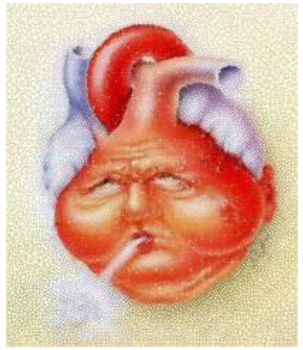
Cardiac hypertrophy and failure



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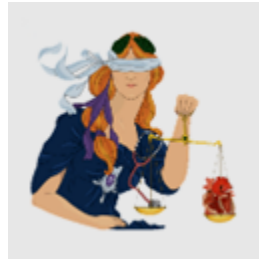


Left ventricular (LV) remodeling: definition and pathophysiology

1. **Change in *size, shape, structure* and *physiology* of the heart** after myocardial injury
2. Compensatory mechanism for the **increased preload and/or afterload**
3. A series of histopathological and structural changes occur in the left ventricular (LV) myocardium, which lead to a progressive decline in LV performance

In heart failure, remodeling results from the *persistent activation of the neurohumoral system*

Macroscopically:

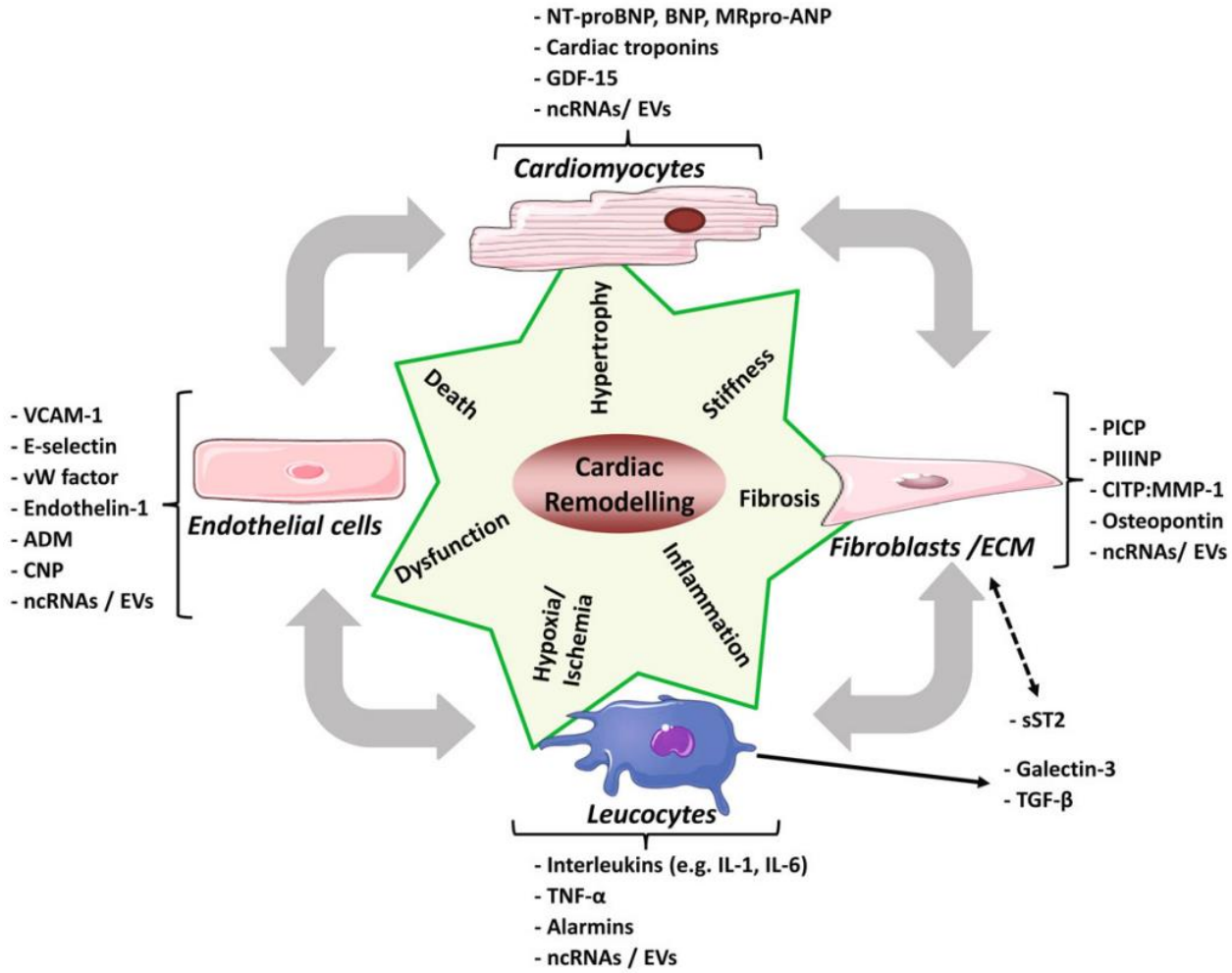
- LV dilatation (spherical)
- Deterioration of the LV systolic function
- Arrhytmias

Histologically:

- Cardiomyocyte hypertrophy/loss
- Connective tissue (reactive/reparative fibrosis)

Cellular/subcellular level:

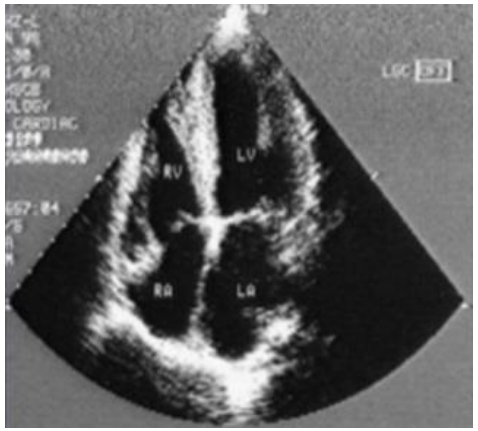
- Reactivation of the fetal gene program
- Ion disturbances
- Changes in mitochondrial energetics

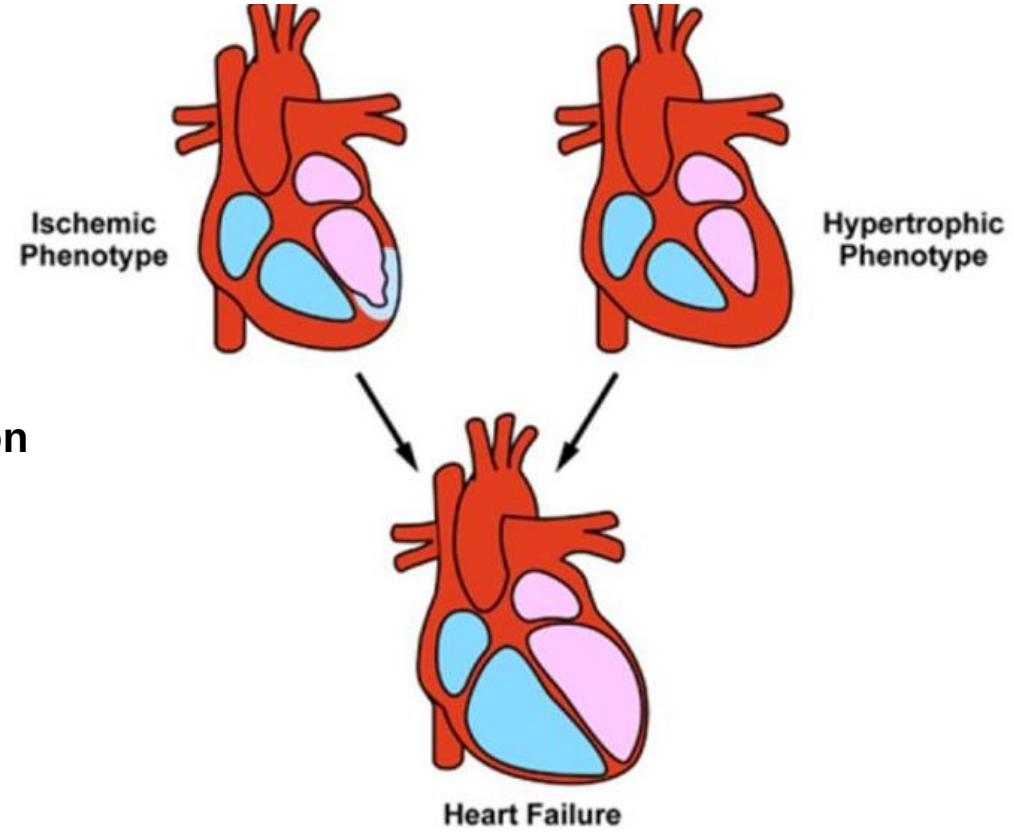


Eur J Heart Fail (2022) 24, 927–943.

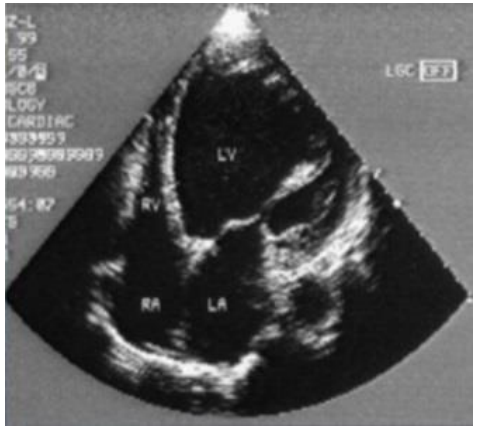
LV hypertrophy, remodeling clinical „phenotypes”

- **Ventricular hypertrophy** develops to maintain systolic wall stress
- ***Pressure* overload** (hypertension, aortic stenosis) - **concentric LV hypertrophy**
  (parallel replication of myofibrils and thickening of individual myocytes)





- ***Volume* overload** (aortic or mitral regurgitation) - **ventricular dilatation**
  (replication of sarcomeres in series and elongation of myocytes)



Heart failure - Definition

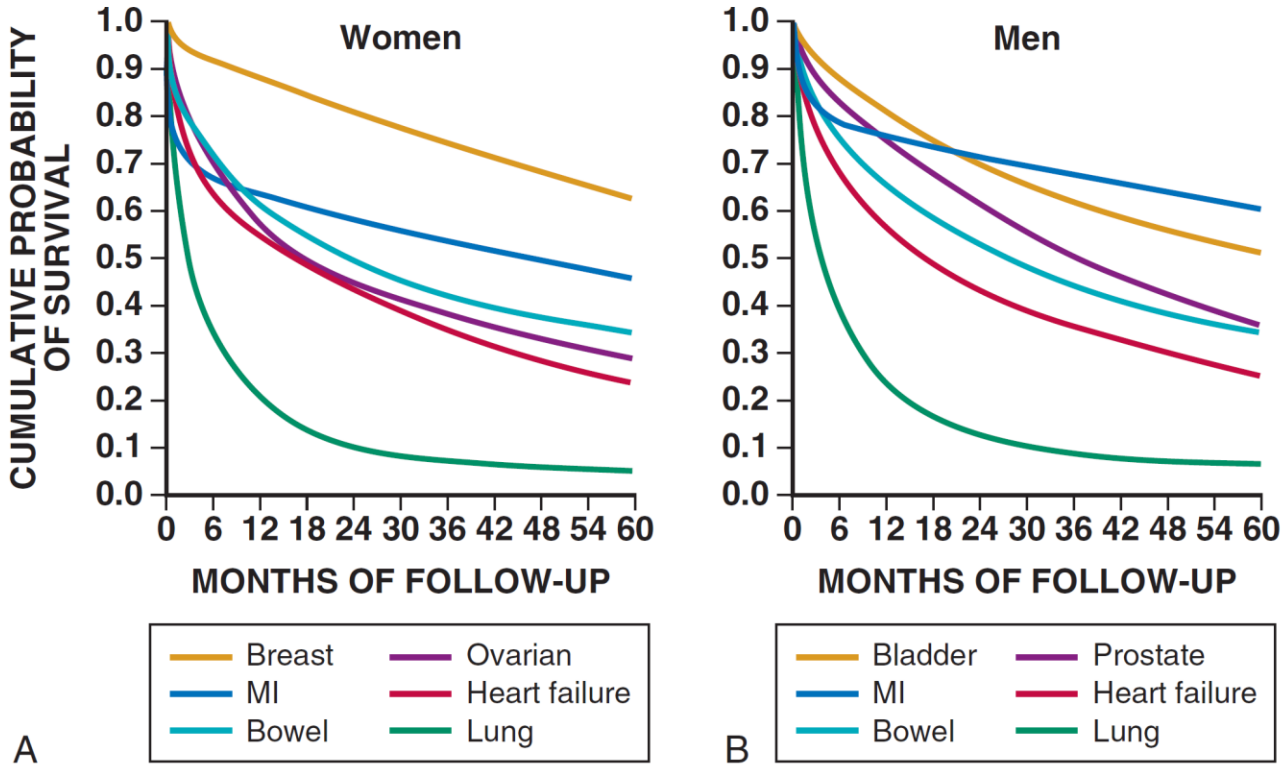
European Society of Cardiology/Heart Failure Association - 2021:

Heart failure is a *clinical syndrome* consisting of cardinal 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). It is due to a *structural and/or functional abnormality of the heart* that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise.

McDonagh TA et al. *Eur Heart J* 2021; 42: 3599-3726.

Epidemiology and prognosis of heart failure

- 64 miilion patients worldwide
- accounts for 5% of the acute hospitalizations (1 million patients/year in the U.S.)
- 2% of the total health expideture (5,4% in the U.S., 38 billion USD/year)
- incidence doubles in every 10 years
- high mortality (20-80%)



Five-year survival following a first admission for heart failure, myocardial infarction, and the four most common sites of cancer specific to men and women.

Modified from Stewart S, *Eur J Heart Fail* 3:315, 2001.

Aetiologies of heart failure I.

Cause	Examples of presentations
CAD	Myocardial infarction Angina or "angina-equivalent" Arrhythmias
Hypertension	Heart failure with preserved systolic function Malignant hypertension/acute pulmonary oedema
Valve disease	Primary valve disease e.g., aortic stenosis Secondary valve disease, e.g. functional regurgitation Congenital valve disease
Arrhythmias	Atrial tachyarrhythmias Ventricular arrhythmias
CMPs	All Dilated Hypertrophic Restrictive ARVC Peripartum Takotsubo syndrome Toxins: alcohol, cocaine, iron, copper
Congenital heart disease	Congenitally corrected/repaired transposition of great arteries Shunt lesions Repaired tetralogy of Fallot Ebstein's anomaly
Infective	Viral myocarditis Chagas disease HIV Lyme disease

McDonagh TA et al. *Eur Heart J* 2021; 42: 3599-3726.

Aetiologies of heart failure II.

Cause	Examples of presentations
Drug-induced	Anthracyclines Trastuzumab VEGF inhibitors Immune checkpoint inhibitors Proteasome inhibitors RAF+MEK inhibitors
Infiltrative	Amyloid Sarcoidosis Neoplastic
Storage disorders	Haemochromatosis Fabry disease Glycogen storage diseases
Endomyocardial disease	Radiotherapy Endomyocardial fibrosis/eosinophilia Carcinoid
Pericardial disease	Calcification Infiltrative
Metabolic	Endocrine disease Nutritional disease (thiamine, vitamin B1 and selenium deficiencies) Autoimmune disease
Neuromuscular disease	Friedreich's ataxia Muscular dystrophy

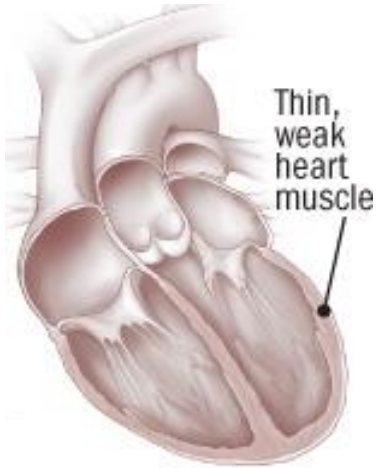
McDonagh TA et al. *Eur Heart J* 2021; 42: 3599-3726.

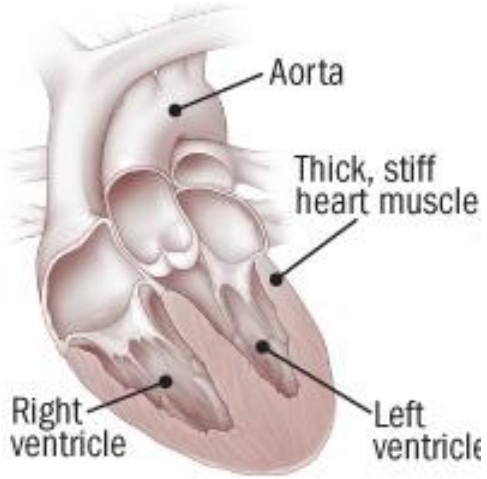
Clinical forms of heart failure

- Right vs. left heart failure (backward vs. forward failure)
- Acute vs. chronic heart failure

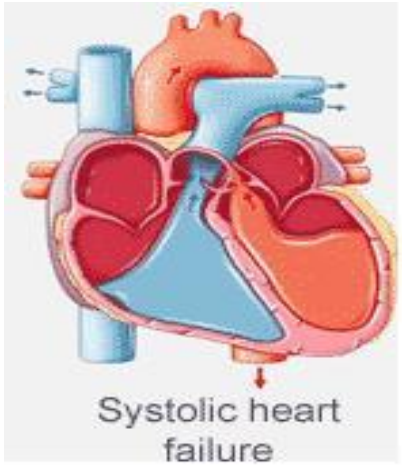
- Heart failure with reduced (**HFrEF**), mid-range (**HFmrEF**) and preserved (**HFpEF**) ejection fraction (EF) (2016-)

HFrEF (EF≤40%)	**HFmrEF** (EF 41-49%)	**HFpEF** (EF≥50%)

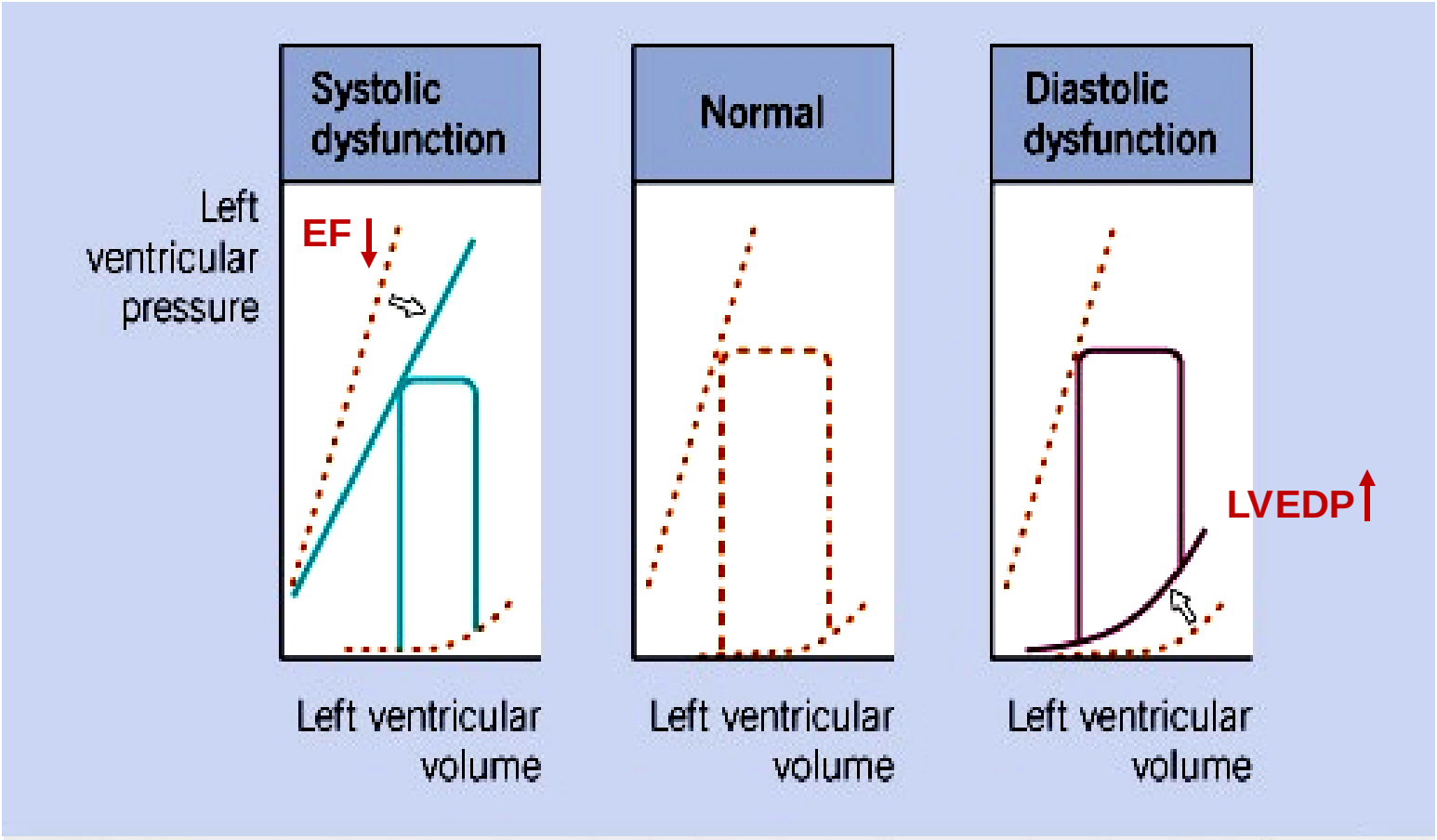


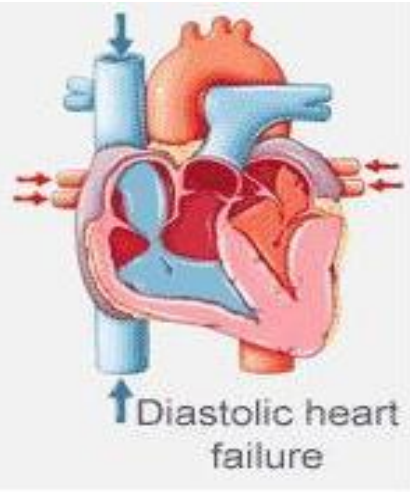


HFrEF vs. HFpEF: distinct heart failure phenotypes



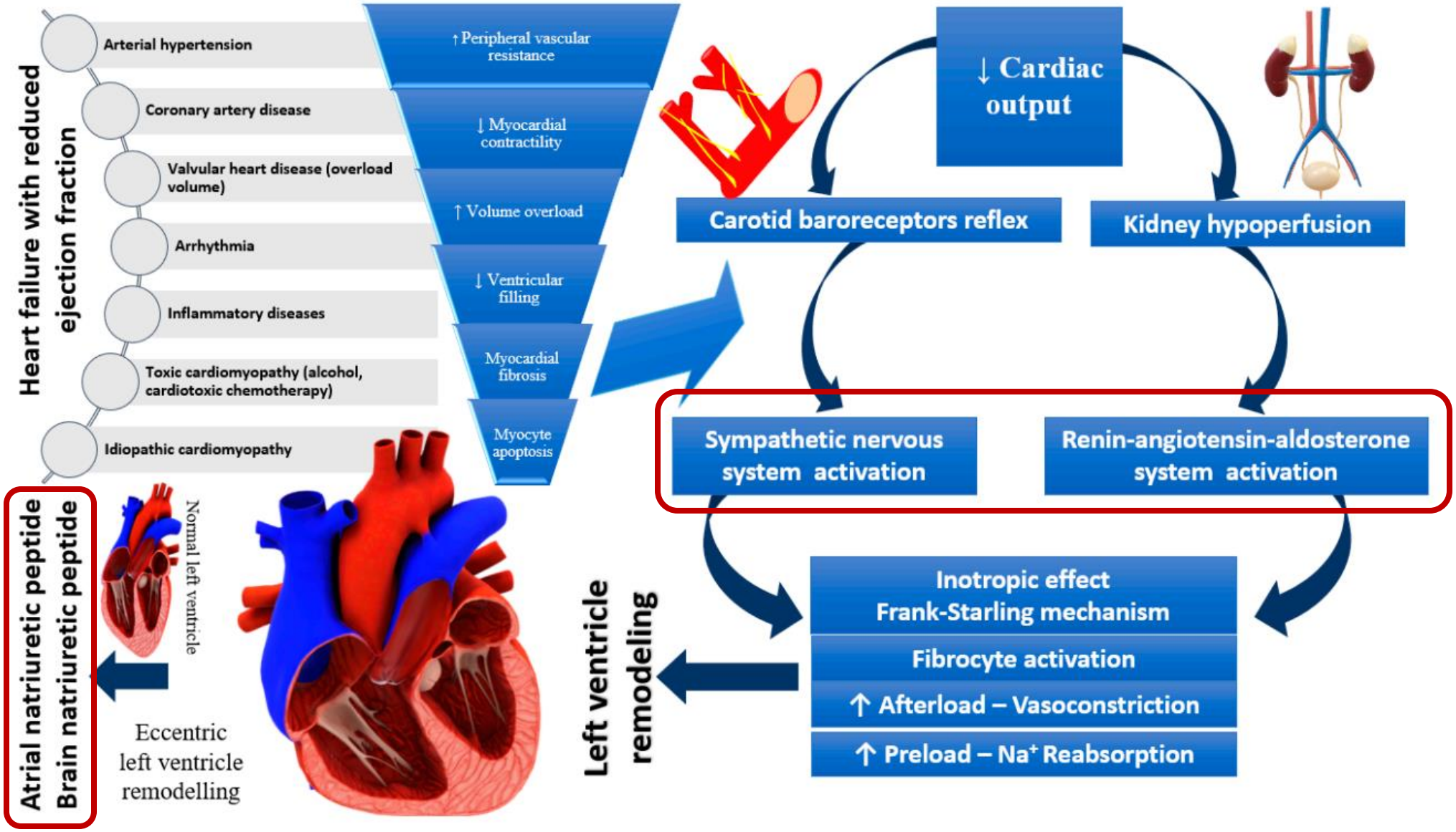
HFrEF





HFpEF

Pathophysiology of HFrEF



Eur J Heart Fail (2022) 24, 927–943.

Important pathological alterations in HFrEF

1. Activation sympathetic nervous system (SNS)
2. Activation of the renin-angiotensin-aldosterone system (RAAS)
3. Activation of the natriuretic peptide system (NPS)

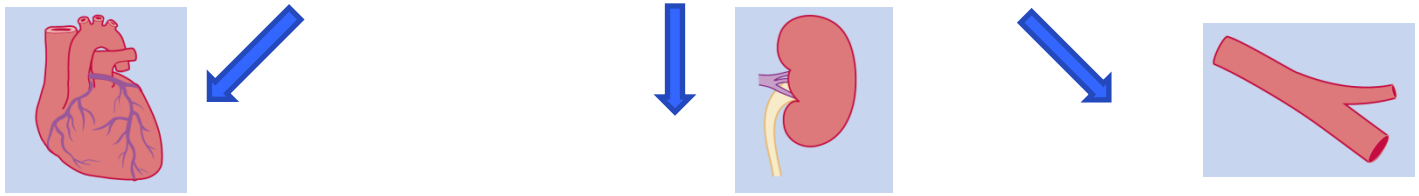
1. Activation sympathetic nervous system (SNS) in HFrEF

1. The **Frank-Starling** mechanism (the law of heterometric autoregulation)
   - rise in preload increases the force of contraction (stroke volume restoration)

2. Activation of **neurohumoral systems**

   The extent of activation of the autonomic nervous system and endogenous hormone production seems to vary with the clinical state of the patient.

   - Circulatory reflexes (increased vasoconstrictor activity)
   - **Sympathetic nervous system activation**



Myocardial effects

- Downregulation of β_1-receptors
- Increased ic. Ca^{2+} concentration
- Arrhythmias
- Cardiomyocyte apoptosis
- Interstitial fibrosis

Renal effects

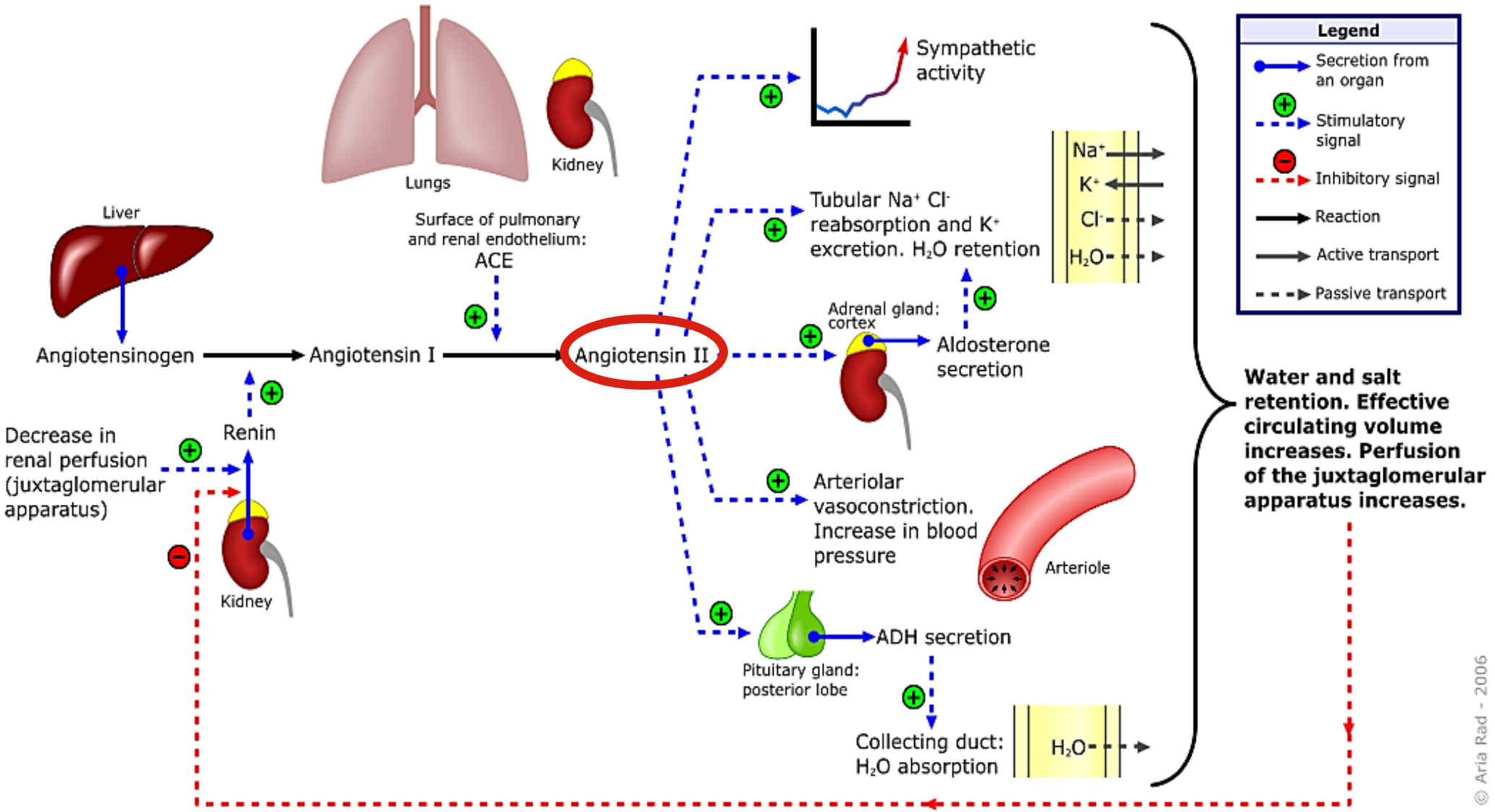
- RAAS activation
- Renal vasoconstriction
- Impaired natriuretic answer

Vascular effects

- Increased peripheral vasoconstriction

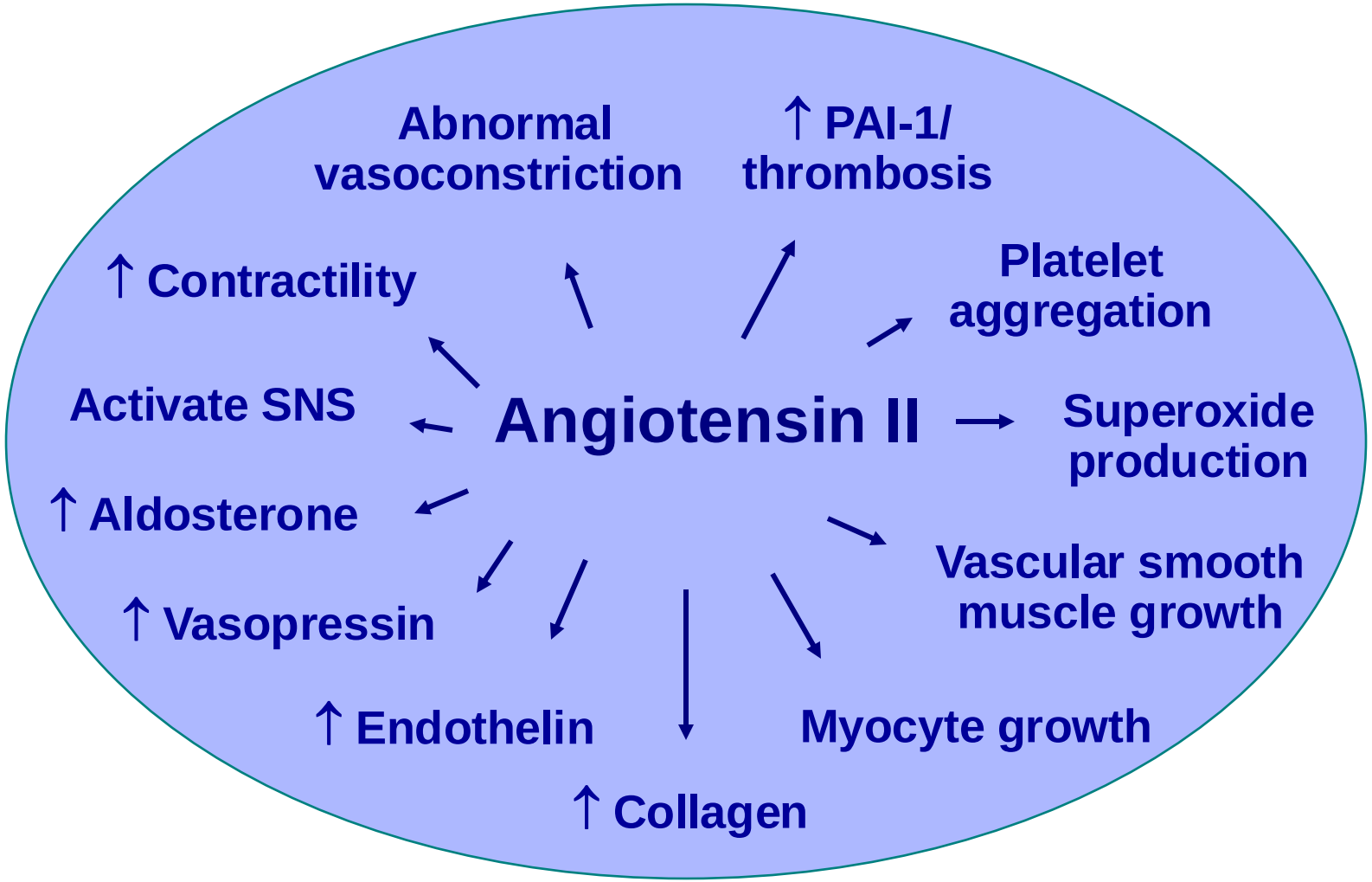
2.

Activation of RAAS in HFrEF



Wikimedia Commons, the free media repository

Pathophysiologic effects of angiotensin II

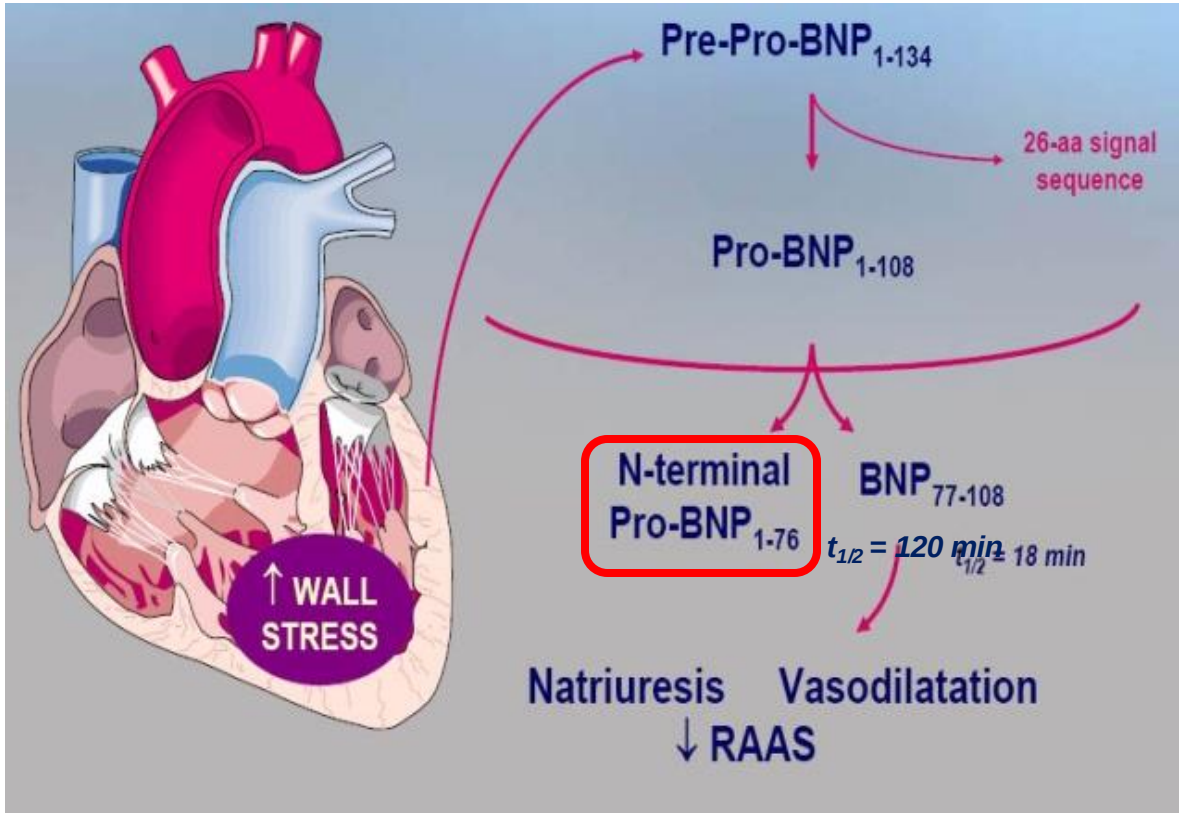


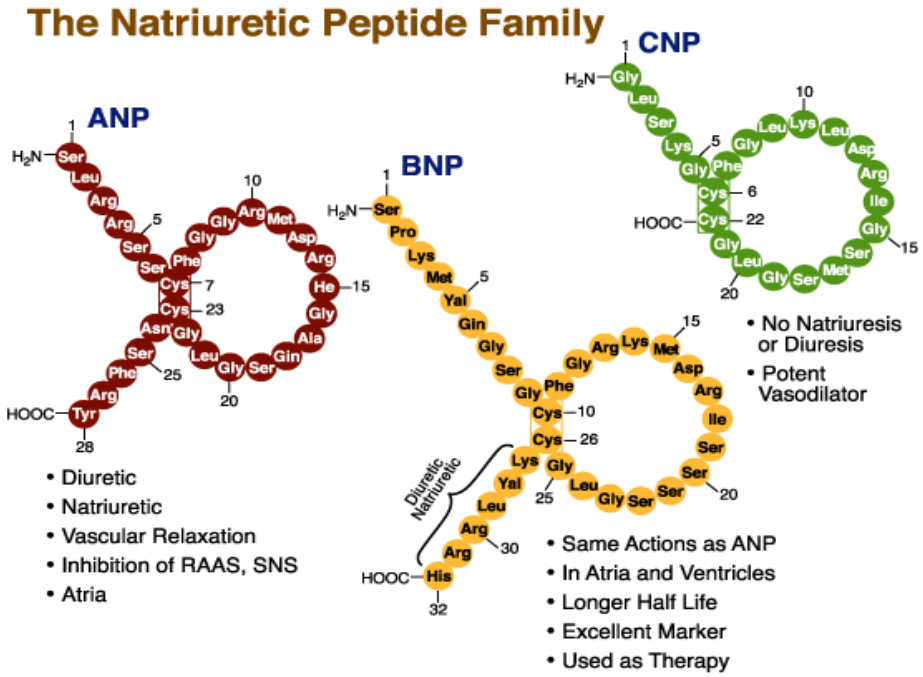
Modified after Burnier & Brunner, *Lancet*, 2000

3. The role of natriuretic peptide system in heart failure

Natriuretic peptides

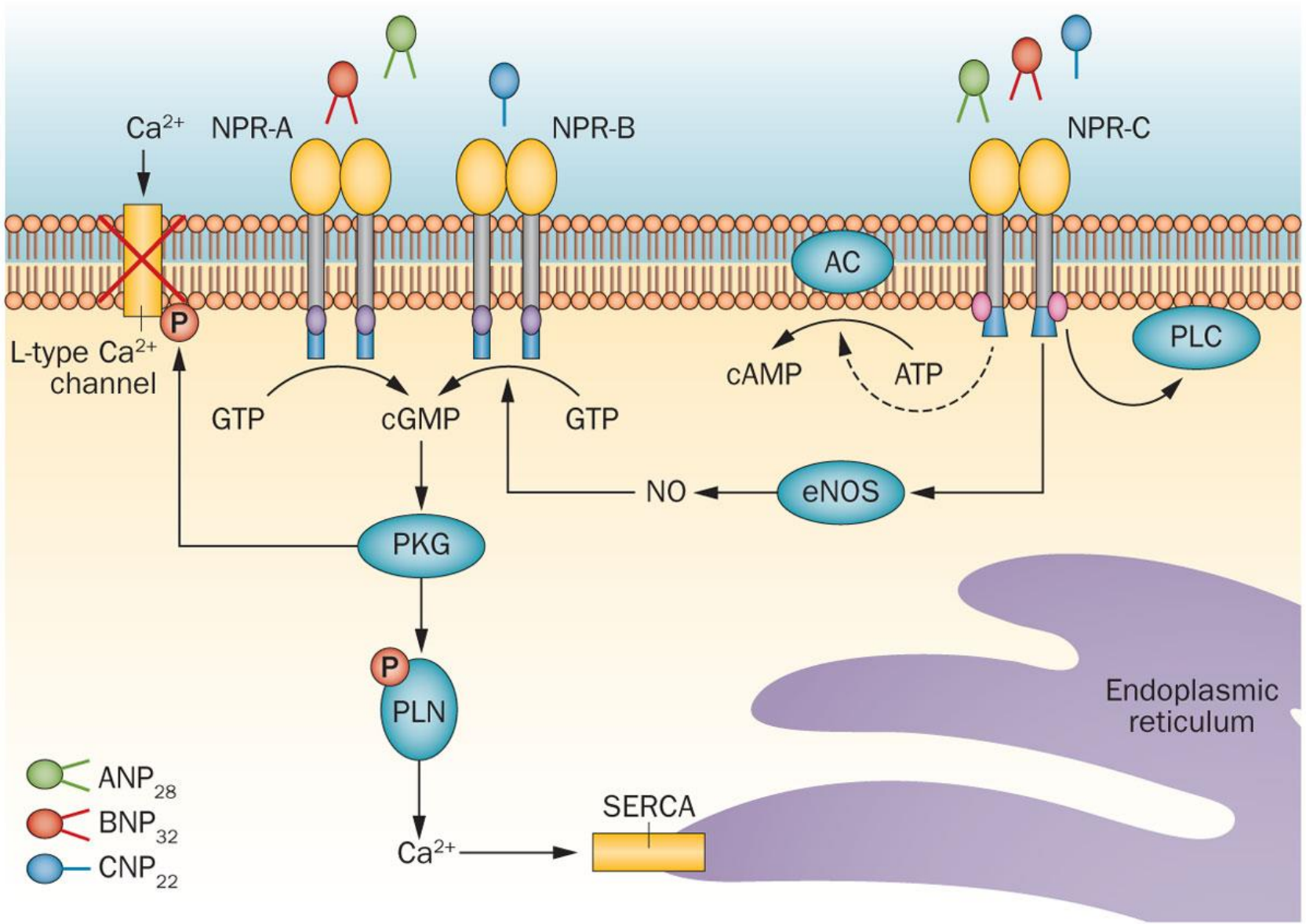
- released from cardiomyocytes in response to atrial and ventricular wall stretch
- ANP, BNP (NT-proBNP), CNP, DNP (dendroaspis), urodilatin





Other hormones: vasopressin, prostaglandins, bradykinin, histamine, EDRF, endothelin-1, relaxin, adrenomedullin, urocortin, apelin, etc.

Natriuretic peptides: signal transduction pathways



Zois NE., *Nature Reviews Cardiology* 11, 403–412. (2014)

Natriuretic peptides: diverse physiological effects

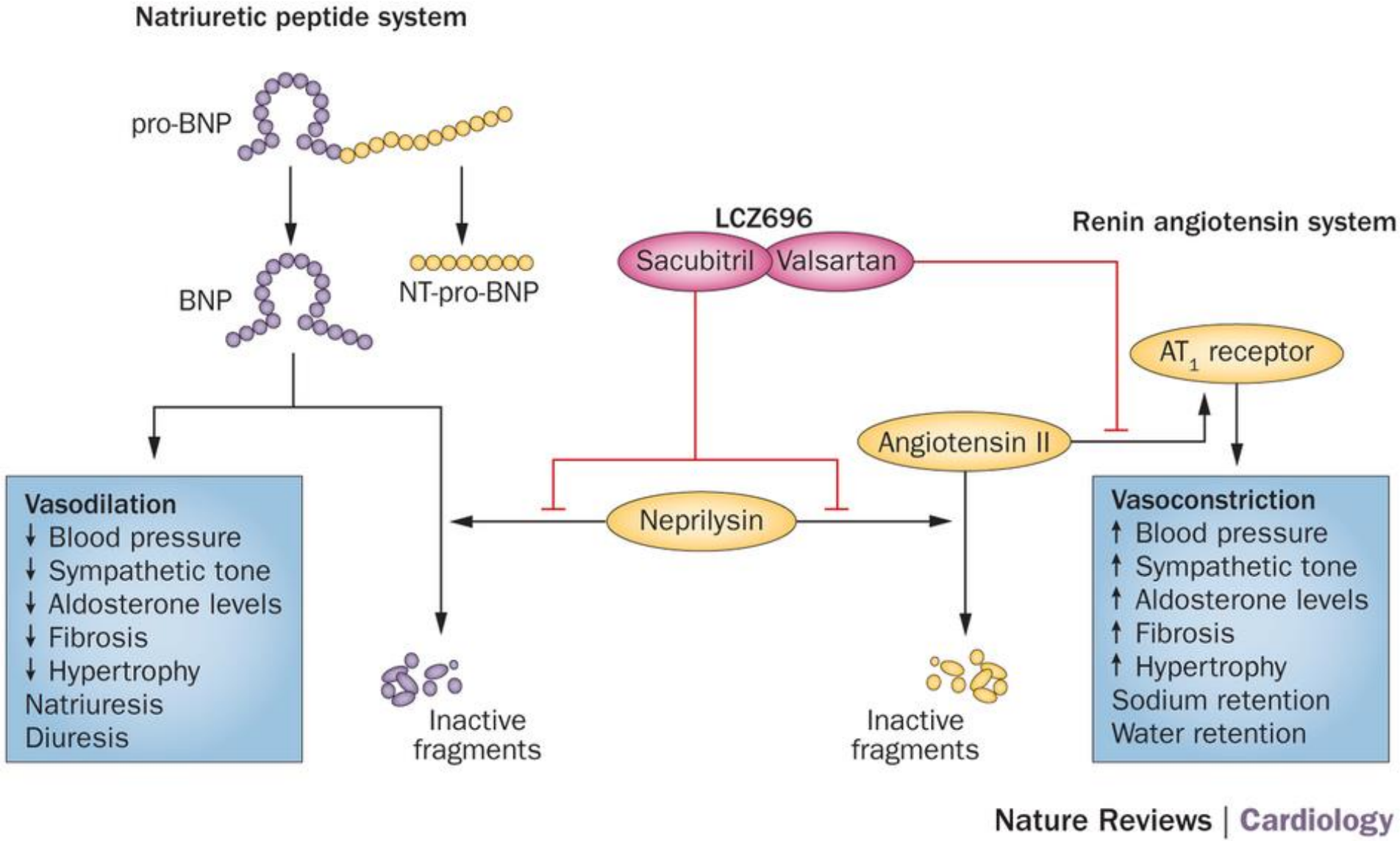
- Inhibition of the sympathetic nervous system and the RAAS
- Natriuretic and diuretic effects (kidney and distal tubules)
- Vasodilatory effects, smooth muscle relaxation (decrease in PVR)
- Vascular system: antiproliferative, antifibrotic and antihypertrophic effects
- Myocardial effects: direct lusitropy (relaxation)

Heart failure: clinical importance of natriuretic peptides

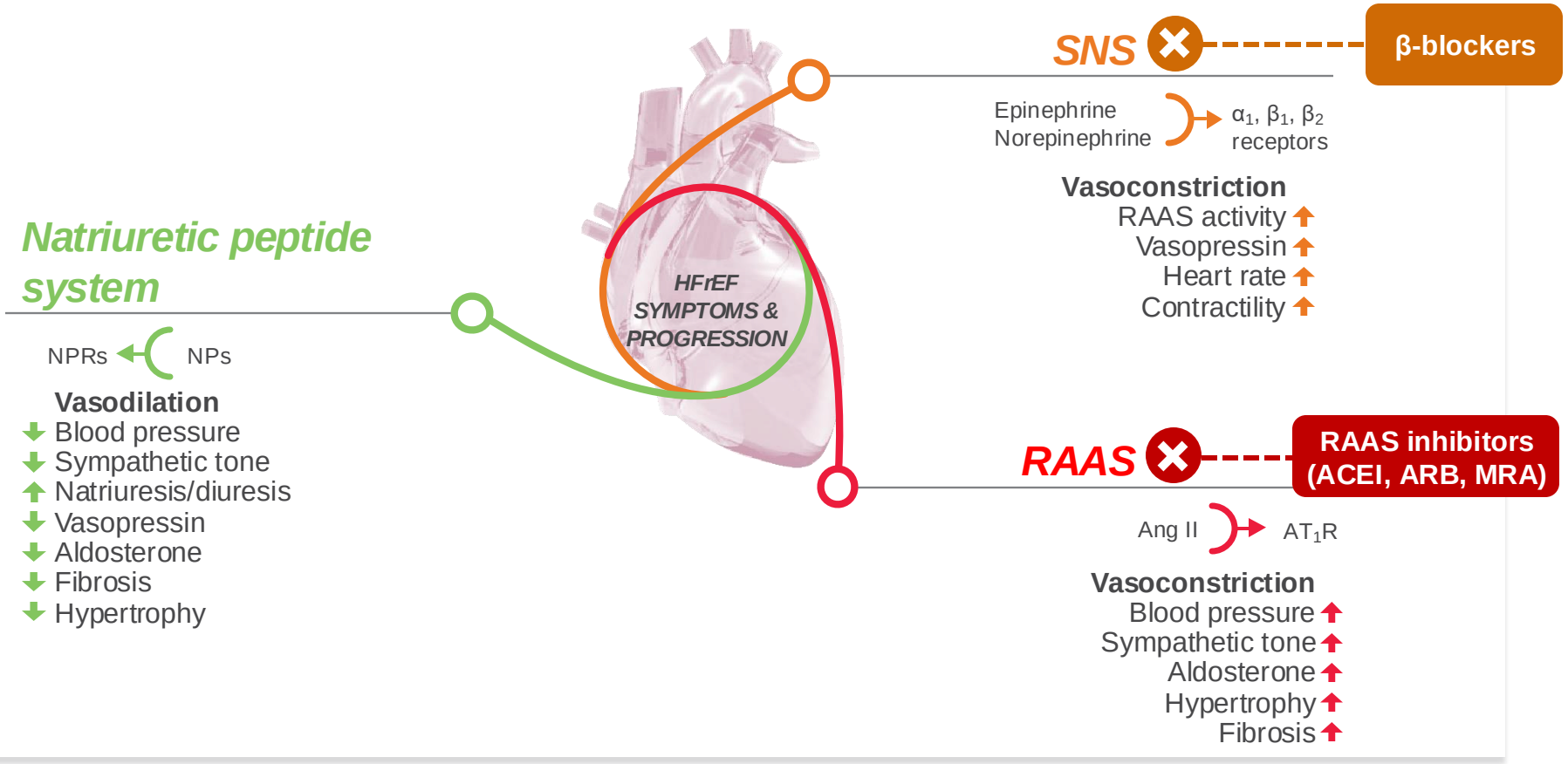
1. Diagnosis (BNP 35 pg/ml and/or NT-proBNP 125 pg/mL)
2. Prognosis
3. Follow-up the effectiveness of HFrEF therapy
4. Therapy (recombinant human BNP (nesiritide), ARNI)

Natriuretic peptides, as therapeutical targets: ARNI

Sacubitril/valsartan (LCZ696) is an **ARNI** (Angiotensin Receptor Neprilysin Inhibitor) which reduces the strain on the failing heart, enhances the levels of natriuretic and other endogenous vasoactive peptides, while also inhibits the RAAS.



Overactivation of the RAAS and SNS is detrimental in HFrEF and underpins the basis of therapy

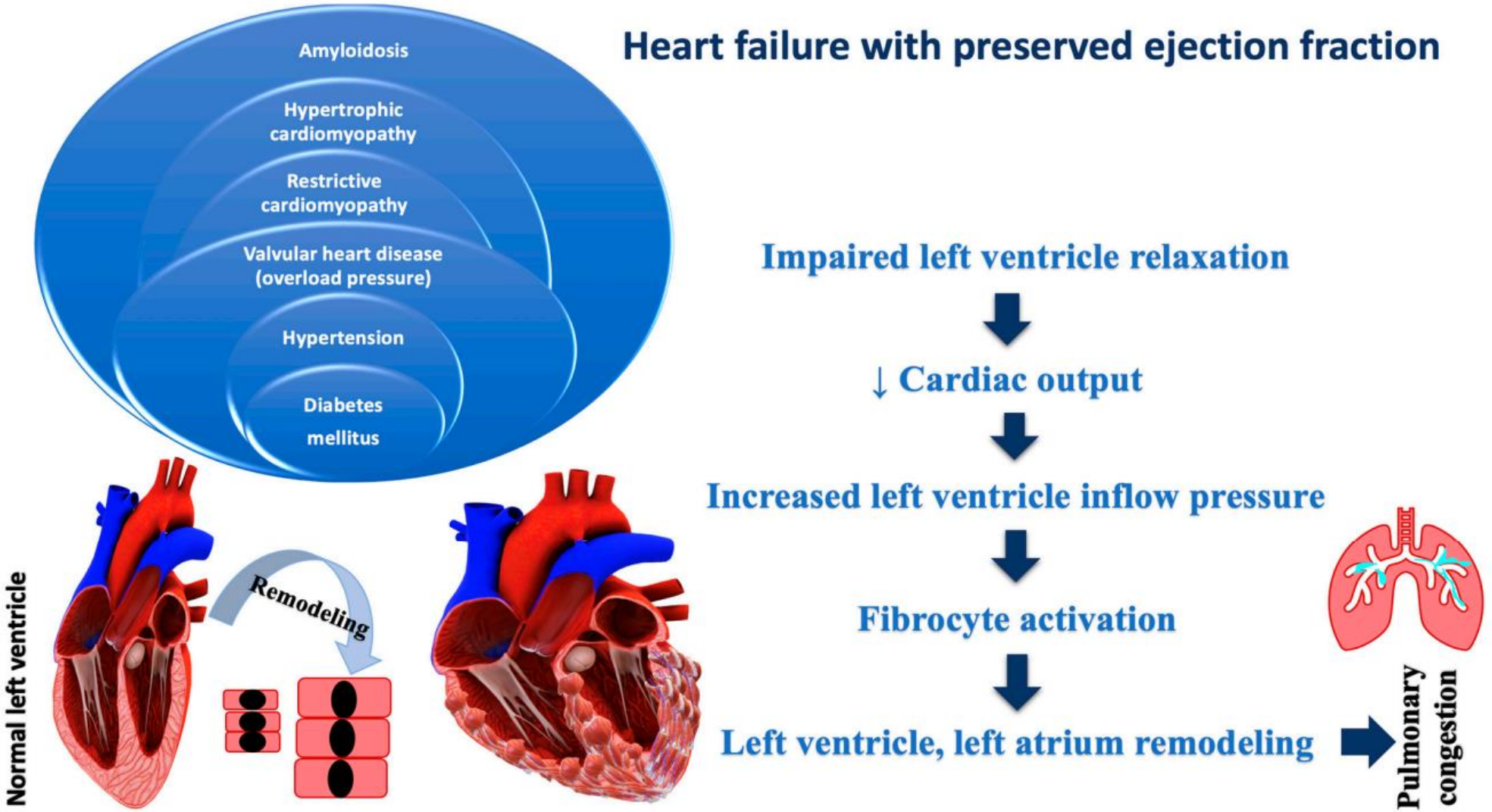


- The crucial importance of the RAAS is supported by the beneficial effects of ACEIs, ARBs and MRAs[1]
- Benefits of β-blockers indicate that the SNS also plays a key role[1]

1. McMurray et al. Eur Heart J 2012;33:1787–847
Figure references: Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42 Kemp & Conte. Cardiovascular Pathology 2012;365–71 Schrier & Abraham. N Engl J Med 1999;341:577–85

See notes for abbreviation definitions

Pathophysiology of HFpEF



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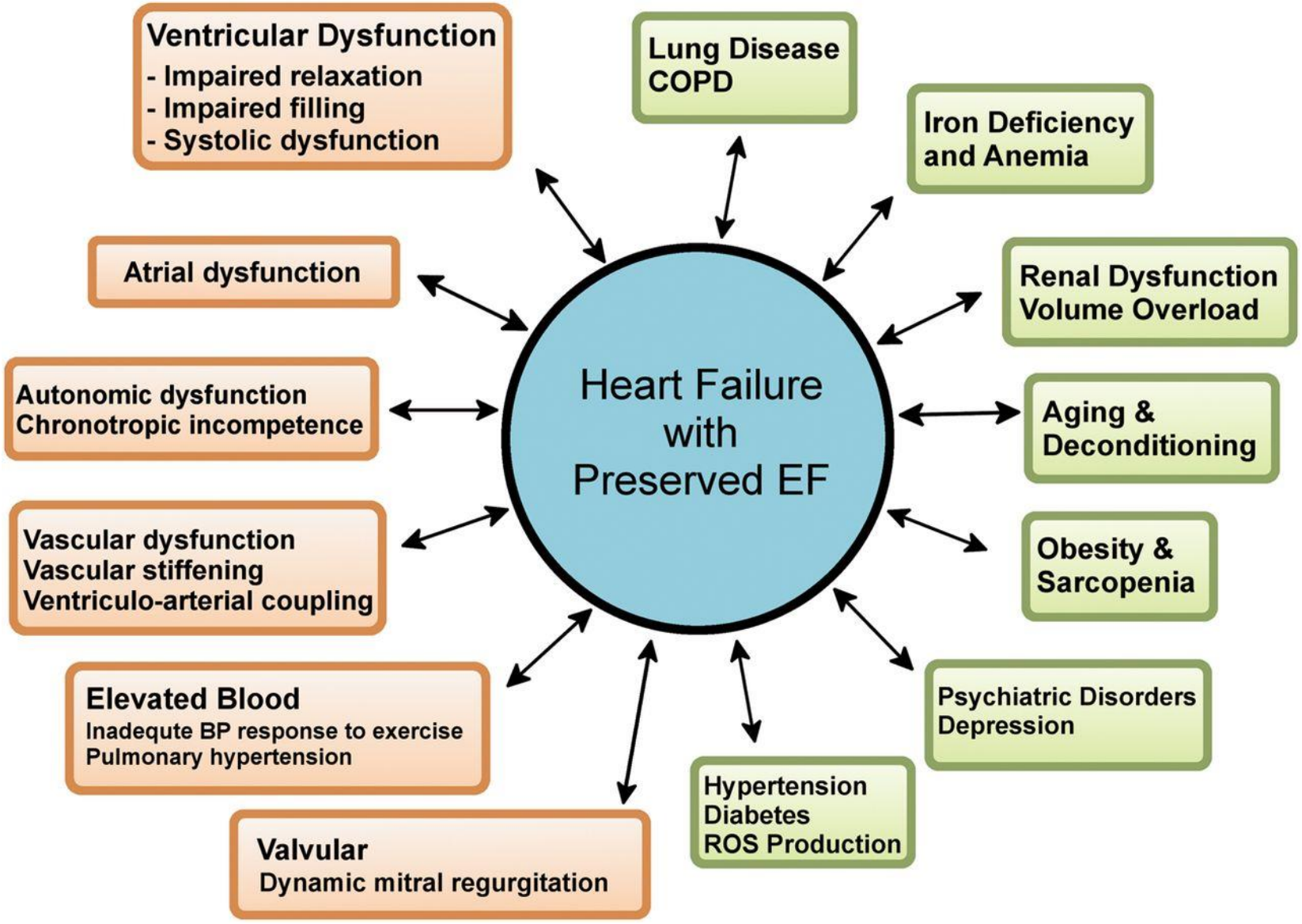
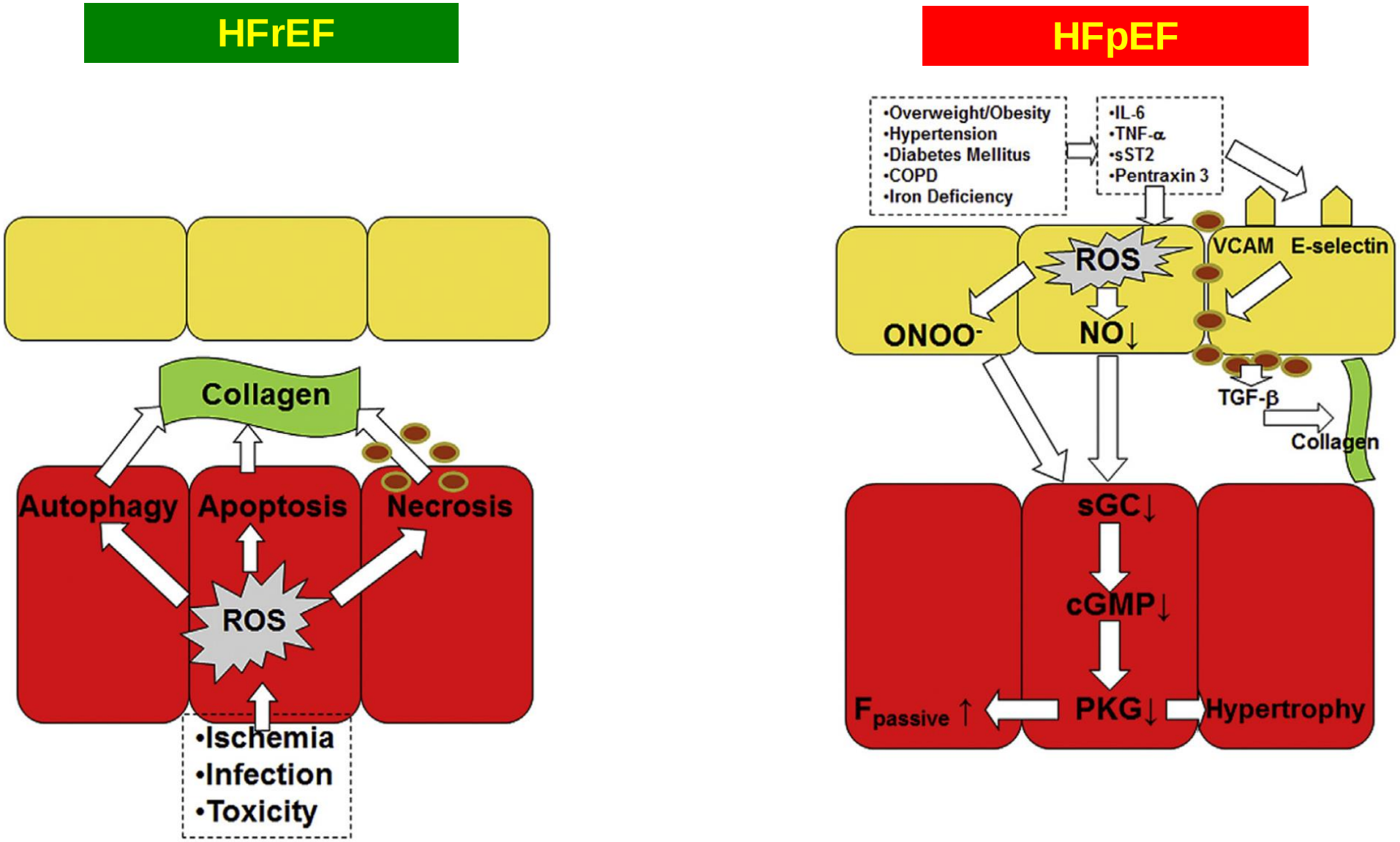
HFpEF: complex, heterogenous pathophysiology



Michele Senni et al. *Eur Heart J* 2014;35:2797-2815

HFrEF vs. HFpEF: distinct pathophysiology



Paulus WJ, JACC, 2013, 62, 263-271.

Symptoms – Left sided failure

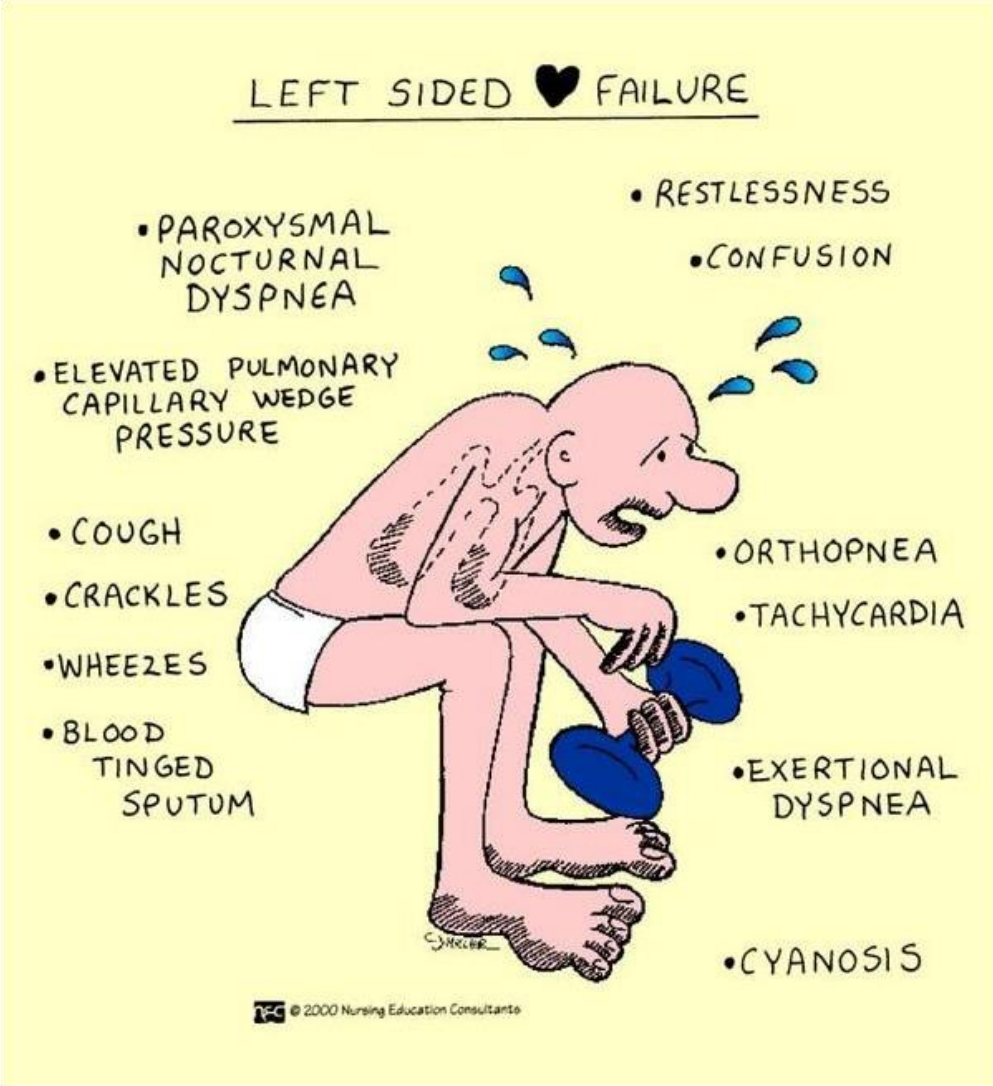
Backward failure:

- **Dyspnea**
  - On exertion and/or at rest
  - Paroxysmal nocturnal dyspnea (PND)
  - Orthopnea
  - Pulmonary edema
  - Cheyne-Stokes

- **Pulmonary crackles** (Killip classification)
- **Cough, sputum** („asthma cardiale")

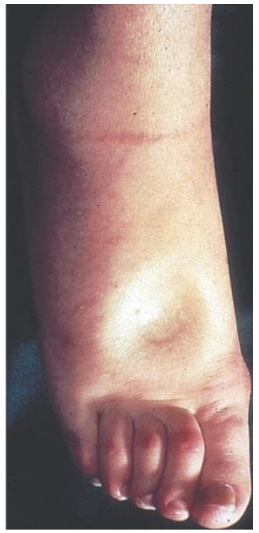
Forward failure:

- **Hypotension**
- **Pallid and cold limbs** (vasoconstriction)
- **„Clear" lungs**

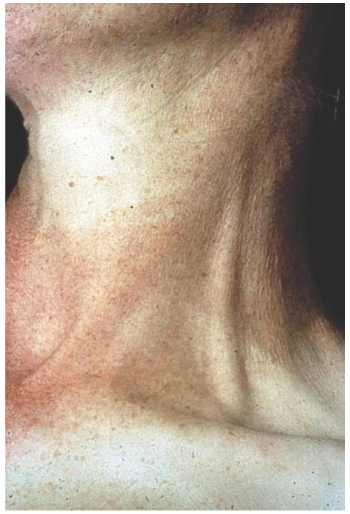


Symptoms – Right sided failure

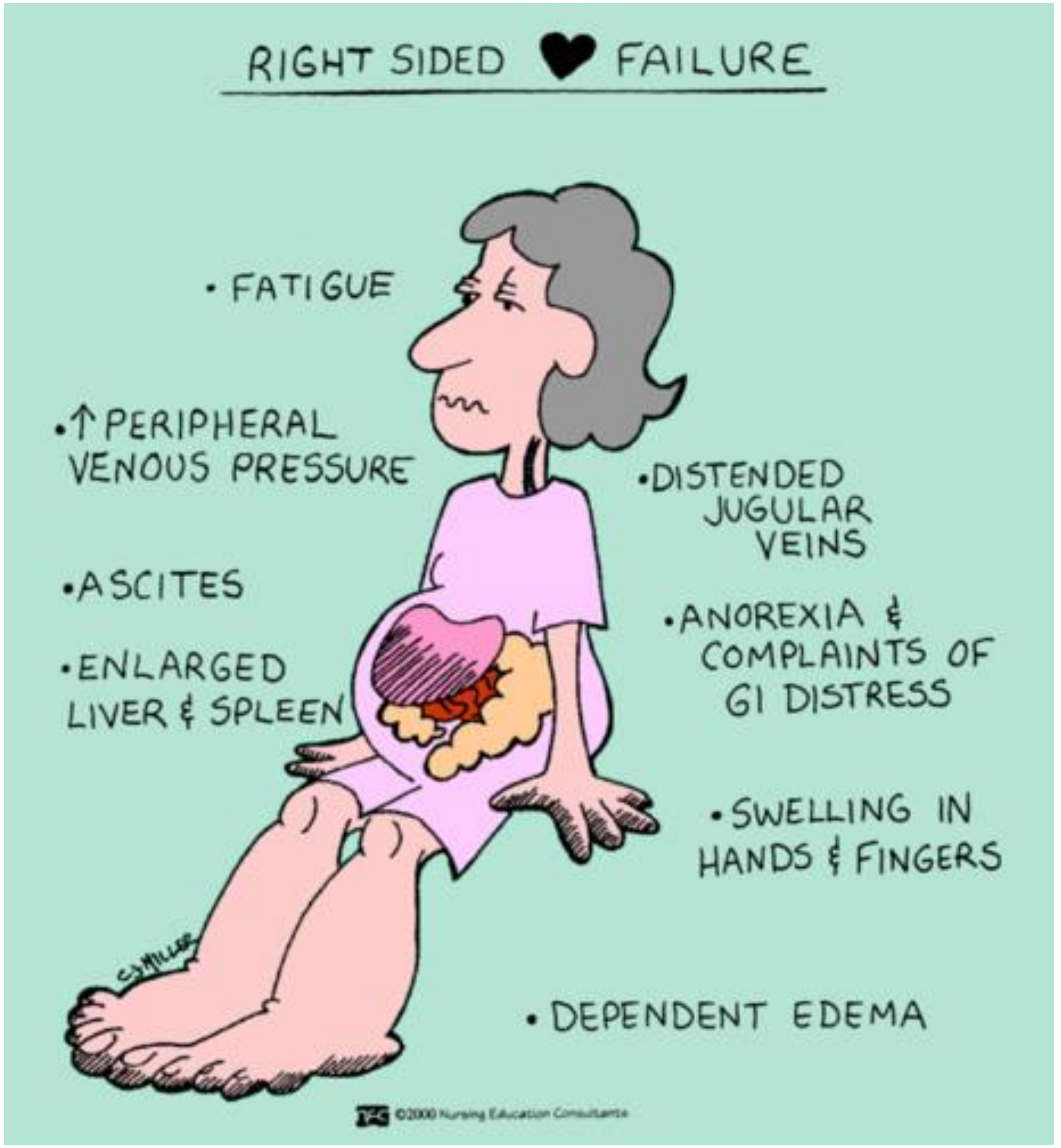
- Fatigue
- Gastrointestinal complains
- Peripheral edema, ascites
- Jugular vein distension
- Spleno- és hepatomegaly („cardiac cirrhosis”)



Ankle swelling



Elevated jugular venous pressure

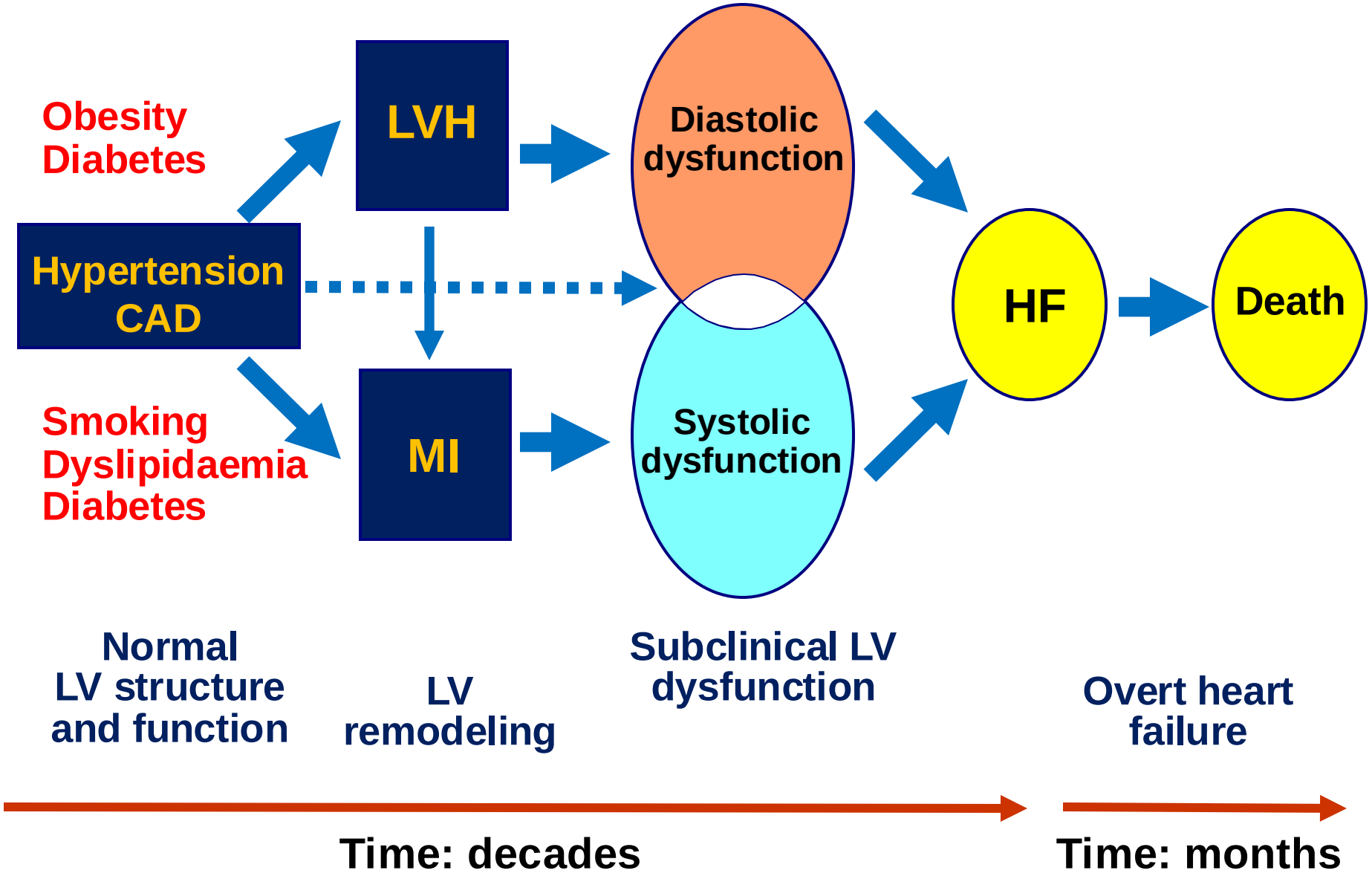


Classification of heart failure by symptoms relating to functional capacity (NYHA) or by structural abnormality (ACC/AHA)

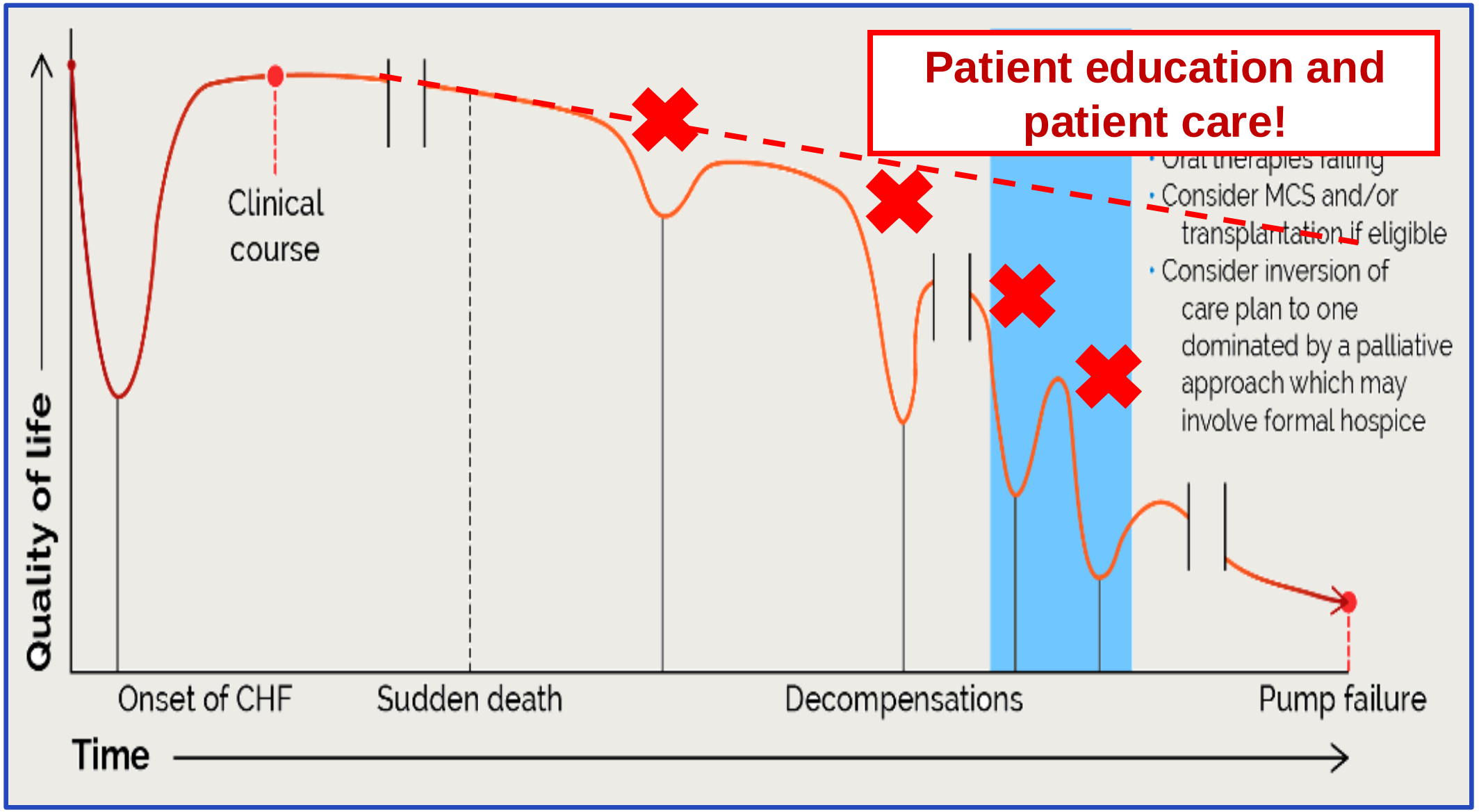
NYHA functional classification	ACC/AHA stages of heart failure
Severity based on ***symptoms and physical activity***	Stage of heart failure based on ***structure and damage*** to heart muscle
Class I No limitation of physical activity. Ordinary physical activity doses not cause undue fatigue, palpitation, or dyspnoea.	**Stage A** At high risk for developing heart failure. No identified structural or functional abnormality; no signs or symptoms.
Class II Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.	**Stage B** Developed structural heart disease that is strongly associated with the development of heart failure, but without signs or symptoms.
Class III Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnoea.	**Stage C** Symptomatic heart failure associated with underlying structural heart disease
Class IV Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.	**Stage D** Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy.

ACC, American College of cardiology; AHA, American Heart Association; NYHA, New York Heart Association.

Progression of heart failure



Progression of heart failure



Allen et al., 2012

Thank you for your attention!