HFrEF vs HFpEF: Pathophysiology and Medical Management

Domain	HFrEF — Reduced EF	HFpEF — Preserved EF
Definition	HF syndrome with **LVEF ≤40%**	HF syndrome with **LVEF ≥50%**, plus evidence of increased filling pressures or structural/functional cardiac abnormalities
Primary ventricular abnormality	Predominantly **systolic dysfunction**: impaired contractility and reduced stroke volume	Predominantly **diastolic dysfunction**: impaired relaxation, **reduced compliance** and elevated filling pressures
Typical ventricular structure	LV dilatation, eccentric hypertrophy and adverse remodelling	Concentric LV hypertrophy, relatively small/stiff LV; left atrial enlargement is common
Common causes	Ischaemic heart disease/MI, dilated cardiomyopathy, myocarditis, cardiotoxicity, genetic cardiomyopathy, chronic volume overload	Ageing, hypertension, obesity, diabetes, CKD, atrial fibrillation, sleep apnoea, infiltrative disease and valvular disease
Core pathophysiology	Myocyte injury → reduced cardiac output → sympathetic nervous system and RAAS activation → vasoconstriction, sodium retention, fibrosis and progressive ventricular remodelling	Systemic inflammation and cardiometabolic disease → endothelial dysfunction, microvascular inflammation, fibrosis and increased myocardial/vascular stiffness
Haemodynamics	Reduced forward flow; elevated LV end-diastolic pressure; frequently increased end-systolic volume	EF remains preserved, but small increases in volume cause marked rises in LV and left atrial pressure, especially during exercise
Neurohormonal activation	Prominent and central to disease progression; explains the benefit of neurohormonal antagonists	Present but less uniformly dominant; disease is heterogeneous and strongly driven by comorbidities
Right-heart/pulmonary effects	Secondary pulmonary hypertension and RV dysfunction may develop in advanced disease	Pulmonary hypertension, RV–pulmonary artery uncoupling and right-sided congestion are **common** adverse phenotypes
Therapeutic objective	Improve survival, reduce HF hospitalization, reverse remodelling and relieve congestion	Reduce HF hospitalization, relieve congestion, improve functional status and aggressively treat the underlying phenotype/comorbidities

Medical management

Treatment	HFrEF	HFpEF
Diuretics	Loop diuretic for clinical congestion; adjust to achieve and maintain euvolaemia	Loop diuretic for congestion; avoid excessive preload reduction because the stiff LV may be volume-sensitive
SGLT2 inhibitor	**Foundational therapy:** dapagliflozin or empagliflozin, irrespective of diabetes, unless contraindicated	Recommended to reduce HF hospitalization and cardiovascular events; currently the most consistently beneficial disease-modifying drug class across HFpEF populations
ARNI / ACE inhibitor / ARB	**Foundational therapy:** sacubitril–valsartan preferred where tolerated; ACE inhibitor or ARB when ARNI is unsuitable	ARNI or ARB may be considered, particularly with EF toward the lower end of the preserved range and where useful for BP control
Evidence-based beta-blocker	**Foundational therapy:** carvedilol, bisoprolol or metoprolol succinate in stable patients	Not routinely prescribed solely for HFpEF; use for another indication such as AF rate control, angina, prior MI or hypertension
Mineralocorticoid receptor antagonist	**Foundational therapy:** spironolactone or eplerenone when renal function and potassium permit	May reduce hospitalization in selected patients, especially with EF closer to 50%; monitor potassium and renal function carefully
Hydralazine–isosorbide dinitrate	Consider when RAAS inhibition is contraindicated; additional benefit in selected symptomatic Black patients despite optimized therapy	No established disease-modifying role
Digoxin	May reduce hospitalization in selected persistently symptomatic patients; does not provide a clear survival benefit	Occasionally used for AF rate control; not routine HFpEF therapy
Blood-pressure management	Avoid hypotension that prevents implementation of prognostic therapy	Central component; generally target **SBP <130 mmHg when tolerated**, individualized to frailty and comorbidity
Atrial fibrillation	Anticoagulation according to thromboembolic risk; rate or rhythm control based on symptoms and HF status	Particularly important because loss of atrial contraction may markedly increase filling pressures; consider early rhythm-control strategies in appropriate patients
Comorbidity treatment	Treat CAD/ischaemia, valvular disease, iron deficiency, diabetes, CKD, sleep apnoea and obesity	Often the principal therapeutic strategy: address obesity, hypertension, diabetes, CKD, AF, sleep apnoea, pulmonary hypertension and coronary/valvular disease
Lifestyle/rehabilitation	Exercise-based cardiac rehabilitation, sodium moderation, daily weight monitoring and vaccination	Structured aerobic and resistance exercise; weight reduction is particularly important in obesity-related HFpEF
Device therapy	ICD and/or CRT in appropriately selected patients after adequate GDMT and reassessment of EF	Generally no indication based on HFpEF alone; use only for conventional pacing or arrhythmia indications

Practical framework

HFrEF: initiate the four foundational therapies early

1. ARNI, ACE inhibitor or ARB
2. Evidence-based beta-blocker
3. Mineralocorticoid receptor antagonist
4. SGLT2 inhibitor

These should generally be introduced rapidly at tolerated doses rather than waiting to maximize one drug before starting the next.

HFpEF: phenotype-directed management

- Confirm that symptoms arise from HF and document elevated filling pressures.
- Use an SGLT2 inhibitor unless contraindicated.
- Treat congestion with diuretics.
- Control blood pressure and manage AF, obesity, diabetes, CKD, sleep apnoea, ischaemia and valvular disease.
- Consider MRA, ARB or ARNI in selected patients, particularly when EF lies near the lower end of the preserved range.

Haemodynamics and Echocardiographic Features: Normal vs HFrEF vs HFpEF

Parameter	Normal	HFrEF (Reduced EF)	HFpEF (Preserved EF)
LVEF (%)	55–70%	≤40%	≥50%
LV End-Diastolic Pressure (LVEDP)	**5–12 mmHg**	**15–30 mmHg** ↑	**15–30 mmHg** ↑ (often normal at rest early, rises markedly with exercise)
Left Atrial Mean Pressure (LAP)	**5–12 mmHg**	**15–25 mmHg** ↑	**15–25 mmHg** ↑
Pulmonary Capillary Wedge Pressure (PCWP)	**6–12 mmHg**	**15–30 mmHg** ↑	**15–25 mmHg** ↑ (often disproportionately elevated during exertion)
Right Atrial Pressure (RAP/CVP)	**2–6 mmHg**	**8–15 mmHg** ↑	**5–15 mmHg** ↑ (late disease)
Pulmonary Artery Systolic Pressure (PASP)	**18–25 mmHg**	**35–60 mmHg** ↑	**35–60 mmHg** ↑
Cardiac Output	4–8 L/min	Reduced	Usually preserved at rest; reduced reserve during exercise
Stroke Volume	60–100 mL	Reduced	Usually normal at rest, reduced with exertion
LV End-Diastolic Volume (LVEDV)	Normal	Increased	Normal or reduced
LV End-Systolic Volume (LVESV)	Normal	Markedly increased	Normal

Pressure Changes During the Cardiac Cycle

Cardiac Cycle	Normal	HFrEF	HFpEF
LV Systolic Pressure	~120 mmHg	Often reduced contractility despite similar arterial pressure	Usually preserved
LV End-Systolic Volume	Normal	↑ Increased (poor emptying)	Normal
LV Diastolic Pressure	Low (5–12 mmHg)	↑ Elevated due to residual volume	↑ Elevated due to stiffness and impaired relaxation
Early Diastolic Filling	Rapid suction	Reduced suction, elevated filling pressure	Impaired relaxation, delayed filling
Late Diastole (Atrial contraction)	Small pressure increase	LA contraction contributes less if dilated	Large dependence on atrial contraction; AF often poorly tolerated
Exercise Response	Small rise in filling pressure	Filling pressures rise further with limited CO increase	Marked rise in LVEDP and PCWP despite preserved EF

Echocardiographic Features

Feature	Normal	HFrEF	HFpEF
LV Size	Normal	**Dilated**	Normal or small
LV Wall Thickness	Normal	Normal or thin	Concentric hypertrophy common
LV Geometry	Normal	Eccentric remodelling	Concentric remodelling
LVEF	55–70%	≤40%	≥50%
Global Longitudinal Strain (GLS)	−18 to −22%	Reduced	Mildly reduced despite preserved EF
Left Atrium	Normal	Enlarged	Enlarged (often marked)
Transmitral E/A Ratio	0.8–2.0	Variable; often restrictive (E/A >2) in advanced disease	Early: E/A <0.8 (Grade I); advanced: pseudonormal or restrictive
Mitral Annular e′ Velocity	Septal >7 cm/s; Lateral >10 cm/s	Reduced	Reduced
Average E/e′ Ratio	<14	>14	>14
Deceleration Time	160–240 ms	Short (<160 ms) in restrictive filling	Prolonged early, shortened with advanced disease
TR Velocity	<2.8 m/s	Often elevated	Often elevated
Pulmonary Vein Flow	Normal S>D	Diastolic predominance	Abnormal with elevated filling pressures
IVC	<2.1 cm with >50% collapse	Dilated if elevated RAP	Dilated if elevated RAP
RV Function	Normal	May be reduced	Often preserved initially, impaired later

Typical Pressure Relationships

Pressure	Normal	HFrEF	HFpEF
LVEDP	5–12	15–30	15–30
Mean LAP	5–12	15–25	15–25
PCWP	6–12	15–30	15–25
RAP	2–6	8–15	5–15
PASP	18–25	35–60	35–60

Key Pathophysiological Difference

HFrEF	HFpEF
Problem: Poor ventricular contraction (systolic dysfunction). The ventricle cannot eject blood effectively → ↑ LVESV → LV dilatation → ↑ LVEDP → ↑ LA pressure → pulmonary congestion.	**Problem:** Stiff, non-compliant ventricle (diastolic dysfunction). Ejection fraction is preserved, but filling requires much higher pressures. Small increases in volume produce large rises in LVEDP and LA pressure, particularly during exercise.

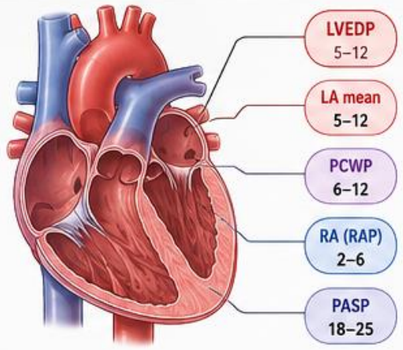
Clinical pearl: Although **HFrEF and HFpEF often have similar elevated filling pressures (LVEDP, LAP, and PCWP)**, the mechanisms differ:

- **HFrEF:** elevated pressures result primarily from **poor systolic emptying and ventricular dilation**.
- **HFpEF:** elevated pressures result from **impaired relaxation and reduced ventricular compliance**, with pressures often becoming dramatically abnormal during exertion even when resting measurements are only mildly elevated.

CHAMBER PRESSURES (mmHg)

- LV — Left Ventricle
- LA — Left Atrium
- PCWP — Pulmonary Capillary Wedge Pressure
- RA — Right Atrium
- PASP — Pulmonary Artery Systolic Pressure

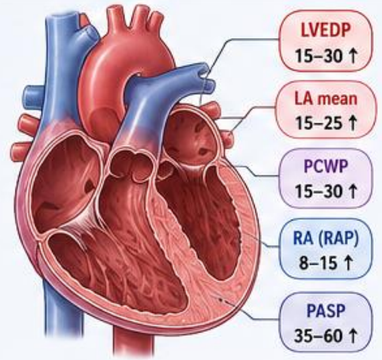
NORMAL



HFrEF (REDUCED EF)

Typical Features

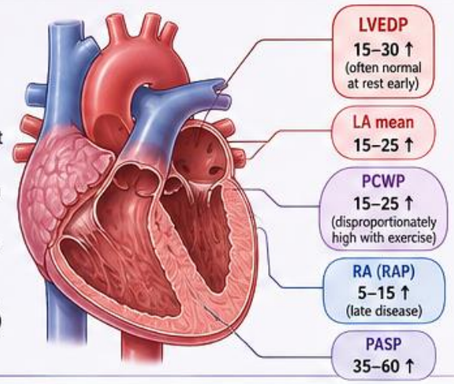
- Dilated LV
- Poor systolic function
- Neurohormonal activation
- ↑ Volumes & filling pressures
- Pulmonary congestion



HFpEF (PRESERVED EF)

Typical Features

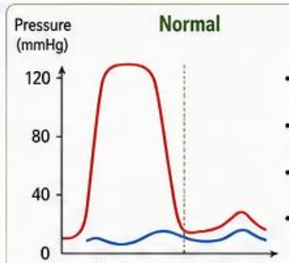
- Concentric LVH
- Stiff, non-compliant LV
- Impaired relaxation
- Comorbidities (HTN, DM, obesity, AF, CKD)
- ↑ Filling pressures (esp. with exercise)



CARDIAC CYCLE PRESSURES

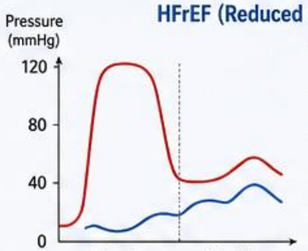
- LV Pressure (mmHg)
- LA Pressure (mmHg)

Normal



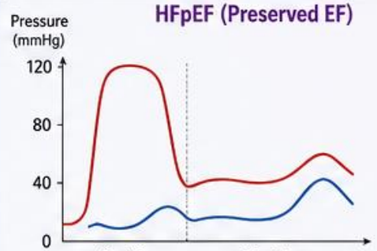
- Low LV diastolic pressure (5–12 mmHg)
- Rapid early diastolic filling (E wave)
- Small rise with atrial contraction (A)
- LA pressure 5–12 mmHg

HFrEF (Reduced EF)



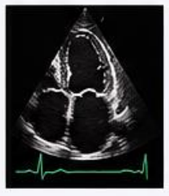
- Poor systolic emptying → ↑ LVESV
- ↑ LV diastolic pressure (15–30 mmHg)
- Reduced early filling (↓ E wave)
- LA pressure ↑ (15–25 mmHg)
- Higher pressures persist through diastole

HFpEF (Preserved EF)

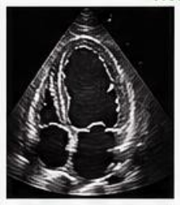


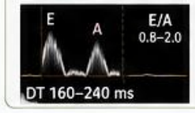
- Preserved systolic pressure
- Impaired relaxation & stiff LV → ↑ diastolic pressure (15–30 mmHg)
- Delayed early filling (small E wave)
- Large A wave – atrial contraction important
- LA pressure ↑ (15–25 mmHg)
- Marked rise in pressures with exercise

ECHOCARDIOGRAPHIC FEATURES



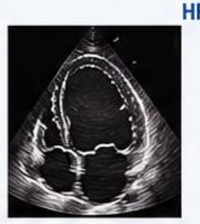
Normal

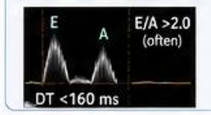




- LV size: Normal
- LV wall thickness: Normal
- LA size: Normal
- LVEF: 55–70%
- E/e' (avg): <14
- e' (septal): >7 cm/s
- e' (lateral): >10 cm/s
- E/A ratio: 0.8–2.0
- Deceleration time: 160–240 ms
- IVC: <2.1 cm, >50% collapse
- RVSP (PASP): 18–25 mmHg
- GLS: −18 to −22%

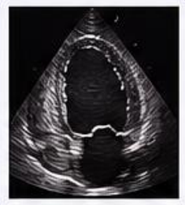
HFrEF (Reduced EF)

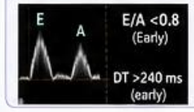




- LV size: Dilated
- LV wall thickness: Normal or thin
- LA size: Enlarged
- LVEF: ≤40%
- E/e' (avg): >14
- e' (septal): Reduced (≤7 cm/s)
- e' (lateral): Reduced (≤10 cm/s)
- E/A ratio: Variable (often >2 in advanced/restrictive)
- Deceleration time: <160 ms in restrictive filling
- IVC: Plethoric if ↑ RAP
- RVSP (PASP): 35–60 mmHg
- GLS: Reduced (−8 to −14%)

HFpEF (Preserved EF)





- LV size: Normal or small
- LV wall thickness: Increased (concentric LVH)
- LA size: Enlarged
- LVEF: ≥50%
- E/e' (avg): >14
- e' (septal): Reduced (≤7 cm/s)
- e' (lateral): Reduced (≤10 cm/s)
- E/A ratio: <0.8 (Grade I) or 0.8–2.0 (pseudonormal) or >2 (restrictive)
- Deceleration time: Prolonged early, shortened if advanced
- IVC: Plethoric if ↑ RAP
- RVSP (PASP): 35–60 mmHg
- GLS: Mildly reduced (−14 to −18%)

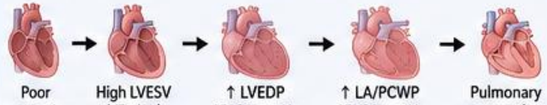
KEY PATHOPHYSIOLOGY

Normal

Efficient contraction and relaxation → low filling pressures and adequate forward flow.

HFrEF (Reduced EF)

Impaired contraction → incomplete emptying → dilatation → elevated filling pressures → congestion, low output.



HFpEF (Preserved EF)

Stiff ventricle with impaired relaxation → high ❄ filling pressures needed to fill → normal EF but symptoms (esp. with exertion).