Management of Acute Heart Failure and Cardiogenic Shock

Brittany D. Bissell, Pharm.D.
PGY-2 Critical Care Pharmacy Resident
Jackson Memorial Hospital | Miami, Florida

www.fshp.org

TECHNICIAN OBJECTIVES

• Explain management principles for left ventricular failure
• Describe treatment options for end-stage heart failure
• List pharmacologic therapies for cardiogenic shock

DISCLOSURE STATEMENT

I have no actual or potential conflicts of interest in relation to this presentation.

PHARMACIST OBJECTIVES

• Assess the hemodynamic dysregulation implicated in the pathophysiology of heart failure
• Develop recommendations for preload optimization
• Investigate evidence for current options for the management of cardiogenic shock
PATHOPHYSIOLOGY OF ACUTE HEART FAILURE

HEMODYNAMIC DYSREGULATION

- Cardiac changes
  - Decreased stroke volume (SV)
  - Increased end-diastolic pressure
- Vascular changes
  - Increased systemic vascular resistance
  - Increased venous pressure
  - Decreased arterial pressure
  - Decreased compliance

CARDIAC PHYSIOLOGY

Inotropy: Contractile force
Afterload: Resistance against ejection
Preload: Pre-contraction stretch of cardiac myocyte

Heart Rate → CARDIAC OUTPUT → Stroke Volume

Sinoatrial node automaticity
Vagal innervation
Sympathetic activity and catecholamines

PATHOPHYSIOLOGY

POOR CARDIAC OUTPUT → ORGAN HYPOPERFUSION

Afterload Mismatch
Diastolic Dysfunction
Neurohormonal Activation
Fluid Overload
Insulting Event
### Acute Management

#### Cardiac Function Parameters

- **Central venous pressure (CVP)**
  - Representative of right ventricular end diastolic pressure / preload
  - Normal: 2 - 6 mmHg
- **Cardiac index (CI)**
  - Correction of cardiac output for body surface area
  - Normal: 2.5 - 4.0 L/min/m²
- **Systemic vascular resistance index (SVRI)**
  - Resistance of blood flow by systemic vasculature corrected for surface area
  - Normal: 800 - 1200 dynes - sec/cm⁵
**Preload Optimization**

**Optimization of Preload**

**Loop Diuretic Resistance**

**Diuretic Resistance Management**

- **Loop Diuretic**
- **Intravenous Loop**
  - **Dose:** No differences in response with continuous infusion
- **Alternative Loop**
- **Combination Therapy**
  - Dose-dependent mortality with furosemide over 300 mg

Alternative Therapies
- Dopamine
- Hypertonic saline
- Ultrafiltration
**CHOICE OF DIURETIC**

**STANDARD THERAPY = FUROSEMIDE**

**TORSEMIDE**
- Liver clearance and increased bioavailability
- Correction of collagen cross-linking and left ventricular stiffness
- Decreased sympathetic nerve response and remodeling
- Significant improvement in NYHA class compared to furosemide
- Decreased mortality compared to furosemide

**COMBINATION THERAPY**

**DOPAMINE**

- 5 mcg/kg/min with furosemide 5 mg/hour
- As effective as furosemide 20 mg/hour with decrease in worsened renal function

**DAD-HF**
- 2 mcg/kg/minute
- No effect on urine volume or cystatin C

**ROSE**
- 5 mcg/kg/minute
- No difference in urine output or mortality

**HYPERTONIC SALINE**

- Mobilization of extravascular fluid into the intravascular space
- Increases cardiac output, renal blood flow, and quick excretion

**SMAC-HF Trial**
- 150 mL of hypertonic saline twice daily
  - Increased diuresis
  - Decreased creatinine
  - Reduction in hospitalization and readmission
  - Decreased mortality
ULTRAFILTRATION

Semipermeable membrane yields iso-osmotic ultrafiltrate
Added benefit of removal of myocardial depressant cytokines

RAPID-CHF
• 8 hour ultrafiltration versus pharmacologic treatment
• Increased fluid removal
• No difference in 24-hour weight loss

UNLOAD
• Ultrafiltration versus intravenous diuretics
• Increased fluid removal
• No difference in dyspnea
• Decrease in rehospitalization and hospital visits

CARRESS-HF
• Fixed-rate ultrafiltration versus stepwise diuretics
• Increased serum creatinine
• Increased adverse events

TERMAATEN, ET AL.

AFTERLOAD OPTIMIZATION

NITRATE THERAPY

Nitroglycerin
• 5-200 mcg/min
• Primarily venodilation with coronary vasodilation
• Decreased rates of endotracheal intubation and ICU admission
• Tachyphylaxis problematic

Nitroprusside
• 0.25-3 mcg/kg/min
• Primarily arterial with some venous vasodilation
• Retrospective study evidence
• Concern in renal dysfunction

**NITRATE ALTERNATIVES**

**NESIRITIDE**
- Arterial and venous vasodilation with natriuretic effects
- Significant improvement in cardiac output and dyspnea
- Increased short-term mortality and symptomatic hypotension

**CLEVIDIPINE**
- Selective arterial vasodilation
- 2 - 32 mg/hour
- Rapid reduction in blood pressure without worsening of heart failure
- Higher rates of target blood pressure and dyspnea improvement compared to standard of care

**CARDIOGENIC SHOCK**

**SEVERE CIRCULATORY FAILURE**

**HYPOTENSION + HYPOPERFUSION**

- Less than 5% of acute heart failure cases
- 80% of cases secondary to acute coronary syndromes with or without mechanical complications
- 40% short-term mortality rates

**INOTROPIC SUPPORT**

**ACUTE MANAGEMENT**

- Cardiogenic Shock
- Identify Cause
- Cath Lab or Surgery
- Respiratory Distress
- Noninvasive Ventilation
- Invasive Ventilation

- Hypoperfusion
- Invasive Monitoring
- Inotropes & Vasopressors
- Mechanical Support
- Renal Replacement
**POSITIVE PRESSURE VENTILATION**

Positive end-expiratory pressure (PEEP) = Aveolar pressure above atmospheric pressure after expiration

- Decreased ...
  - Transthoracic pulmonary pressure decreases LV afterload
  - Venous return decreases preload
  - Breathing efforts decreases metabolic demand
  - Hypoxia decreases pulmonary vasoconstriction
- Studies show increased cardiac output, decreased pulmonary pressures, improved oxygenation, increased ventilator weaning, and increased survival

**DOSE-DEPENDENCY OF DOPAMINE**

Low doses (<5 mcg/kg/minute) vasodilate, including coronary and renal arteries
- Increased renal perfusion not seen in cohort studies

Intermediate doses (5 - 10 mcg/kg/minute) produce inotropic and chronotropic effects

High doses (>10 mcg/kg/minute) induce vasoconstriction and increases in afterload

**INOTROPIC SUPPORT**

DOPAMINE  DOBUTAMINE  MILRINONE

**DOPAMINE**

Comparison of Dopamine and Norepinephrine in the Treatment of Shock

Daniel De Backer, M.D., Ph.D., Patrick Biston, M.D., Jacques Devriendt, M.D., Christian Mail, M.D., Didier Choukroun, M.D., Cesar Mafeza, M.D., Alexandre Brassard, M.D., Pierre Defrance, M.D., Philippe Cottignies, M.D., and Jean-Louis Vincent, M.D., Ph.D., for the SOAP II Investigators.

1679 patients receiving dopamine 2–20 mcg/kg/minute or norepinephrine 0.02-0.19 mcg/kg/minute for shock
**DOBUTAMINE**

- Dose range: 5-20 mcg/kg/minute
- β effects improve myocardial contractility and output
- Increased left ventricular end diastolic pressure
- May induce hypotension
- Risk of eosinophilic myocarditis and arrhythmias
- Increased myocardial oxygen demand

---

**MILRINONE**

- Inhibits phosphodiesterase-3, preventing cAMP degradation
- Positive inotrope activity independent of β stimulation
- Reduction of pulmonary artery pressure
- Significantly higher rates of hypotension compared to placebo
- Dose range: 0.25 - 0.75 mcg/kg/min
- 949 patients receiving milrinone or placebo for 48-72 hours

---

**Heart Failure Etiology and Response to Milrinone in Decompensated Heart Failure**

Results From the OPTIME-CHF Study

G. Michael Felker, MD,⁎ Raymond L. Bzura, MD,⁎ A. Brakley Chadwick, MD,⁎ Jeffrey D. Leinberger, PhD,⁎ Michael S. Cuff, MD,⁎ Robert M. Califf, MD,⁎ Mihai Ghemeneh, MD,⁎ Christopher M. O'Connor, MD,⁎ for the OPTIME-CHF Investigators

---

**In-Hospital Mortality in Patients With Acute Decompensated Heart Failure Requiring Intravenous Vasoactive Medications**

An Analysis From the Acute Decompensated Heart Failure National Registry (ADHERE)

Mortality Odds Ratios in Pair-Wise Treatment Comparisons

<table>
<thead>
<tr>
<th>Test</th>
<th>NTG (n = 6,598)</th>
<th>NTG (n = 5,310)</th>
<th>NES (n = 4,683)</th>
<th>NES (n = 4,270)</th>
<th>NES (n = 4,933)</th>
<th>NES (n = 3,943)</th>
<th>DOB (n = 3,493)</th>
<th>DOB (n = 3,168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEL (n = 1,806)</td>
<td>0.99 (0.97-1.02)</td>
<td>0.99 (0.97-1.02)</td>
<td>0.98 (0.96-1.01)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.99 (0.97-1.01)</td>
<td>1.00 (0.98-1.03)</td>
<td>1.00 (0.98-1.03)</td>
</tr>
<tr>
<td>MEL (n = 1,806)</td>
<td>0.99 (0.97-1.02)</td>
<td>0.99 (0.97-1.02)</td>
<td>0.98 (0.96-1.01)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.99 (0.97-1.01)</td>
<td>1.00 (0.98-1.03)</td>
<td>1.00 (0.98-1.03)</td>
</tr>
<tr>
<td>NTG (n = 6,598)</td>
<td>0.99 (0.97-1.02)</td>
<td>0.99 (0.97-1.02)</td>
<td>0.98 (0.96-1.01)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.99 (0.97-1.01)</td>
<td>0.99 (0.97-1.01)</td>
<td>1.00 (0.98-1.03)</td>
<td>1.00 (0.98-1.03)</td>
</tr>
</tbody>
</table>

MECHANICAL CIRCULATORY SUPPORT

Blood removed from femoral vein or inferior vena cava
Blood returned to right heart or femoral artery
Separate modes for goal outcomes

MECHANICAL CIRCULATORY SUPPORT

Inflation facilitates coronary perfusion with increased diastolic pressure
Deflation augments left ventricular (LV) ejection through negative pressure

IABP INDICATIONS FOR USE

Refractory Heart Failure
Ventricular Arrhythmias

Acute Coronary Syndromes
- Cardiogenic shock in STEMI
- High-risk PCI or CABG
- STEMI and NSTEMI complications
- Refractory angina
**Anticoagulation with IABP**

- **Randomized controlled trial**
- Heparin vs. placebo
- Ischemia 0.2 vs. 2.4%
- Bleeding 14.2 vs. 2.4%

- **2008**
  - Prospective cohort
  - Heparin vs. selective
  - Ischemia 0.5 vs. 0%
  - Bleeding 38.5 vs. 25.4%

- **2012**
  - Retrospective study
  - No anticoagulation
  - Ischemia 3.4%
  - Bleeding 4.2%

**Bottom Line:** Anticoagulation warranted for primary indications

**Mechanical Support**

- 2005: LVAD, RVAD, LVAD+RVAD
- 2006: LVAD, RVAD, LVAD+RVAD
- 2007: LVAD, RVAD, LVAD+RVAD
- 2008: LVAD, RVAD, LVAD+RVAD, TAH
- 2009: LVAD, RVAD, LVAD+RVAD, TAH
- 2010: LVAD, RVAD, LVAD+RVAD, TAH, VAD+ECMO, ECMO
- 2011: LVAD, RVAD, LVAD+RVAD, TAH, VAD+ECMO, ECMO
- 2012: LVAD, RVAD, LVAD+RVAD, TAH, VAD+ECMO, ECMO

**Intermacs Heart Failure Profiles**

- 7 - Advanced NYHA III
- 6 - Exertion limited
- 5 - Exertion intolerant
- 4 - Resting symptoms
- 3 - Inotrope dependent
- 2 - Progressive decline
- 1 - Critical cardiogenic shock

**Definitive Therapy Required**

- Months
- Days
- Hours

**Criteria for Implantation**

- Peak oxygen consumption <14 mL/kg/min or Inability to perform exercise test
- NYHA functional class IV
- Failed optimal management for 45/60 days or 7 days IABP-dependent or 14 days inotrope-dependent
- Left ventricular ejection fraction <25%
**MECHANICAL SUPPORT**

**HEARTMate II**
- Axial flow
- Mechanical bearings
- Larger in size
- FDA approved for BTT: 75-90% survival
- FDA approved for DT: 58-61% survival
- Increased hemolysis and thrombosis

**HEARTWare**
- Centrifugal flow
- Hydrodynamic bearings
- Less experience with use
- FDA approved for DT: 90.7% survival
- DT trial completed
- Increased stroke and bleeding

---

**ANTICOAGULATION BRIDGING**

**HEARTMate II Retrospective Sub-analysis**
- Stratified by PTT values
- PTT <40 associated with significantly less transfusions
- No difference in stroke or pump thrombosis
- Post-operative heparin an independent risk factor for bleeding

HeartMate II: No bridge
HeartWare: Heparin 10 unit/kg/hour
Target PTT: 40-50 sec to 50-60 sec

---

**ANTIPLATELET THERAPY**

**HeartWare ADVANCE Trial**
- Aspirin (ASA)
- Warfarin to INR 2-3
- INR<2 or ASA ≤81 mg associated with increased thrombotic events
- Pump exchange rates decreased 55% with increase to aspirin 325 mg

HeartWare: ASA 325 mg daily

**HeartMate II Retrospective Cohort**
- Aspirin 325 mg
- Warfarin to INR 2-3
- ~50% dipyridamole use
- Significantly higher bleeding rates versus thrombotic events
- Aspirin dose changed to 81 mg

HeartMate II: ASA 81 mg daily

---

**ANTICOAGULANT THERAPY**

**General Consensus:** Warfarin after chest-tube removal days two to three

**Warfarin**
- Wide range of INR goals
- Increased thrombosis with INR <1.5
- 31-51% of time spent within goal
- Increased bleeding with INR >2.5

**Dabigatran**
- Decreased major bleeding compared to warfarin (n=7)
- Increased thromboembolism in mechanical valve population
- Ongoing study (EudraCT: 2010-024534-38)

HeartWare: Warfarin to INR 2-3
HeartMate II: Warfarin to INR 2-2.5
EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

VENOVENOUS (VV)
- Removes venous blood
- Returns to venous system
- CO₂ and O₂ exchange
- Pulsatile flow

VENOARTERIAL (VA)
- Returns to arterial system
- CO₂ and O₂ exchange
- Augmentation of cardiac output
- Nonpulsatile flow

Heparin Anticoagulation

- Historical standard with most evidence
- Xa and thrombin inhibition
- 40-80 units/kg once followed by 10-30 units/kg/hour
- 1-2 hour half-life
- Problematic in antithrombin deficiency and heparin-induced thrombocytopenia

Anticoagulation Alternatives

Heparin Anticoagulation

- Historical standard with most evidence
- Xa and thrombin inhibition
- 40-80 units/kg once followed by 10-30 units/kg/hour
- 1-2 hour half-life
- Problematic in antithrombin deficiency and heparin-induced thrombocytopenia

Antithrombin (AT) Deficiency
- Antithrombin decreases with ECMO
- Hemodilution & coagulation
- Decreased heparin responsiveness
- Sudden rise in plasma-free hemoglobin
- FFP administration may overcome

Argatroban
- 0.25 - 1 mcg/kg/minute
- T₁/₂: 39-51 min
- Evidence in case series only
- Significant thrombin decrease compared to heparin
- Higher bleeding rates seen – lower doses warranted

Bivalirudin
- 0.08-0.2 mg/kg/hour
- T₁/₂: 0.25-3.5 hours
- Operative use more common
- Guideline HIT recommendation
- Metabolized by thrombin - levels depleted in areas of stasis
**LEVOSIMENDAN**

Increased inotropy via increased calcium sensitivity through troponin C binding

Increased vasodilation through potassium channels and reduction of preload and afterload

**MORTALITY**

LIDO Trial (n=203)
- Increased cardiac output and decreased PCWP
- Lower 1- and 6-month mortality

SURVIVE Trial (n=1327)
- No mortality difference at 180 days

**ADVERSE EVENTS**

RUSSLAN Trial (n=504)
- No association with hypotension or clinically significant ischemia

REVIVE-II Trial (n=600)
- Increased adverse events, including hypotension and arrhythmias despite symptom improvement

---

**ULARITIDE**

Natriuresis

Diuresis

Vasodilation

Synthetic form of urodilatin with resistance to degradation

**MORTALITY**

SIRIUS I
- 15- and 30-ng/kg/min
- Improvement in dyspnea
- Decreased mortality

SIRIUS II
- 15- and 30-ng/kg/min
- Improved dyspnea
- Improvement pulmonary pressures
- Decreased hospitalization
- Decreased mortality

TRUE-AHF
- 15- and 30-ng/kg/min

---

TRUE-AHF

Co-Primary Outcome:
- Improved global assessment at 6, 24, and 48 hours without meeting criteria for worsening, including:
  - Death within 48 hours
  - Worsening of disease warranting intervention
  - Worsening global assessment

Co-Primary Outcome:
- Freedom from cardiovascular mortality

Secondary Outcomes:
- N-terminal pro-BNP changes
- All-cause mortality and rehospitalization
- Cardiovascular rehospitalization

RELAX-AHF

30 mcg/kg/day serelaxin versus placebo

Significant improvement in symptomatic visual analog scale

Significantly reduced hospital stay, time to dyspnea improvement, and worsening of heart failure

SERELAXIN

Human recombinant form of relaxin

Anti-inflammatory and anti-fibrotic properties

Inhibition of angiotensin II and endothelin receptors, systemic and renal vasodilation

Upregulator of endothelin B receptors and nitric oxide production

RELAX-AHF

**Beta-Blocker Considerations**

- Bisoprolol, carvedilol, and metoprolol succinate
- Medication correlation with decompensation
- Half-life longer than initial critical period
- Paradoxical activation of sympathetic nervous system

**Beta-Blocker Therapy**

**Short-Term Mortality or Rehospitalization**

**Assessment Question**

*Increasing preload and/or inotropy are strategies for optimization of cardiac output.*

**TRUE**
A primary principle in the management of left heart failure is reduction of venous congestion.

**TRUE**

The patient receives a HeartMate II ventricular assist device. The patient should be bridged with heparin.

**FALSE**

**REFERENCES**

REFERENCES