Heart Failure

Andrew Ying-Siu Lee, MD,PhD.

Cardiac cycle:

1. ***Left ventricular contraction:***(= isovolumic contraction; maximal ejection)

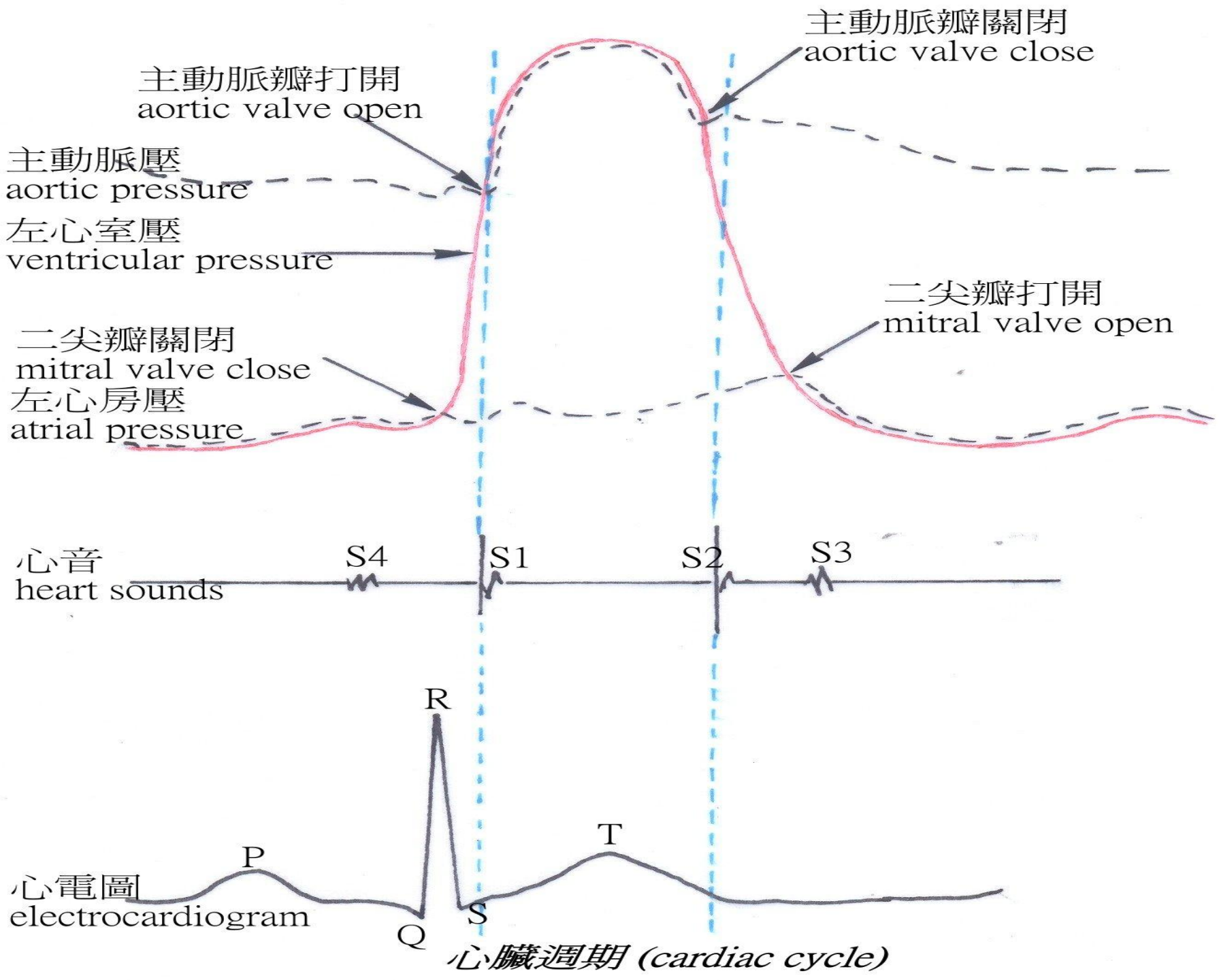
   when mitral valve close and aortic valve open, S1 heart sound, R wave

2. ***Left ventricular relaxation:***(= reduced ejection; isovolumic relaxation)

   when mitral valve open and aortic valve close, S2 heart sound, T wave

3. ***Left ventricular filling:***(= rapid filling; slow filling or diastasis; atrial systole)

   S3 heart sound



心臟週期 (cardiac cycle)

Factors controlling myocardial function:

1. ***Preload:*** estimated by pulmonary capillary wedge pressure
2. ***Afterload:*** estimated by systolic arterial pressure (in absence of aortic stenosis)
3. ***Myocardial contractility:*** estimated by left ventricular ejection fraction
4. Heart rate and rhythm

Heart failure = ***syndrome*** characterized by dyspnea, fatigue, sodium water retenton (congestion and edema), caused by ***heart abnormality*** (eg. myocardial disease, valvular disease, pericardial disease, arrhythmias) that impair pumping action of heart (reduced cardiac output) to meet metabolic need of body.

= principal complication of virtually all forms of heart diseases

- Acute heart failure syndromes
- Heart failure with reduced ejection fraction (= systolic heart failure)
- Heart failure with normal ejection fraction (diastolic heart failure)

Pathophysiology of heart failure

cardiac event

(eg. myocardial infarction (acute), pressure or volume overloading (chronic), hereditary (genetic cardiomyopathies), which damage the heart thereby loss or dysfunction of myocytes)

neurohormonal activation

- adaptive responses
- maladaptive responses

ventricular remodeling

oxidative stress,

endothelin, nitric oxide,inflammatory mediators, growth factors etc

heart failure

- ***Adaptive responses (short-term compensatory benefits) :-***

  Frank-Starling mechanism → increased preload to substain heart function

  sympathetic nervous system activation → increase heart rate and contractility, activation of renin-angiotensin-aldosterone system (RAAS)

  RAAS activation → restore circulating volume maintaining perfusion of vital organs

  release natriuretic peptides → increase peripheral vasodilation, natriuresis ad diuresis, inhibit sympathetic and RAAS activation

- ***Maladaptive responses (long-term decompensatory harms):-***

blunted Frank-Starling mechanism → less cardiac reserve

excessive maladaptive activation of sympathetic and RAAS → heart hypertrophy (ventricular remodeling) → apoptosis and necosis → heart failure

increase collagen deposit in interstitial matrix

increase release of neurohormones, peptides and cytokines eg. vasopressin, BNP, endothelin, TNF

abnormal circulatory homeostasis (eg. Increase vascular tone, redistribution of blood flow, reduced cardiac output, impair reflexes) → multiorgan failure

Renin-Angiotensin System (RAS)

- ***Systemic RAS:-***

liver secrete → angiotensinogen

Kidney (juxtaglomerular cells) secrete renin →

angiotensin I

Lung endothelial cells secrete angiotensin converting enzyme (ACE)→

angiotensin II (in circulation)

AT1 **(angiotensin type 1 receptor)**

Aldosterone secretion, Sodium & water retention, Vasoconstriction, Increase contractility, hypertrophy, inflammatory & oxidative stress, endothelial dysfunction,sympathetic Activation, diminished thrombolysis)

AT2

bradykinin, vasodilation, remodeling, antiproliferative antifibrotic effects, cardioprotective

AT3

(observed in cell lines)

AT4

vasorelaxation, plasminogen activation inhibitors

- ***Local RAS:-***

  - heart, brain, vessels, kidney, eyes, pancreas, reproductive organ etc.

  - express all components of RAS de novo and synthesize angiotensin II locally at tissue sites

  - cardiac RAS and the intracellular cardiac RAS

Ventricular remodeling

= genomic expression resulting in molecular, cellular and interstitial changes that are manifested clinically as changes in size, shape and function of heart after cardiac injury.

- Alternations in heart cell biology eg. excitation contraction coupling, myocardial gene expression, B adrenergic desensitization etc.
- Alternations in myocardium eg. loss of heart cell (necrosis, apoptosis), alternations in extracellular matrix, fibrosis
- Alternations in ventricular chambers eg dilatation,thinning
- Inadequate growth of myocardial microvasculature → decrease coronary reserve
- “Reverse remodeling” → myocardial recovery

Oxidative Stress

- Aerobic metabolism → reactive oxygen species (ROS) eg. $O2^-$ (=free radicals, react with organic molecules including lipids, nucleic acid, protein, leading to cellular *dysfunction)*
- Body's antioxidant defense system = antioxidant enzymes eg. superoxide dismutases, glutathione peroxidase, vitamin antioxidants
- Oxidative stress = production of ROS > antioxidant defense system

Causes of heart failure

1. ***Underlying causes:*** **hypertension, congenital or acquired disorders of peripheral and coronary vessels, pericardium, myocardium, valves.**
2. ***Functional causes:*** **biochemical and physiological**
3. ***Precipitating causes:*** **incompliance, arrhythmias, myocardial ischemia or infarction, infection, pulmonary embolism, physical, emotional and environmental stress, inflammation, systemic illness, high output failure (eg anemia, hyperthyroidism) etc.**

Manifestation of heart failure

1. **respiratory distress: cough, dyspnea, exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, dyspnea at rest, acute pulmonary edema**
2. **exercise intolerance**
3. **other symptoms: fatigue and weakness, nocturia, confusion, anxiety, headache, insomnia, cyanosis, weak pulse, hypotension, cold extremities, pulmonary rales, hepatomegaly, splenomegaly, pedal edema, pleural effusion, ascite, cardiomegaly, gallop heart sounds etc.**

Framingham criteria for heart failure

Major Criteria:

Paroxysmal nocturnal dyspnea
neck vein distention
pulmonary rales
radiographic cardiomegaly
acute pulmonary edema
S3 heart sound

Minor Criteria:

pedal edema
nocturnal cough
exertional dyspnea
hepatomegaly
pleural effusion
tachycardia (>120 beats/min)

Diagnosis of heart failure require 2 major, or 1 major plus 2 minor criteria

New York Heart Association Functional classification of heart failure

Class I : asymptomatic with ordinary activity

II : ordinary activity results in fatigue, palpitation, dyspnea or angina

III: less than ordinary activity results in symptoms

IV: symptomatic at rest

American Heart Association Classification of Heart Failure

Stage A : high risk for heart failure but without structural heart disease or symptoms of heart failure eg. hypertension, diabetes

Stage B : structural heart disease but without signs or symptoms of heart failure eg. previous myocardial infarction, left ventricular hypertrophy, valvular disease

Stage C : structural heart disease with prior or current symptoms of heart failure

Stage D : refractory heart failure requiring specialized interventions

New York Heart Asso	***ACC/AHA (American heart asso)***
III, IV	D, refractory end-stage heart failure
I , II	C, symptomatic heart failure
	B, aysmptomatic heart failure, with structural and functional abnormalities eg. previous MI, LV dysfunction, valvular dysfunction
	A, risk factors for heart failure, eg. Hypertension, coronary artery ds,diabetes, valvular heart ds.

European Society of Cardiology diagnostic criteria for heart failure

- Symptoms of heart failure
- Objective evidence of cardiac dysfunction (eg. cardiac echo LVEF, diastolic indices)
- Symptom improvement by antifailure drugs

Diastolic heart failure

- Heart failure with preserved left ventricular ejection fraction (systolic heart failure = decreased contractility; diastolic heart failure = impaired relaxation)
- Common in elderly female, 50% of heart failure patients. Mortality similar to systolic heart failure
- Symptoms and treatment similar to systolic heart failure

Biomarkers in heart failure

- ***Natriuretic peptides:-***
  - 1. Atrial natriuretic peptide (ANP, synthesized in atria); 2. B-type natriuretic peptide (BNP, due to left ventricular pressure or volume overload → myocardial wall stress); 3. C-type natriuretic peptide (product of endothelial cells)

  - increased in heart failure, acute coronary syndrome, hyperdynamic states (eg. sepsis, cirrhosis, hyperthyroidism, renal dysfunction etc)

  - bind to various tissues inducing vasodilation, natriuresis and diuresis, inhibit sympathetic and RAS activation.

- ***Adrenomedullin, inflammatory markers (CRP, tumor necrosis factor, interleukins)***

Prognosis of heart failure

- Overall 5-year mortality 50%
- 1-year mortality for severe heart failure 35-40%

Mortality	1 year	5 year
Class II-III	52%	34%
Class IV	66%	82%

Severity and prognostic factors in heart failure patients

Clinical: **age, male, coronary artery disease, New York Heart Association class, exercise capacity, heart rate at rest, systolic arterial pressure, cardiac cachexia, history of hospitalization**

Hemodynamic: **ejection fraction, cardiac output**

Biochemical: **plasma norepinephrine, renin, vasopressin, atrial and brain natriuretic peptides, endothelin, interleukin, sodium(hyponatremia signifies advanced heart failure and fluid retention), potassium, magnesium**

Electrophysiological: **LBBB, wide QRS, arrhythmias**

Treatment of heart failure

- Avoid risk factors (eg. Hypertension, diabetes, hyperlipidemia, coronary artery disease)
- Patient and family education (eg. Lifestyle modification, appropriate exercise, psychological support)
- Identify and treat causes of heart failure

Treatment of heart failure

Class IV : triple therapy (digoxin, ACEI, diuretic) for life

Class II-III : triple therapy

Class I : ACEI (if ejection fraction <40%)

Diuretics:

- reduce preload
- improve congestive symptoms and slow remodeling by reducing left ventricular filling pressure and wall stress

Vasodilators: nitrate, amlodipine, etc.

Inotropic agents:

1. ***Digitalis (digoxin):***

mechanism of action: inhibit Na^+,K^+-ATPase sodium pump → increase intracellular Na^+ → increase intracellular Ca^{++} → increase systolic function

Side effects: when serum level > 2 ng/ml

- disturbances in cardiac impulse formation, conduction or both (hallmark of digitalis toxicity) eg. ectopic beats,heart block,bradycardia
- gastrointestinal : anorexia, nausea, vomiting, diarrhea
- neurologic : malaise, fatigue, confusion, insomnia, vertigo, colored vision (green or yellow halos around lights)
- blood : high digoxin level, hypokalemia

2. Adrenergic agonists (most powerful way to increase contractility):

Dobutamine:

mechanism of action: stimulate beta 1 and 2 adrenergic receptors → increase cardiac output and decrease systemic vascular resistance

side effects: arrhythmias, hypotension

Dopamine:

mechanism of action: norepinephrine precursor, stimulate dopamine D1 and 2 receptors with low affinity for adrenergic receptors

side effects: arrhythmias

Neurohormonal inhibitors :-

Angiotensin-converting enzyme inhibitors (ACEI)

Angiotensin II receptor blocking agents (ARB)

Aldosterone antagonists (eg spironolactone)

Beta-adrenergic receptor blocking agents (for all patients with stable mild, moderate, severe heart failure)

Antiarrhythmic agents:

for symptomatic arrhythmias or for rapid atrial fibrillation

Anticoagulation:

for atrial fibrillation with left ventricular thrombus, or history of thromboembolic events

Statins:

- inhibit oxidative stress
- upregulate endothelial nitric oxide synthetase in endothelium and heart → increase angiogenesis and myocardial perfusion, decrease myocardial apoptosis, improve endothelial and cardiac function
- improve survival in patients with ischemic and non-ischemic heart failure

Device Therapy:

intraaortic balloon counterpulsation

ultrafiltration - for severe heart failure refractory to conventional therapy

resynchronization (CRT, biventricular pacing)

implantable defibrillation

ventricular assist devices

artificial heart

heart transplantation

Cardiac Resynchronization Therapy (CRT)

- **Heart failure → electrical conduction delay → discoordinate contraction (dysynchrony) → maladaptive (molecular, cellular, electrical) ventricular remodeling → reduce heart function**
- **Ventricular dysynchrony = abnormal ventricular contraction resulting in paradoxical septal wall motion, reduced left ventricular contractility, suboptimal ventricular filling → reduced stroke volume → heart failure**
- **Presence of ventricular dyssynchrony (=QRS prolongation ≥ 120 ms) associated with increased morbidity and mortality in heart failure**
- **CRT → electrical activation of heart → mechanical activation of heart via excitation-contraction coupling**

- ***Inclusion criteria of CRT*** **:-**
  1. **NYHA class III-IV heart failure (symptomatic despite medical treatment)**
  2. **Sinus rhythm**
  3. **QRS duration ≥ 120 ms**
  4. **LVEF ≤ 35%**

- **CRT → reverse remodeling of failing heart making heart smaller and stronger**

- **Nonrespond to CRT about 25-35%**

- **CRT improves quality of life, functional status, exercise capacity, cardiac structure and function, and reduces morbidity and mortality**