Pathophysiology of HEART FAILURE

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The prognosis is as bad as for many cancers

One year survival rate %

- Skin
- Breast
- Uterus
- Bladder
- Prostate
- Non-Hodgkins Lymphoma
- Colon
- Heart failure
- Ovary
- Kidney
- Leukaemia
- Stomach
- Oesophagus
- Lung
- Pancreas

British Heart Foundation, 2002
What do we mean by “heart failure”? 

- Right v’s Left … or biventricular
- Acute or chronic?
- Systolic or diastolic?
- Related to vascular disease .. or valvular disease .. or metabolic disease ........
What is heart failure?

- A “syndrome” = set of signs and symptoms that appear together and characterize a disease or medical condition/abnormality

- Multiple causes … and the “diagnosis” of Heart Failure demands that a cause be identified!
Definition of heart failure

“Heart failure is a complex syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the heart to function as a pump to support a physiological circulation. This syndrome is associated with a characteristic pattern of haemodynamic, renal and neurohormonal responses”
Causes of Heart Failure

• Ischaemic heart disease – commonest cause
• Hypertension
• Cardiomyopathies
  - *Dilated* cardiomyopathies - infection (viral/bacterial), alcohol, drugs, pregnancy, idiopathic
  - *Hypertrophic* cardiomyopathy (HOCM)
  - *Restrictive* cardiomyopathy (amyloid)
• Valvular heart disease
• Arrythmias (Atrial fibrillation)
• Metabolic (Thyrotoxicosis)
• Pericardial disease
Coronary artery disease is the leading cause of heart failure

- Coronary artery disease (52%)
- Hypertension alone (4%)
- Valve disease (10%)
- Alcohol (4%)
- AF alone (3%)
- Other (5%)
- Idiopathic (no CAD) (13%)
- Undetermined (no angiographic data) (10%)

Full investigation (including coronary angiography) in new patients aged <75 in a UK population-based study

“The good news is, you have a healthy heart. The bad news is, it’s in someone else’s chest right now.”
Basic Physiology of the Heart
What stops us from doing better?
Overview - Circulation

Lung

Right atrium

Left atrium

Ventricles

Systemic capillaries
Cardiac cycle

diastole  systole
Basic Physiology of the Heart
“STATISTICS”

- Cardiac output – 5 litres per minute
- Stroke volume – 75 ml per beat
- LV end systolic volume - 75 ml
- LV end diastolic volume - 150 ml
- Ejection fraction 50% or more
- Weight 330 gm
- 42,050,000 cardiac cycles per year
Cardiac Output

Stroke volume \times \text{Heart rate}
Physiological factors influencing CARDIAC OUTPUT

- Heart rate
- LV preload - venous capacitance (stretch on the ventricle muscle fibres influences strength of contraction)
- LV afterload (systemic vascular resistance to LV contraction)
- Myocardial contractility
LV Preload
Frank-Starling law of the heart

- The Frank-Starling law of the heart (also known as Starling's law or the Frank-Starling mechanism) states that the more the ventricle is filled with blood during diastole (end-diastolic volume), the greater the volume of ejected blood will be during the resulting systolic contraction (stroke volume).

- an intrinsic adaptive response which serves to adjust each ventricular output to its inflow by increasing the force of contraction of the myocardium proportionally to any increase in the length of the muscle fibers.
Frank-Starling law

Cardiac output vs. end-diastolic pressure
LV Afterload
Heart, arteries and arterioles

Heart (cardiac output)  Arteries (blood pressure)  Arterioles ( peripheral resistance)
The control of peripheral arteriolar resistance

Vasodilating systems
- Parasympathetic
- Kallikrein-kinin system
- Prostaglandins
- Endothelial derived relaxant factor
- Atrial natriuretic factor

Vasoconstricting systems
- Sympathetic
- Calcium
- Local renin-angiotensin systems
- Circulating renin-angiotensin system
- Endothelin
- Ouabain
- ? Vasopressin

Vascular growth factors
- Insulin like growth factor
- Growth hormone
- Parathyroid hormone
- Tissue oncogenes
Myocardial contractility
Figure 3 - Schematic representation of the ventricular preload/stroke volume relationship of a normal and a failing ventricle. The increase in stroke volume (ΔSV) as a result of cardiac preload increase (ΔP) depends on ventricular function shown by the slope of the curve (dotted line); assessing baseline preload is not useful in predicting ΔSV.
Developments in our understanding of the pathophysiology of heart failure have been essential for recent therapeutic advances in this area.
Left ventricular systolic dysfunction
Apical 4 Chamber

- Apex of heart
- Septum
- Tricuspid valve
- Aortic valve
- Right atrium
- Interatrial septum
- Mitral valve
- Left atrium
- Papillary muscles
Parasternal Long Axis
Commonest cause of LVSD?....

Ischaemic heart disease
SCHEMATIC ILLUSTRATION OF LV REMODELING FOLLOWING MYOCARDIAL INJURY

Stage 1

Early infarct expansion, myocyte thinning and slippage, and disruption of extracellular matrix

Stage 2

Stretching and thinning of non-infarcted myocardial segments, adaptive myocyte hypertrophy, extracellular collagen growth, and fibrosis

There is an increased end-systolic and end-diastolic volume, and altered shape and geometry
A  Ventricular remodeling after acute infarction

- Initial infarct
- Expansion of infarct (hours to days)
- Global remodeling (days to months)

B  Ventricular remodeling in diastolic and systolic heart failure

- Normal heart
- Hypertrophied heart (diastolic heart failure)
- Dilated heart (systolic heart failure)
Process of ventricular remodelling

Myocardial infarction

Reduced systolic function

Increased left ventricular end diastolic volume and pressure

Increased wall stress

Non-infarcted segment: regional hypertrophy

Infarcted segment: infarct expansion

Increased cardiac output

Neurohormonal activation

Heart failure

Death

Heart Failure
Compensatory mechanisms

- Increased heart rate
- Increased peripheral resistance
- Vasoconstriction
- Redistribution of fluid in circulation (oedema)
- Alteration in heart structure (LVH)
Neurohormonal Regulation of Heart Function.

- Sympathetic Nervous System
- Renin-Angiotensin-Aldosterone system
- Natriuretic hormones
- Anti-diuretic hormone
- Endothelin
Neurohormonal Activation

Poor ventricular function

Decreased cardiac output

**NEUROHORMONAL RESPONSE**

Sympathetic activation

RAS activation

**Vasoconstriction:** increased sympathetic tone, angiotensin II, endothelins, impaired NO release

**Sodium and fluid retention:** increased ADH and aldosterone release

**COMPENSATORY SUPPORT**
Neurohormonal Activation

Poor ventricular function

Decreased cardiac output

**NEUROHORMONAL RESPONSE**

Sympathetic activation

RAS activation

**Vasoconstriction:** increased sympathetic tone, angiotensin II, endothelins, impaired NO release

**Sodium and fluid retention:** increased ADH and aldosterone release

Initial compensatory support

Further stress on ventricular wall and dilatation leading to worsening of ventricular function
VICIOUS CYCLE OF HEART FAILURE

- Impaired LV function
- Outflow resistance
- Systemic vascular resistance
- Neurohormonal activation
- Cardiac output and stroke volume
- Ventricular dilatation
- Increased wall stress
- Renal perfusion
- Sodium/water retention
- Blood volume
- Filling pressure
- Preload

Sympathetic
Renin-Angiotensin-Aldosterone
Vasopressin
Neurohormonal Regulation of Heart Function.

Sympathetic Nervous System
Sympathetic Nervous system
Initial response

- Baroreceptor mediated response
- Initial neurohormonal response
- Increased central sympathetic flow
  - increases plasma noradrenaline
- Increases neuronal release of noradrenaline
Sympathetic Nervous system
Initial response

• Activation via low and high pressure baroreceptors resulting in:
  - increase cardiac contractility
  - vascular constriction (arterial and venous)
  - increase heart rate
Sympathetic Nervous system
Late response

- Beta adrenergic receptors down regulated
- RAA system up regulated
- LV hypertrophy (eccentric) and fibrosis
- Myocyte apoptosis and necrosis
Summary
Sympathetic activation in chronic heart failure

Myocardial damage

Activation of sympathetic nervous system

Renin-angiotensin system

Vasoconstriction

Increased heart rate and contractility

Direct cardiotoxicity

Fluid retention

Increased wall stress

Increased myocardial oxygen demand

Myocardial hypertrophy

Decreased contractility

Myocyte damage

Norepinephrine concentrations and prognosis in chronic heart failure

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Neurohormonal Regulation of Heart Function.

Renin-Angiotensin-Aldosterone system
Figure 1 (A) Components of the renin-angiotensin-aldosterone system. (B) The four regulators of renin secretion. JGA, juxtaglomerular apparatus.
Renin-angiotensin-aldosterone system

- Angiotensinogen → Angiotensin I → Angiotensin II
- Renin
- Decrease in renal perfusion (juxtaglomerular apparatus)
- Lungs
- Kidney
- Surface of pulmonary and renal endothelium: ACE
- Sympathetic activity
- Tubular Na^+ Cl^- reabsorption and K^+ excretion, H_2O retention
- Adrenal gland: cortex
- Aldosterone secretion
- Arteriolar vasoconstriction, Increase in blood pressure
- Pituitary gland: posterior lobe
- ADH secretion
- Collecting duct: H_2O absorption
- Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.
Renin-angiotensin–aldosterone axis in heart failure

1. Liver - Renin substrate (angiotensinogen)
2. Vessels - Angiotensin I
   - Angiotensin converting enzyme (lungs and vasculature) - Angiotensin II
     - Vasoconstriction
     - Aldosterone release
     - Enhanced sympathetic activity
     - Salt and water retention
3. Brain - Enhanced sympathetic activity
**Angiotensin II actions**

- Arterial hypertrophy and constriction
- Adrenal – stimulates release of aldosterone
- Brain – stimulates AVP (antidiuretic hormone) release/stimulates thirst
- Heart – increase myocardial contractility and stimulates hypertrophy
- Kidney-inhibits renin release/increase Na reabsorption/vasoconstriction
- Sympathetic NS-stimulates central sympathetic outflow/peripheral sympathetic transmission/adrenal release of adrenaline
- Increased susceptibility to arrhythmias
Local versus systemic renin-angiotensin systems

Local endothelial angiotensin affects local smooth muscle cells (paracrine or epicrine action)

Blood vessel

Endocrine angiotensin from circulating renin-angiotensin system

Beevers, G. et al. BMJ 2001;322:912-916
Origins and actions of myocardial tissue

ACE-A2
Neurohormonal Regulation of Heart Function.

Natriuretic and other hormones
Pathophysiology - ANP/BNP

Stretch or increase in cardiac chamber volume leads to release of natriuretic peptides

- Atrial natriuretic peptide
- N-terminal atrial natriuretic peptide
- Brain natriuretic peptide

Vasodilatation
Increased urinary sodium excretion
**Pathophysiology - Other hormones**

**Natriuretic peptides:**

- ANP (atria); BNP (ventricles)
  - increase in response to volume expansion and pressure overload and counteracts effects of RAAS (antagonists to Angiotensin II and aldosterone)
  - promote natriuresis (renal - constrict afferent and dilates efferent arterioles, decrease Na reabsorption in collecting duct, inhibit secretion of renin and aldosterone)
  - vasodilatation (arteries and veins)
  - interest in use as diagnostic marker of heart failure
Pathophysiology - Other hormones

- **Antidiuretic hormone (ADH) or Vasopressin (AVP)**
  - Increased in severe heart failure /diuretic therapy
  - Secreted by posterior pituitary
  - Causes moderate vasoconstriction raising BP
  - Leads to excretion of sodium in urine while conserving water producing concentrated urine and reducing urine volume (increasing risks of hyponatraemia in diuretic therapy)

- **Endothelins:**
  - Secreted by vascular endothelial cells
  - Potent renal vasoconstrictor leading to sodium retention
  - Important prognostic marker related to symptomatic and haemodynamic severity
Other hormonal mechanisms in chronic heart failure

- The arachidonic acid cascade leads to increased concentrations of prostaglandins (prostaglandin E₂ and prostaglandin I₂), which protect the glomerular microcirculation during renal vasoconstriction and maintain glomerular filtration by dilating afferent glomerular arterioles.
- The kallikrein-kinin system forms bradykinin, resulting in both natriuresis and vasodilatation, and stimulates the production of prostaglandins.
- Circulating concentrations of the cytokine tumour necrosis factor (TNF) are increased in cachectic patients with chronic heart failure. TNF has also been implicated in the development of endothelial abnormalities in patients with chronic heart failure.
Kidney in Heart failure

- Renal function (Glomerular filtration rate) is maintained initially by haemodynamic changes at the glomerulus.
- Increased salt and water retention through neurohormonal activation.
- As disease progresses there is a fall in renal blood flow leading to reduction in GFR.
Vascular endothelium in heart failure

- Normally VE has role in regulating tone.
- In heart failure increased peripheral resistance related to
  - activation of SNS
  - activation of RAAS
  - increased endothelin
  - reduced EDRF (nitric oxide)
- Exercise and drug rx (ACE inhibitors) may improve VE function in heart failure
MECHANISMS AND PREVENTION OF HEART FAILURE

Myocardial necrosis

Left ventricular dysfunction

Vasodilatory, natriuretic, anti-mitogenic systems
- Atrial & brain natriuretic peptides
- Prostacyclins
- Endothelium-derived relaxing factors
- Nitric oxide
- Antioxidants

Left ventricular dilatation
- Left ventricular wall stress
- Myocyte hypertrophy
- Myocyte loss
- Matrix structural derangements

Vasoconstrictive, anti-natriuretic, mitogenic systems
- Catecholamines
- Angiotensins
- Aldosterone
- Cytokines
- Endothelins
- Free radicals

Balance
Prevents heart failure

Imbalance
Progression of heart failure
"Yes! That was very loud Mr. Trainer, but I said I wanted to hear your HEART!"
Pharmacological Rx of Heart Failure

Renin-Angiotensin-Aldosterone System

↑ RENIN → ↑ AT I

ACE

↑ Aldosterone receptors (renal)

↑ Aldosterone (adrenal gland)

↑ AT II

SNS

↑ Noradrenaline

↑ Adrenaline

β-1-adrenoreceptors

↓ ATII type I receptor
Pharmacological Rx of Heart Failure

Renin-Angiotensin-Aldosterone System

↑ RENIN → ↑ AT I → X → AT II → AT II type I receptor

ACE inhibitor

ACE

Aldosterone receptors (renal)

↑ Aldosterone (adrenal gland)

SNS

↑ Noradrenaline

↑ Adrenaline

β-1-adrenoreceptors
Pharmacological Rx of Heart Failure

**Renin-Angiotensin-Aldosterone System**

↑ RENIN → ↑ AT I → X

ACE inhibitor

↓ Aldosterone (renal)

↓ ↑ Aldosterone (adrenal gland)

X

ACE

AT II

β-1-adrenoreceptors

↓ SNS

↑ Noradrenaline

↑ Adrenaline

ATII type I receptor

Angiotensin receptor blocker
Pharmacological Rx of Heart Failure

Renin-Angiotensin-Aldosterone System

↑ RENIN → ↑ AT I

ACE

Aldosterone receptors (renal)

↑ Aldosterone (adrenal gland)

ACE inhibitor

β-1-adrenoreceptors

↑ Noradrenaline

↑ Adrenaline

Beta blockers

AT II

Angiotensin receptor blocker

ATII type I receptor
Pharmacological Rx of Heart Failure

Renin-Angiotensin-Aldosterone System

\[ \text{RENIN} \rightarrow \text{AT I} \rightarrow \text{AT II} \]

**Renin**

**ACE**

**AT II**

**SNS**

\[ \uparrow \text{Noradrenaline} \]

\[ \uparrow \text{Adrenaline} \]

**ACE inhibitor**

**Beta blockers**

\[ \beta-1\text{-adrenoreceptors} \]

**Aldosterone antagonists**

**Angiotensin receptor blocker**

**ATII type I receptor**
A  Ventricular remodeling after acute infarction

Initial infarct → Expansion of infarct (hours to days) → Global remodeling (days to months)

B  Ventricular remodeling in diastolic and systolic heart failure

Normal heart → Hypertrophied heart (diastolic heart failure) → Dilated heart (systolic heart failure)
Systolic vs Diastolic Classification

- On echocardiography determine left ventricular function
- Measured by ejection fraction - the amount of blood in left ventricle that is expelled with each contraction of cardiac cycle
- Ejection fraction:
  - <40%: left ventricular systolic dysfunction (LVSD)
  - >40%: diastolic dysfunction
Pathophysiology - Diastolic dysfunction

- Results from impaired myocardial relaxation with normal LV systolic function associated with concentric hypertrophy
- Due to increased stiffness of ventricle wall and reduced compliance causing impaired ventricular (diastolic) filling
- Unable to compensate with Starling effect resulting in reduced cardiac output
- Approx 30-50% of patients
- Commonly seen in hypertension
- Difficulties in diagnosis
- Similar activation of neurohormonal response as in systolic failure due to low cardiac output
- No clear outcome evidence for management
Summary

• Heart failure is a clinical syndrome
• Regardless of underlying cause, pump failure triggers neuroendocrine activation
• ‘Compensatory’ mechanisms becomes counterproductive in the longer term
• Treatment with ACE inhibitors, beta-blockers and Spironolactone has demonstrated significant reduction in mortality
Knowledge is the antidote to fear.

- Ralph Waldo Emerson

Thank you