Heart Failure: Pathophysiology, Diagnosis, and Hemodynamic Targets

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Heart Failure Rages Through American Cities
The Boys Go Out For A ‘Heart Healthy’ Lunch…
And Then Walk the Dog For Exercise
Acute Heart Failure
Magnitude of the Problem

- 1 million admissions annually in the U.S. (↑50% over the past 10 years)
- Most common admitting diagnosis for patients ≥ 65 years
- Hospitalization costs are considerable (>60% of amount spent on heart failure)
Acute Heart Failure
Have We Made Progress?

- The good news:
  - In-hospital mortality 5% (↓40% in 10 years)
  - Mean length of stay 5-6 days (↓30% in 10 years)

- The bad news:
  - Readmission rates remain high
    - 25% within 30 days
    - 50% within 6-12 months
  - High mortality rates persist
    - 5-10% at 30 days
    - 20-40% at 6-12 months
HCFA Hospitalization Costs

Chronic Heart Failure: 5.4 billion dollars
Cancer: 2.4 billion dollars
Myocardial Infarction: 3.3 billion dollars

Worsening Chronic Heart Failure Is the Major Reason for Heart Failure Hospitalizations

- Worsening chronic heart failure (75%)
- De novo heart failure (23%)
- Advanced or end-stage heart failure (2%)

Compliance with medications
Compliance with a low-salt diet
### Acute Decompensated Heart Failure: Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ADHERE N = 105,388</th>
<th>OPTIMIZE-HF N = 48,612</th>
<th>Euro-HF N = 11,327</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yrs)</td>
<td>72.4</td>
<td>73</td>
<td>71</td>
</tr>
<tr>
<td>&gt; 75 years (%)</td>
<td>50</td>
<td>ND</td>
<td>30 men</td>
</tr>
<tr>
<td>Male (%)</td>
<td>48</td>
<td>48</td>
<td>53</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>72</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Prior HF history (%)</td>
<td>75</td>
<td>87</td>
<td>65</td>
</tr>
<tr>
<td>Systolic dysfunction (%)</td>
<td>54</td>
<td>46</td>
<td>45</td>
</tr>
</tbody>
</table>

Heart Failure as a Symptomatic Disorder Functional Class

- NYHA
  - Class I: normal exercise tolerance
  - Class II: symptoms with ordinary exertion
  - Class III: symptoms with only mild exertion
  - Class IV: symptoms at rest

Problem: the underlying disease progresses, even in the absence of symptoms!!
Rationale for a New Way of Classifying Patients With HF in 2009

- HF represents a continuum beginning with risk factors and culminating in end-stage or refractory disease
- There are known risk factors and structural prerequisites leading to the development of LV systolic and/or diastolic dysfunction and the clinical syndrome of HF
- HF is a preventable disorder
Revised Staging System for HF

Stage A

At high risk of HF but without structural heart disease or HF symptoms

Revised Staging System for HF

Stage B
- Structural heart disease but without signs or symptoms of HF

Stage A
- At high risk of HF but without structural heart disease or HF symptoms

Revised Staging System for HF

Stage C
Structural heart disease with prior or current HF symptoms

Stage B
Structural heart disease but without signs or symptoms of HF

Stage A
At high risk of HF but without structural heart disease or HF symptoms

Revised Staging System for HF

Stage A
At high risk of HF but without structural heart disease or HF symptoms

Stage B
Structural heart disease but without signs or symptoms of HF

Stage C
Structural heart disease with prior or current HF symptoms

Stage D
Refractory HF requiring specialized interventions

The Cardiovascular Disease Continuum

Risk Factors:
- Obesity
- Insulin Resistance

Endothelial Dysfunction
- Vascular Disease (Atherosclerosis)
- Endothelial Dysfunction

Pathological Remodeling (LVH)

Heart Attack (Myocardial Dysfunction)
- Left Ventricular Enlargement
- Heart Failure
- DEATH

Maladaptive Remodeling

Heart Failure: A Changing Paradigm

1950’s - 1980’s

- Hemodynamic Model
  - Reduced contractility, pump dysfunction
  - Treatment:
    - Positive inotropic drugs to stimulate contractility
    - Vasodilators to "unload" the heart
    - Conventional drugs
      - Diuretics
      - Digitalis

1980’s - 2004

- Neurohormonal Model
  - Progressive remodeling with impaired myocardial performance
  - Treatment:
    - Prevention of progression with neurohormonal blockers:
      - ACE inhibitors, aldo blockers
      - β-adrenergic blockers, ARBs
    - Conventional drugs
      - Diuretics
      - Digitalis
    - Emerging therapies
      - Bi-Ventricular Pacing
      - Bi-V Pacing + ICD
      - LV Reconstruction surgery (Dor)
      - Acorn, Myosplint
Structural Remodeling Post-MI

**Days**
MI due to coronary occlusion

**Weeks**
Scarring and reshaping of the heart (remodeling)

**Months - Years**
Heart enlarges and leads to congestive heart failure
Remodeling Is The Major Cause of Progressive Cardiac Dysfunction

6 months post-MI

14 months post-MI
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Role of Neurohormonal Activation in Remodeling

ACE = angiotensin-converting enzyme; ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; RAAS = renin-angiotensin-aldosterone system

Progression of Heart Failure

Myocardial injury to the heart (CAD, HTN, CMP, valvular disease)

Initial decrease in LV performance, increased wall stress

Activation of RAAS and SNS

Remodeling and progressive worsening of LV function

Fibrosis, apoptosis, hypertrophy, cellular/molecular alterations, myotoxicity

Peripheral vasconstriction, hemodynamic alterations

Heart failure symptoms:
- Fatigue
- Chest congestion
- Shortness of breath
- Activity altered
- Edema

Morbidity and mortality, arrhythmias, pump failure

CAD = coronary artery disease; CMP = cardiomyopathy; HTN = hypertension; LV = left ventricular; RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system

Pathophysiologic Effects of Angiotensin II

Ang II

Abnormal vasoconstriction

↑Contractility

Activate SNS

↑Aldosterone

↑Vasopressin

↑Endothelin

Myocyte growth

Vascular smooth muscle growth

↑Collagen

Remodeling

↑PAI-1/ thrombosis

Platelet aggregation

Superoxide production
Effects of CHF on Renal Function

- **Primary Pathophysiology**
  - BP = Blood Pressure
  - CO = Cardiac Output
  - SNS = Sympathetic Nervous System
  - RAA = Renin-Angiotensin-Aldosterone Axis
  - AII = Angiotensin II
  - GFR = Glomerular Filtration Rate

- **Direct Renal Effects**
  - BP ↓
  - CO ↓
  - Renal Perfusion ↓
  - GFR ↓

- **Neurohormonal Activation**
  - SNS ↑
  - RAA ↑

- **Secondary Pathophysiology**
  - Norepinephrine
  - Renal Vasoconstriction
  - Na and Water Retention
    - Intravascular Volume ↑
    - Preload ↑
    - Heart Failure symptoms and signs

- **Cardiomyopathy**
  - Effects of CHF on Renal Function

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BP = Blood Pressure
CO = Cardiac Output
SNS = Sympathetic Nervous System
RAA = Renin-Angiotensin-Aldosterone Axis
AII = Angiotensin II
GFR = Glomerular Filtration Rate
The Cardio-Renal Syndrome of Heart Failure

- Decreased cardiac performance
- Increased water & Na\(^+\) retention
- Impaired renal function
- Decreased cardiac output
- Neurohormonal Activation
- Diminished blood flow
- Decreased renal perfusion
Diagnosis of Heart Failure

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Case- MA- 1

- **HPI**: 65 year old male was visiting relatives in San Diego when over the course of 24 hours he developed progressively worsening dyspnea, occurring first with minimal exertion and culminating with shortness of breath at rest. He denied any chest pain or nausea but said he felt his heart skipping some beats.

- **PMH**: Hypertension, COPD, remote myocardial infarction. He was told he had a normal “ejection fraction” one year ago.
MA-2

- **Meds**: Two inhalers, clonidine, simvistatin
- **PE**: vitals: 170/100-100-26; JVP-14 cm, rhonchi and wheezing throughout all lung fields. No gallops or edema.
- **ECG**: sinus tachycardia, multifocal pacs, LVH, LAE and old Q waves inferiorly.
- **CXR**: (poor quality) no cardiomegally. Possible cephalization.
- **Bedside echo** (fellow): mild inferior wall hypokinesis (old). Overall systolic function was normal.
MA- Questions-a

- What is the diagnosis?
- How can you differentiate between COPD and CHF?
- If this is CHF, what has precipitated it?
- What other tests would you order?
MA-3

- Labs:
  - TnI <0.4
  - CBC normal
  - Electrolytes: normal
  - BNP: not done
The diagnosis was COPD exacerbation.

He was given oxygen, nebulization treatments, and a steroid bolus.

He felt slightly better and was discharged home two hours later at 8pm.
Goals in Diagnosis

- For your mother
  - Rapid
  - Highly accurate
  - Non-invasive, if at all possible
  - Spare no expense
Goals in Diagnosis

- For your mother-in-law
  - No rush
  - Mistakes happen
  - Invasive studies, got no problem with that
  - She is cheap, don’t go wasting money
The Short of Breath Pie
We need to make rapid, accurate diagnoses and triage patients accordingly.
The Hall and the physical exam
The Challenge of Diagnosing Heart Failure: Physical Examination

JVP on Physical Exam
  Great if well seen
  In OPTIMIZE and ADHERE, in the majority of hospitalized HF patients, initial exam missed it
  Obesity epidemic: good luck

S3 on Physical Exam
  Great if heard
  Missed 4/5 times
How Good Is the History and Physical in AHF?

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx of HF</td>
<td>62</td>
<td>94</td>
<td>80</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>56</td>
<td>53</td>
<td>54</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>47</td>
<td>88</td>
<td>72</td>
</tr>
<tr>
<td>Rales</td>
<td>56</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>S3</td>
<td>20</td>
<td>99</td>
<td>66</td>
</tr>
<tr>
<td>JVD</td>
<td>39</td>
<td>94</td>
<td>72</td>
</tr>
<tr>
<td>Edema</td>
<td>67</td>
<td>68</td>
<td>68</td>
</tr>
</tbody>
</table>

Chest X-Ray in Heart Failure
The CXR is not all it’s cracked up to be

- Misses 20% of echo proven cardiomegaly
- Detection of pleural effusion if supine
  - 67% sensitivity
  - 70% specificity
- Even worse if done portable
How sure are we about the diagnosis of CHF?

Significant Indecision Exists 43%
The Challenge of Diagnosing Heart Failure

- **Primary care diagnosis**
  
  Correct diagnosis on initial presentation
  
  18% of females
  
  36% of males

- **Emergency department diagnosis**
  
  12% entirely wrong diagnosis
  
  6% over diagnosed
  
  6% under diagnosed

Cardiorenal Axis

ANP, BNP, and CNP
- Natriuretic
- Diuretic
- Vasodilating
- Renin and aldosterone inhibiting
- Anti-fibrotic

Renin-angiotensin-aldosterone system
- Sodium retaining
- Antidiuretic
- Vasoconstricting
- Fibrosis
Pre-Pro-BNP$_{1-134}$

Pro-BNP$_{1-108}$

N-terminal Pro-BNP$_{1-76}$

BNP$_{77-108}$

t$_{1/2} = 18$ min

WALL STRESS

Natriuresis

Vasodilatation

lusitropy

RAAS
History
Physical exam
CXR
NP levels
EURETHRA!

IT'S EUREKA!
BNP & NT ProBNP: They Look Similar But May Be “Different Animals”
BNP and NT-proBNP Summary

- BNP is a more widely used marker
- Values of the two molecules are NOT interchangeable
- Both are good diagnostic markers in heart failure
- Diagnostic algorithms and cut-offs are more complex for NT-proBNP than for BNP
- Both can be used to screen for LV dysfunction
- Both are good prognostic markers in heart failure
- NT-proBNP values appear to be more effected by renal function
- BNP is a more dynamic marker due to differences in half-lives
The Cardiovascular Disease Continuum

Risk Factors:
- Obesity
- Insulin Resistance

Endothelial Dysfunction

Vascular Disease (Atherosclerosis)

Maladaptive Remodeling

Left Ventricular Enlargement

Heart Attack (Myocardial Dysfunction)

Heart Failure

Death

BNP = 0

Breathing Not Properly STUDY

Clinical Investigation and Reports

B-Type Natriuretic Peptide and Clinical Judgment in Emergency Diagnosis of Heart Failure
Analysis From Breathing Not Properly (BNP) Multinational Study

Peter A. McCullough, MD, MPH; Richard M. Nowak, MD, MBA; James McCord, MD; Judd E. Hollander, MD; Howard C. Herrmann, MD; Philippe G. Steg, MD; Philippe Duc, MD; Arne Westheim, MD, PhD; Torbjorn Omland, MD, PhD, MPH; Cathrine Wold Knudsen, MD; Alan B. Storrow, MD; William T. Abraham, MD; Sumant Lamba, MD; Alan H.B. Wu, PhD; Alberto Perez, MD; Paul Clopton, MS; Padma Krishnaswamy, MD; Radmila Kazanegra, MD; Alan S. Maisel, MD; for the BNP Multinational Study Investigators
Specificity, Sensitivity, and Accuracy of BNP Cutoff Value

**Optimal cut-off point determined @ 100 pg/mL**

<table>
<thead>
<tr>
<th>BNP Cutoff Value</th>
<th>Final Diagnosis Heart Failure</th>
<th>Final Diagnosis NOT Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP = 100 pg/mL</td>
<td>673</td>
<td>227</td>
</tr>
<tr>
<td>BNP &lt; 100 pg/mL</td>
<td>71 Sensitivity = 90%</td>
<td>615 Specitivity = 73%</td>
</tr>
</tbody>
</table>
Clarification of Diagnosis & BNP

BNP reduces clinical indecision by 74%
Acute Dyspnea: BNP ROC Curve

Area Under ROC Curve
- 0.86 (0.84-0.88) E.D. Probability
- 0.90 (0.88-0.91) BNP
- 0.93 (0.92-0.94) Combined
## Results of the BNP for Acute Shortness of Breath Evaluation (BASEL) Study

<table>
<thead>
<tr>
<th>End Point</th>
<th>Routine Assessment (n=227)</th>
<th>Routine Assessment + BNP (n=225)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to treatment</td>
<td>90 (20-205)</td>
<td>63 (16-153)</td>
<td>0.03</td>
</tr>
<tr>
<td>Time to discharge</td>
<td>11.0 (5.0-18.0)</td>
<td>8.0 (1.0-16.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospitalization (%)</td>
<td>85</td>
<td>75</td>
<td>0.008</td>
</tr>
<tr>
<td>Intensive-care unit admission (%)</td>
<td>24</td>
<td>15</td>
<td>0.01</td>
</tr>
<tr>
<td>Total treatment cost</td>
<td>7264 (6301-8227)</td>
<td>5410 (4516-6304)</td>
<td>0.006</td>
</tr>
<tr>
<td>In-hospital mortality (%)</td>
<td>9</td>
<td>6</td>
<td>0.21</td>
</tr>
<tr>
<td>30-d mortality (%)</td>
<td>12</td>
<td>10</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Caveats to NP testing

- Gray Zone
- Renal dysfunction
- Obesity
- Heart Failure with normal levels
“Grey Zone” BNP

Usually from Right Ventricle

- Pulmonary disease
  - COPD with cor pulmonale
  - pulmonary hypertension
- Right ventricular failure
  - from long-standing left ventricular failure
  - right ventricular infarction
- Pulmonary embolism

- Knowledge of baseline BNP levels are important
Renal dysfunction

- NP are retained in patients with renal dysfunction
- Level much higher in HF with same amt of renal dysfunction
- Need to know baseline values
- Even in dialysis patients- NP above baseline might represent volume overload
Obesity

http://go.to/funpic
There appears to be a linear inverse relationship between BMI and NP levels.

Patients who are obese (BMI >30kg/m²) should have their NP doubled to use the standard cut-points.
Refractory Edema

- 63 year old non-obese man with history of coronary artery disease and bypass surgery 6 years ago
- Complains that he has had leg swelling for several years and is now developing abdominal pain
- Physical exam with elevated JVP, hepatomegaly and ascites with a third heart sound
- Echo reveals normal right and left ventricular function
- BNP 84 pg/ml
Why is the BNP level low?

- This is a falsely negative BNP. This patient has heart failure.
- The right ventricle makes BNP when overloaded, so this is a false negative reading.
- The patient has neither left nor right heart failure. Another test is in order.
Constrictive pericarditis
The presence of pericardial calcification on chest x-ray strongly suggests pericardial constriction in patients with symptoms of heart failure.
Normal levels of BNP

- Heart failure
  - Flash pulmonary edema
  - Acute atrial fibrillation
  - Acute papillary muscle rupture
  - Mitral stenosis

- Looks like HF but not!
  - Tamponade
  - Pericarditis
IN ACS--Time Is Myocardium!

So we strive to shorten door to balloon time
So in Acute Decompensated Heart Failure, why don’t we strive to improve door to Diuretic time!!
Sunday in the ER

Is speed important?
Delayed BNP Equals Delayed Treatment

Maisel, Peacock, Fonarow, Jesse et al  JACC 2008
% Rales vs. Quartiles of Diuretic Time & BNP Level

Time to diuretic

Maisel, Peacock, Fonarow, Jesse et al JACC 2008
Mortality (%) vs. Time to IV Diuretic (hours) for different iBNP Levels (pg/mL):

- <1.05
- 1.05-2.22
- 2.23-4.98
- >4.98

- <449
- 450-864
- 865-1738
- >1738
Lets talk about things that lead to a bad pronosis
There is no cardiac biomarker that is as good as a NP level for prognosis.
Multicenter blinded BNP study
N= 464, 90% admitted
If admitted: 11% with BNP < 200
90 day events (CHF visit, admit, death)
  9% if BNP < 200
  29% if BNP > 200
Disconnect between perceived severity and BNP

Maisel AS, JACC. 2004 Sep 15;44(6):1328-33
REDHOT BNP Values & Patient Disposition

- Previous data link high BNP to morbidity & mortality
- Actual BNP values blinded to ED physician
- BNP median values ~22% higher in patients discharged home from ED

At 11 pm that same night, he awoke with severe shortness of breath. His wife called 911 and he was brought back to the same emergency room (different physician).

MA-questions b

- What is going on?  COPD
  Pulmonary embolism
  CHF
  If CHF- what kind and why?

- What test(s) might be helpful at this point?
  - Cardiac markers
  - D-dimer
  - Lower extremity dopplers
  - BNP
The BNP level was 900 pg/ml

- What is going on and why?
- How would you treat this patient?
He was brought to the ICU where he was given lasix 40 mg ivp, diltiazem 10 mg/hour iv (heart rate control) and Natrecor 2mcg/kg bolus followed by .01 mcg/kg/min infusion.

Twenty four hours later he felt much better. His heart rate was back in NSR. His lungs were clear. He had diuresed 3 liters of fluid. Four hours after the discontinuation of Natrecor his BNP level was 150 pg/ml.
Full doppler echocardiographic exam revealed diastolic dysfunction with E/A < .7 and Deceleration time 320 ms (impaired relaxation).

He was placed on an ACE inhibitor and beta blocker and discharged 2 days later.
MA-8- final points

- Patient had COPD with underlying diastolic dysfunction.
- Atrial fibrillation led to severe CHF.
- A BNP level was able to help separate CHF from COPD exacerbation
- Diastolic function is common in the emergency room.
- BNP is elevated in diastolic dysfunction
Assessment of Patient with Dyspnea

For Your Mother

- History, physical exam by top gun attending
- Pulse oximetry
- ECG within 5 minutes
- CBC, chem panel
- BNP or NT-pro BNP
- Troponin
- D-dimer, if indicated
- CXR PA and Lateral
- Other testing and imaging as indicated

Mother-in-law

- Wait in a side room for a few hours
- History, physical exam by 1st year med student
- ABG
- CBC, chem panel
- Portable CXR
History
Physical exam
CXR

NP levels