

Be Still My Heart

A case study of a patient with refractory
heart failure

Presented by Sarah Smith, Pharm.D.



Objectives

- Review anatomy and physiology of the heart
- Discuss the pathophysiology of heart failure
- Evaluate the patient with heart failure or cardiomyopathy
- Overview of therapy in systolic heart failure
- Discuss evidence-based treatment strategies for patients with refractory heart failure
- Review medications to avoid in Heart Failure

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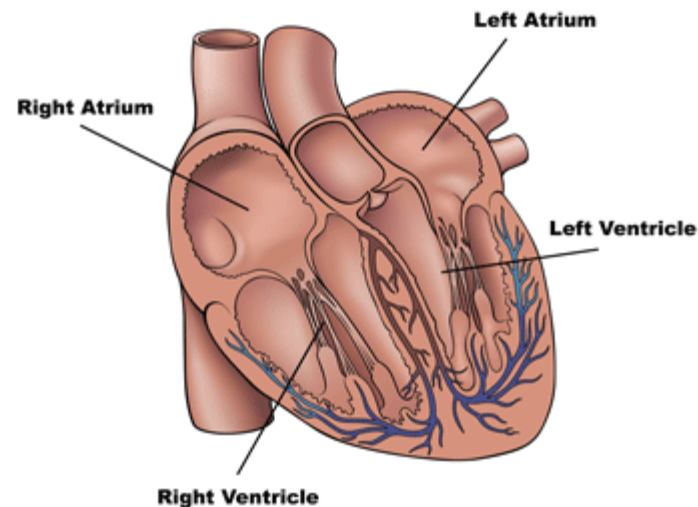
Anatomy and Physiology of the Heart

2 Separate Pumps

- Right side receives blood from the body and sends it to the lungs (pulmonary)
- Left side receives blood from the lungs and sends it to the body (systemic)

Cardiac cycle involves systole and diastole

- Systole = contraction or ejection of blood from ventricles
- Diastole = relaxation or filling of blood into ventricles



Pathophysiology of Heart Failure

- Normal Left Ventricular Pressure-Volume Relationship
 - Stroke volume represents efficiency
 - Preload = amount of blood allowed into the ventricle during diastole
 - Contractility = strength or force the muscle fibers are capable of generating
 - Afterload = impedance during ejection
 - Cardiac Output = Stroke Volume x Heart Rate
- Heart Failure Left Ventricular Pressure-Volume Relationship
 - Contractility reduction = developed force reduced
 - Frank-Starling curve

Definition of Heart Failure

- Chronic Heart Failure
 - Complex syndrome that can result from any structural or functional disorder that impairs the ability of the ventricle to fill or eject blood
 - Clinical symptoms and signs of low cardiac output and/or pulmonary or systemic congestion include dyspnea, fatigue, and fluid retention
- Acute Decompensated Heart Failure
 - Gradual or rapid change in heart failure signs and symptoms resulting in the need for urgent therapy
- Refractory Heart Failure
 - Recognized when patients continue to be symptomatic or develop recurrence of heart failure despite optimal contemporary pharmacotherapy proven to be of benefit in clinical trials

Heart Failure Classification

Classification of Heart Failure: ACC/AHA Stage vs NYHA Class

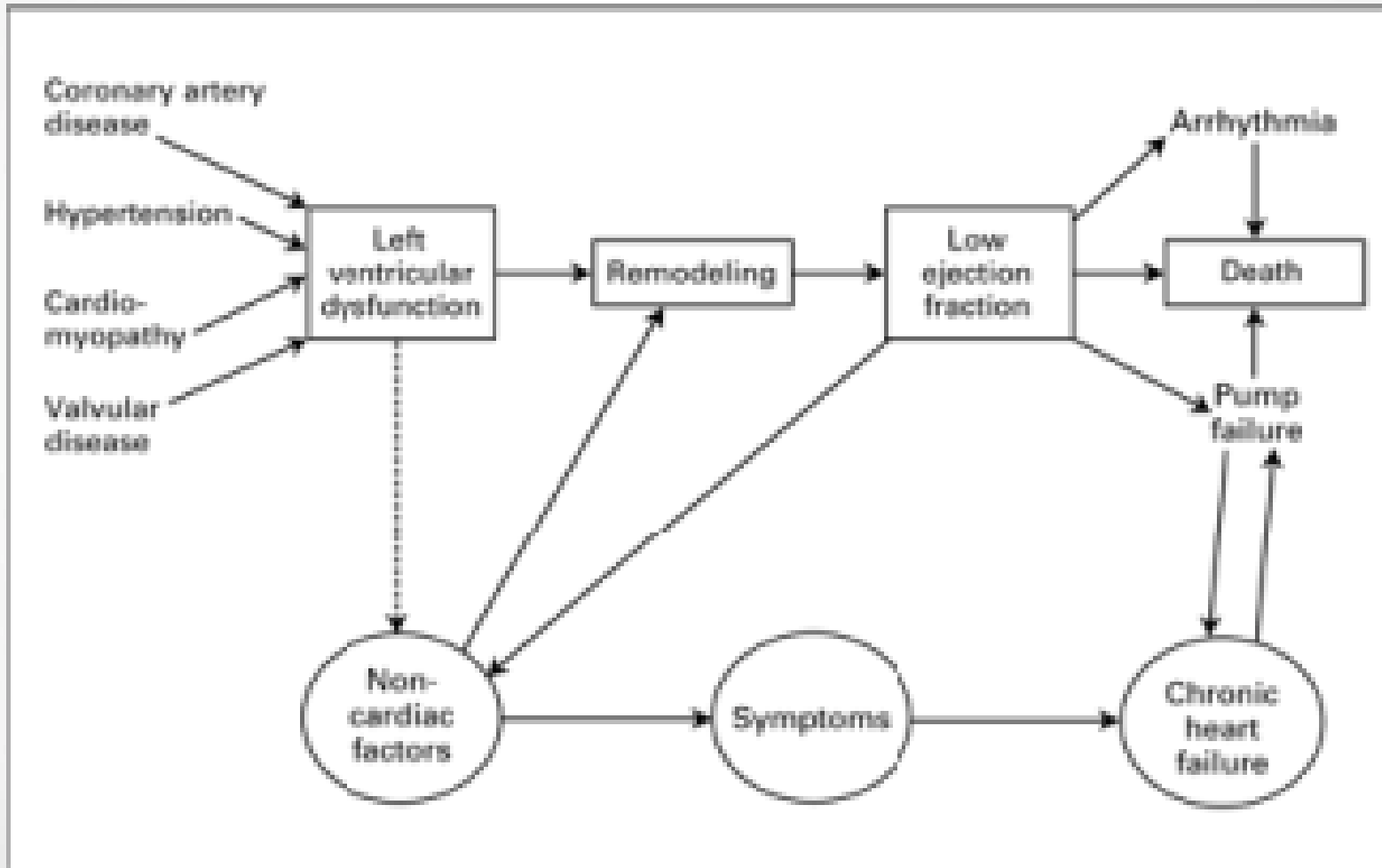
ACC/AHA Heart Failure Stage	NYHA Functional Class
A. At risk for heart failure but without structural heart disease or symptoms	None
B. Structural heart disease but without heart failure	I. Asymptomatic HF: no symptoms
C. Structural heart disease with prior or current heart failure symptoms	II. Mild HF: symptomatic with moderate exertion III. Moderate HF: symptomatic with minimal exertion
D. Refractory heart failure requiring specialized interventions	IV. Severe HF: symptomatic at rest

Hunt SA et al. *Circulation*. 2001;104:2996-3007.
Farrall MH et al. *JAMA*. 2002;287:830-837.



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Causes of Heart Failure



Clinical Manifestations of Heart Failure

Symptoms from Right Ventricle Impairment	Symptoms from Left Ventricle Impairment	Symptoms of reduced pumping function (systolic)
<ul style="list-style-type: none"> • Lower extremity swelling 	<ul style="list-style-type: none"> • Dyspnea on exertion 	<ul style="list-style-type: none"> • Fatigue
<ul style="list-style-type: none"> • Abdominal girth increase 	<ul style="list-style-type: none"> • Orthopnea (breathless when at rest) 	<ul style="list-style-type: none"> • Weakness
<ul style="list-style-type: none"> • Abdominal pain (right) 	<ul style="list-style-type: none"> • Paroxysmal nocturnal dyspnea 	<ul style="list-style-type: none"> • Inability to concentrate
<ul style="list-style-type: none"> • Weight gain 	<ul style="list-style-type: none"> • Difficulty ambulating 	<ul style="list-style-type: none"> • Loss of appetite
<ul style="list-style-type: none"> • Loss of appetite 		<ul style="list-style-type: none"> • Weight loss
<ul style="list-style-type: none"> • Possible liver enlargement 		<ul style="list-style-type: none"> • Feels cold
		<ul style="list-style-type: none"> • Shortness of breath

Case Study

- 63 year old male
- CC: 8 lb weight gain with increasing abdominal girth and lower extremity edema
- CXR: pulmonary edema
- BNP: 1200



Case Study

Pertinent Labs on Admission

Vital Signs

BP 94/57

HR 80 (paced)

Electrolytes

Na 135 mmol/L

K 5.2 mmol/L

Glucose 50 mg/dL

Calcium 9.5 mg/dL

Albumin 2.6 g/dL

SCr 1.44 mg/dL

CrCL~ 50 L/min

Cardiac Enzymes

BNP 1200 →

1022.5

Troponin I → 0.21

CK-MB → 3.8

Liver Function

Tests

T Bili 0.8

Alk Phos 200

AST/ALT 18/35

LDH 240

Drug Level

Digoxin 2.0 (2.3)



Case Study

- PMH:
 - Hypertension
 - Diabetes
 - Increased LFTs
 - History of acute kidney injury with a baseline SCr ~1.2
 - Non-occlusive coronary artery disease
 - Non-ischemic cardiomyopathy
 - Vtach/Aflutter/LBBB – s/p biventricular pacing and AICD
 - Class IV CHF with EF <20%
 - Lung disease secondary to amiodarone

Case Report

- HPI:
 - Echo in 2011 suggested stable non-occlusive CAD
 - LVEF 25% - 30% (severe LV systolic dysfunction) with markedly elevated end-diastolic pressure out of proportion to CAD
 - Non-ischemic dilated cardiomyopathy
 - Atrial fibrillation/atrial flutter with placement of AICD early 2012
 - Ventricular tachyarrhythmias, declining cardiac function
 - Amiodarone started
 - Developed Left BBB and marked first-degree AV block
 - By end of 2012 he was functional class IV heart failure

Case Report

- 4 prior hospitalizations in 2013
 - February
 - biventricular pacing after failed LV lead placement
 - May
 - 4+ pitting edema to groin with 6 lb weight gain in one week
 - June
 - Increased weight and abdominal girth – refractory to diuretics
 - Echo with severely decreased LV systolic function and EF 20%
 - Biatrial dilation, mitral and tricuspid regurgitation, pulmonary hypertension, right-sided chamber dilation with severe right ventricular hypokinesis
 - Referred to Advanced Heart Failure program at Vanderbilt
 - September
 - Fall due to weakness resulted in hip fracture and L-ORIF

Official Diagnosis: Mixed picture of cardiomyopathy, largely non-ischemic, with class IV CHF with LVEF of 20%

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Case Report

Outpatient Medications

- Dobutamine continuous IV infusion 5 mcg/kg/min
- Demadex 100 mg twice daily
- Zaroxolyn 2.5 mg daily
- Spironolactone 50 mg twice daily
- KCL 40 mEq twice daily if tolerated
- Magnesium 400 mg daily
- Digoxin 0.125 mg daily
- SSI (Novolog) and Levemir 20 units daily
- Ferrous sulfate 325 mg daily
- Vitamins B-12, C and D
- Ativan 0.5 mg daily
- Robaxin 750 mg daily
- Warfarin 4 mg daily

Medications in Heart Failure

- Guidelines
 - 2013 American College of Cardiology Foundation / American Heart Association (ACCF/AHA) guideline
 - 2008 European Society of Cardiology (ESC) guidelines
 - 2010 Heart Failure Society of America guidelines
- Goals
 - Treat underlying causes and exacerbating co-morbidities
 - Slow the progression and preserve cardiac function
 - Prevent hospitalizations and mortality

Medications in Heart Failure

- Order of Initiation
 - Loop diuretics
 - Symptomatic relief in patients with overt heart failure
 - ACE-Inhibitors
 - Initiate during or after optimization of loop diuretic dose
 - Start with low doses and titrate to goal slowly
 - Beta Blockers
 - Initiate after patient is stable on loop diuretics and ACE-Inhibitors
 - Start with low doses and titrate to goal slowly
 - Recommended agents include carvedilol, metoprolol ER, and bisoprolol

Medications in Heart Failure

- Select Populations

- Aldosterone Antagonists (MRAs)

- NYHA Class II - IV HF with EF < 35%
 - STEMI and on therapeutic ACE-I, EF <40%, and symptomatic or diabetic

- Angiotensin II Receptor Blockers (ARBs)

- Patients who are intolerant to ACE-Is (e.g. cough)

- Digoxin

- To reduce hospitalizations
 - In patients with Atrial Fibrillation for rate control

- Hydralazine + nitrate

- Persistent symptoms despite optimal doses of ACE-I and Beta Blocker

- Aspirin

- Patients with known coronary artery disease

Optimization of Medication Regimens

- ACE Inhibitors
 - Lisinopril 20-40 mg daily
 - Enalapril 10-20 mg BID
 - Captopril 50 mg TID
- ARB
 - Losartan 50-100 mg daily
- Loop Diuretics
 - Furosemide titrate to effect: Max 240-480 mg once or twice daily
 - Volume overload Add-Ons
 - HCTZ 25-50 mg daily (target)
 - Metolazone 2.5 mg daily or PRN Max 10 mg daily or PRN
- Vasodilators
 - Hydralazine + isosorbide dinitrate 40 mg TID/QID + 100 mg TID
- Beta-Blockers
 - Carvedilol BID dose 25 mg <185 lb 50 mg >185 lb
 - Metoprolol LA 200 mg daily
 - Bisoprolol 10 mg daily
- MRA
 - Spironolactone 50 mg daily or 25 mg BID*
 - Eplerenone 50 mg daily
- Anti-arrhythmic
 - Digoxin based on level and symptoms
 - Adjust based on age and renal function
 - Consider Q48H dosing in age >70 or decreased renal function
 - Target level 0.5 – 0.8 (<1.2)

Case Report

Outpatient Medications

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Impact of Heart Failure

- Cardiac
 - Hypertrophy, Hypokinesia, Dilation of ventricle
 - Left ventricular failure can eventually lead to right ventricular heart failure
 - Systolic heart failure can lead to diastolic heart failure
- Hepatic
 - Mild alterations in liver function tests
 - Cardiogenic ischemic hepatitis
 - Congestive liver fibrosis
 - Cardiac cirrhosis
- Renal
 - Cardiorenal syndrome
- CNS
 - Decline in mental processes and loss of gray matter

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Treatment of Refractory Heart Failure

- General Considerations
 - Confirm the accuracy of the diagnosis and recognize any contributing co-morbidities
 - Optimize medical therapy and avoid medications that exacerbate heart failure
 - Recommendations that apply to other classes of heart failure are appropriate in Class IV/Stage D
 - Referral to a heart failure treatment center is useful
- Options
 - Natriuretic doses of mineralcorticoid antagonists
 - IV positive inotropic therapy
 - Cardiac Resynchronization Therapy (CRT)
 - Ultrafiltration
 - Mechanical circulatory support
 - Cardiac Transplantation

Treatment of Refractory Heart Failure

- Mineralcorticoid/Aldosterone Receptor Antagonists
 - Aldosterone has pleiotropic effects on the heart, kidney, and vasculature
 - Contributes to hypertrophy and remodeling of heart
 - Sodium and water retention
 - Enhances atherosclerosis, platelet aggregation, and reduces nitric oxide bioavailability
 - Natriuretic doses of Spironolactone in HF patients
 - Cardioprotective dose 25-50 mg daily
 - Natriuretic doses >50 mg daily (up to 400 mg daily)
 - Necessary in loop diuretic, volume overloaded patients
 - Dose is related to amount of RAAS activity
 - **Clinical Pearl: Spironolactone is a potent inhibitor of P-gp** (digoxin substrate)
 - may also cross react with some digoxin assays giving falsely elevated digoxin concentrations

Treatment of Refractory Heart Failure

- Intravenous inotropes and vasodilators
 - Acute improvement of hemodynamics and symptomatic relief
 - Dobutamine, Milrinone, Nitroprusside, Nitroglycerin, Nesiritide
 - Increased cardiac output via dose-dependent inotropic and chronotropic mechanisms
 - Myocardial oxygen demand is also increased, increasing the risk of myocardial ischemia, tachyarrhythmias and ventricular dysfunction
 - Long term use may actually increase mortality
 - Considered palliative care
 - Continuous IV infusion is recommended by ACC/AHA HF guidelines for palliative management of symptoms
 - Use of beta-blockers (provide mortality benefit by decreasing incidence of sudden cardiac death) incompatible

Treatment of Refractory Heart Failure

- Cardiac Resynchronization Therapy (CRT)
 - Improve pump performance and reduce cardiac remodeling
 - Bi-ventricular pacing +/- ICD
 - Mortality benefit by reducing sudden cardiac death
 - Recommended in patients with Class II-IV heart failure, severe systolic dysfunction (LVEF <35%) and intraventricular conduction delay (QRS \geq 120 msec)
 - Increased mortality shown in RCT of patients with QRS < 130 msec

Treatment of Refractory Heart Failure

- Ultrafiltration
 - Decreased neurohormonal activity, controlled diuresis with little to no effect on serum electrolytes
 - Aquadex UF system example
 - Small portable device that utilizes a major vein system
 - Multiple RCTs demonstrate efficacy (RAPID-CHF, CARRESS-HF, UNLOAD)
 - Decreased hospitalization; Increased adverse event rates
 - Hematologic abnormalities, worsening heart failure or renal failure, etc
 - Reserved for patients refractory to aggressive diuretic therapy

Treatment of Refractory Heart Failure

- Mechanical Circulatory Support Devices
 - Intraaortic Balloon
 - Cardiogenic shock, refractory heart failure bridge to transplant
 - Intractable angina
 - Low cardiac output after cardiopulmonary bypass
 - Complications
 - Vascular
 - Limb and visceral ischemia
 - Major hemorrhage, vascular lacerations
 - Non-vascular
 - Cholesterol embolization
 - Suspect in patients with thrombocytopenia – chronic anticoagulation may be detrimental and promote further embolization
 - Sepsis
 - Fall in platelet count, hemolysis

Treatment of Refractory Heart Failure

- Mechanical Circulatory Support Devices
 - Centrifugal Pump
 - Extracorporeal Pump
 - Left Ventricular Assist Device (LVAD)
 - Right Ventricular Assist Device (RVAD)
 - Bi-ventricular Assist Device (BiVAD)
 - Axial Flow Pump
 - **Impella microaxial flow device** (Memorial)
 - Total Artificial Heart (TAH)
 - Recommend continuous flow LVADs (second and third generation devices) over pulsatile flow (first generation) in patient with left ventricular dysfunction
 - Early intervention key to success

Medications to Avoid in Heart Failure

- NSAIDS
 - COX-2
 - Aspirin
 - Possible role if other compelling indications (CAD)
- Calcium Channel Blockers
 - Amlodipine and felodipine have neutral effect on mortality
- Antidepressants
 - TCAs > SSRIs adverse effects
 - Depression worse than antidepressant use
- Oral Hypoglycemic Agents
 - Metformin – lactic acidosis
 - Thiazolidinediones – fluid retention
- PDE-Inhibitors
 - Cilostazole (PDE-3)
 - Anagrelide (PDE-4)
 - Vardenafil (PDE-5)
- Antiarrhythmics
 - Amiodarone less pro-arrhythmic so considered DOC for HF patients with arrhythmias
- Chemotherapy
 - Anthracyclines
 - HER-2 agents
- Antiandrogens
 - Recommendations against testosterone therapy in unstable HF patients

Summary

- Heart failure is a progressive disease
- Medications play a key role in preventing morbidity and mortality associated with heart failure
- Refractory heart failure patients have special needs for managing symptoms of heart failure
- Pharmacists can play a key role in monitoring medication regimens and making suggestions regarding optimization of therapy
- Pharmacists need to monitor for appropriateness of medications that can potentially exacerbate symptoms or accelerate heart failure progression

