Pathophysiology of heart failure

Prof. Maria Pallayova, MD, PhD.
maria.pallayova@upjs.sk
20.02.2026
DM

Pathophysiology of Heart Failure

From cardiac dysfunction to congestion, hypoperfusion, and multi-organ injury

Session overview

- Definition and mechanistic classifications (HFrEF, HFpEF, acute vs chronic)
- Hemodynamics: preload, afterload, compliance, pressure–volume logic
- Neurohormonal activation and maladaptive remodeling
- Congestion biology and organ cross-talk (kidney, lungs, liver, muscle)
- Clinical phenotypes, triggers of decompensation, and exam pitfalls

How to use this lecture

- Always ask: “Is the problem pressure, flow, or both?”
- Explain symptoms using filling pressures and reserve—not EF alone
- Think in loops: compensation → remodeling → decompensation

Heart failure is a syndrome (not a single diagnosis)

A final common pathway of diverse cardiac and systemic diseases

Core definition (mechanistic)

- Symptoms/signs due to structural or functional cardiac abnormality
- Inadequate output and/or elevated filling pressures
- Systemic consequences: neurohormonal activation + organ dysfunction
- Phenotype depends on tempo: acute vs chronic compensation

Teaching pearl

- Patients feel pressures (congestion) more than EF
- “Normal BP” can coexist with poor perfusion or severe congestion

Learning objectives

What you should be able to explain after this session

By the end, you can…

- Link preload/afterload/compliance to symptoms and signs
- Contrast HFrEF vs HFpEF dominant mechanisms
- Explain neurohormonal compensation and why it becomes maladaptive
- Describe congestion as a pressure/distribution problem
- Use clinical profiles (wet/dry, warm/cold) to reason mechanistically

Assessment focus

- Mechanism-first explanations (not memorized lists)
- Cause→effect chains from heart → organs → bedside findings

Classification axes that matter for pathophysiology

Tempo, side, EF phenotype, and clinical profile

Four useful axes

- Tempo: acute vs chronic (time for remodeling?)
- Side: left vs right vs biventricular (where is congestion?)
- EF phenotype: HFrEF vs HFpEF vs HFmrEF (dominant mechanism)
- Clinical profile: wet/dry and warm/cold (congestion/perfusion)

Practical takeaway

- Different phenotypes share symptoms but differ in mechanisms
- Always label: (1) congestion, (2) perfusion, (3) trigger

Hemodynamics 1: the minimum toolkit

CO, SV, MAP, and filling pressures

Key equations (conceptual)

- CO = HR × SV (forward flow)
- MAP ≈ CO × SVR (pressure depends on flow + resistance)
- LV filling pressure ↔ LA/PCWP; RV filling pressure ↔ RA/CVP
- Symptoms correlate strongly with elevated filling pressures

Clinical translation

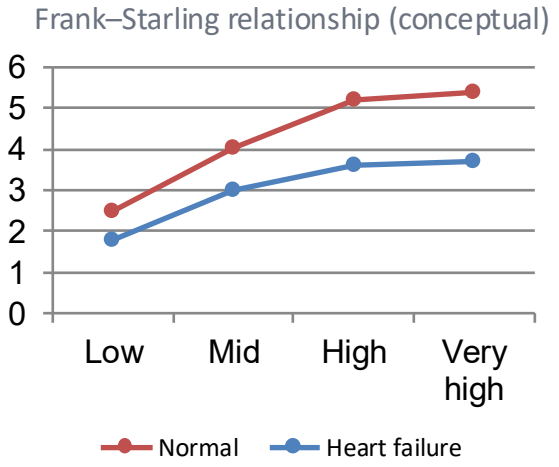
- Dyspnea/orthopnea/PND = elevated left-sided filling pressures
- JVP/edema/hepatomegaly = elevated right-sided filling pressures

Hemodynamics 2: preload and Frank–Starling reserve

Why increasing filling pressures stops helping (and starts hurting)

Starling curve logic

- Early compensation: ↑ preload → ↑ SV (up the curve)
- Plateau: further preload raises pressures more than SV
- Pulmonary/systemic congestion appears when pressures rise
- HF shifts curve down/right (reduced contractile reserve)



Exam pearl

- A “wet” patient is often on the flat part of the Starling curve
- Reducing filling pressures can improve symptoms without raising CO

Hemodynamics 3: afterload and wall stress

Why vasoconstriction can worsen the failing heart

Afterload effects

- ↑ Afterload → ↓ SV (especially in systolic dysfunction)
- SNS/RAAS raise SVR to defend MAP
- Chronic ↑ wall stress → remodeling (hypertrophy/dilation)
- Subendocardial ischemia risk rises as wall stress increases

Clinical translation

- “High SVR with low CO” can look normotensive but underperfused
- Reducing afterload often increases forward SV in HFrEF

Hemodynamics 4: compliance and diastolic function

How a “normal EF” heart can be a high-pressure heart

Diastolic physiology

- Relaxation (active) + stiffness (passive) determine filling pressure
- Low compliance → large pressure rise for small volume increase
- HFpEF: exertional dyspnea from exercise-induced pressure rise
- Atrial contribution becomes critical (loss in AF is poorly tolerated)

Bedside implication

- HFpEF patients can be “euvolemic” yet congested during exercise
- Tachycardia reduces diastolic filling time → pressure spikes

Congestion vs hypoperfusion: the two outputs

A practical physiologic framework for symptoms and signs

Congestion (pressure/venous) dominates

- Pulmonary: dyspnea, orthopnea, PND, crackles, hypoxemia
- Systemic: JVP↑, edema, hepatomegaly, ascites, gut edema
- Driven by elevated filling pressures and venous pressures

Hypoperfusion (flow) clues

- Cool extremities, narrow pulse pressure, oliguria, confusion
- Can coexist with congestion (“cold & wet” is highest risk)

Neurohormonal model: compensation → maladaptation

SNS, RAAS, vasopressin/endothelin vs natriuretic peptides

Primary responses to “low effective perfusion”

- SNS: ↑ HR/contractility, vasoconstriction, renin release
- RAAS: Ang II vasoconstriction + aldosterone Na^+/H_2O retention
- Vasopressin: free water retention; endothelin: vasoconstriction
- Natriuretic peptides: counter-regulation (natriuresis/vasodilation)

Why it matters

- Chronic activation drives remodeling, congestion, and arrhythmias
- Many effective HF therapies work by antagonizing these pathways

Sympathetic nervous system (SNS)

Short-term hemodynamic support; long-term toxicity

Adaptive effects

- ↑ HR and contractility (β1)
- Peripheral vasoconstriction (α1) → maintains MAP
- Renal vasoconstriction + renin release → volume retention

Maladaptive consequences

- ↑ myocardial O_2 demand, ↓ diastolic filling time
- Pro-arrhythmic remodeling and myocyte apoptosis
- Down-regulation/desensitization of β-receptors → reduced reserve

RAAS and aldosterone

Volume retention, vasoconstriction, fibrosis, and remodeling

Ang II + aldosterone effects

- Systemic vasoconstriction → ↑ afterload
- Na^+/H_2O retention → ↑ preload and congestion
- Myocardial and vascular fibrosis (ECM remodeling)
- Potassium wasting and arrhythmia vulnerability

Conceptual loop

- RAAS defends pressure but feeds congestion and remodeling
- Congestion + low output perpetuate further RAAS activation

Natriuretic peptides: counter-regulation

Physiologic brakes on RAAS/SNS—often overwhelmed

Physiologic actions

- Released with myocardial stretch (ANP/BNP)
- Promote natriuresis and vasodilation
- Suppress renin, aldosterone, and sympathetic tone
- Reflect filling pressures and wall stress (biomarker logic)

Clinical link

- High levels often indicate high pressures, but interpret in context
- HFpEF and acute HF can produce very high values from stretch

Remodeling patterns: HFrEF vs HFpEF

Geometry, stiffness, and reserve determine phenotype

HFrEF (typical pattern)

- Eccentric remodeling: dilation + increased wall stress
- Reduced contractility and systolic reserve
- Often post-MI, dilated cardiomyopathy, chronic volume overload

HFpEF (typical pattern)

- Concentric remodeling/hypertrophy and increased stiffness
- Impaired relaxation; high filling pressures with exertion
- Often driven by HTN, obesity, diabetes, CKD, aging

Cellular dysfunction (high-yield, not exhaustive)

Calcium handling, energetics, oxidative stress, and apoptosis

Common cellular themes

- Impaired Ca^{2+} cycling → weak contraction + delayed relaxation
- Mitochondrial dysfunction → reduced ATP and increased ROS
- Myocyte hypertrophy and cell death (apoptosis/necrosis)
- β-adrenergic desensitization → reduced inotropic reserve

Why students should care

- Cell biology explains loss of reserve and progression over time
- Fibrosis + ion handling changes create an arrhythmogenic substrate

Fibrosis and extracellular matrix remodeling

Stiffness, impaired relaxation, and conduction heterogeneity

Matrix biology in HF

- Interstitial fibrosis increases stiffness → higher filling pressures
- Replacement fibrosis after injury (e.g., MI) reduces contractile mass
- MMP/TIMP imbalance alters structure and chamber shape
- Fibrosis disrupts electrical coupling → AF/VT vulnerability

Clinical translation

- Fibrosis is a mechanism for HFpEF symptoms and HFrEF progression
- Arrhythmias are not “complications” but part of pathophysiology

Inflammation and systemic biology

Cytokines, endothelial dysfunction, and progression loops

Inflammatory drivers

- HF activates innate and adaptive immune pathways
- Endothelial dysfunction → impaired vasodilation and reserve
- Inflammation promotes fibrosis and catabolism
- Comorbidities amplify inflammation (obesity, DM, CKD)

HF as multi-system disease

- Symptoms arise from heart + vessels + lungs + kidneys + muscle
- HFpEF especially reflects systemic comorbidity biology

HFrEF: systolic pump failure

Reduced contractility, dilation, and reduced forward reserve

Mechanistic core

- Reduced contractility → ↓ SV and CO
- Higher EDV as compensation → dilation (eccentric remodeling)
- Neurohormonal drive maintains MAP but raises afterload and preload
- Progression: dilation → MR, arrhythmias, worsening wall stress

Bedside cues

- Low pulse pressure and fatigue suggest limited forward reserve
- Decompensation is often triggered by salt load, ischemia, AF, infection

HFpEF: a high-pressure, low-reserve state

Stiff ventricle, impaired relaxation, and exercise intolerance

Mechanistic core

- Preserved EF at rest, but filling pressures rise excessively
- Concentric remodeling and fibrosis → stiffness
- Microvascular/endothelial dysfunction → impaired relaxation
- Peripheral limitations: chronotropic and vasodilator reserve

Key paradigm

- Comorbidities can “drive” myocardial dysfunction via inflammation
- Exercise unmasks the physiology (pressures spike with small volumes)

HFmrEF and “improved EF”

Transitional phenotypes and why EF is not destiny

Concepts

- HFmrEF often shares features with both HFrEF and HFpEF
- Improved EF: EF rises above reduced range, but biology may persist
- Symptoms may remain driven by filling pressures and comorbidities
- Use phenotype to reason, not just the EF number

Teaching point

- EF is a snapshot; remodeling and neurohormonal state drive prognosis

Left-sided congestion: why patients get dyspnea

Pulmonary venous hypertension → interstitial edema → air hunger

Mechanism to symptoms

- ↑ LVEDP/LA pressure → ↑ pulmonary venous and capillary pressure
- Fluid shifts into interstitium/alveoli → ↓ compliance, ↑ work of breathing
- Orthopnea: supine venous return + fluid redistribution
- PND: delayed nocturnal redistribution and reduced adrenergic drive

Bedside translation

- Dyspnea/orthopnea/PND are “pressure symptoms”
- Treating congestion reduces symptoms even if EF is unchanged

Right-sided failure and systemic congestion

Venous hypertension as a driver of symptoms and organ dysfunction

Clinical physiology

- RV failure or pulmonary hypertension → RA pressure rises
- JVP elevation reflects high RA/CVP
- Peripheral edema from increased hydrostatic pressure + Na^+ retention
- Hepatomegaly/ascites from hepatic–splanchnic congestion

Examination maneuvers

- Hepatojugular reflux suggests limited RV reserve
- Systemic congestion can exist without major pulmonary symptoms

Ventricular interdependence & pericardial constraint

How right and left filling pressures influence each other

Key concept

- Within a constrained pericardium, one ventricle’s volume affects the other
- RV dilation shifts septum → reduces LV filling and output
- High RA pressures can limit LV preload despite systemic congestion
- Relevant in acute RV failure and advanced biventricular HF

Clinical insight

- Treating RV overload can improve LV output (and vice versa)
- Look for septal shift and disproportionate JVP elevation

Pulmonary hypertension in left HF

Passive venous congestion can become reactive vascular disease

Two components

- Post-capillary PH: elevated LA pressure transmitted backward
- Reactive component: vascular remodeling raises PVR over time
- Higher RV afterload → RV dilation and failure
- Worsening: reduced RV output → more systemic congestion

Why RV fails

- RV is afterload-sensitive (thin-walled, low-pressure chamber)
- Rising PVR converts left HF into biventricular HF

Cardiorenal syndrome: forward vs backward failure

Why kidney function worsens even with preserved arterial pressure

Mechanisms

- “Forward”: reduced renal perfusion from low CO
- “Backward”: renal venous congestion reduces filtration gradient
- Neurohormones: SNS/RAAS promote Na^+ retention and vasoconstriction
- Inflammation and tubular injury amplify dysfunction

Clinical punchline

- Venous congestion is a major driver of renal dysfunction in HF
- Decongestion can improve renal perfusion pressure gradient

Diuretic resistance (mechanistic view)

Why congestion can persist despite escalating loop diuretics

Pathophysiologic contributors

- Reduced renal perfusion and high venous pressure reduce delivery to tubule
- RAAS/SNS activation increases distal Na^+ reabsorption
- Gut edema reduces oral absorption
- Hyponatremia and low albumin alter effective volume distribution

Clinical reasoning

- Resistance is often a congestion + neurohormone problem
- Assess adherence, bioavailability, and venous congestion

Hepatic–splanchnic congestion and the “gut”

Edema, inflammation, and metabolic consequences in advanced HF

What venous congestion does

- Congestive hepatopathy: hepatomegaly, cholestatic labs
- Ascites from portal venous hypertension and fluid shifts
- Gut edema → impaired absorption and altered barrier function
- Systemic inflammation can increase catabolism and cachexia

Why it matters

- Venous congestion is a multi-organ disease
- Symptoms include early satiety, abdominal discomfort, weight gain

Skeletal muscle and exercise intolerance

Why patients fatigue even when resting hemodynamics look “okay”

Peripheral limitations

- Reduced peak CO reserve + impaired peripheral vasodilation
- Muscle deconditioning and fiber shift → early anaerobic metabolism
- Mitochondrial dysfunction and reduced capillary density
- Inflammation contributes to sarcopenia and cachexia

Clinical translation

- Fatigue is not “psychological”: it is physiologic and systemic
- Exercise unmasks reduced reserve in both HFrEF and HFpEF

Ventilatory inefficiency & periodic breathing

Cheyne–Stokes respiration as a consequence of HF physiology

Mechanistic ingredients

- Low CO prolongs circulation time → unstable feedback control
- Hyperventilation lowers $PaCO_2$ toward apneic threshold
- Central apneas alternate with crescendo–decrescendo ventilation
- Associated with sympathetic activation and poorer prognosis

Clinical link

- Sleep-disordered breathing can worsen HF via neurohormonal stress
- Treat as part of the systemic HF phenotype (not an isolated problem)

Arrhythmias in HF: bidirectional worsening

AF and VT are both consequences and drivers of HF progression

Why arrhythmias occur

- Atrial dilation + fibrosis → atrial fibrillation
- Scar/fibrosis + ion channel changes → ventricular arrhythmias
- SNS activation increases automaticity and triggered activity

Why arrhythmias worsen HF

- Loss of atrial kick increases filling pressures (esp. HFpEF)
- Rapid rates shorten diastole and reduce perfusion
- Irregularity reduces effective stroke volume

Valvular disease as an HF amplifier

Load mismatch: stenosis (pressure) vs regurgitation (volume)

Mechanistic roles

- Aortic stenosis: fixed afterload → hypertrophy → HF symptoms
- Mitral regurgitation: volume overload → dilation → worsening MR
- Functional MR/TR arise from chamber dilation (HF causing valve disease)
- Acute valve failure can cause fulminant pulmonary edema/shock

Exam pearl

- Always ask whether valvular load is the primary driver or secondary
- Treating the driver can reverse “functional” regurgitation

Ischemia and post-MI remodeling

Infarction, hibernation, and progressive dilation

Mechanisms

- Loss of contractile myocardium → reduced systolic function
- Infarct expansion and scar → geometric remodeling
- Neurohormonal activation promotes further remodeling
- Ischemia can cause functional MR via papillary displacement

Clinical translation

- HFrEF often represents remodeling after ischemic injury
- Symptoms may worsen with recurrent ischemia or new infarction

Acute decompensated HF: why stable patients crash

Triggers, pressure shifts, and loss of reserve

Common triggers

- Dietary salt/fluid excess or medication nonadherence
- Infection, anemia, thyroid disease (increased demand)
- Arrhythmia (AF with RVR), ischemia, hypertensive crisis
- Renal dysfunction or iatrogenic fluid load

Physiology of decompensation

- Small changes in volume/distribution can spike filling pressures
- Neurohormonal surge and venous capacitance shifts worsen congestion

Bedside hemodynamic profiles: warm/cold and wet/dry

A fast physiology snapshot with prognostic value

Profiles (clinical assessment)

- Warm & dry: compensated
- Warm & wet: congestion without hypoperfusion (most common)
- Cold & wet: hypoperfusion + congestion (highest risk)
- Cold & dry: hypoperfusion without overt congestion

Why this works

- Perfusion signs approximate CO; congestion signs approximate filling pressures
- Profiles correlate with outcomes and guide physiologic priorities

Cardiogenic shock continuum (brief)

When hypoperfusion dominates and a vicious cycle accelerates

Pathophysiology

- Primary pump failure → ↓ CO and coronary perfusion
- SNS/RAAS vasoconstriction ↑ afterload → worsens output
- Rising lactate and acidosis impair contractility and catecholamine response
- Microcirculatory dysfunction can persist despite normal MAP

Clinical cue

- Think “cold & wet” with rising lactate
- Treat cause + restore perfusion + relieve congestion

Biomarkers (mechanistic interpretation)

What BNP/NT-proBNP and troponin reflect in HF

Mechanistic meaning

- BNP/NT-proBNP: myocardial stretch, wall stress, filling pressures
- Troponin: ongoing injury/strain (not only acute MI)
- Renal function alters levels (reduced clearance)
- Trends can reflect decongestion or worsening load

Clinical caveats

- Interpret biomarkers with phenotype (HFrEF vs HFpEF, CKD, obesity)
- A single value is less informative than context + trajectory

Volume vs congestion

Total body fluid, venous capacitance, and redistribution

Why “too much water” is incomplete

- Congestion = elevated venous/filling pressures
- Can occur via redistribution (venous tone) without big weight change
- Splanchnic venous reservoir is a major capacitance compartment
- Venous congestion impairs kidneys and drives further retention

Bedside clue

- Look at JVP and orthopnea, not only peripheral edema or scale weight
- Treat pressure/distribution as well as volume

Cachexia, sarcopenia, anemia/iron deficiency

Late systemic consequences that worsen functional capacity

Mechanisms

- Chronic inflammation and neurohormones → catabolic state
- Reduced appetite + gut congestion → malnutrition
- Anemia/iron deficiency reduce oxygen delivery and exercise tolerance
- Muscle wasting lowers peak VO_2 and reserve

Clinical impact

- Advanced HF is multi-organ and metabolic, not only “pump failure”
- Functional decline often reflects peripheral physiology

Comorbidities that drive HFpEF

Obesity, DM, HTN, CKD and systemic inflammation

Upstream drivers

- Hypertension → hypertrophy and stiffness
- Obesity/DM → inflammation, endothelial dysfunction, volume expansion
- CKD → fluid retention and vascular stiffness
- Aging → reduced compliance and chronotropic reserve

Paradigm

- HFpEF is often a systemic cardiometabolic disease
- Treating comorbid biology is part of treating HF physiology

Putting it together: a progression model

Initiation → compensation → remodeling → decompensation

Four stages (mechanistic)

- Initiation: injury or chronic load (ischemia, HTN, valve disease)
- Compensation: Starling + neurohormonal support
- Remodeling: geometric + fibrotic changes reduce reserve
- Decompensation: pressure spikes, organ dysfunction, recurrent admissions

Loop thinking

- Each stage strengthens feedback loops that accelerate progression
- Breaking loops explains why therapy targets neurohormones and congestion

Case 1: HFrEF decompensation

Explain symptoms using pressures, flow, and triggers

Presentation

- 58-year-old with prior MI, EF 30%, weight +2 kg in 5 days
- Dyspnea, orthopnea, PND, leg edema, JVP elevated
- BP 118/70, HR 105, cool extremities?
- Question: congestion only or congestion + hypoperfusion?

Mechanistic interpretation

- Orthopnea/PND + JVP = high filling pressures (wet)
- BP can be preserved via high SVR despite low CO
- Look for perfusion signs to classify warm vs cold

Case 2: HFpEF exertional dyspnea

Normal EF, severe symptoms: explain the physiology

Presentation

- 72-year-old with HTN and obesity; EF 60%
- Marked exertional dyspnea, minimal edema at rest
- AF paroxysms; symptoms worsen with tachycardia
- Question: why dyspnea with “normal EF”?

Mechanistic interpretation

- Stiff LV: small volume increases → large pressure rises
- Exercise and tachycardia shorten diastole → filling pressure spikes
- Loss of atrial kick in AF worsens LV filling in stiff ventricle

Common exam pitfalls

Where students lose points in HF pathophysiology

Pitfalls

- Equating HF with low EF (HFpEF is common and symptomatic)
- Equating BP with perfusion (SVR can mask low CO)
- Equating edema with congestion severity (JVP/orthopnea matter)
- Missing tempo: acute vs chronic regurgitation behave differently
- Ignoring triggers (AF, infection, ischemia) in decompensation

How to score full marks

- State the phenotype + pressures + perfusion + trigger
- Use mechanism words: preload/afterload/compliance/neurohormones

10 take-home mechanisms

A compact mental model for clinical reasoning

Remember these

- HF = inadequate output and/or elevated filling pressures
- Symptoms correlate strongly with filling pressures (congestion)
- Starling reserve is finite: beyond plateau, pressure rises dominate
- Neurohormonal activation is initially adaptive, chronically harmful
- Remodeling (dilation or stiffness) reduces reserve and raises pressures

And these

- Venous congestion drives kidney dysfunction and retention
- Right HF often follows left HF via pulmonary hypertension
- HFpEF is a stiffness + systemic comorbidity syndrome
- Arrhythmias are part of the substrate and worsen hemodynamics
- Think in loops: trigger → pressure rise → organ dysfunction → worse HF

Questions & discussion

Use the framework: phenotype → pressures → perfusion → trigger

Prompt questions

- Explain orthopnea and PND in one mechanistic chain
- Why can creatinine worsen during congestion?
- How does AF worsen HFpEF more than HFrEF?
- What bedside signs define “cold & wet”?

Suggested reading

- ESC 2021 HF guideline (definitions/phenotypes)
- AHA/ACC/HFSA 2022 guideline (conceptual framework)
- Neurohormonal activation review; venous congestion kidney review