**Remembering the forgotten ventricle:**
Management of acute right ventricular failure in Pulmonary Hypertension

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**Objectives**

- Review the descriptive and hemodynamic classification of pulmonary hypertension
- Discuss the significance of acute right heart failure (ARHF) in PH
- Discuss management principles for ARHF in setting of pre-capillary vs. post-capillary PH, including the role of:
  - Oxygenation
  - Pulmonary vasodilator therapies
  - Inopressors
  - MCS, transplantation

**Pulmonary Hypertension (PH)**

Sustained elevation of mean pulmonary artery pressure*:

\[ \text{mPAP} > 25 \text{ mmHg} \]

* mPAP = Normal: 8 - 20 mmHg
  ePASP Echo Doppler > 40 mmHg

**PH ≠ PAH**
GROUP 1 – Pulmonary Arterial Hypertension (PAH)

1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and Toxin-Induced
1.4 Associated with:
   1.4.1 Connective Tissue Disease
   1.4.2 Human Immunodeficiency Virus (HIV) Infection
   1.4.3 Portal Hypertension
   1.4.4 Congenital Heart Disease
   1.4.5 Schistosomiasis

GROUP 2 – PH Due to Left Heart Disease

2.1 LV Systolic Dysfunction (HFrEF)
2.2 LV Diastolic Dysfunction (HFpEF)
2.3 Valvular Disease
2.4 Congenital/Acquired Left Heart Inflow/Outflow Tract Obstruction and Congenital Cardiomyopathies

GROUP 3 – PH Due to Lung Disease and/or Hypoxia

3.1 Chronic Obstructive Pulmonary Disease
3.2 Interstitial Lung Disease
3.3 Other Pulmonary Diseases With Mixed Restrictive and Obstructive Pattern
3.4 Sleep-disordered Breathing
3.5 Alveolar Hypoventilation Disorders
3.6 Chronic Exposure to High Altitude
3.7 Developmental Lung Diseases

GROUP 4 – Chronic Thromboembolic PH (CTEPH)

GROUP 5 – PH With Unclear Multifactorial Mechanisms

5.1 Hematologic Disorders: Chronic Hemolytic Anemia, Myeloproliferative Disorders, Splenectomy
5.2 Systemic Disorders: Sarcoidosis, Pulmonary Histiocytosis, Lymphangioleiomyomatosis
5.3 Metabolic Disorders: Glycogen Storage Disease, Gaucher Disease, Thyroid Disorders
5.4 Others: Tumoral Obstruction, Fibrosing Mediastinitis, Chronic Renal Failure, Segmental PH


• Single center study from Australia
• 6,994 screened → 936 pts (9.1%) with PH on ECHO Doppler (defined as ePASP >40 mmHg)

Etiology of PH on Echocardiogram:

PH Hemodynamic Profiles:

Vachiery JL et al, J Am Coll Cardiol 2013;62: D100-8
Fang J et al, J Heart Lung Transplant 2012;31:153-33
**Group 1 – PAH**

Group 3, 4, 5

Pre-capillary PH
- PA mean ≥ 25mmHg
- PAWP < 15 mmHg
- TPG > 12
- PVR > 3 Wu

Modified from:
- Vachiery JL et al. *J Am Coll Cardiol*. 2013;62:D100-8

**Group 2:** PH due to left heart disease

- LV systolic dysfunction
- LV Diastolic dysfunction
- Valvular disease
- LH obstruction & Congenital CMP

**Isolated Post-Capillary PH**
- PAWP>15 mmHg
- TPG > 12
- PVR in range

**Combined post- & pre-capillary PH**

- Left sided filling pressure
- Neurohormones, cytokines, other mediators

**Normal**

**Endothelin Receptor Antagonists (oral)**
- Bosentan
- Ambesnten
- Macitentan

**Phosphodiesterase Type-5 Inhibitors (oral)**
- Sildenafil
- Tadalafil

**Soluble Guanylate Cyclase Stimulators (oral)**
- Riociguat (also approved for CTEPH)

**Prostacyclin Receptor Agonist (oral)**
- Selexipag

**Prostacyclin Derivatives**

- Epoprostenol: IV
- Iloprost: inhalational
- Treprostinil: inhalational, oral, SQ or IV
Pulmonary hypertension (PH) from any etiology is associated with:

- Worse prognosis due to right heart failure
- Increased morbidity and mortality
- Reduced exercise capacity

Working Definition of Right Heart Failure

A clinical syndrome due to an alteration of structure and/or function of the right heart system that leads to a sub-optimal delivery of blood flow to the pulmonary circulation and/or elevated venous pressures - at rest or with exercise.
**PAH: It's all about the RV!!**


![Graph showing survival rates for different RV function levels](image1)

- RVEF > 35%, PVR < 650 (n=36)
- RVEF > 35%, PVR > 650 (n=20)
- RVEF < 35%, PVR < 650 (n=13)
- RVEF < 35%, PVR > 650 (n=41)

**p < 0.01**

**PH in LHD: It's all about the RV!**


![Graph showing survival rates for different RV function levels](image2)

- Group 1: Normal PAP, preserved RVEF
- Group 2: Normal PAP, low RVEF
- Group 3: High PAP, preserved RVEF
- Group 4: High PAP, low RVEF

**P<0.001**

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**Prediction of right ventricular failure after ventricular assist device implant: systematic review and meta-analysis of observational studies**

**LVAD outcomes: It's all about the RV (RV/PA coupling)**


<table>
<thead>
<tr>
<th>Category</th>
<th>High Risk Variables Predicting RVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td>Age, Female gender</td>
</tr>
<tr>
<td>Clinical setting</td>
<td>Need for mechanical ventilation, Need for dialysis/CRRT</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>High INR, High NT-proBNP (heterogenous)</td>
</tr>
<tr>
<td>Hemodynamic (RHC)</td>
<td>Low RVSWI, High CVP</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Moderate to severe RVD, Elevated RV/LV ratio, Low RV free wall longitudinal systolic strain</td>
</tr>
</tbody>
</table>

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**Pathophysiology of RV Failure in PH**

De Marco T. Advances PH. 2005;4:16
Voelkel et al. Circ. 2006;114:1883
Pathophysiology of RV Failure in PH

- Pulmonary hypertension → RV Pressure overload
- Adaptive RV hypertrophy
- Decreased wall stress
- Maladaptive RV hypertrophy & fibrosis
- Diastolic dysfunction

Compensated Phase
- Normal CO
- Normal RAP

Decompensating Phase
- Higher RAP to maintain adequate CO
- RV remodeling

De Marco T. Advances PH 2005;4:16
Nootens et al. J Am Coll Cardiol 1995;26:1581
Voelkel et al. Circ 2006;114:1883

Cont.

RV dilation & systolic failure

RV ischemia:
- ↑ Wall stress & heart rate
- ↑ MVO₂
- ↓ Coronary perfusion gradient (↓ DBP, ↑RV/EDP)
- Tricuspid regurgitation
- Decreased LV compliance/preload (VI):
  - Inter-ventricular septal shift
  - ↑ Intrapericardial pressure
  - LV transmural FP = LVEDP-IPP
  - ↓ LV myocardial congestion

Compensated Phase
- ↑ RAP ↓ CO
- Congestive hepatopathy/ascites/peripheral edema
- Renal congestion
- Hypoperfusion
- Hypoxemia (PFO)
- Acidosis
- Life-threatening dysrrhythmias

De Marco T. Advances PH 2005;4:16
Haddad et al. Circ 2008;117;1717

Measuring RV systolic function

- TAPSE (Tricuspid annular plane systolic excursion)
  - TAPSE < 1.6 indicates RV systolic dysfunction
- Fractional area change (FAC)
  - Two-dimensional FAC (as a percentage) provides an estimate of RV systolic function.
  - Two-dimensional FAC < 35% indicates RV systolic dysfunction.
- Tissue doppler S'
  - Easy to measure, reliable and reproducible
  - S' velocity < 10 cm/s indicates RV systolic dysfunction.

De Marco T. Advances PH 2005;4:16
Haddad et al. Circ 2008;117;1717
Management of Acute Right Heart Failure (ARHF) in PH

ARHF: Goals of Management

- **Immediate**
  - Restore oxygenation
  - Treat congested/volume overload state
  - Restore vital organ perfusion (kidneys, brain, heart, liver)

- **Short Term**
  - Identify and treat precipitating factors
  - Initiate/readjust maintenance regimen
  - Minimize ICU time and length of stay

- **Intermediate and Long Term**
  - Prevent early readmission
  - Optimize medical regimen to
    - Alleviate symptoms
    - Slow disease progression
    - Reduce morbidity & mortality
    - Successfully bridge patients to more definitive therapy
      - PAH → lung tx
      - PH in LHD with VAD → Heart Transplant

Medical Management Principles in ARHF

- **Identify and Treat Triggering Factor(s)**

- **Reduce RV Afterload**
  - External (PVR, PAC)
  - Internal (Wall Stress)

- **Optimize Preload**

- **Optimize Cardiac Output**
  - CVO2 >65%, CI >2.0 l/min/m²

- **Optimize Perfusion Pressure**

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Medical Management Principles in ARHF

- Identify and Treat Triggering Factor(s)

- Reduce RV Afterload:
  - External (PVR, PAC)
  - Internal (Wall Stress)
  - iNO, IV and/or inhaled Prostanoids (PAH)
  - PDE5 inhibitors (IV, oral); others
  - Optimal fluid management

- Optimize Preload

- Optimize Cardiac Output
  - CVO2 >65%, CI >2.0 l/min/m²

- Optimize Perfusion

Reducing RV External Afterload (PVR): Pulmonary Vasodilators - General Considerations:

- Use of pulmonary vasodilators in chronic PAH differs from acute PH/RH failure
- Potential adverse hemodynamic effects of non-selective pulmonary vasodilators
  - V/Q mismatch
  - Inhaled treatments most selective
  - iNO most selective; no effect on SVR, but may lead to pulmonary edema in PH due to LHD
  - Systemic administration of pulmonary vasodilators can induce hypotension
  - In presence of fixed pulmonary venous hypertension (PVOD), worsen RV ischemia
  - Monitor renal function closely!!

Reducing RV External Afterload (PVR): Pulmonary Vasodilators

- Oxygen
  - Aim for SpO2 >90%
  - Avoid intubation in severe PAH → cardio-circulatory collapse
- Inhaled NO in pre-capillary PH (PAH)
  - selective pulmonary vasodilator
  - PVR, no Δ on SVR, MAP
  - no V/Q mismatch
- Other inh. Prostanoids (iloprost, epoprostenol) beneficial in pre-capillary PH (PAH)
  - enhanced effect with PDE 5-Inhibitors
- IV, oral PDE-5 Inhibitors

PH in LHD: iNO

19 patients with class III (n=5) to IV (n=14) HF; mean PVR 2.8 WU

Protocol: 80 ppm inhaled nitric oxide (iNO) over 10 minutes
Effect of INO On Pulmonary Circulatory In Setting of PVH

- PA Vasodilation
- PA flow
- No venous dilation (inactivated by Hgb)

Reducing RV External Afterload (PVR, ↓PAC): Pulmonary Vasodilators

- IV prostacyclin derivatives initial treatment of choice in PAH (epoprostenol, treprostinil, iloprost)
  - All reduce PVR and improve RV performance
  - Epoprostenol preferred agent in ARHF
    - Short acting
    - Shown to improve survival
- Caveat: systemic hypotension which can limit use
  - May need concomitant pressors
  - Avoid tachyarrhythmia

Reducing RV External Afterload (PVR, ↓PAC): Pulmonary Vasodilators

- In severe HF: ↓PCWP and ↓CO
  - Oral or IV sildenafil may provide a transition method from INO or inhaled epoprostenol

Sildenafil in PH due to Advanced HF

- 14 pts with AHF (EF<24±14%) and Cpc PH refractory to milrinone, dobutamine, nitroprusside, nesiritide
  - Sildenafil 25-50 mg administered orally q 8hr <3 doses
  - 93% of pts ↓mPAP >20%; 20% pts ↓PVR/SVR (relative PA selectivity); 50 mg more effective; sildenafil safe & effective to improve candidacy for OHT

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Post-sild.</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPAP (mmHg)</td>
<td>44±11</td>
<td>31±14</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>25±2</td>
<td>18±2</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>2.4±0.9</td>
<td>2.0±1.0</td>
</tr>
<tr>
<td>SVR (dyns-sec-cm⁻⁵)</td>
<td>311±119</td>
<td>193±114</td>
</tr>
<tr>
<td>PVR (dyne-sec-cm⁻⁵)</td>
<td>106±23</td>
<td>101±21</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>102±15</td>
<td>102±11</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td>82±13</td>
<td>82±11</td>
</tr>
</tbody>
</table>

Wall SJ et al. J Am Coll Cardiol 2000;36:1940
Kazemi S et al. Am J Cardiol 2001;87:1161
Dugas B et al. J Am Coll Cardiol 2000;36:1940
Haddad R et al. J Am Coll Cardiol 2000;36:1161
De Marco T. Advances PH 2005; 4:16

De Marco T. Advancing Heart Failure: From Basic to Clinical Science 2008; 4:15
Hemodynamics were collected and analyzed both pre and post (within 48-72 hrs) LVAD implantation on a cohort of 64 HFrEF pts. RV afterload almost always declines with LVAD insertion and does so rapidly.

### LVADs Decrease "Fixed" PH in Cardiac Transplant Candidates (Reduction in Left Sided Filling Pressures)

- Prospective, 6 week study
- N= 35 pts
- Severe HF and indication for LVAD
- "Fixed" Cpc-PH, PVR >3.5 WU despite vasodilators/inodilators
- RV cath before LVAD, then 3 days and 6 weeks post- LVAD
- Device: MicroMed DeBakey (24), DuraHeart (3), Novacor (8)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 Days</th>
<th>6 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPA pressure</td>
<td>44.9 ±6.3</td>
<td>25.4 ±4.3*</td>
<td>18.4 ±3.9*</td>
</tr>
<tr>
<td>PAP pressure</td>
<td>50.4 ±9.6</td>
<td>33.0 ±7.1*</td>
<td>26.8 ±4.6*</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>3.1 ±0.6</td>
<td>5.7 ±0.7*</td>
<td>4.0 ±0.9**</td>
</tr>
<tr>
<td>PVR (Wu units)</td>
<td>5.1 ±2.6</td>
<td>2.9 ±1.3*</td>
<td>2.0 ±0.8*</td>
</tr>
</tbody>
</table>

* P< .0001; **P< .002

**TPG ↓ from >16 to <8 mmHg**

### PDE-5 Inhibitor Treatment for Persistent PH after MCS

- **Study**
  - Tedford et al. 2008
- **N**
  - LVAD: 138
- **Design**
  - N=58, no-in PVR 1-2 wks post LVAD despite ↓ in RVAP
  - 26 consecutive pts received sildenafil (mean dose 52 mg TID)
  - 32 controls
- **Results**
  - Sildenafil Group (12-15 wks post-LVAD)
    - PVR ↓ 5.87± 1.9 to 2.96± 0.92**
    - MPAP↓ 36.5 ±24.3 to 24.3 ± 9.6**
  - PVR sign. lower in sildenafil vs P placebo vs control
  - Sildenafil resulted in improved RV function (dp/dt, TAPSE) vs control

* *P< .001

**In patients with persistent mixed PH after LVAD, sildenafil is a useful adjunctive therapy to ↓ PVR and potentially facilitate heart transplantation**

### Medical Management Principles in ARHF

- Identify and Treat Triggering Factor(s)
  - Reduce RV Afterload:
    - External (PVR, PAC)
    - Internal (Wall Stress)
  - Optimize Preload
    - Hypovolemia ➔ IV diuresis/hemofiltration
    - Hypovolemia with hypoperfusion (no evidence for congestion, rare) ➔ Administer fluid
  - Optimize Cardiac Output
    - COV2 >55%, CI >2.0 l/min/m2
  - Optimize Perfusion Pressure

Reduce RV internal afterload (Wall Stress ≈ P x R/h)
Decompress RV to ↓ preload/wall stress ➔ ↓MVO₂, ↑ CPP, ↓ RV ischemia; ➔ improve LV filling and systemic CO; relieve organ congestion

- Avoid volume loading in setting of hypotension or pre-renal azotemia
  - No benefit from RV Frank-Starling mechanism
  - Dilates RV ➔ ↓ LV filling, ↓ CO
- Diuretics
  - Intermittent or continuous infusion loop diuretics, +/- thiazide, +/- aldosterone antagonists
- Mechanical fluid removal: CVVH/Aquapheresis

Augment RV contractility
- Inotropes
  - Dobutamine/dopamine
  - Other adrenergic agents (NE, epinephrine)
  - Milrinone in PH due to LHD (Ipc-PH, Cpc-PH)
  - Addition of IV epoprostenol (PAH)
  - Combination
    - Caveat: tachyarrhythmias, hypotension (HTN concerning esp with milrinone in PAH)

Medical Management Principles in ARHF

- Identify and Treat Triggering Factor(s)
- Reduce RV Afterload:
  - External (PVR, ↓ PAC)
  - Internal (Wall Stress)

- Optimize Preload
  - Dobutamine/dopamine (monitor for tachyarrhythmia)
  - Milrinone (caveat: systemic hypotension in PAH)
  - Favored in PH due to LHD

- Optimize Cardiac Output
  - CVO₂ >65%, CI >2.0 l/min/m²

Optimize Perfusion Pressure
- Norepinephrine
- Vasopressin

Medical Management Principles in ADRHF
Proposed Algorithm: Treatment of ADRHF in PAH

Identify and treat underlying precipitating factors
- Dietary indiscretion, infection, anemia/erythrocytosis, thyroid disorders, dysrhythmia, ischemia, PE, NSAID

Restore oxygenation
- Supplemental high flow O2
- Avoid mechanical ventilation
- Avoid excess PEEP
- Avoid acidosis

Restore vital organ perfusion
- Pulmonary vasodilators (afterload)
- O2/iNO/prostanoids (IV, inh.)
- Combination therapy
- Inotropes / vasopressors
- Antithrombotics / IV epoprostenol

Relieve congestion
- IV loop diuretics
- IV oral thiazide diuretic
- Oral aldosterone antagonist
- Mechanical fluid removal (CVVH or Aquapheresis)

Unresponsive/refractory
- Transplant Candidate: Bridge to Transplant
- Continuous IV inotropes
- Atrial Septostomy
- ECLS (ECMO, Artificial lung)
- Transplant Candidate
- Relief of symptoms
- Hospice Care

Stabilization achieved
- Transition to chronic therapy
- Wean NO with epoprostenol
- Wean IV inotropes
- Optimize chronic therapies
- Evaluate for transplantation

Proposed Algorithm for Management of Cpc-PH due to LHD

On optimal, guideline directed therapy for HFrEF
- Transplant eligible
- Not transplant eligible
- Vasoreactive
- Not vasoreactive

Acute vasoreactivity testing

Vasoreactive
- Continuous IV inotropes
- Atrial Septostomy
- ECLS (ECMO, Artificial lung)
- Transplant Candidate
- Relief of symptoms
- Hospice Care

Not vasoreactive
- Frequent RHC q 3-6 mos

 Persistent PH
- PH resolves or becomes vasoreactive
- Consider heart-lung transplantation

Heart transplant
- Investigational VAD
- Continuous HF Therapy
- DT VAD

Adapted from Murray SJ, Adv in PH 2006;5:33
Mehra et al., J Heart Lung Transplant 2005;25:1024
Conclusions

- ARHF in PH is associated with ↑ morbidity and mortality
- ARHF is a syndrome with complex pathophysiology
  - Characterized by dyspnea, fatigue, edema, syncope, ↑ CVP, vital organ congestion +/- hypoperfusion
- Pharmacologic strategies should be aimed at:
  - Restoring oxygenation
  - Relieving congestion and hypoperfusion
  - Maintaining vital organ perfusion is critical
- Management includes judicious- individualized use of:
  - Pulmonary vasodilators
  - Diuretics/ hemofiltration
  - Inotropes
  - Vasopressors
  - Atrial septostomy, mechanical circulatory support (BTT), and transplantation

Thank you!!