Medical Management of Acutely Decompensated Heart Failure

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Goals of Acute Heart Failure Therapy

- Alleviate symptoms
- Reduce extracellular fluid volume excess (“congestion”)
- Improve hemodynamics
  - Decrease left and right ventricular filling pressures
  - Increase cardiac output (?)
- Maintain perfusion to vital organs
How Do We Accomplish These Goals?

- With hemodynamic interventions
  - Diuretics
  - Nitrovasodilators
  - Natriuretic peptides
  - Positive inotropic agents
    - Sympathomimetic agents
    - Phosphodiesterase inhibitors
    - Calcium channel sensitizers
  - Mechanical interventions that improve hemodynamics
Pharmacological Approach To Acute Heart Failure Therapy

- **Diuretics to reduce ECF volume**
  - IV loop diuretics ± metolazone/thiazide

- **Intravenous vasodilators to reduce ventricular filling pressures**
  - Nesiritide, nitroglycerin, nitroprusside

- **Intravenous inotropic agents to improve cardiac output**
  - Sympathomimetic agents
  - Phosphodiesterase inhibitors
Importance of Diuretic Therapy in Acutely Decompensated Heart Failure

- Beneficial effects of diuretic therapy:
  - ↓ End-diastolic volume (preload)
  - ↓ Systemic vascular resistance (acutely, may ↑ SVR)
  - ↑ Cardiac output / stroke volume
  - ↓ Congestive symptoms
  - ↑ Exercise capacity

- Key to successful initiation and titration of ACE inhibitors, β-blockers, vasodilators
Tubular Sites of Action of Commonly-used Diuretics

Abraham and Schrier, 1994
Limitations Of Diuretic Therapy

- Electrolyte abnormalities
  - Hypokalemia
  - Hypomagnesemia
  - Hyponatremia
- Volume depletion
- Pre-renal azotemia
- Hyperuricemia
- Diuretic resistance
Loop Diuretics Diminish GFR In Patients with Heart Failure

Gottlieb et al., 2000

Glomerular Filtration Rate (ml/min)

Placebo: 81.5
Furosemide: 63.4

n = 12

p < 0.001
The “Iatrogenic” Cardio-Renal Syndrome of Heart Failure

Diuretic Therapy

- Increased Morbidity and Mortality
- Development of Diuretic Resistance
- Impaired Renal Function
- Decreased Renal Perfusion
- Diminished Blood Flow
- Neurohormonal Activation

Abraham WT, 2004
Ultrafiltration Fluid Removal System

- FDA approved
- Uses peripheral venous access (can also use central access)
- Total extracorporeal blood volume 33 mL
- Designed to remove up to 500 ml of fluid per hour with adjustable flow rates of 10-40 mL/min
- Highly automated, computer controlled operation with simple operator interface
Ultrafiltration versus IV Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure: A Prospective Randomized Clinical Trial

The UNLOAD Trial

Costanzo MR, et al., JACC 2007
Primary End Point: Weight Loss at 48 Hr

- **Ultrafiltration Arm**
  - Weight Loss: $m = 5.0$, CI $\pm 0.68$ kg
  - $(N = 83)$
  - $p = 0.001$

- **Standard Care Arm**
  - Weight Loss: $m = 3.1$, CI $\pm 0.75$ kg
  - $(N = 84)$
### Effects on Worsening Heart Failure Over 90 days

<table>
<thead>
<tr>
<th></th>
<th>UF</th>
<th>SC</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Re-hospitalized %</td>
<td>18</td>
<td>32</td>
<td>0.022</td>
</tr>
<tr>
<td>Re-hospitalizations/patient</td>
<td>0.22</td>
<td>0.46</td>
<td>0.037</td>
</tr>
<tr>
<td>Number of Re-hospitalization days/patient</td>
<td>1.4</td>
<td>3.8</td>
<td>0.022</td>
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<tr>
<td>Days Re-hospitalized</td>
<td>123</td>
<td>330</td>
<td>0.022</td>
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<tr>
<td>(Unscheduled office + ED visits) %</td>
<td>21</td>
<td>44</td>
<td>0.009</td>
</tr>
</tbody>
</table>
Intravenous Positive Inotropic Agents

- Phosphodiesterase inhibitors
  - milrinone
  - enoximone

- Sympathomimetics
  - dopamine
  - dobutamine
  - isoproterenol
  - epinephrine
  - norepinephrine

- Calcium channel sensitizers
  - levosimendan
## Selection of an Inotropic Agent

<table>
<thead>
<tr>
<th></th>
<th>Dobutamine</th>
<th>Milrinone</th>
</tr>
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<tbody>
<tr>
<td>SBP&lt;80</td>
<td>1st choice</td>
<td>Usually in combination with pressor</td>
</tr>
<tr>
<td>Pulmonary HTN</td>
<td>Not a good pulmonary vasodilator</td>
<td>1st choice lowers PVR</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>↑ myocardial O$_2$ demand</td>
<td>1st choice ↓↔ myocardial O$_2$ demand</td>
</tr>
</tbody>
</table>
Limitations Of Positive Inotropic Therapy

- Tolerance/Tachyphylaxis
- Hypotension
- Tachycardia
- Other arrhythmias
  - Ventricular tachycardia
  - Atrial fibrillation/flutter
- Increased mortality?
IV Milrinone During Hospitalization for Decompensated Heart Failure

OPTIME-CHF: In-hospital Adverse Events

- Treatment Failure From Adverse Event (48 h): *P* < 0.001
- Sustained Hypotension: *P* < 0.001
- Acute MI: *P* = 0.18
- Afib: *P* = 0.004
- Mortality: *P* = 0.19

# Hemodynamic Effects of Vasodilators

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>CO</th>
<th>LVFP</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroprusside</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic hBNP</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

CO = cardiac output; HR = heart rate; LVFP = left ventricular filling pressure; SVR = systemic vascular resistance.
Limitations Of Nitrovasodilators

- Tolerance/Tachyphylaxis
- Hypotension
- Toxicity
  - Thiocyanate
  - Cyanide
- Vasoconstrictor activation
- Fluid retention
Natriuretic Peptides

- Produce selective renal afferent arteriolar vasodilation
- Inhibit sodium reabsorption in the collecting duct
- Improve/maintain glomerular filtration
- Inhibit renin and aldosterone (and possibly vasopressin and adrenergic activity)
- Improve systemic hemodynamics
The Natriuretic Peptide Family

- Naturally Occurring
  - ANP - Atrial or A-Type Natriuretic Peptide
  - BNP - Brain or B-Type Natriuretic Peptide
  - CNP - C-Type Natriuretic Peptide
  - DNP - Dendroaspis or D-Type Natriuretic Peptide
  - Urodilatin - Extended form of ANP

- Designer
VMAC Trial: PCWP Through 3 Hours

Added to standard therapy; N = 242

*P<0.05 for nesiritide or placebo vs placebo
† P<0.05 for nesiritide vs. nitroglycerin

Publication Committee for the VMAC Investigators. JAMA. 2002;287:1531
ASCEND-HF Trial

- Landmark trial presented at AHA LBCT Session November 2010
- Largest RCT in ADHF (7,141 subjects)
- Results clearly demonstrate the safety of natriuretic peptides in the treatment of ADHF
- Unambiguously answers the critical questions raised by meta-analyses published in 2005
ASCEND-HF Trial: Primary Endpoint

Co-primary outcome: 30-day all-cause mortality or HF rehospitalization

- **P = 0.31**
- **Hazard Ratio 0.93 (95% CI: 0.81, 1.08)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Nesiritide</th>
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<tbody>
<tr>
<td>30-day Death/HF Rehospitalization</td>
<td>10.1</td>
<td>9.4</td>
</tr>
<tr>
<td>30-day Death</td>
<td>4.0</td>
<td>3.6</td>
</tr>
<tr>
<td>HF Rehospitalization</td>
<td>6.1</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Risk Diff (95% CI)
- 30-day Death/HF Rehospitalization: -0.7 (-2.1; 0.7)
- 30-day Death: -0.4 (-1.3; 0.5)
- HF Rehospitalization: -0.1 (-1.2; 1.0)
Investigational Strategies in ADHF

- Second-Generation Natriuretic Peptides
  - Urodilatin
  - CD-NP
- Relaxin
- Nitroxylin Donors
- Vasopressin Antagonists
- Others
Approach to Acute Therapy in Volume Overloaded Heart Failure Patients

Clinical Congestion
- Adequate Perfusion: IV Diuretics
- Reduced Perfusion: IV Diuretics plus IV Vasodilators
- Cardiogenic Shock: IV Diuretics plus IV Inotropes