DIASTOLIC HEART FAILURE

By

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INTRODUCTION

- HF is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/ or elevated intracardiac pressures at rest or during stress.

- Heart failure is a diagnosis associated with considerable morbidity and mortality.
- More than 5 million people in the USA carry this diagnosis with a mortality rate of 50% at 5 years from diagnosis.

Basaraba JE, Barry AR. Pharmacotherapy of heart failure with preservedejection fraction. Pharmacotherapy 2015

- The prevalence of HF 1–2% of the adult population in developed countries, rising to ≥10% among people >70 years of age.
- 12-month all-cause mortality rates for hospitalized HF patients is 17% and stable/ambulatory HF patients is 7%.

EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail 2013

Classification of HF according to EF:

1. **HF with preserved EF (HFpEF) :** patients with normal LVEF ≥50%.(diastolic heart failure)
2. **HF with reduced EF (HFrEF) :** patients with reduced LVEF <40%.(systolic heart failure)
3. **HF with mid-range (HFmrEF) :** Patients with an LVEF in the range of 40–49% represent a ‘grey area’

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.

[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

[b]BNP>35 pg/ml and/or NT-proBNP>125 pg/mL.

Diastolic heart failure (DHF)

DEFINITION:

- It is defined by the American College of Cardiology and American Heart Association as the presence of clinical symptoms or signs of heart failure in a patient with a left ventricular ejection fraction (LVEF) greater than 50% with evidence of diastolic dysfunction by Doppler echocardiography or cardiac catheterization.

ACCF/AHA guideline for the management of heart failure: 2013

OTHER NAMES:

- Heart failure with preserved ejection fraction .
- Heart failure with normal ejection fraction .

Epidemiology

- It accounts for at least 50% of all heart failure cases .
- Its incidence will increase in the coming years as the population ages; Among people >65 years of age presenting to primary care with breathlessness on exertion, one in six will have unrecognized HF (mainly HFpEF).

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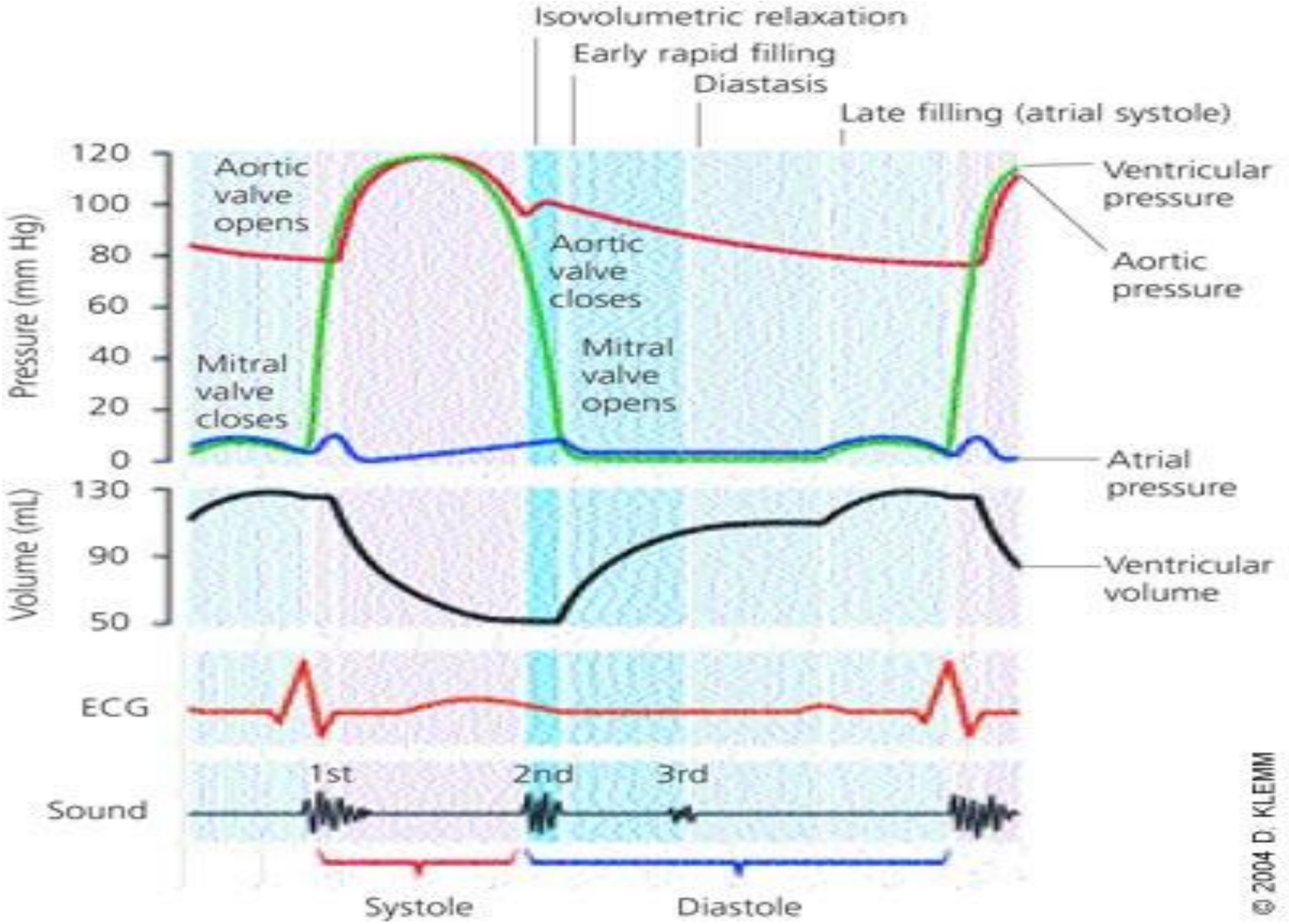
PATHOPHYSIOLOGY

- Traditionally, it was assumed that the only pathology responsible for this disorder is impaired filling and diastolic dysfunction, hence the label of DHF. It is now understood that diastolic dysfunction plays a central role, but is not the solitary contributor to the diagnosis of DHF.

- Diastole is the process by which the heart returns to its relaxed state; it is also the time for cardiac perfusion.
- During diastole, drastic changes in cardiac pressure-volume relationships occur. The relaxation process has four phases:

1. Isovolumetric relaxation; from the time of aortic valve closure to mitral valve opening
2. Early rapid filling; after mitral valve opening
3. Diastasis; a period of low flow during mid-diastole
4. Late filling of the ventricles from atrial contraction


Isovolumetric relaxation
Early rapid filling
Diastasis
Late filling (atrial systole)
Pressure (mm Hg)
120
100
80
60
40
20
0
Aortic valve opens
Aortic valve closes
Mitral valve closes
Mitral valve opens
Ventricular pressure
Aortic pressure
Atrial pressure
Volume (mL)
130
90
50
Ventricular volume
ECG
Sound
1st
2nd
3rd
Systole
Diastole
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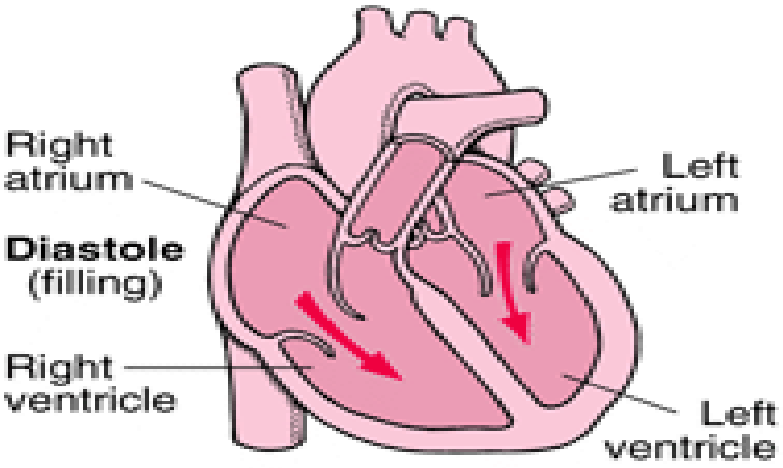
- Diastole is a complex process that is affected by a number of factors, including ischemia, heart rate, velocity of relaxation, cardiac compliance (i.e., elastic recoil and stiffness), hypertrophy, and segmental wall coordination of the heart muscle.

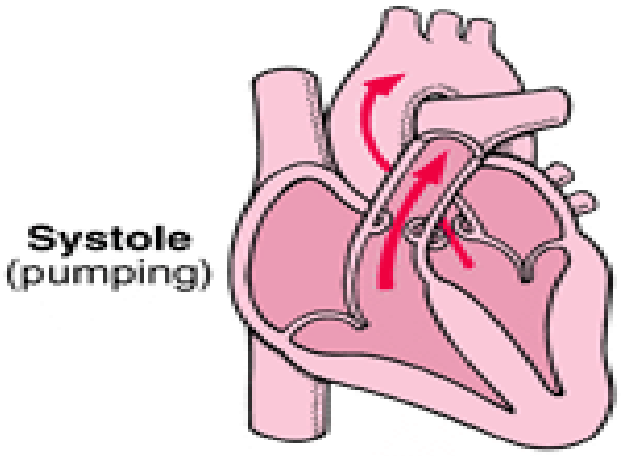
Diastolic dysfunction

- In patients with isolated diastolic heart failure, the heart often is able to meet the body's metabolic needs, but at higher diastolic pressures.
- The left ventricle is stiff, with decreased compliance and impaired relaxation.
- Transmission of the higher end-diastolic left ventricular pressure to the pulmonary circulation may lead to pulmonary congestion, dyspnea, and other symptoms of heart failure.

Normal

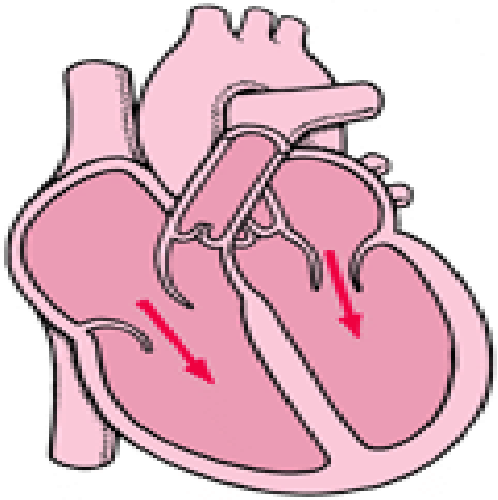


The ventricles fill normally with blood.

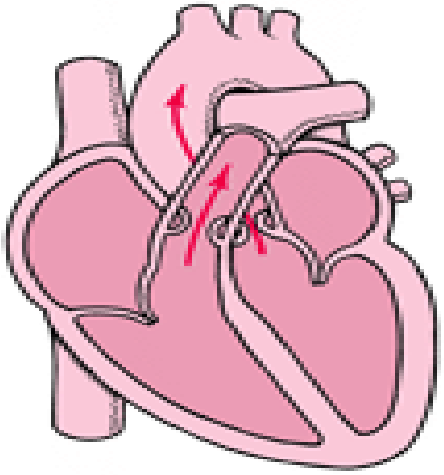


The ventricles pump out about 60% of the blood.

Systolic Dysfunction

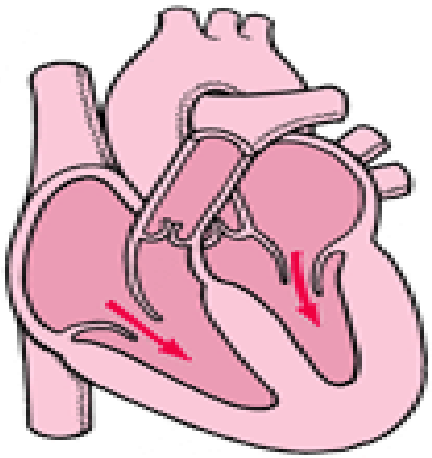


The enlarged ventricles fill with blood.

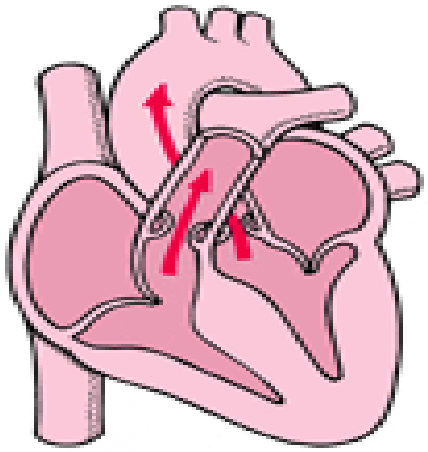


The ventricles pump out less than 40 to 50% of the blood.

Diastolic Dysfunction



The stiff ventricles fill with less blood than normal.



The ventricles pump out about 60% of the blood, but the amount may be lower than normal.

Factors contributing in DHF

Hypertension

- Chronic hypertension is the most common cause of diastolic dysfunction and failure.
- It leads to left ventricular hypertrophy and increased connective tissue content, both of which decrease cardiac compliance.
- The hypertrophied ventricle has a steeper diastolic pressure-volume relationship; therefore, a small increase in left ventricular end-diastolic volume (which can occur with exercise, for example) causes a marked increase in left ventricular end-diastolic pressure.

Ischemia

- Relaxation of the ventricles involves the active transport of calcium ions into the sarcoplasmic reticulum, which allows the dissociation of myosinactin crossbridges.
- Hypoxia inhibits the dissociation process by altering the balance of the adenosine triphosphate–to–adenosine diphosphate ratio, which may contribute to diastolic dysfunction.

Heart rate

- The heart rate determines the time for diastolic filling, coronary perfusion, and ventricular relaxation.
- Tachycardia affects diastolic function by several mechanisms:

1. It decreases left ventricular filling and coronary perfusion times
2. Increases myocardial oxygen consumption, and causes incomplete relaxation because the stiff heart cannot increase its velocity of relaxation as heart rate increases.

Atrial fibrillation

- Patients with heart failure are at increased risk for atrial fibrillation.
- As the ventricle stiffens and develops higher end-diastolic pressures, the atria are distended and stressed; this often results in atrial fibrillation.
- The loss of atrial contraction worsens the symptoms of heart failure, because patients with diastolic dysfunction often are dependent on atrial filling of the left ventricle (“atrial kick”).
- Atrial fibrillation also can worsen symptoms if the ventricular rate is uncontrolled.

Ventricular load

- At the end of normal systole, a small residual volume of blood remains in the left ventricle.
- If this residual volume increases, it interferes with the normal elastic recoil of the heart, the relaxation of the heart, and the development of a negative pressure gradient between the ventricle and atria. As a result, rapid early diastolic filling is impaired.

Aging

- Diastolic dysfunction is more common in elderly persons, partly because of increased collagen cross-linking, increased smooth muscle content, and loss of elastic fibers.
- These changes decrease ventricular compliance, making patients with diastolic dysfunction more susceptible to the adverse effects of hypertension, tachycardia, and atrial fibrillation.

Right ventricle-pulmonary vascular unit dysfunction

- Chronic pulmonary venous hypertension and the resultant increase in right ventricle (RV) afterload have been considered the main causes of RV dysfunction in patients with DHF.
- Compared with patients with normal RV function, patients with any RV dysfunction were more likely to have atrial fibrillation, and associated with clinical and echocardiographic evidence of more advanced heart failure and with poorer outcome.

Systolic dysfunction

- There is recent evidence that there is slow but progressive decline in ejection fraction in patients with DHF; therefore, these patients will eventually be diagnosed with heart failure with reduced ejection fraction.

- Dunlay SM, Roger VL, Weston SA, et al. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. Circ Heart Fail 2012;
- Ueda T, Kawakami R, Nishida T, et al. Left ventricular ejection fraction (EF) of 55% as cutoff for late transition from heart failure (HF) with preserved EF to HF with mildly reduced EF. Circ J 2015;

- Dunlay et al. showed that in patients with DHF, ejection fraction decreased by 5.8% over 5 years with greater declines in older individuals and in those with coronary artery disease. Overall, 39% of the patients initially diagnosed with DHF had a LVEF<50% at some point after the diagnosis.

Dunlay SM, Roger VL, Weston SA, et al. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. Circ Heart Fail 2012

- A third population of heart failure patients has been described**, heart failure with recovered ejection fraction**. These patients may be misclassified as DHF.
- Although systolic function is seemingly normal or near-normal at rest, patients with DHF demonstrate a blunted hemodynamic response to exercise through the inability to increase accordingly LVEF, stroke volume, and cardiac output.

Basuray A, French B, Ky B, et al. Heart failure with recovered ejection fraction: clinical description, biomarkers, and outcomes. Circulation 2014

@Diastolic heart failure: diagnosis and therapy Nicoara and Jones-Haywood 2016 Wolters Kluwer Health, Inc

Diagnosis

- The diagnosis of DHF remains challenging.
- LVEF is normal and signs and symptoms for HF are often non-specific and do not discriminate well between HF and other clinical conditions.
- To improve the specificity of diagnosing DHF, the clinical diagnosis needs to be supported by objective measures of cardiac dysfunction at rest or during exercise.

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Symptoms	Signs
Typical	**More specific**
Breathlessness Orthopnoea Paroxysmal nocturnal dyspnoea Reduced exercise tolerance Fatigue, tiredness, increased time to recover after exercise Ankle swelling	Elevated jugular venous pressure Hepatojugular reflux Third heart sound (gallop rhythm) Laterally displaced apical impulse
Less typical	**Less specific**
Nocturnal cough Wheezing Bloated feeling Loss of appetite Confusion (especially in the elderly) Depression Palpitations Dizziness Syncope Bendopnea[53]	Weight gain (>2 kg/week) Weight loss (in advanced HF) Tissue wasting (cachexia) Cardiac murmur Peripheral oedema (ankle, sacral, scrotal) Pulmonary crepitations Reduced air entry and dullness to percussion at lung bases (pleural effusion) Tachycardia Irregular pulse Tachypnoea Cheyne Stokes respiration Hepatomegaly Ascites Cold extremities Oliguria Narrow pulse pressure

HF = heart failure.

The diagnosis of DHF requires the following:

1- The presence of symptoms and/or signs of HF.

2- A ‘preserved’ EF (defined as LVEF ≥50% or 40–49% for HFmrEF).

3- Elevated levels of NPs (BNP >35 pg/mL and/or NT-proBNP >125 pg/mL.)

4- Objective evidence of other cardiac functional and structural alterations underlying HF.

5- In case of uncertainty, a stress test or invasively measured elevated LV filling pressure may be needed to confirm the diagnosis.

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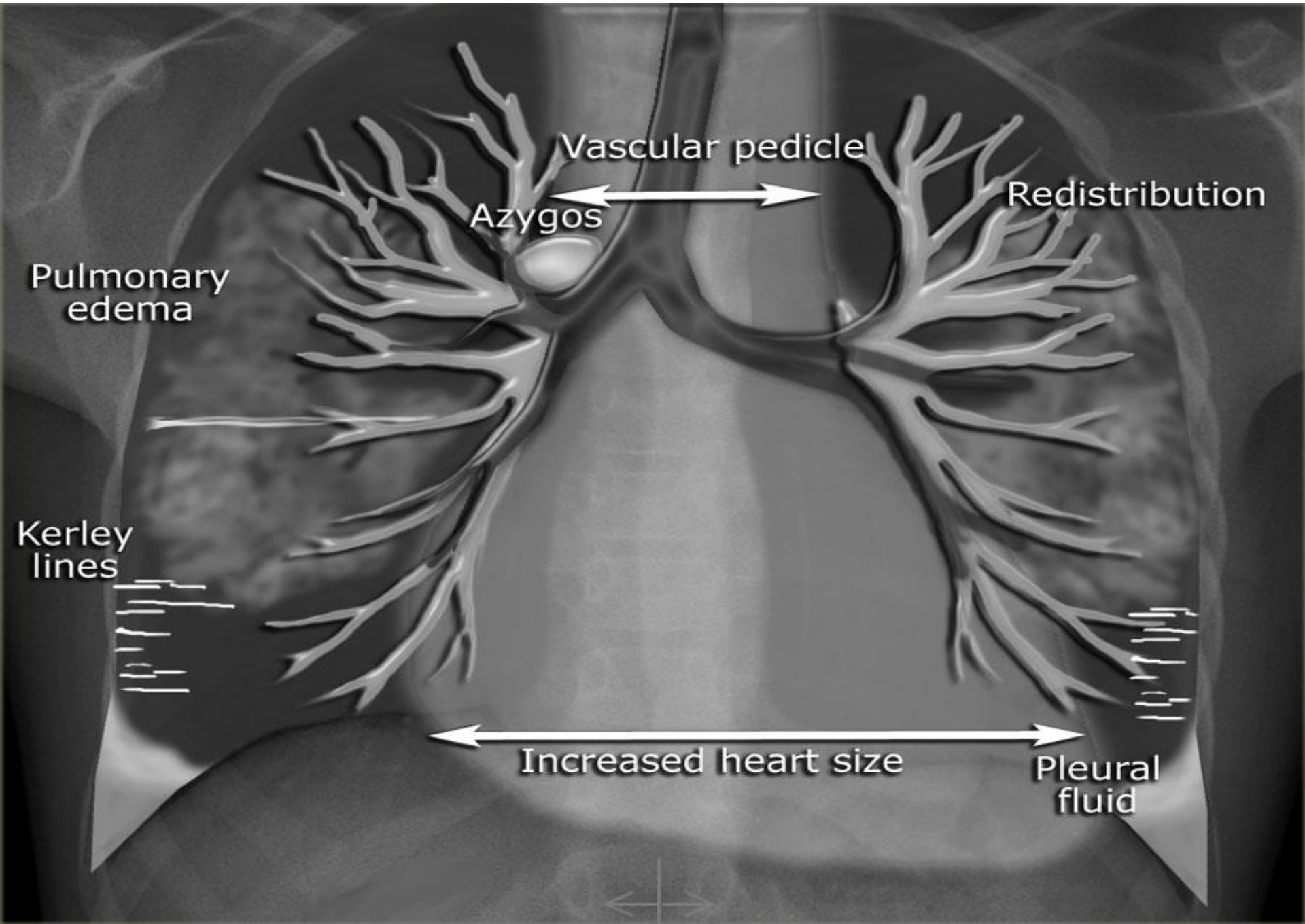
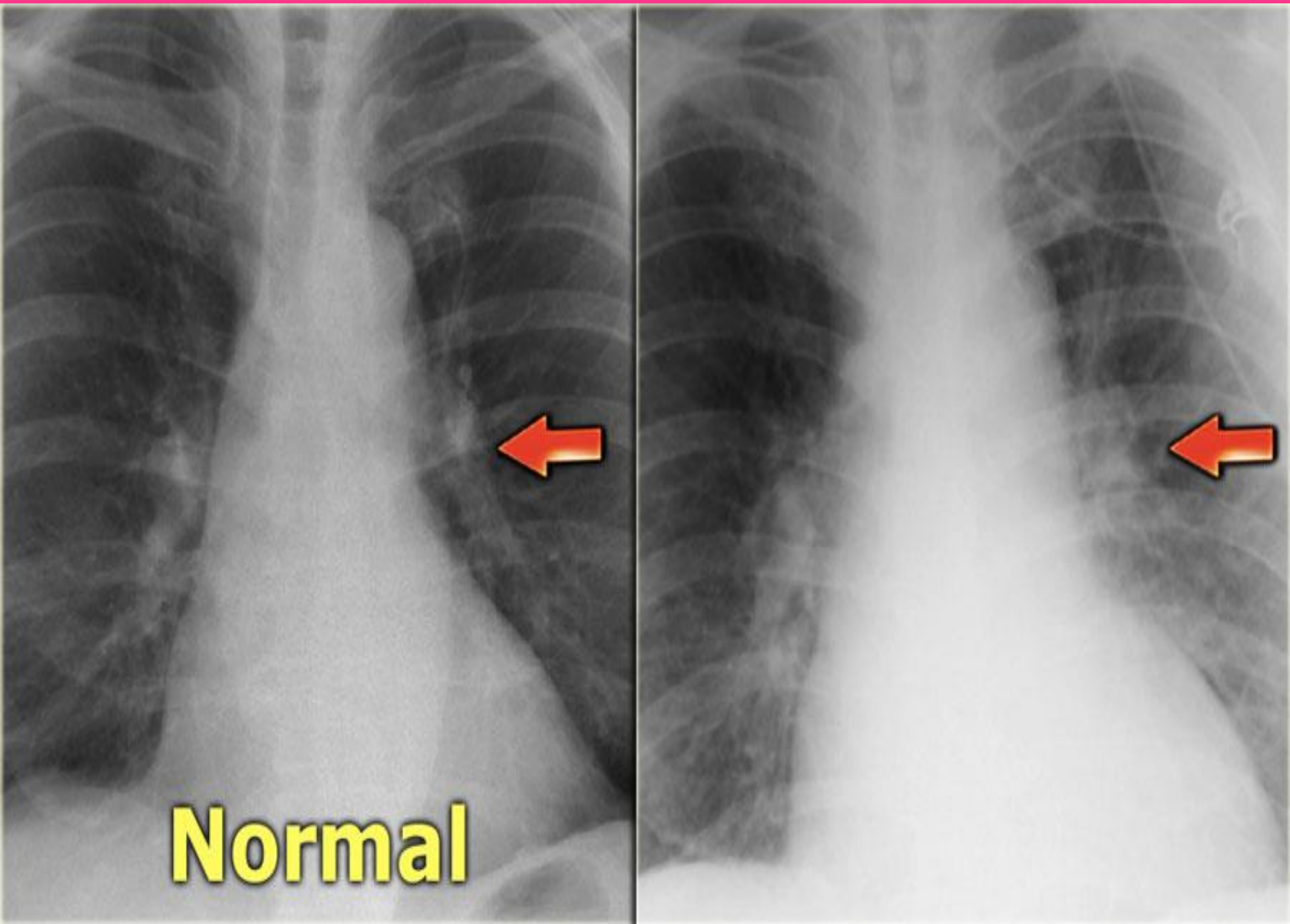
Cardiac imaging and other diagnostic tests

1- Chest X-ray

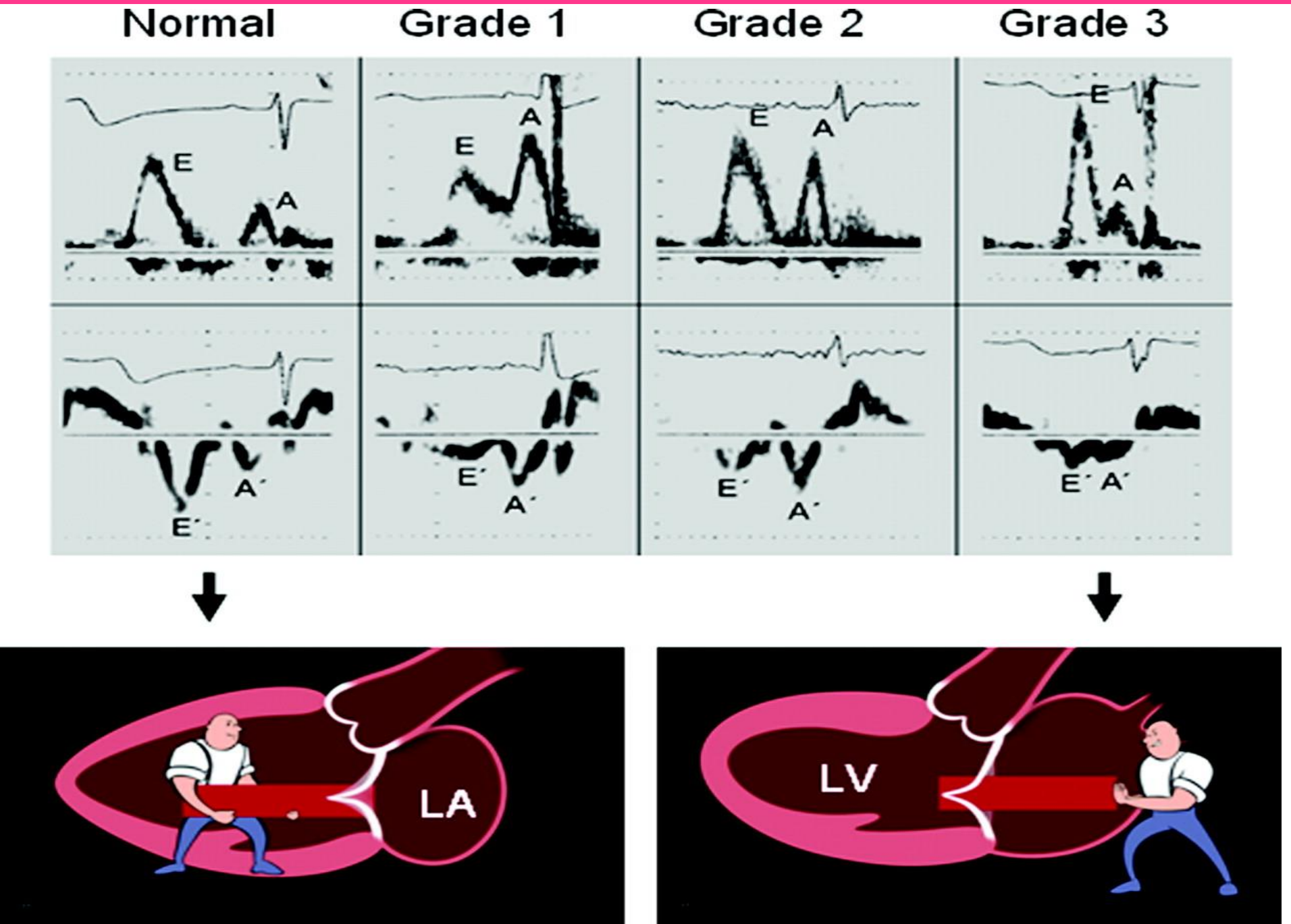
- A chest X-ray is of limited use in the diagnostic work-up of patients with suspected HF.
- It is probably most useful in identifying an alternative, pulmonary explanation for a patient's symptoms and signs, i.e. pulmonary malignancy and interstitial pulmonary disease.
- The chest X-ray may, however, show pulmonary venous congestion or oedema in a patient with HF
- It is important to note that significant LV dysfunction may be present without cardiomegaly on the chest X-ray.


Vascular pedicle
Azygos
Redistribution
Pulmonary edema
Kerley lines
Increased heart size
Pleural fluid


Normal

2- Transthoracic echocardiography (TTE)

- TTE is the method of choice for assessment of myocardial systolic and diastolic function of both left and right ventricles.
- Although echocardiography is at present the only imaging technique that allows the diagnosis of diastolic dysfunction, but a comprehensive echocardiography examination incorporating all relevant two-dimensional and Doppler data is recommended.


Normal
Grade 1
Grade 2
Grade 3
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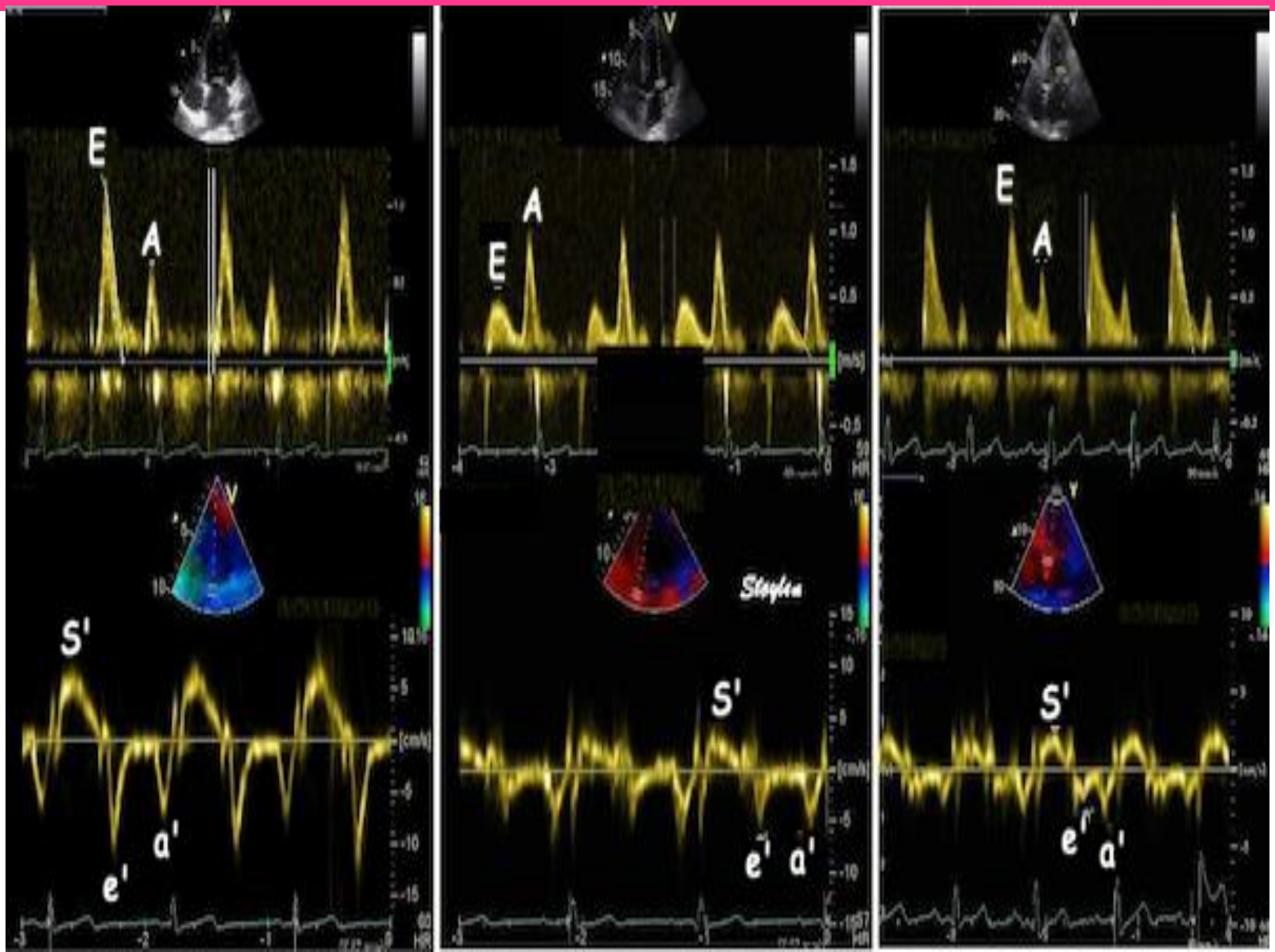
E´
A´
LA
LV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3- Transoesophageal echocardiography

- Transoesophageal echocardiography (TOE) is not needed in the routine diagnostic assessment of HF.
- It may be valuable in patients with valve disease, suspected aortic dissection, suspected endocarditis or congenital heart disease and for ruling out intracavitary thrombi in AF patients requiring cardioversion.
- When the severity of mitral or aortic valve disease does not match the patient's symptoms using TTE alone, a TOE is needed.

5- Cardiac magnetic resonance

- CMR is the gold standard for the measurements of volumes, mass and EF of both the left and right ventricles.
- It is the best alternative cardiac imaging modality for patients with nondiagnostic echocardiographic studies (particularly for imaging of the right heart) and is the method of choice in patients with complex congenital heart diseases.

Treatment

- Since the patients with DHF are often elderly and highly symptomatic, and often have a poor quality of life, an important aim of therapy may be to alleviate symptoms and improve well-being.

Recommendations for treatment of patients with heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction

Recommendations	Class [a]	Level [b]	Ref [c]
it is recommended to screen patients with HFpEF or HFmrEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.	I	C	
Diuretics are recommended in congested patients with HFpEF or HFmrEF in order to alleviate symptoms and signs.	I	B	178, 179

HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction.

[a]Class of recommendation.

[b]Level of evidence.

[c]Reference(s) supporting recommendations.

1- Effect of treatment on symptoms

- Diuretics usually improve congestion, if present, thereby improving symptoms and signs of HF.
- Evidence that beta-blockers and mineralocorticoid receptor antagonist (MRAs) improve symptoms in these patients is lacking.
- There is inconsistent evidence for an improvement in symptoms in those treated with ARBs (only for candesartan was there an improvement) and ACEIs.

2- Effect of treatment on hospitalization

- For patients in sinus rhythm, there is some evidence that nebivolol, digoxin, spironolactone and candesartan might reduce HF hospitalizations.
- For patients in AF, beta-blockers do not appear to be effective and digoxin has not been studied.
- The evidence in support of either ARBs or ACEIs is inconclusive.

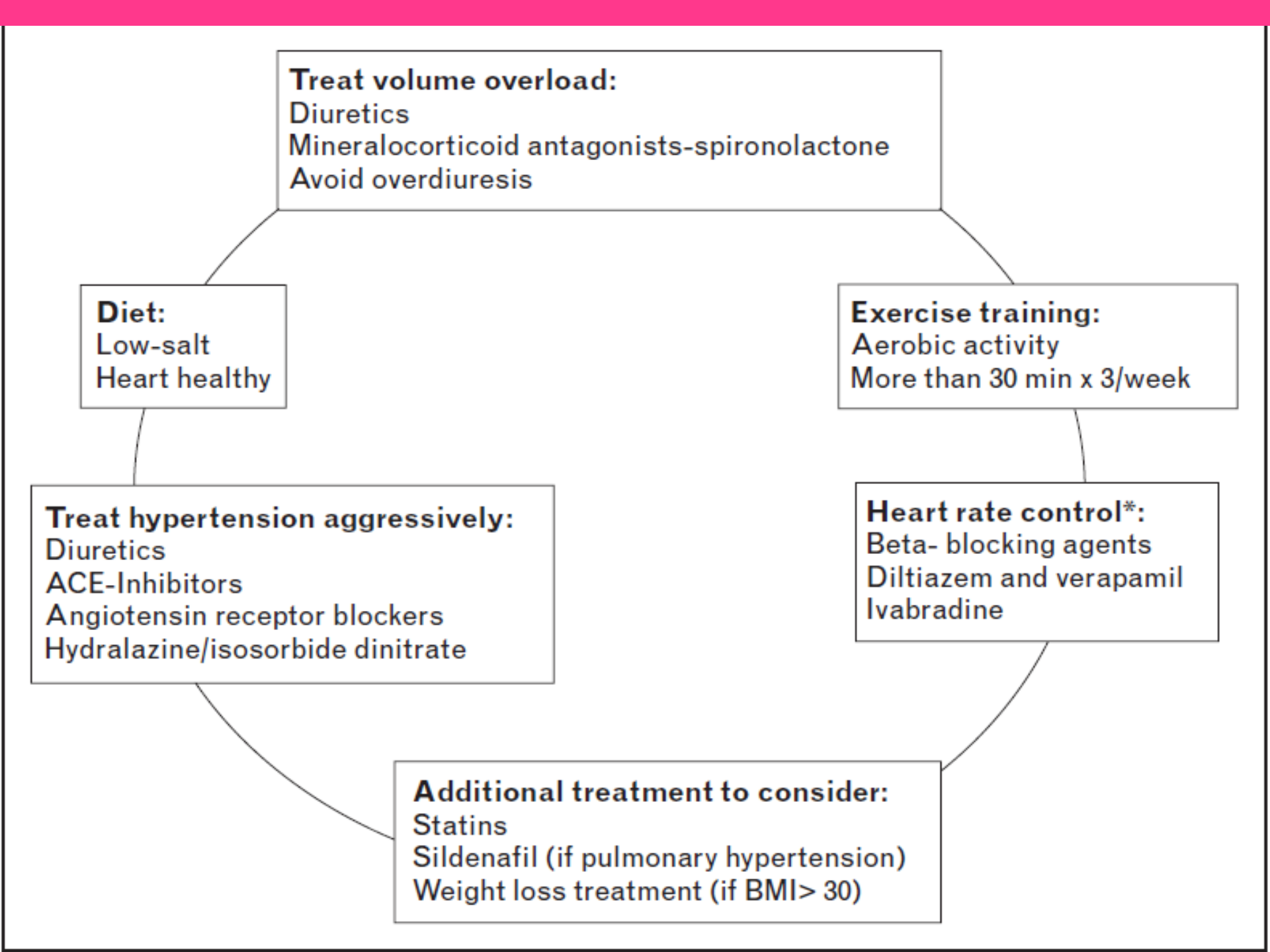
3 Effect of treatment on mortality

- Trials of ACEIs, ARBs, beta-blockers and MRAs have all failed to reduce mortality in patients with HFpEF or HFmrEF.

Management of contributing factors

HFpEF Characteristic	Treatment Recommendations
Volume overload symptoms	Diuretic
Hypertension	ACE inhibitor, ARB, β-blocker
Atrial fibrillation	β-blocker, non-DHP CCB, digoxin, amiodarone
Diabetes/CKD	ACE inhibitor, ARB
Coronary artery disease	ACE inhibitor or ARB + β-blocker

Therapy	Hypothesized mechanism
Sildenafil	Reduction in pulmonary pressure; reduction in cardiac fibrosis
Soluble guanylate cyclase antagonists	Pulmonary and systemic vasodilation; inhibition of smooth muscle proliferation
Endothelin receptor antagonists	Reduction in pulmonary pressure
Neprilysin inhibitors	RAAS and inhibition of breakdown of natriuretic peptides
Ivabradine	Increase time for diastolic filling
Iron supplements	Antioxidant
Ranolazine	Reduce intracellular calcium via reduction in late sodium current
Mitochondrial enhancement	Restoration of ATP production and energy deficit
Serelaxin	Pleiotropic effects
Statins	Endothelial redox balance restoration; effects on collagen turnover
Isosorbide dinitrate and hydralazine	Altered ventricular hemodynamics
Perhexiline	Correct myocardial energy deficiency


Treat volume overload:
Diuretics
Mineralocorticoid antagonists-spironolactone
Avoid overdiuresis
Diet:
Low-salt
Heart healthy
Exercise training:
Aerobic activity
More than 30 min x 3/week
Treat hypertension aggressively:
Diuretics
ACE-Inhibitors
Angiotensin receptor blockers
Hydralazine/isosorbide dinitrate
Heart rate control*:
Beta- blocking agents
Diltiazem and verapamil
Ivabradine
Additional treatment to consider:
Statins
Sildenafil (if pulmonary hypertension)
Weight loss treatment (if BMI> 30)

CONCLUSION

- The prevalence of DHF is likely to continue to grow over the next several decades.
- Currently, the key to the treatment of DHF is aggressive management of contributing factors.
- The understanding of the multifactorial pathophysiology of DHF may lead to novel therapeutic targets in the future.


Thank You