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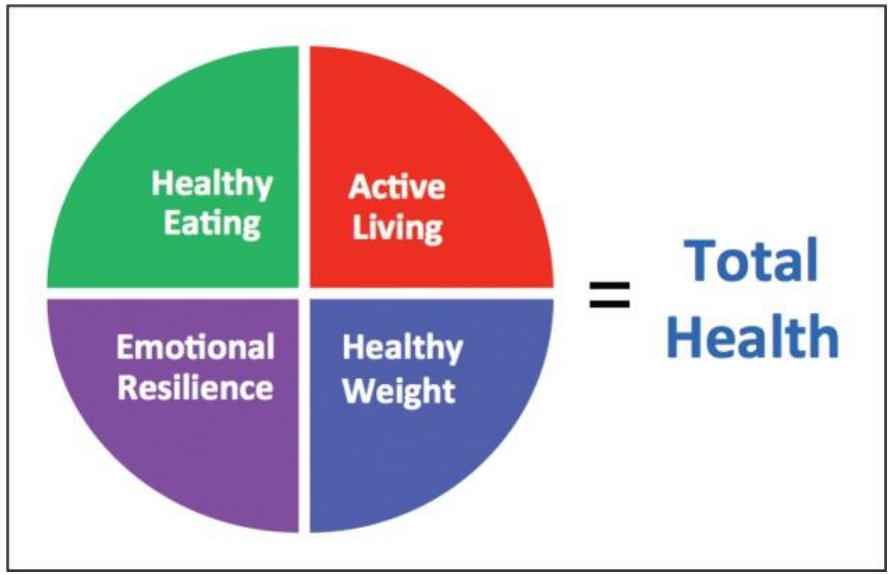
Pathophysiology of cardiovascular systém III

Pressure and volume overload.

Heart failure

27.10.2020



Normal cardiac function

- Cardiac output = heart rate x stroke volume
- Heart rate – controled by SNS and PNS
- Stroke – dependent on preload, afterload and contractility
- Preload = LVEDP and is measured as PCWP (Pulmonary Capillary Wedge Pressure)
- Afterload = SVR
- Contractility: ability of contractile elements to interact and shorten against a load
  (+ inotropy- inotropy)

Heart rate

- The heart rate is modulated from beat to beat by efferent vagal and sympathetic fibers, the former being the predominant mediators of the chronotropic influence of arterial baroreceptors and respiration and the latter being important in the cardiac responses to physical and mental stress.
- Cardiac vagal influences are modulated by a number of factors. These can be grouped as: 1) neural factors, such as the wakefulness-sleep cycle, the alerting reaction, and exercise; 2) humoral-pharmacological factors, such as angiotensin II, angiotensin 1-7, atrial natriuretic factor, cardiac glycosides; 3) normal aging; 4) a number of cardiovascular and other diseases, such as arterial hypertension, coronary artery disease, congestive heart failure and diabetes mellitus.

Journal of Cardiovascular Electrophysiology 14; 8, 2003, 791-799

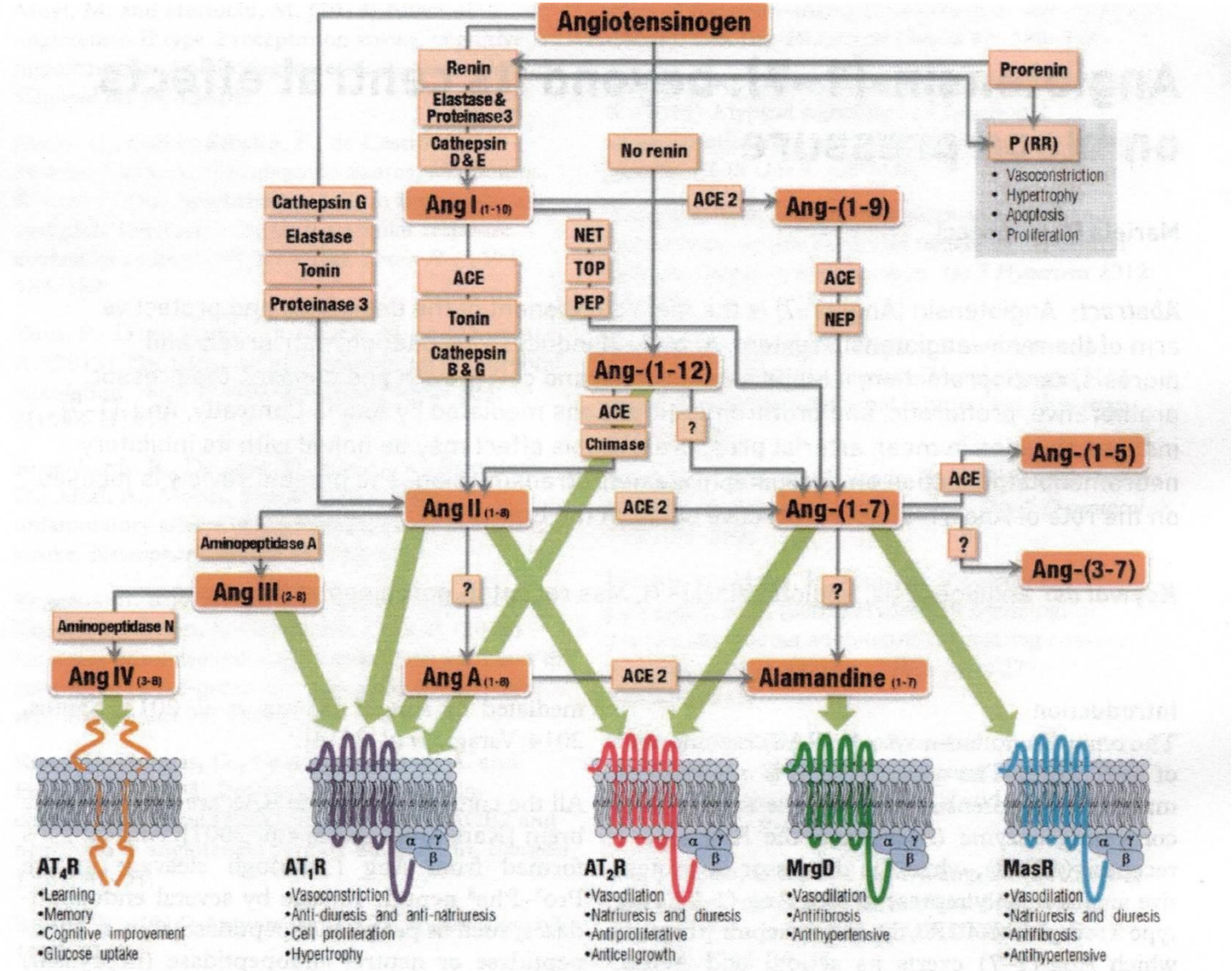
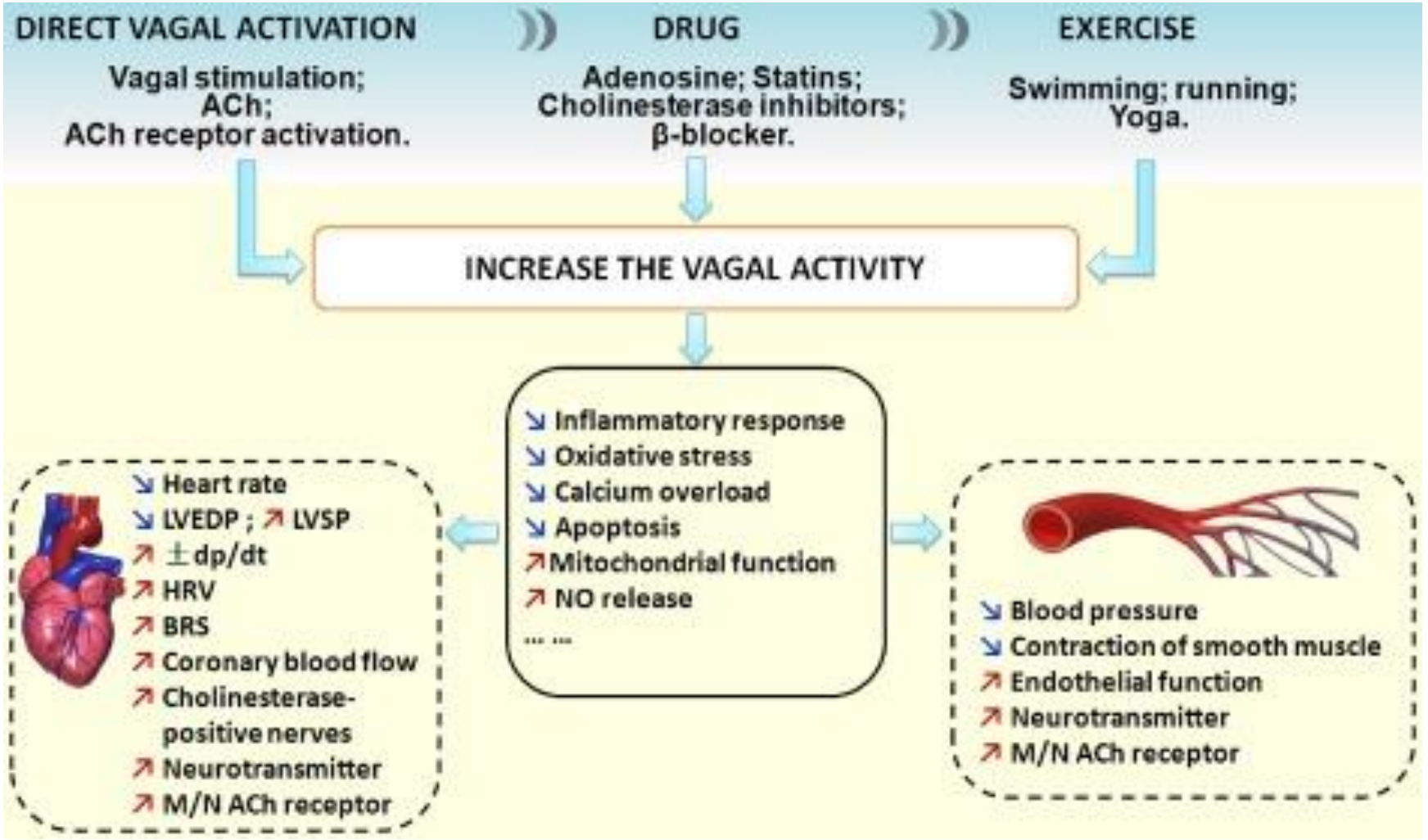
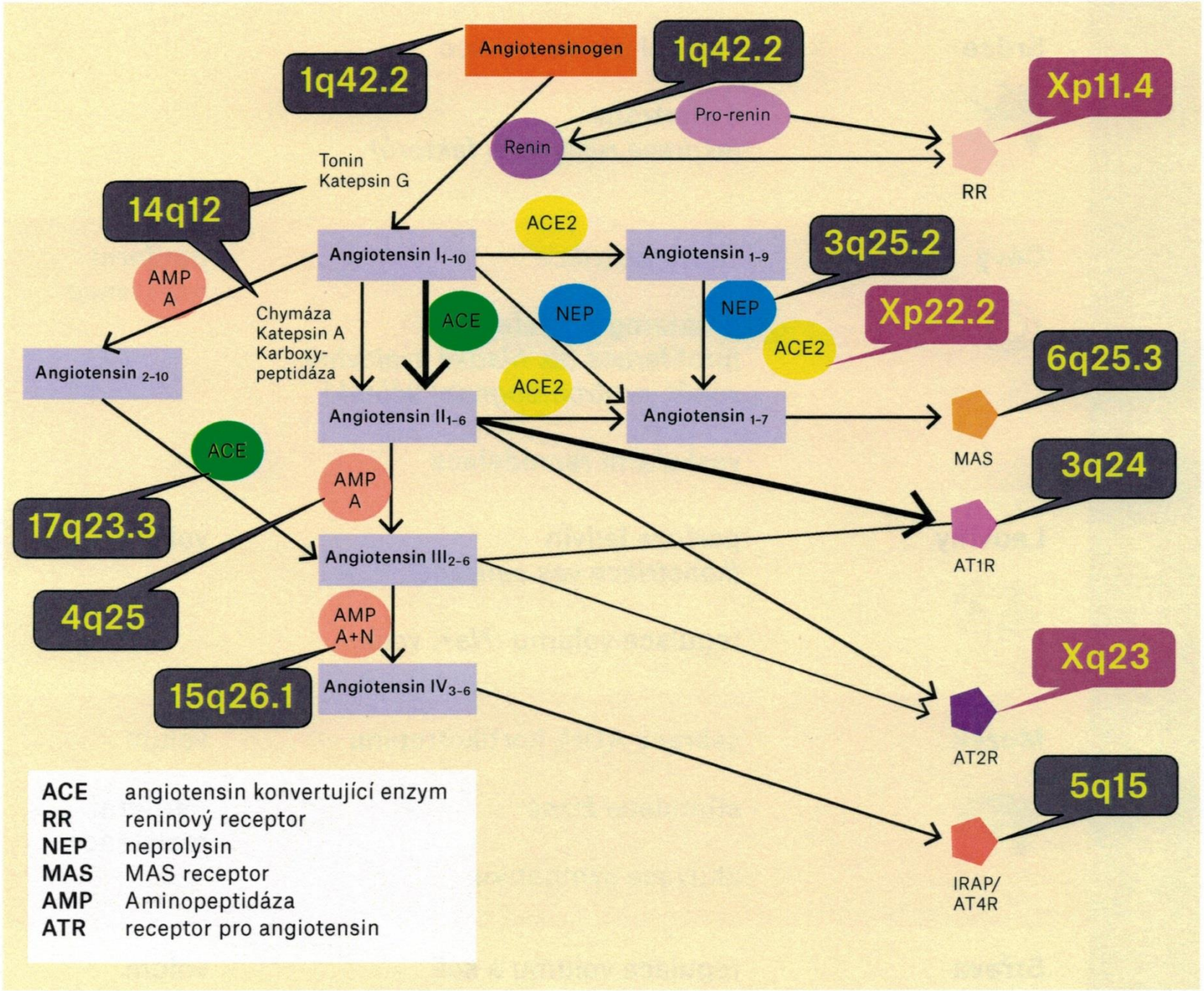


Figure 1. Brain renin–angiotensin system.
ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; Ang, angiotensin; AT_1 R, angiotensin type 1 receptor; AT_2 R, angiotensin type 2 receptor; AT_4 R, angiotensin type 4 receptor; Mas R, Mas receptor; MrgD, Mas related G-protein coupled receptors; NEP, neutral endopeptidase (neprilysin); PEP, prolyl endopeptidase; (P)RR, prorenin receptor; TOP, thimet oligopeptidase.

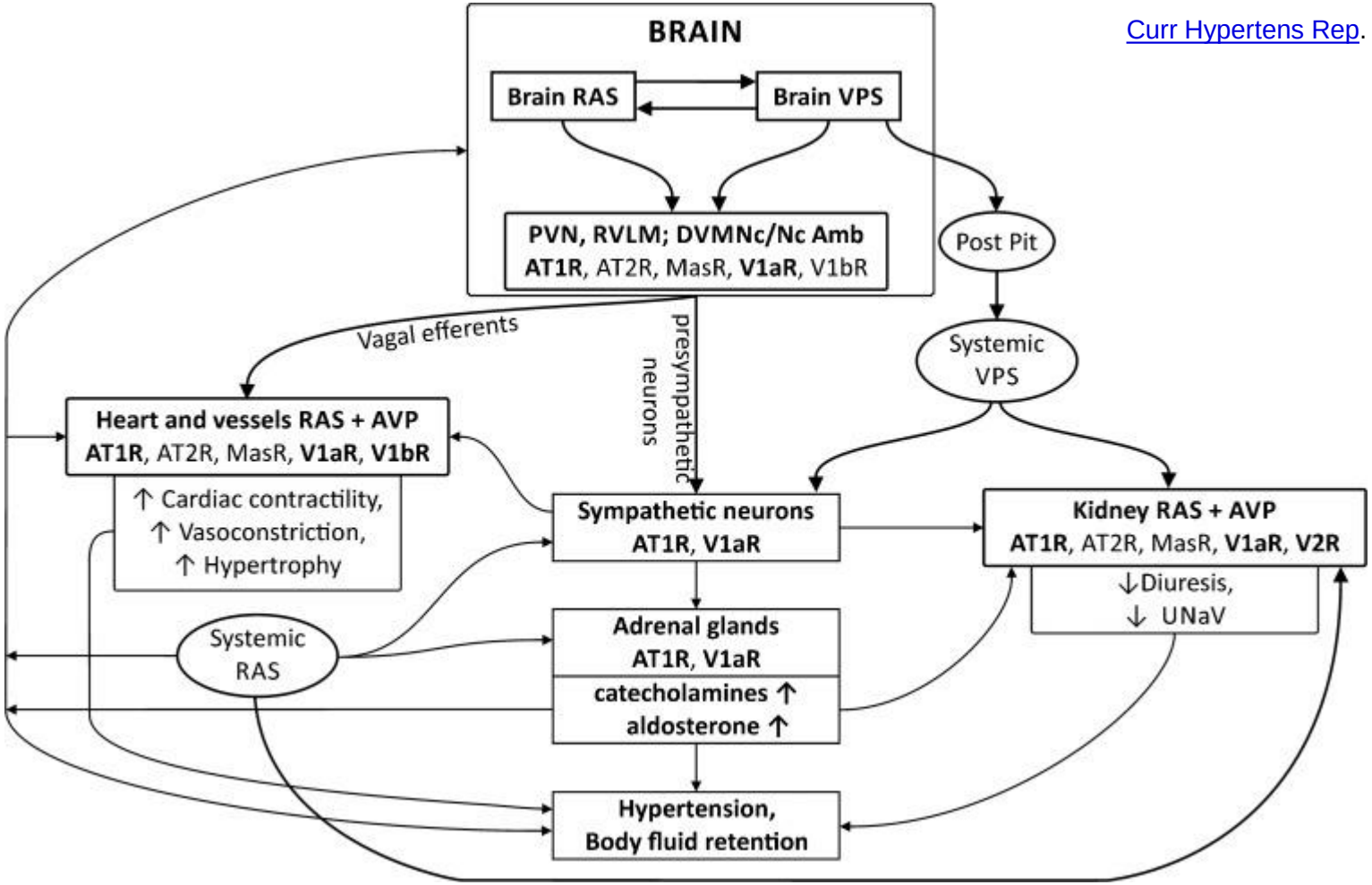


Beneficial effects on cardiac and vascular function are provided by the modulation of vagal activity, including direct vagal activation (vagal stimulation, ACh administration and ACh receptor activation), pharmacological modulation (adenosine, cholinesterase inhibitors, statins) and exercise training.

Br J Pharmacol. 2015 Dec; 172(23): 5489–5500.


Angiotensinogen
1q42.2
1q42.2
Xp11.4
Pro-renin
Renin
RR
Tonin
Katepsin G
14q12
ACE2
Angiotensin I1-10
Angiotensin 1-9
3q25.2
AMP
A
Chymáza
Katepsin A
Karboxy-
peptidáza
ACE
NEP
NEP
Xp22.2
ACE2
Angiotensin 2-10
6q25.3
ACE2
Angiotensin II1-6
Angiotensin 1-7
MAS
ACE
3q24
AMP
A
17q23.3
Angiotensin III2-6
AT1R
4q25
AMP
A+N
Xq23
15q26.1
Angiotensin IV3-6
AT2R
5q15
IRAP/
AT4R
ACE angiotensin konvertující enzym
RR reninový receptor
NEP neprolysin
MAS MAS receptor
AMP Aminopeptidáza
ATR receptor pro angiotensin

Curr Hypertens Rep. 2018; 20(3): 19.



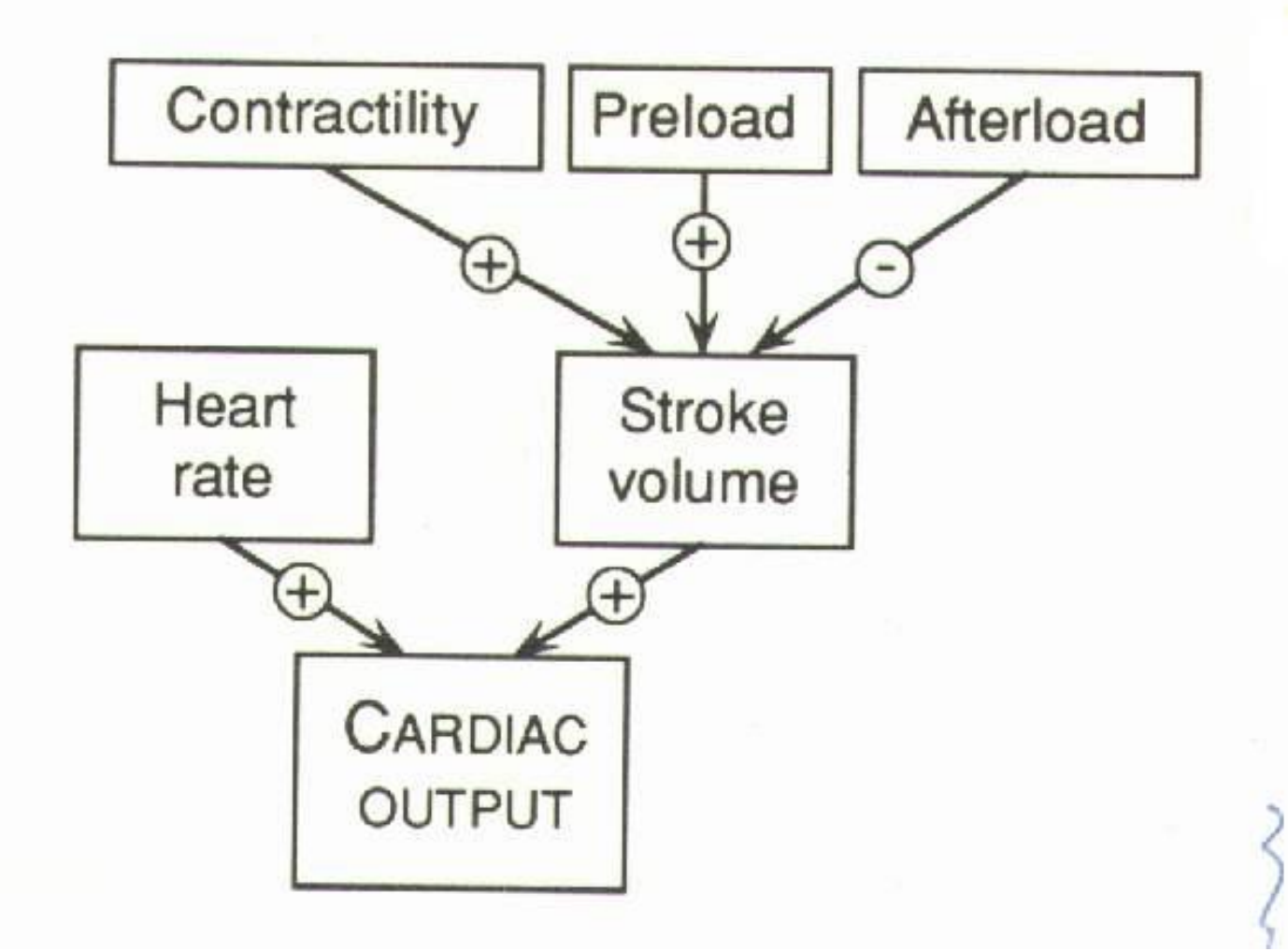
Interactions of the renin-angiotensin system (RAS) with the vasopressinergic system (VPS) in the regulation of blood pressure and body fluid volume.

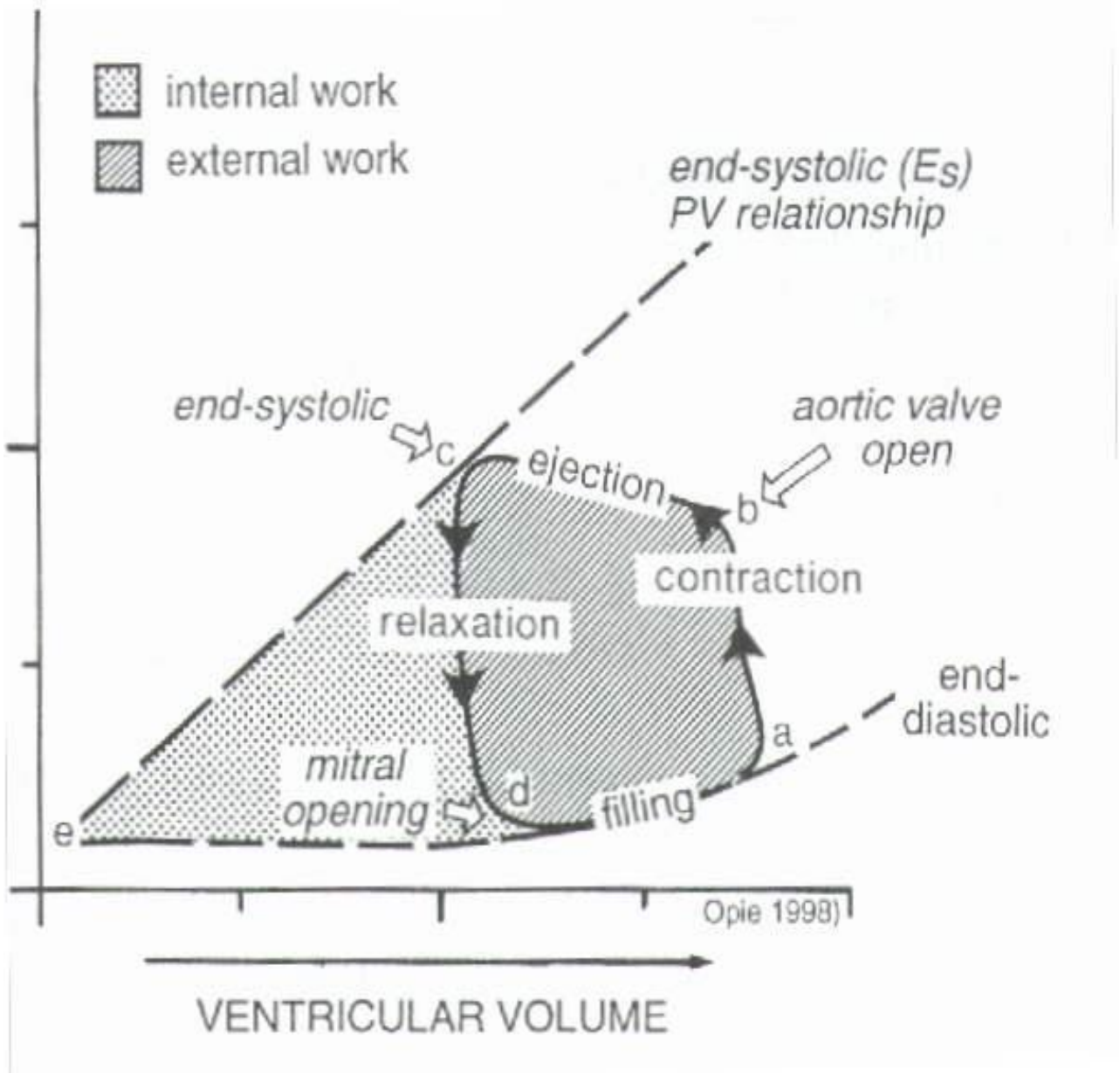
AT2R, angiotensin AT2 receptors; AVP, arginine vasopressin; DVMNc/Nc Amb, complex of the dorsoventromedial nucleus of the vagus and the nucleus ambiguous; MasR, Mas receptor of angiotensin- (1-7); Post Pit, the posterior pituitary; PVN, the paraventricular nucleus of the hypothalamus; RVLM, the rostral ventrolateral medulla of the brain; UNaV, sodium excretion

Interactions of the renin-angiotensin system (RAS) with the vasopressinergic system (VPS) in the regulation of blood pressure and body fluid volume.

- RAS and VPS closely cooperate in adjusting blood pressure to cardiovascular challenges. The cooperation takes place in the cardiovascular regions of the brain, in the cardiovascular and the sympathoadrenal systems, and in the kidney.
- Multiple synergistic and/or antagonistic actions of angiotensin peptides and vasopressin, as well as positive and negative feedbacks between RAS and VPS are involved in the regulation of cardiovascular functions.
- Dysregulated interaction of RAS and VPS in the brain and in the peripheral tissues results in excessive stimulation of angiotensin AT1 receptors (AT1R), and vasopressin V1a (V1aR) and V2 (V2R) receptors, and in the development of hypertension and/or body fluid retention.

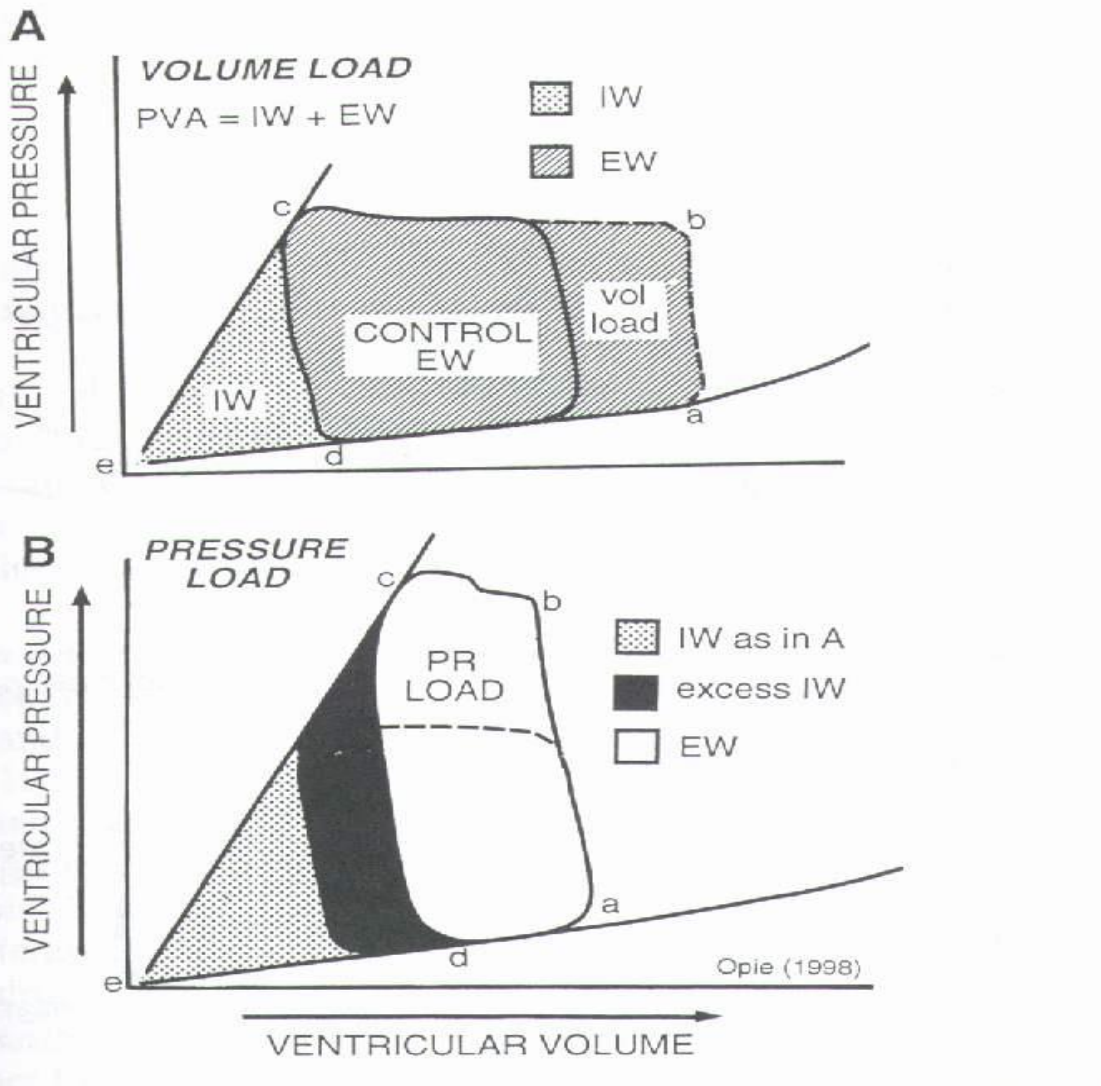
Curr Hypertens Rep. 2018; 20(3): 19.


Contractility
Preload
Afterload
+
+
-
Heart rate
Stroke volume
+
+
CARDIAC OUTPUT



Working diagram

- Sum of the external and internal work represents the total mechanical work of contraction and this is directly proportional to oxygen consumption of the myocardium.
- Pressure work of the heart consumes more oxygen than volume work, so that the effectivity of the former is lower than that of the latter.


A
VOLUME LOAD
PVA = IW + EW
IW
EW
VENTRICULAR PRESSURE
c
b
vol load
CONTROL EW
IW
a
e
d
B
PRESSURE LOAD
c
b
PR LOAD
IW as in A
excess IW
EW
a
d
e
Opie (1998)
VENTRICULAR VOLUME

Systolic dysfunction

- Impairment of the contraction of the left ventricle such that stroke volume (SV) is reduced for any given end-diastolic volum (EDV)
- Ejection fraction (EF) is reduced (below 40-45%)
- EF=SV/EDV

Systolic dysfunction-etiology

– **Dilated cardiomyopathy**

- Ischemic disease
  - Myocardial ischemia
  - Myocardial infarction

- Non-ischemic disease
  - Primary myocardium muscle dysfunction
  - Valvular abnormalities
  - Hypertension
  - Alcohol and drug-induced
  - Idiopathic

Diastolic dysfunction

- Ventricular filling rate and the extent of filling are reduced or a normal extent of filling is associated with an inappropriate rise in ventricular diastolic pressure.

Diastolic dysfunction-etiology

- **Hypertrophic cardiomyopathy**
- Gene mutation in sarcomere proteins
- Hypertension
- Myocardial ischemia and infarction

- **Restrictive cardiomyopathy**
- Amyloidosis
- Sarcoidosis

Compensatory mechanisms for decreased cardiac output

Increased SNS activity

Increase HR and SV which increases BP

Frank-Starling mechanism:

⇑ LVEDP = ⇑ SV

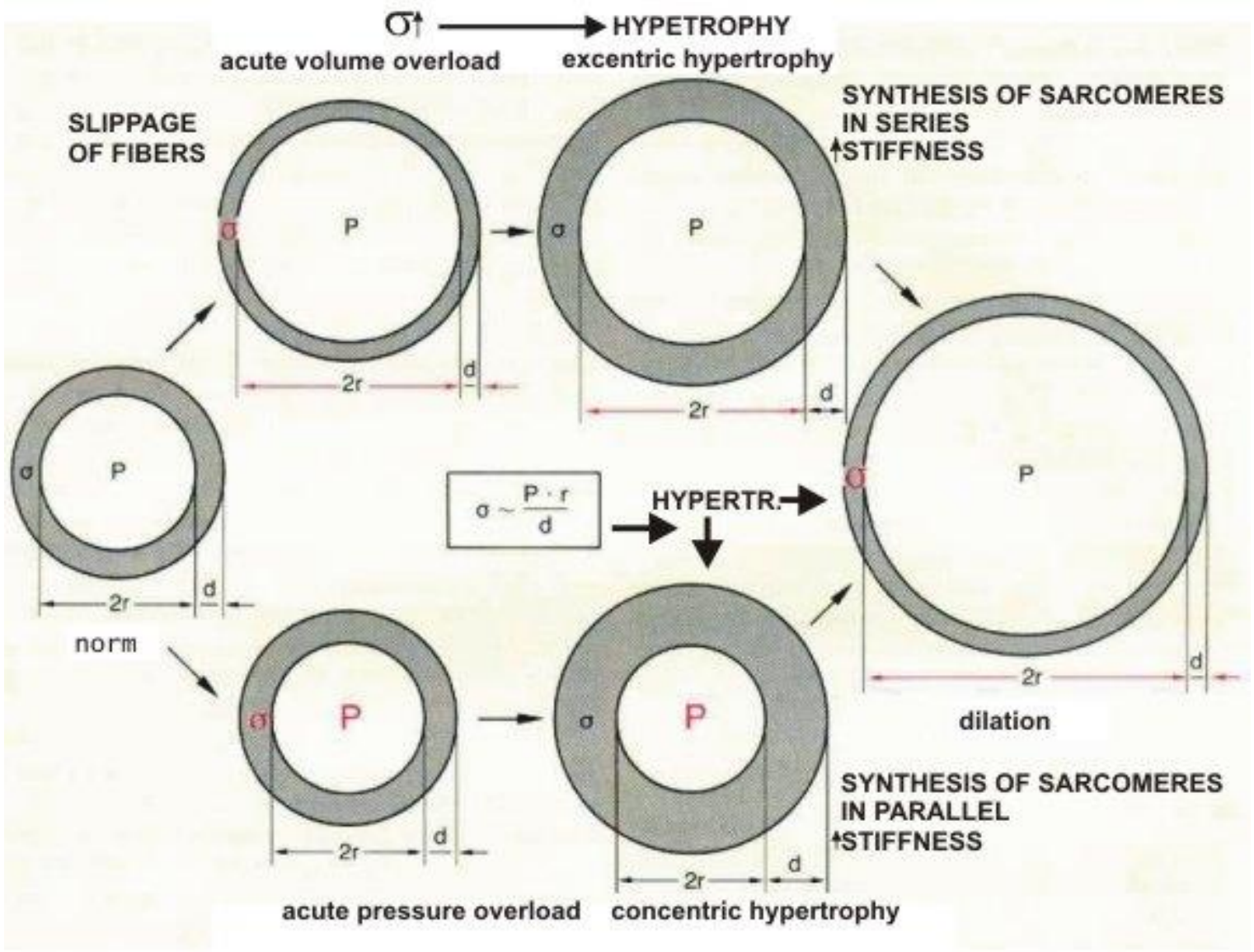
Activation of Renin-angiotensin-aldosterone system (RAAS)

Myocardial Remodeling

- Concentric hypertrophy
- Eccentric hypertrophy

Table 1 Summary of characteristics for the hypertrophy patterns (concentric and eccentric) and haemodynamic mechanisms influencing pathological and physiological left ventricular hypertrophy (LVH)

	Pathological LVH		Physiological LVH	
	Concentric	Eccentric	Concentric	Eccentric
Stimulating haemodynamic mechanism	Increased pressure (afterload)	Increased volume (preload)	Increased pressure (afterload)	Increased volume (preload)
Potential aetiology of stimulus	Hypertension, aortic stenosis	Valvular disease	Strength training	Long-term endurance exercise
Ventricle morphology	Parallel addition of new myofibrils (wall thickening), frequently with myocyte necrosis and increased fibrosis	Series addition of sarcomeres (wall dilation and thinning) frequently with myocyte necrosis	Parallel addition of new myofibrils (wall thickening) with increased capillary density	Series addition of new sarcomeres (chamber volume enlargement)
Ventricular mechanics	Diastolic dysfunction with stiffness and decreased contractility	Decreased contractility often associated with side-to-side slippage of myocytes	Normal or enhanced contractility and myocardial efficiency	Normal or enhanced contractility and myocardial efficiency
Ventricular function	Abnormal	Abnormal	Normal	Normal or supranormal
Potential to regress	No	No	Yes	Yes



Pathological hypertrophy of the myocardium

Cardiomyopathies classification

- Dilated (congestive)
- Hypertrophic
- Restrictive

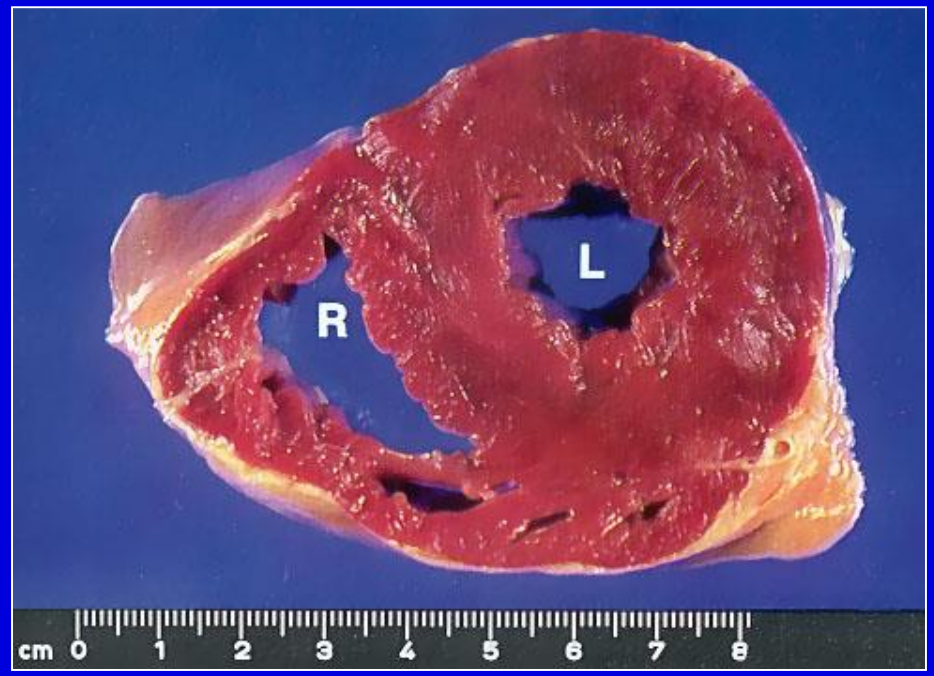
Cardiomyopathies dilated (congestive)

Ejection fraction-- <40%

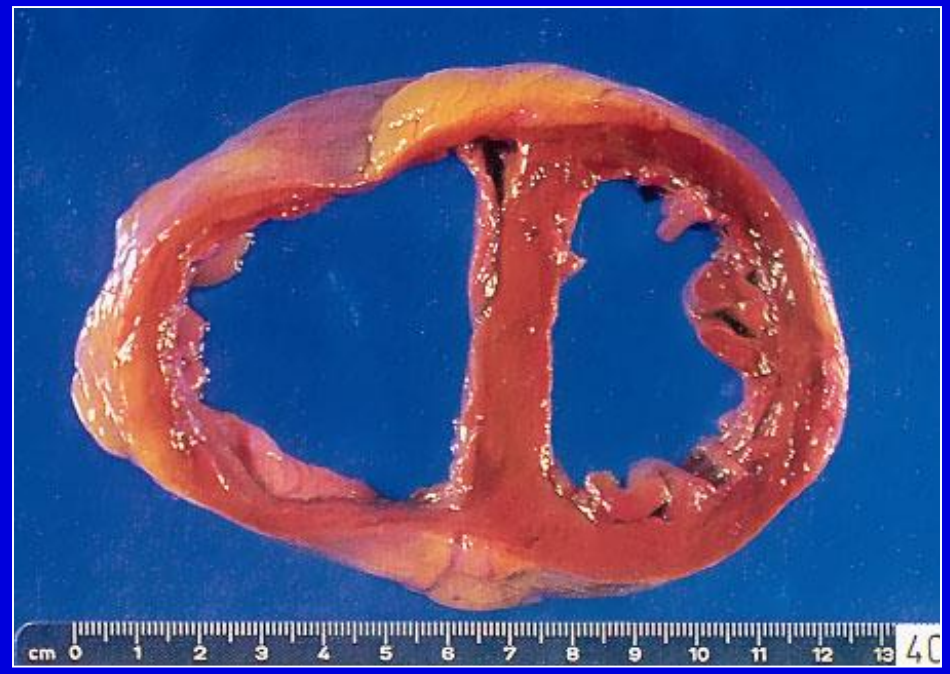
- Mechanism of failure--
  - Impairment of contractility (systolic dysfunction)
- Causes--
  - Idiopathic, alcohol, peripartum, genetic, myocarditis, hemochromatosis, chronic anemia, doxorubicin, sarcoidosis
- Indirect causes (not considered cardiomyopathies)--
  - Ischemic heart disease, valvular disease, congenital heart disease

Cross section of a normal heart, with right and left ventricles (R &L) having normal myocardial thickness and chamber size.

normal thickness LV 1.3-1.5 cm; RV 0.3-0.5 cm



Dilated cardiomyopathy (cross section), with both right and left ventricular chambers showing dilatation. The myocardium appears to be normal or slightly thin in this case.



Cardiomyopathies hypertrophic

- Ejection fraction-- 50-80%
- Mechanism of failure-- impairment of compliance (diastolic dysfunction)
- Causes-- idiopathic, genetic, Friedreich ataxia, storage diseases, DM mother
- Indirect causes– hypertesion heart, aortic stenosis

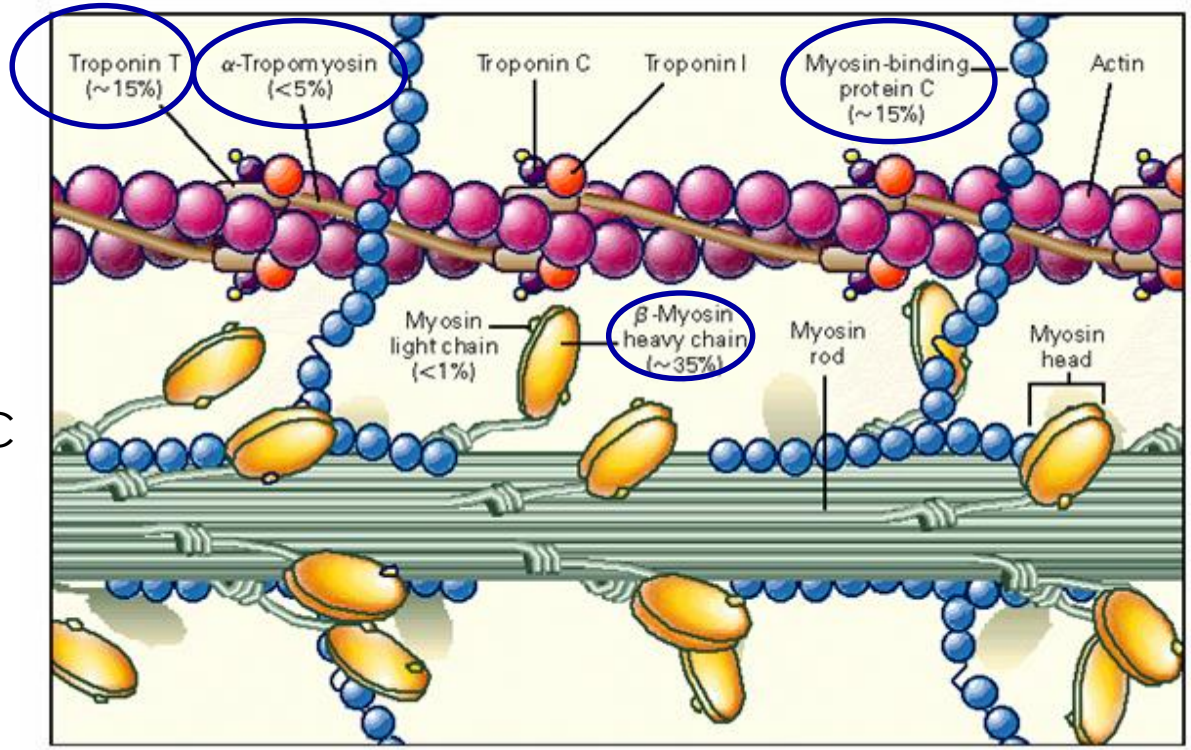
Etiology

Familial in ~ 55% of cases with autosomal dominant transmission

Mutations in one of 4 genes encoding proteins of cardiac sarcomere account for majority of familial cases

Remainder cases are spontaneous mutations

- β-MHC
- cardiac troponin T
- myosin binding protein C
- α-tropomyosin



Cardiomyopathies restrictive

- Ejection fraction-- 45-90%
- Mechanisms of failure- impairment of compliance (diastolic dysfuntion)
- Causes-- Idiopathic, amyloidosis, radiation-induced fibrosis
- Indirect causes-- pericardial constriction, heart tamponade

Restrictive (infiltrative) cardiomyopathy- etiology

- Infiltration of the myocardium with something other than muscle

- Stiff heart that cannot fill or pump well

  (Filling appears to be the main problem)

Etiologies

TABLE 4. CAUSES OF RESTRICTIVE CARDIOMYOPATHY.

Myocardial

Noninfiltrative disorders
- Idiopathic disease
- Familial disease
- Hypertrophy
- Scleroderma
- Diabetes mellitus
- Pseudoxanthoma elasticum

Infiltrative disorders
- Amyloidosis
- Sarcoidosis
- Gaucher's disease
- Hurler's syndrome
- Fatty infiltration

Storage disorders
- Hemochromatosis
- Fabry's disease
- Glycogen storage disease

Endomyocardial

Endomyocardial fibrosis
Hypereosinophilic (Löffler's) syndrome
Carcinoid syndrome
Metastatic cancer
Exposure to radiation
Toxins
Anthracycline (doxorubicin or daunorubicin)
Serotonin
Methysergide
Ergotamine
Mercurial agents
Busulfan

Heart failure

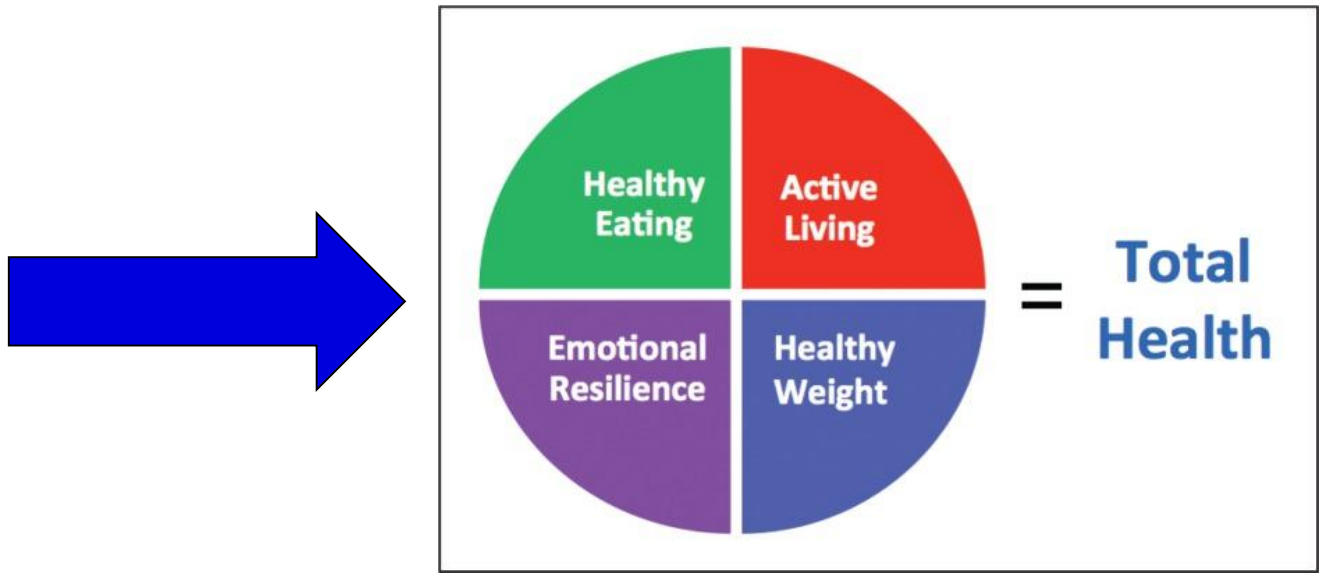
- A condition that exist when the heart is unable to pump sufficient blood volume to meet the metabolic needs of the body.
- Heart failure (HF) is a growing health problem and a major cause of mortality and morbidity in the world.

Heart failure

- The pathophysiological concept of HF has changed dramatically during the last decade with an increased understanding of the heart as an endocrine organ, leading to a multiorgan neurohormonal response and an activation of systemic inflammation.

Heart failure and gut

– Gut microbiota play critical physiological roles in the extraction of energy from our food and in the control of local or systemic immunity.



Curr Heart Fail Rep. 2016 Apr;13(2):103-9.
doi: 10.1007/s11897-016-0285-9.

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Gut microbiota

- The colon has two mucus layers, which is different from the small intestine with a single layer of mucus. The inner layer is a mucous lining that is closely linked to the intestinal epithelium, which provides a sterile environment. Outer layer is a mucous layer of varying thickness, composed of mucins, trefoil peptides, and secretory IgA. Although there is bidirectional effects between the microbiota and the host, its direct effects on intestinal epithelial cells are limited by mucus layers and antimicrobial peptides (AMPs) such as defensins and regenerating islet-derived 3 gamma (Reg3g).

Front Immunol. 2017; 8: 1674.

Gut microbiota

- Gut microbiota participates in food digestion through two main catabolic pathways.
- In the saccharolytic pathway, the gut microbiota is responsible for production of short-chain fatty acids, which are known to exert a protective action and a positive immune-modulating activity, guaranteeing a general healthy status.
- The second catabolic pathway is represented by protein fermentation, which also induces short-chain fatty acid formation and leads to other co-metabolites such as ammonia, amines, thiols, phenols and indoles, some of which are potentially toxic and are considered microbial uremic toxins.
- The microbiota exerts a fundamental influence on systemic immunity and metabolism. A healthy gut microbiota is largely responsible for the overall health of the host.

Curr Heart Fail Rep. 2016 Apr;13(2):103-9. doi: 10.1007/s11897-016-0285-9.

Gut microbiota

- The healthy and complete mucus layer only enables intestinal microbiota to attach to the mucus layer instead of the direct touch of intestinal epithelial cells. There are four phyla of microbiota in normal human intestine including *Bacteroidetes, Firmicutes, Actinobacteria*, and *Proteobacteria*, two of which (*Bacteroidetes* and *Firmicutes*) are dominant in the gut. In the intestinal tract of healthy people, *Firmicutes*, a community of Gram-positive bacteria, are classified into two main groups: *Bacilli* and *Clostridia* (primarily *Clostridium* cluster IV and *Clostridium* XIVa). The Gram-negative *Bacteroidetes* resides in the gut as one of the most abundant genera.

Front Immunol. 2017; 8: 1674.

Heart failure and gut

- Gut microbiota and microbiome compositions appear to be involved in the pathogenesis of diverse diseases such as obesity, diabetes, gastrointestinal diseases, cancer and cardiovascular (CV) diseases, including HF.

Curr Heart Fail Rep. 2016 Apr;13(2):103-9. doi: 10.1007/s11897-016-0285-9.F.

Heart failure and gut

- Trimethylamine N-oxide (TMAO), which is derived from gut microbiota produced metabolites of specific dietary nutrients, has emerged as a key contributor to CV disease pathogenesis.
- Changes in composition of gut microbiota, called dysbiosis, can contribute to higher levels of TMAO and the generation of uremic toxins, progressing to both HF and renal impairment.

Curr Heart Fail Rep. 2016 Apr;13(2):103-9.
doi: 10.1007/s11897-016-0285-9.

Types of heart failure

- **Systolic & Diastolic**
- **High Output Failure**
  - Pregnancy, anemia, thyreotoxicosis
- **Low Output Failure**
  - **Acute**
    - large MI, aortic valve dysfunction---
  - **Chronic**

Precipitating causes of heart failure

1. ischemia
2. change in diet, drugs or both
3. increased emotional or physical stress
4. cardiac arrhythmias (eg. atrial fib)
5. infection
6. concurrent illness
7. uncontrolled hypertension
8. new high output state (anemia, thyroid)
9. pulmonary embolism
10. mechanical disruption

Heart failure
Clinical Manifestations

Symptoms

dyspnea
fatigue
exertional limitation
weight gain
poor appetite
cough

Signs

tachycardia, tachypnea
edema
jugular venous distension
pulmonary rales
pleural effusion
hepato/splenomegaly
ascites
cardiomegaly
S3 gallop

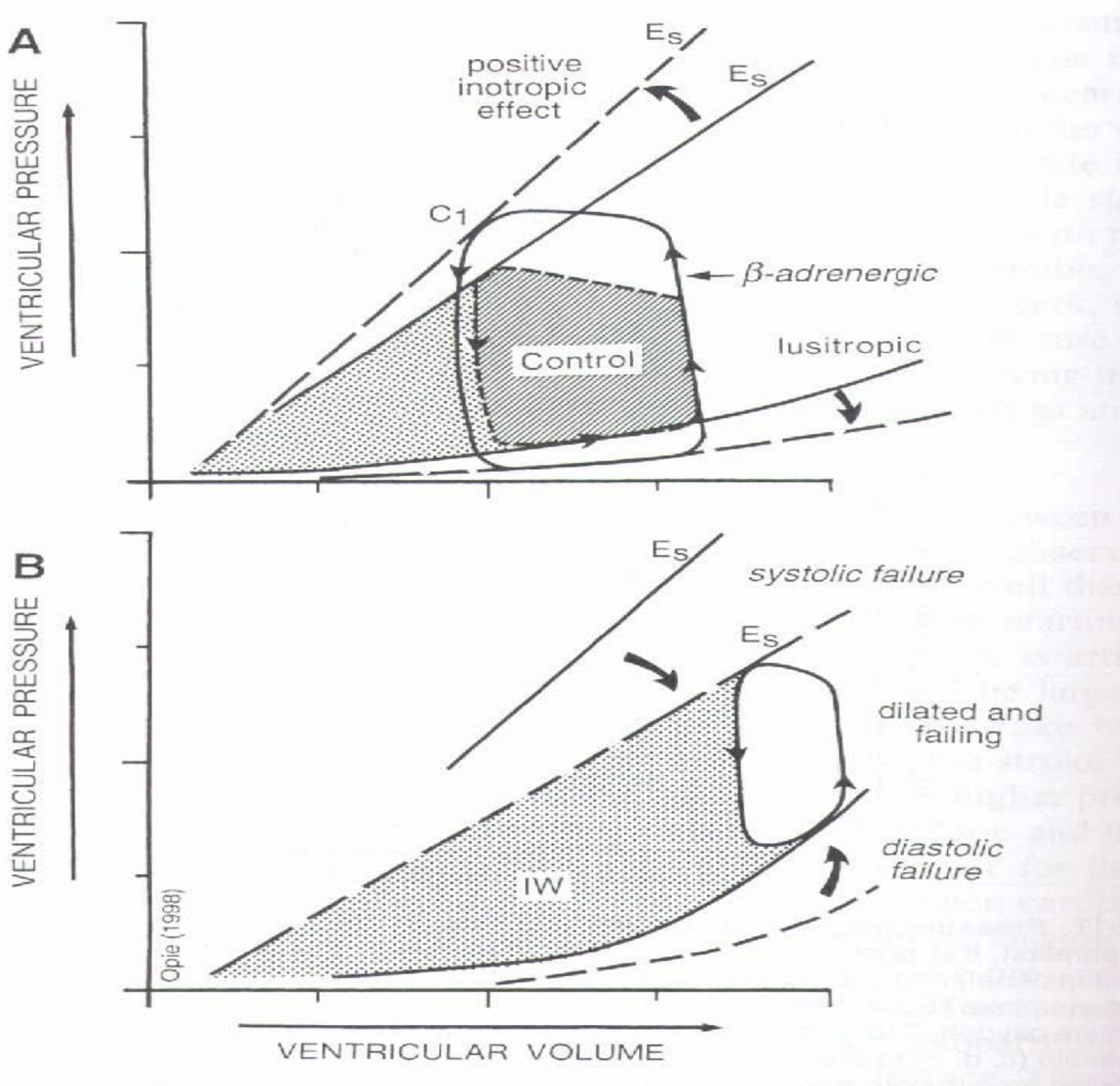
Left vs. Right Heart Failure

Left Heart Failure

pulmonary congestion

Right Heart Failure

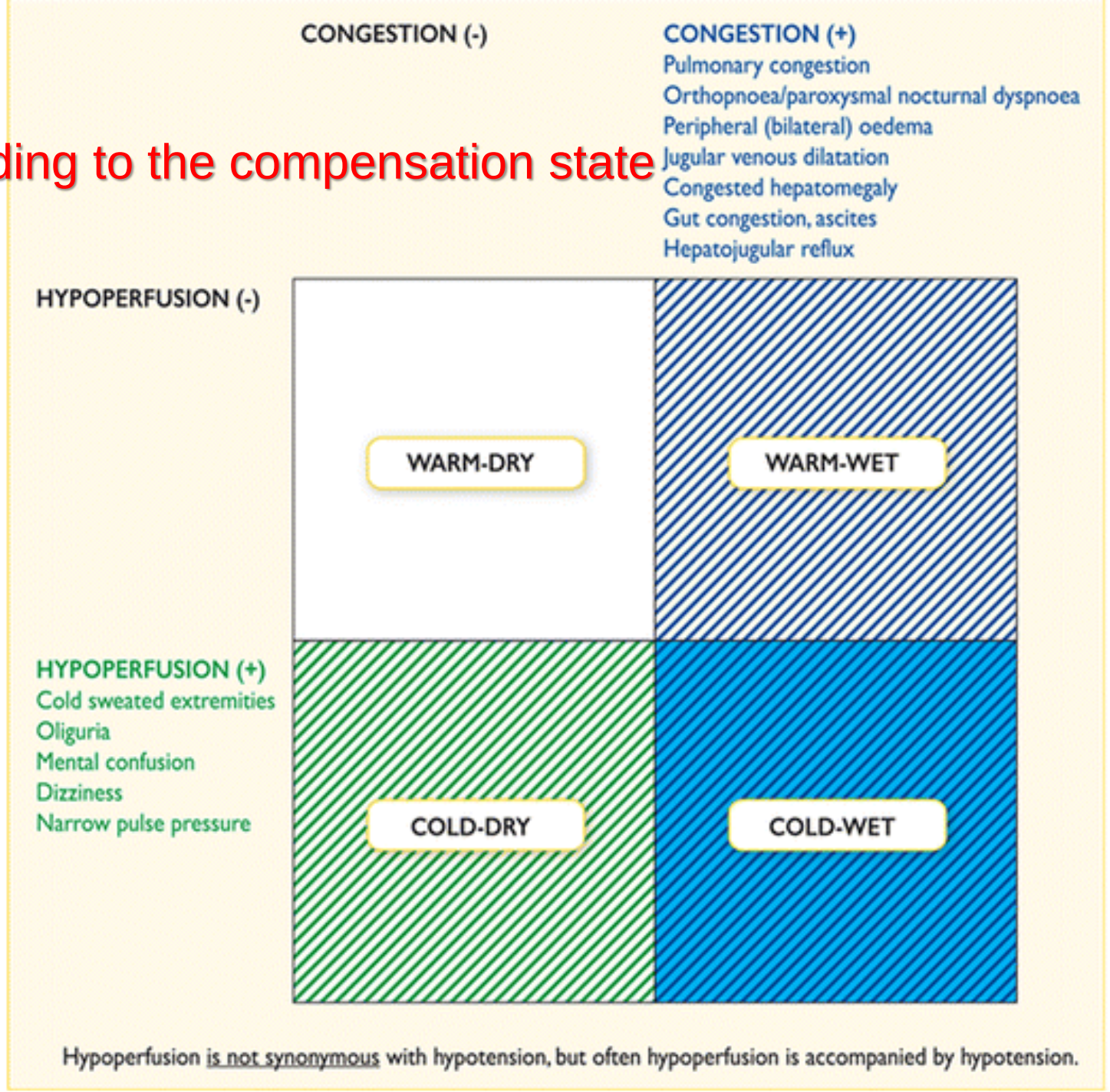
peripheral edema
sacral edema
elevated JVP
ascites
hepatomegaly
splenomegaly
pleural effusion


A
VENTRICULAR PRESSURE
positive
inotropic
effect
Es
Es
C1
β-adrenergic
Control
lusitropic
B
VENTRICULAR PRESSURE
Es
systolic failure
Es
dilated and
failing
diastolic
failure
IW
Opie (1998)
VENTRICULAR VOLUME

Compensatory Mechanisms in Heart Failure

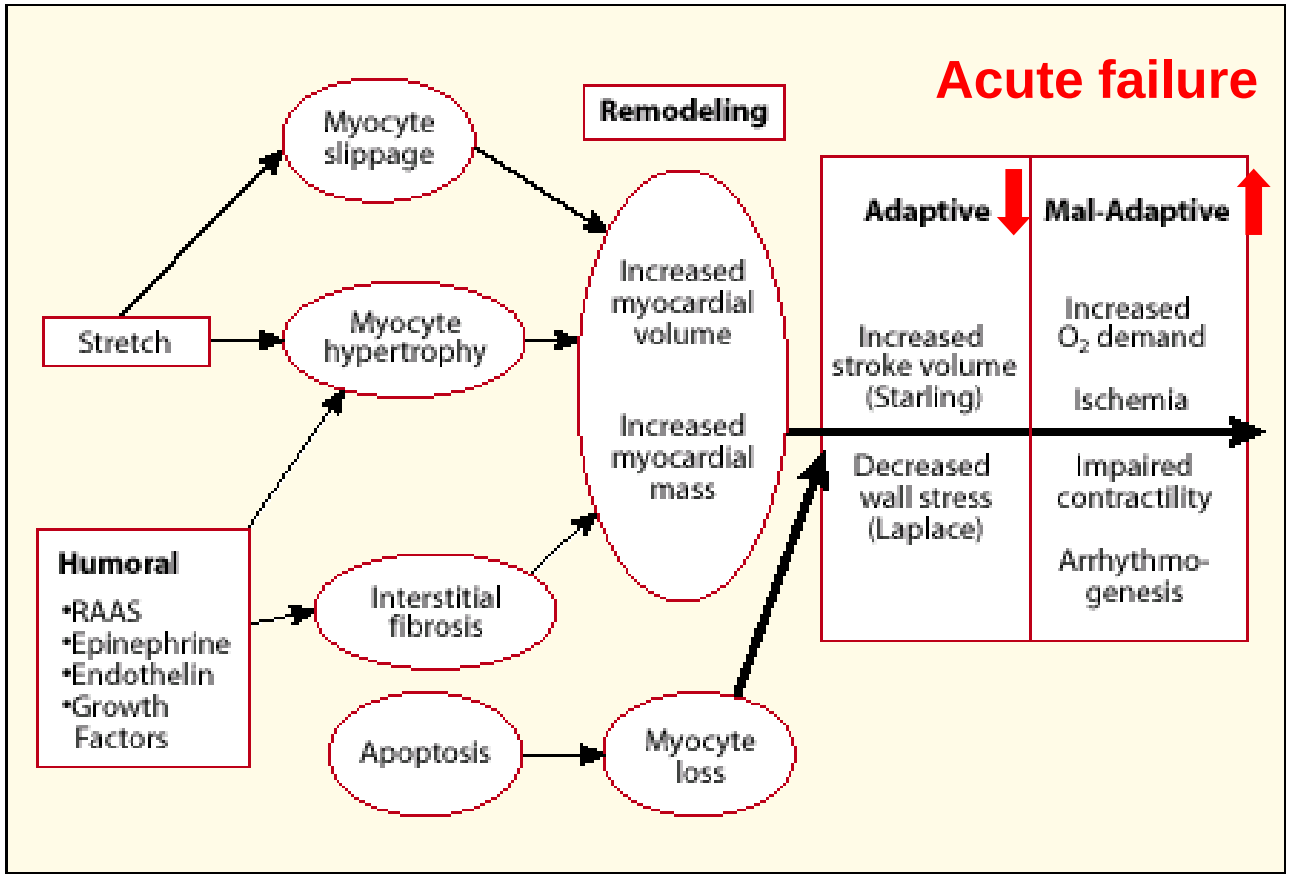
- increased preload
- increased sympathetic tone
- increased circulating catecholamines
- increased renin-angiotensin-aldosterone
- increased vasopressin (↑ CRH)
- increased atrial natriuretic factor

Heart failure according to the compensation state



Current Heart Failure Reports October 2017, Volume 14, Issue 5, pp 393–397

Pathophysiology of Acute Congestive Heart Failure



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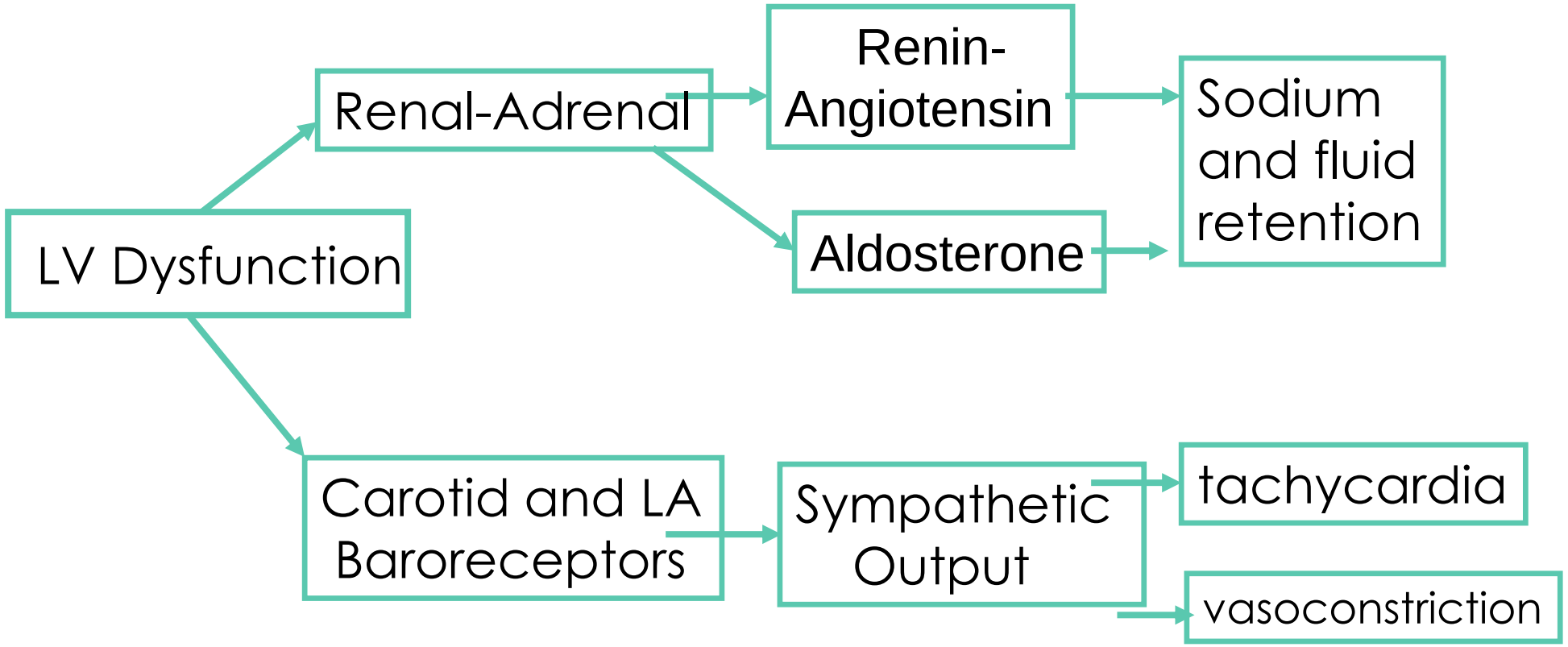
Pathophysiological response to heart failure



Neurohumoral mechanismus during chronic heart failure (CHF)

- Direct toxic effects of Norepinephrine (NE) and Angiotensin II (AII) (Arrhythmias, Apoptosis)
- Impaired diastolic filling
- Increased myocardial energy demand
- Increased pre- and after-load
- Platelet aggregation
- Desensitization to catecholamines (ischemia of adrenergic receptors)

Neurohormonal mechanism of CHF

- **Components**
- Endothelin
- Vasopressin (ADH)
- Natriuretic Peptides
- Endothelium-Derived Relaxing Factor
- RAAS
- SNS
- Cytokines
- HIF

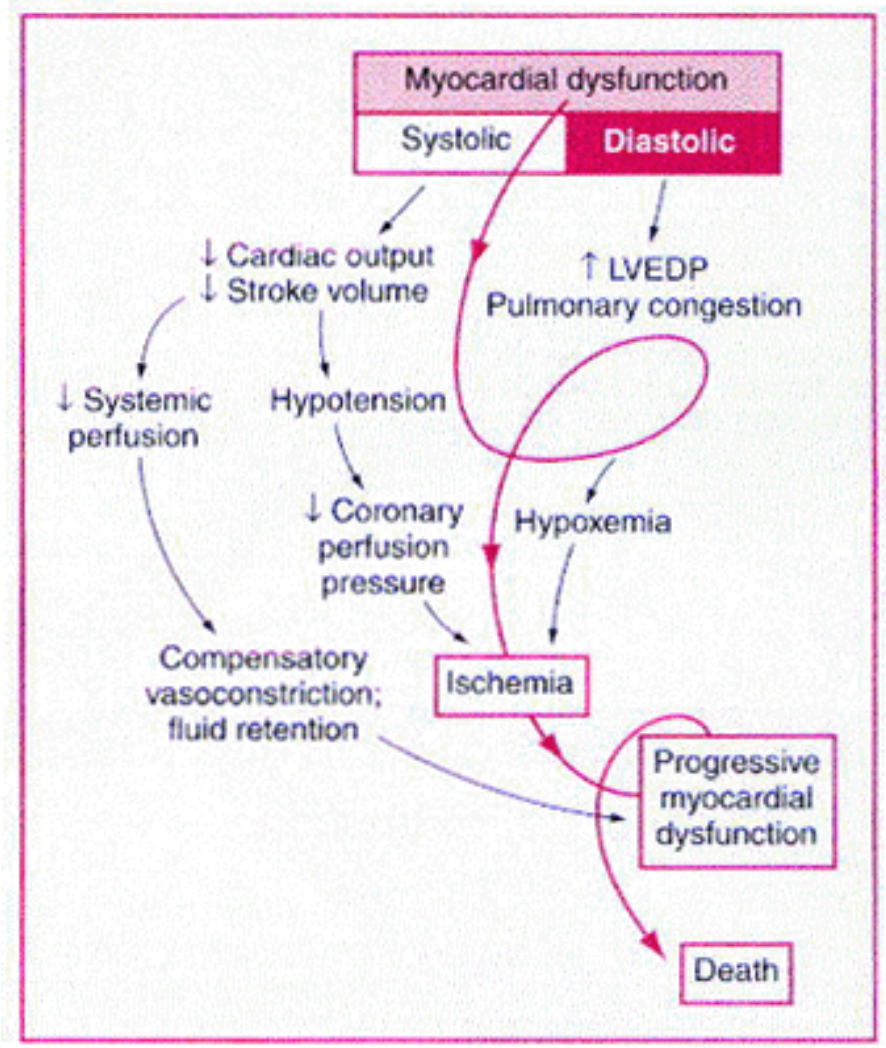
NYHA Functional Classification

- **Class I:** patients with cardiac disease but no limitation of physical activity
- **Class II:** ordinary activity causes fatigue, palpitations, dyspnea or anginal pain
- **Class III:** less than ordinary activity causes fatigue, palpitations, dyspnea or angina
- **Class IV:** symptoms even at rest

Stages of Heart Failure

- Stage A
  - High risk for development of heart failure
- Stage B
  - Structural heart disease
  - No symptoms of heart failure
- Stage C
  - Symptomatic heart failure
- Stage D
  - End-stage heart failure

The vicious circle in cardiogenic shock



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PREDICTORS OF MORTALITY IN PATIENTS WHO DEVELOP CS

- Age

Multiple studies have identified age as an independent predictor of poor outcomes.

- Clinical History and Risk Factors

Prior MI can lead to worse outcomes in those who develop CS, presumably because of a lower reserve to tolerate additional injury. Diabetes mellitus (DM) has been identified as an independent risk factor in some studies but not in others. Anoxic brain injury,higher body mass index, cerebrovascular disease, stroke, peripheral vascular disease, history of angina, prior percutaneous coronary intervention (PCI), dialysis, and white race are other risk factors for mortality. Cardiac arrest, as expected, is a significant risk factor for mortality.

Cardiol Rev. 2018 Sep-Oct; 26(5): 255–266.

PREDICTORS OF MORTALITY IN PATIENTS WHO DEVELOP CS

- CardiacTiming of Shock Development

Although the influence of timing of shock development may differ due to changes in management approaches, most patients develop CS once admitted, therefore, providing an opportunity for early diagnosis and management.

- Duration of Shock

The duration of shock is important because a longer time in shock can lead to systemic inflammatory response failure and multisystem organ failure, after which time the benefit of treatment (revascularization or mechanical support) becomes more limited.

Cardiol Rev. 2018 Sep-Oct; 26(5): 255–266.

PREDICTORS OF MORTALITY IN PATIENTS WHO DEVELOP CS

- Hemodynamic Parameters

The shock index (SI), defined as HR/SBP, is a simple measure with significant prognostic significance. In addition to macrocirculatory hemodynamic disturbances, patients with shock can also have microcirculatory dysfunction.

- STEMI Versus Non-STEMI

Cardiogenic shock occurs in a smaller proportion of patients with non-STEMI (NSTEMI) compared to those with STEMI, but mortality is high in either condition once shock develops. The NSTEMI group was more likely to develop shock after hospitalization, whereas the STEMI group was more likely to present with shock. The NSTEMI group also had more 3-vessel disease and lower LVEF. Mortality risk was higher in NSTEMI versus STEMI (40.8 versus 33.1%).

Cardiol Rev. 2018 Sep-Oct; 26(5): 255–266.

PREDICTORS OF MORTALITY IN PATIENTS WHO DEVELOP CS

- Metabolic and Laboratory Derangements

Hyperlactatemia can reflect impaired tissue perfusion, intracellular metabolic derangements, and hepatic dysfunction.

- Renal Failure

Acute renal failure is an important predictor of mortality, both as a marker of the severity of shock, and also as a direct mediator of poor outcomes.

- Inflammatory Response

There is increasing recognition that CS is not simply a low perfusion state. Particularly with severe or late-stage shock, there is systemic inflammation associated with a low systemic vascular resistance and vasopressor resistance.

- Integrated Multisystem Scores

Further supporting the influence of the systemic inflammatory response in outcomes, several investigators have found that risk scores initially created for sepsis or medical intensive care unit patients have prognostic value in MI-CS patients.

Cardiol Rev. 2018 Sep-Oct; 26(5): 255–266.

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