Pathophysiology of Heart Failure

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Overview

• 5.7 million Americans > age 20 have HF
• Projected to increase by 46% by 2030 resulting in > 8 million with HF
• Survival improving, but still ≈ 50% die within 5 years after diagnosis
• Approximately 55% of those with symptomatic HF have preserved EF
• Total cost $30.7 billion, of which 68% are direct medical costs


Cardiac Cycle

https://upload.wikimedia.org/wikipedia/commons/1/1c/Cardiac_Pressure_Volume_Loop.jpg
Definitions

• Preload: stretch of cardiac myocytes prior to contraction. Indicated by EDV or EDP
• Afterload: pressure generated by ventricle to eject blood
• Stroke Volume: Amount of blood ejected during ventricular systole. SV = EDV-ESV.
• Inotropy: contractility. Changes in inotropy affects SV and ESV
• Necrosis – cell death
• Apoptosis- programmed cell death aggravated by inflammatory cytokines, angiotensin II, catecholamines, elevated wall stress

The Laws

• Frank-Starling Mechanism – Stroke volume increases as the volume of blood in the heart increases (in a normal heart)
• LaPlace’s Law: Wall tension (T) is proportional to pressure (P) times the radius (r) divided by 2 times the wall thickness (h)
  \[ T \propto \frac{P \cdot r}{2h} \]

Pathophysiology – the beginning

• Injury \( \rightarrow \) wall stress (myocyte hypertrophy and remodeling)
• Fall in cardiac output \( \rightarrow \) filling pressures and volume
• Activation of central baroreceptors and chemoreceptors \( \rightarrow \) Sympathetic stimulation (release of norepinephrine, angiotensin II and endothelin)
• Decrease pressure in baroreceptors stimulated release of vasopressin
Pathophysiology – Continuing downward

- Sympathetic stimulation causes down regulation of β1 receptors and uncoupling of β2 receptors
- Sustained sympathetic stimulation causes changes in the expression of contractile proteins that alter calcium homeostasis (G Proteins: Gs and Gi) lead to decreased inotrophy

What’s happening in the kidneys?

- Falling CO decreases stretch in afferent arteriole → release of renin → angiotensin I → converts with angiotensin converting enzyme to → angiotensin II → aldosterone (RAAS)
- Angiotensin II stimulates angiotensin II receptors near hypothalamus which causes release of vasopressin

Pro-inflammatory Cytokines

- Elevated in HF
- IL 1, IL6, TNFα
- Cytokine – a small protein molecule secreted from cells due to certain stimuli
- Pro-inflammatory – initiate the inflammatory response
- Can cause structural changes in myocardium leading to LV dysfunction

All this results in...

- Peripheral vasoconstriction
- Sodium/water retention
- Worsening LV function

......Heart Failure Symptoms

The good guys

- ANP and BNP are released in response to atrial and ventricular stretch (volume and pressure)
- BNP vasodilates afferent arterioles inhibits Na reabsorption, renin release, and aldosterone release
- Vasodilatation and natriuresis

Heart Failure with Reduced Ejection Fraction (HFrEF)

- Definition:
  EF ≤ to 40%
systolic HF

  Majority of RCT enrollment, thus evidence based therapies effective in this population
Conditions/Risks that may lead to HFrEF

- Ischemia/atherosclerotic disease
- Valvular disease
- HTN
- Obesity
- Diabetes
- Thyroid disease
- Cardiotoxins (cocaïne, ETOH, cytotoxic antineoplastic drugs, ephedra, anabolic steroids, etc)
- Growth hormone deficiency or excess
- Tachycardia induced
- Viral/Bacterial
- Peripartum
- Nutritional deficiencies
- Iron overload
- Amyloidosis
- Sarcoidosis
- Stress (Takotsubo CM)
- Chagas’ Disease

Echocardiography

- Estimate EF
- Evaluate LV structure, geometry, wall motion
- Evaluate RV function
- Measure ventricular and atrial dimensions
- Assess LV volume
- Assess wall thickness
- Evaluate valves
- Estimate PA pressure

Heart Failure with Preserved EF

- HFrEF – EF >50% with signs and symptoms of HF and noncardiac causes have been excluded. Formerly called Diastolic HF
- HFrEF, borderline – EF 41-49%. Treatment and outcomes are similar to HFrEF group
- HFrEF, improved - EF>40% in patients with previously documented HFrEF

Yancy C., et al. 2013 ACCF/AHA HF Guideline
European Society of Cardiology Perspective on HfPEF

- Referred to HfNEF (normal EF) because preserved implies previous measurement
- Also were clearer on need for evidence of diastolic dysfunction as prerequisite for diagnosis of HfNEF

Review of Left Sided Diastole

- Isovolumetric relaxation – AoV and MV closed. Ventricle relaxes. Energy dependent phase
- Rapid filling – MV opens, rapid, passive filling of LV. Blood flows from pulmonary veins into LA.
- Diastasis – minimal volume change. LV pressure approached LA pressure
- Isovolumetric contraction – MV and AoV closed. Ventricular contraction begins at the base and pulls the MV toward apex, stretching LA. Pul veins empty into LA

Review of Diastole

Rosenberg MA & Manning WJ. Circ. 2012:126:2353-2362
Important Concepts in HFpEF

- Relaxation (lusitropy) – ventricular pressure drops below atrial pressure allowing blood to flow into lower pressure chamber
- Compliance – refers to pressure-volume relationship as blood flows into ventricle. With decreased compliance the pressure is higher per volume of blood

Echocardiographic Evidence of HFpEF

- Normal EF
- Increased LA size
- Increased LV wall thickness
- Abnormal mitral Inflow patterns
  - E wave reflects early diastole, passive filling.
  - A wave reflects late diastole, atrial systole

Mitral Inflow Patterns
Grades of Diastolic Dysfunction

- Grade I – Impaired LV relaxation, less filling in early diastole (reversal E:A ratio)
- Grade II – Decreased LV compliance so pressure gradient is low (small A wave, pseudonormalization)
- Grade III – Decreased compliance, high LA pressures. Most filling occurs early
- Grade IV – Irreversible restrictive pattern

Contributing/Risk Factors

- HTN
- Obesity
- Diabetes
- Renal disease
- Valvular heart disease
- Aging
- Infiltrative diseases
- Restrictive CM
- Not just older Caucasian women

Pressure Volume Curves in HF

[Diagram showing pressure volume curves in HF]
RV Pathophysiology

- Same SV as LV, but to much lower pressure – so RV is thin walled
- Because of low pressure, no isovolumetric relaxation of RV
- Ventricular interdependence – when RV dilates acutely it impairs LV diastolic filling
- RV cannot adjust rapidly to acute pressure changes, but can accommodate more gradual volume changes

Causes of RV Failure

- Pulmonary HTN (primary or secondary) – may be final pathway in LV failure
- RV and tricuspid valve pathologies
- Diseases of the pericardium

Echocardiography

- RV size, shape
- Tricuspid valve
- Shift of IVS – loss of LV sphere (D shape)
- Distended IVC with loss of inspiratory collapse indicates elevated RA pressure
- Flow across PA, dilated PA
Current Medications - where and why they work

- ACE –I
- ARB
- Beta blockers
- Aldosterone antagonists (MCRA)
- Neprilysin inhibitors
- Vasopressin receptor antagonists (hypervolemic hyponatremia)

Summary

- The SNS, RAAS, pro-inflammatory cytokines and other changes at the cellular level contribute to the progression of heart failure
- Compliance and relaxation during diastole are important elements in HFrEF
- Evidence based medications focus on addressing pathophysiologic contributions to HFrEF