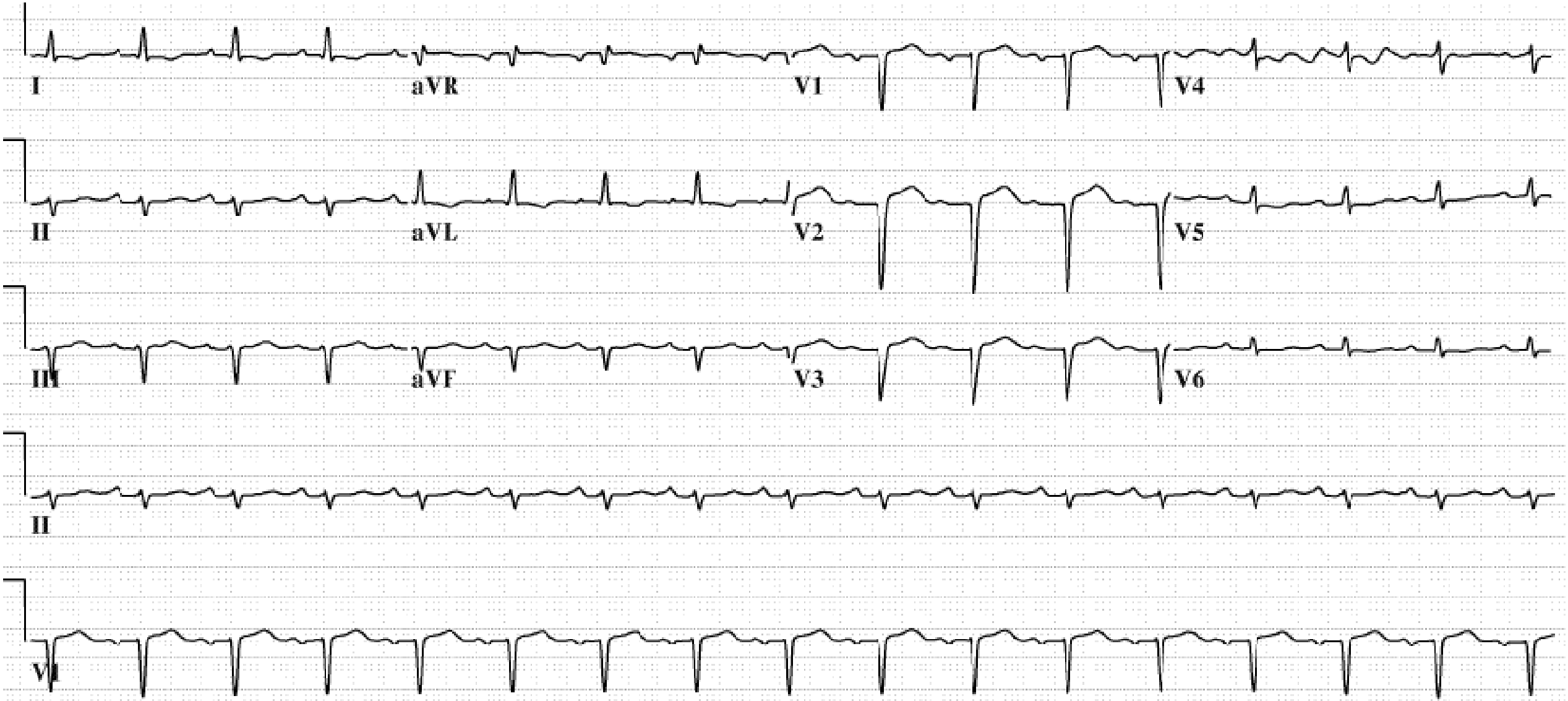
- **Restrictive cardiomyopathy (RCM) has no diagnostic ECG criteria**
  - The **ECG is always abnormal** in RCM
  - **Echocardiography** is used for diagnosis

Most common ECG changes in restrictive cardiomyopathy

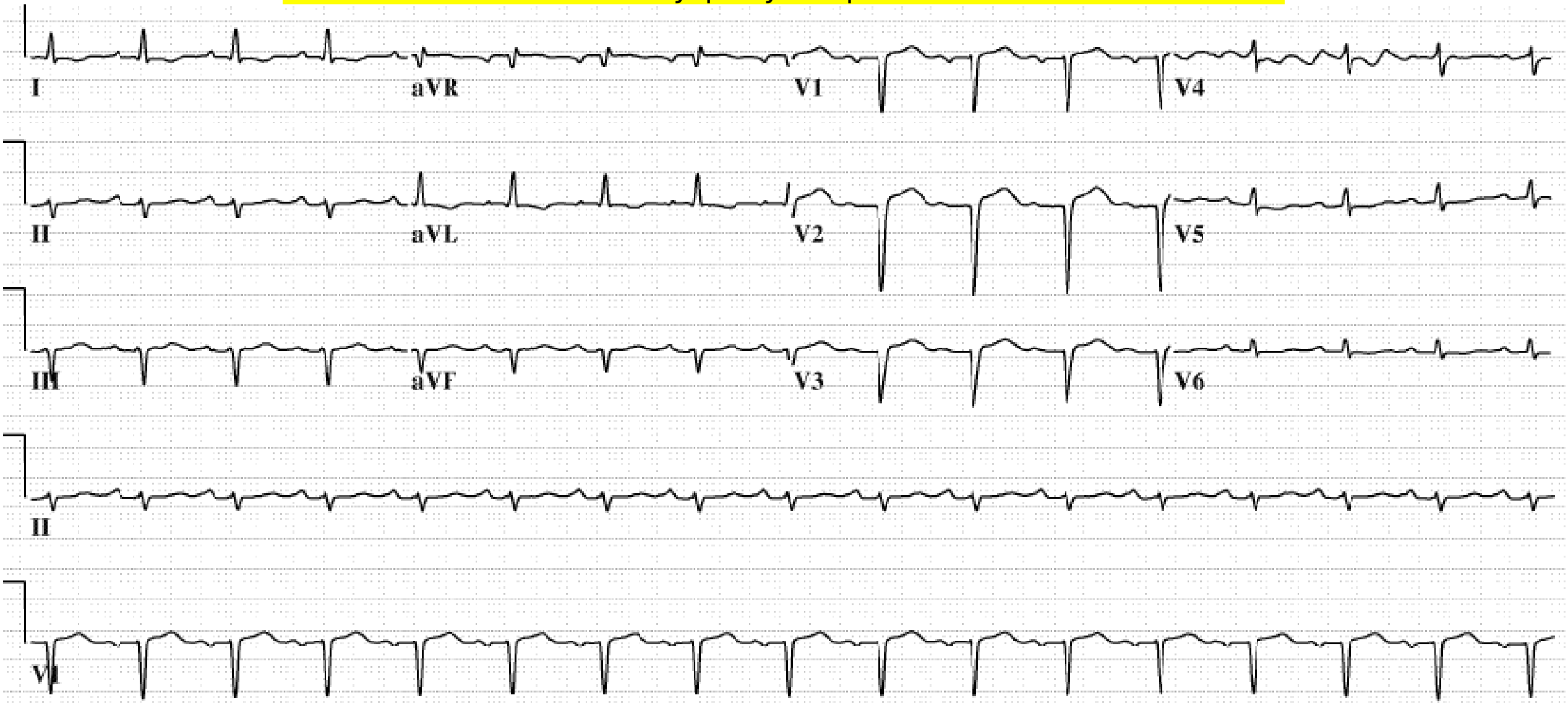
- **Low QRS voltage**

  (Substances in the heart – iron, proteins, molecules – act as an electrical insulator)
- **Nonspecific ST-segment and T-wave changes**
- **Conduction system disorders**
  - **Bundle branch blocks**
  - **AV blocks**
- **Pathological Q waves**
  - In **sarcoidosis**, **granulomas form in the heart and alter the ventricular electrical vector**
- Because the heart is **structurally abnormal**, the following may occur:
  - **Ventricular arrhythmias**
  - **Supraventricular arrhythmias**

Case report – patient with sarcoidosis



Restrictive cardiomyopathy: Low ECG voltage (I, II, aVR, V4, V5, V6), Nonspecific changes: flat T waves, ST elevations (V1–V3), pathological Q waves (V1–V3). Nonspecific changes and pathological Q waves can also suggest myocardial infarction. The patient had sarcoidosis; echocardiography confirmed restrictive cardiomyopathy. The patient did not have an infarction.



ARVC + LVNC + specific secondary forms

A) ARVC (Arrhythmogenic Right Ventricular Cardiomyopathy)

- **Pathophysiology:** defect of **cell–cell junctions** → **myocyte loss under stress** → **fibro-fatty replacement** (especially the **right ventricle**) → **substrate for ventricular tachycardia (VT)**
- **Clinical features:** palpitations, syncope, **VT with LBBB morphology** (originating in the RV)

B) LVNC (Left Ventricular Noncompaction)

- **Pathophysiology:** developmental **non-compaction of the trabecular layer** → risk of **systolic dysfunction, arrhythmias, and thromboembolism** in some patients

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C) Takotsubo (stress cardiomyopathy)

- **Catecholamine toxicity + microvascular spasm + energetic dysfunction** → **transient ventricular dysfunction** (often **apical**)

D) Peripartum cardiomyopathy

- **Multifactorial:** angiogenic imbalance, oxidative stress, genetic predisposition

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E) Toxic / iatrogenic cardiomyopathy

- **Alcohol, anthracyclines, some targeted therapies** → **mitochondrial injury, reactive oxygen species (ROS), apoptosis**

Arrhythmogenic right ventricular cardiomyopathy (ARVC): mechanism and why VT occurs

- Arrhythmogenic right ventricular cardiomyopathy primarily leads to electrical instability.
- With defects in cell junctions/desmosomes, myocytes die under mechanical load and are replaced by fibrofatty tissue.
- This creates a strong re-entry substrate in the right ventricle; clinically VT and syncope dominate, often before overt RV failure develops.

LVNC + secondary cardiomyopathies

- LVNC: hypertrabeculation; in some patients HFrEF, arrhythmias, thrombosis.
- Takotsubo cardiomyopathy: catecholamine toxicity + microvascular dysfunction → transient dysfunction.
- Peripartum cardiomyopathy: multifactorial (angiogenic imbalance, oxidative stress, predisposition).
- Toxic/iatrogenic: damage mitochondria/increase ROS (alcohol, some drugs).

3 questions

1) Why can HCM cause angina with normal coronaries?
2) Why does dilatation worsen DCM?
3) What is the hemodynamic core of RCM?

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2) Why does dilatation worsen DCM? Laplace – ↑ wall stress;
3) What is the hemodynamic core of RCM? a steep diastolic pressure–volume curve.

Questions

Why can HCM cause angina with normal coronary arteries?

→ Microvascular ischemia + increased O_2 demand of the hypertrophied myocardium.

Why does LV dilatation worsen DCM even without new injury?

→ **↑ wall stress (Laplace), ↑ energy demand, secondary MR.**

What is the hemodynamic core of RCM?

→ **A very steep diastolic pressure–volume curve: a small ↑ in volume → a large ↑ in pressure.**