Objectives

• To discuss the relationship between pulmonary venous and arterial hypertension, and potential cardiac causes
• To discuss the impact of pulmonary hypertension in left heart diseases
• To discuss diagnostic and treatment options for pulmonary hypertension in left heart diseases
**Definitions**

- **Pulmonary hypertension**: raised mean pulmonary artery pressures (PAP)  
  \[
  \text{PAP}_{\text{mean}} = \frac{2 \times \text{PAP}_{\text{diastolic}} + \text{PAP}_{\text{systolic}}}{3}
  \]
  - Normal: 7-18 mmHg
  - Pulmonary hypertension: > 25 mmHg at rest
    > 30 mmHg with exercise

- **Heart failure**: Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.

  Focused Update ACC/AHA Guidelines, Circulation 2009

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**Pulmonary Hypertension in Heart Failure**

*Also known as:*

- Pulmonary venous hypertension ("WHO Group 2")
- Post-capillary pulmonary hypertension
- Pulmonary hypertension with left heart disease
  - Systolic heart failure
  - Diastolic heart failure
  - Valvular heart disease
  - Restrictive or constrictive cardiomyopathy
- Secondary pulmonary hypertension in heart failure
  - "Passive" – proportionate to elevated filling pressures
  - "Reactive" – disproportionate to elevated filling pressures
  - "Intrinsic" or "Fixed" – vascular remodeling

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**Venice Classification of Pulmonary Hypertension**

- **Sporadic (IPAH)**
- **Familial (FPAH)**
- **PH Related to:**
  - Collagen vascular diseases
  - Congenital L-to-R shunt
  - Portal-pulmonary HTN
  - HIV (AIDS), HIV-A
  - Drugs / toxins (e.g. anorectic drugs, cocaine/amphetamines)
  - Others
- **Pulmonary venous occlusive disease**
Pulmonary Hypertension in Mitral Stenosis

Determine the “Lesion” in Pulmonary Hypertension

"Pre-capillary" PH
(Normal PCWP, ↑ PVR, ↑ TPG)
COPD
IPF
IPAH
Hypoxia
Mitrail valve disease
Myxoma, TAPVR
Cor Triatriatum
"Post-capillary" PH
(↑ PCWP, Normal PVR, ↑ TPG)
Hypertension
Aortic valve disease
Pulmonary veno-occlusive disease
Mycardial disease

Diagnosis: Right Heart Catheterization
Pulmonary Vascular Resistance

“Ohm’s Law”: Δ Pressure = Flow x Resistance
\[\text{TPG} \times \text{CO} = \text{PVR}\]

Trans-Pulmonary Gradient (TPG)
\[= \text{PA}_{\text{mean}} - \text{PCWP}_{\text{mean}}\]
Normal: <12 mmHg

Pulmonary vascular resistance (PVR)
\[= \frac{\text{TPG}}{\text{Cardiac output (CO)}\ \text{in Woods units}}\]
(or x80 in dynes-sec-cm²)
Normal: <1.5 Wood units
Pulmonary hypertension: > 3 Wood units
(or >250 dynes-sec-cm²)

Diagnosis: Echocardiography

Kirkpatrick et al, JACC 2007

Hemodynamic Definitions of Pulmonary Hypertension

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Mild PH</th>
<th>Moderate PH</th>
<th>Severe PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean PA (mmHg)</td>
<td>9-24</td>
<td>25-40</td>
<td>41-55</td>
<td>&gt;55</td>
</tr>
<tr>
<td>TPG (mmHg)</td>
<td>2-10</td>
<td>10-15</td>
<td>&gt;15</td>
<td></td>
</tr>
<tr>
<td>PVR (Woods)</td>
<td>0.5-2</td>
<td>2-5</td>
<td>&gt;5</td>
<td></td>
</tr>
</tbody>
</table>

Spectral Echocardiography

|                |        |         |             |           |
| TR Velocity (m/s) | <3.4   | 2.8-3.3 | 3.4-4.2     | >4.2      |
| Estimated RVSP (mmHg) | 15-37  | 36-50   | 50-75       | >75       |

* assumes RAP=5 mmHg
**Important Caveats for Echocardiographic Estimates**

- RV systolic pressure (RVSP) does not necessarily reflect severity of TR
- RVSP can overestimate mPAP in non-PAH pts while underestimate in PAH pts
- Always look for intracardiac shunting ("bubble study")

\[
\text{RVSP} = \text{RAP} + 4v^2 = 10 + 4 \times (4)^2 = 74 \text{ mmHg}
\]

**Other Echocardiographic Parameters in PH**

- Pulse Wave at RVOT for Peak Systolic Pulmonary Acceleration Velocities
- Ventricular interdependence
- RV volumes
- Right atrial area or volume index
- Diastolic eccentricity index (c/d)
- Mean right ventricular fractional area change
- Tricuspid annular plane systolic excursion (TAPSE)
- Right Myocardial Performance ("Tei") index
- RV Peak Systolic Strain

**Echocardiographic Assessment of Diastology**
Determinants of Pulmonary Hypertension

- 102 consecutive patients with LVEF <50%
- Multivariate analysis suggested 3 strongest determinants of systolic PA pressures were:
  - Patient age
  - Diastolic dysfunction
    mitral decel time <150 ms
  - Mitral regurgitation
    effective regurg orifice >20 mm²

Other Diagnostic Considerations for PH in HF

- Left Heart Catheterization
  - Useful in direct measurement of LV end-diastolic pressure to confirm or rule out pulmonary venous hypertension (elevated LA pressure)
  - Simultaneous LV-RV measurements to assess constriction vs restriction, determine valvular dysfunction
  - Determine vasoreactivity
- Cardiopulmonary Exercise Testing
  - Characterize and quantify functional limitations
  - Risk stratification and serial monitoring
- Cardiac CT
  - Especially after PV ablation for AF to rule out PV stenosis

Natriuretic Peptides in Left Heart Failure: ADEPT

Troughton et al, JACC 2004
Tang et al (unpublished) 2009
**Definition, Epidemiology, & Diagnostics: Summary**

- Common: over two thirds of patients with chronic systolic heart failure or symptomatic valvular stenosis have associated PH
- Degree of PH often correlates with symptoms (e.g. mitral stenosis)
- Presence of PH is independent predictor of mortality in systolic heart failure, post-MI, or post-transplant
  - Some challenged the presence of RV systolic dysfunction as major determinant of prognosis rather than RVSP
- Persistent or “Fixed” PH is a contraindication for transplantation
  - TPG and PVR are important determinants

**Pathophysiology: LV Impedance (“Afterload”)**

**Pulmonary Hypertension and Exercise Capacity**

- Butler et al, J Am Coll Cardiol 1999
**Hemodynamic Correlates for Ambulatory CHF**

![Graph showing hemodynamic correlates for ambulatory CHF](image)

**Pulmonary Hypertension in Diastolic HF**

![Graph showing pulmonary hypertension in diastolic HF](image)

**Pathophysiology of Pulmonary Hypertension**

![Diagram illustrating pathophysiology of pulmonary hypertension](image)
Pathophysiology: Vasoconstrictor Excess

**Vasoconstrictors**
- Norepinephrine
- Angiotensin II
- Aldosterone
- Vasopressin
- Endothelin
- Cytokines

**Vasodilators**
- Natriuretic peptides

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Pathophysiology of Right Heart Failure and Cor Pulmonale in Pulmonary Hypertension

**Pulmonary Hypertension**
- RV Pressure Overload

**Compensated Phase**
- Normal CO, RAP
- Adaptive concentric RV hypertrophy
- RV chamber size normal or ↓
- Decreased and shear

**Declining Phase**
- Inadequate CO
- Maladaptive RV hypertrophy, fibrosis
- RV diastolic dysfunction
- Neurohormonal and other mediator activation
- RV remodeling
- RV diastolic & systolic failure
- ↑ Wall stress, ↑ Heart rate, ↓ RV compliance, ↓ LV preload, ↓ CO

**Decompensated Phase**
- Inadequate CO
- Hypoxia
- Dysrhythmia
- Septal shift / interdependence
- RV Ischemia
- ↓ LV preload, ↓ CO

Pathophysiology: Summary

- Mechanical complication of disturbed left ventricular filling
- ↑ Hydrostatic pressure from:
  - Passive "backward" transmission of elevated intracardiac pressures
  - Reactive response due to endothelial dysfunction and structural abnormalities in pulmonary microcirculation
- Damage ? Surfactant Protein Type B
- Progressive pulmonary vascular remodeling similar to PAH
- Chronic hypoxia or high pulmonary artery flow
- Cyanotic congenital heart defects or shunts
- Sleep apnea
Prognosis of PH Related to Left Heart Disease

Cappola et al., Circ 2002

Consequences: Independent Predictors of Adverse Events in Patients with Advanced Heart Failure

Mullens et al., Am J Cardiol 2008

Arterial and venous pressure in blood and urine flow

Winton et al., J Physiol 1931

Firth et al., Lancet 1988
Pulmonary Hypertension and Worsening Renal Function in Advanced Heart Failure

Mullens et al., J Am Coll Cardiol 2009

Consequences: Hepatic Congestion


- ↓ serum albumin and protein-losing enteropathy
- ↑ serum cobalamin (vitamin B12), and liver function tests (e.g. bilirubin)
- Lymphocytopenia and anemia

Visceral Edema: Raised Intra-Abdominal Pressure

Mullens et al., J Am Coll Cardiol 2008
Consequences: Summary

Determination of heart transplant candidacy
- Acute: vasoreactivity testing in cath lab
- Sub-acute: Sodium nitroprusside challenge in ICU
- Chronic: LVAD implantation

Determination of treatment strategy
- Identify reversible causes (valve surgery, heart failure Rx)
- Add-on vasodilator therapy:
  - Acute: nitroprusside, nesiritide, nitroglycerin
  - Chronic: isosorbide dinitrate, hydralazine
  - Inodilators: milrinone/dobutamine in low-output states

Management: ACC/AHA Guideline Updates

“Reversibility Testing” in Left Heart Disease
Inhaled Nitric Oxide in Left Heart Disease

- Selective vasodilatory effects on pulmonary vasculature
- Currently used for PH due to RV dysfunction (post-op or MI)
- Advantage: Only reaches ventilated alveoli, without worsening V/Q mismatch
- Disadvantage: May lead to pulmonary edema in the setting of raised LA pressure as increased flow in the absence of decrease in LVEDP


Sodium nitroprusside in Left Heart Disease

Mullens et al, J Am Coll Cardiol 2008

Add-on Oral vasodilators in Advanced Heart Failure

A-HeFT (African-Americans)
Cleveland Clinic (low-output HF)

Taylor et al, NCAI 2004
Mullens et al, AUC 2009
Epoprostenol in Severe Heart Failure: FIRST (n=471)

- NYHA 3b-4, LVEF <25-30%, CI <2.2 l/min/1.73m2, PCWP >15 mmHg
- Median mPAP 38 mmHg, PCWP 25 mmHg, CI 1.8 l/min/1.73m2
- Events included death, heart failure hospitalization, IV inotropes, mechanical circulatory assistance, tracheotomy, CPR, MI
- Improved hemodynamics but no impact on functional capacity
- Some case series on inhaled iloprost with hemodynamic benefits

Califf et al, Am Heart J 1997

Bosentan Clinical Trials in Chronic Heart Failure

- REACH-1: (n=370) Increased incidence of worsening heart failure during 1st month of treatment in CHF patients related to starting dose (125 and 250 mg bid) and speed of up titration (weekly to 500 mg bid)
- ENABLE: (n=1,613) Bosentan 125 mg bid vs placebo

Kalra et al, Int J Cardiol 2002

Sildenafil in Secondary Pulmonary Hypertension

Lewis et al, Circulation 2007

Tedford et al, Circ HF 2008
Sildenafil combined with nitric oxide/nitrate therapy

Leopore et al, Chest 2005
Stehlik et al, J Card Fail 2009
Ongoing study: RELAX (sildenafil in diastolic HF, n=190)

Vasoactive Drugs in Heart Failure: Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>Endpoint</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol</td>
<td>LVEF</td>
<td>Acute increase in LVEF and hemodynamic improvement, but can induce ischemia or pulmonary edema, no long-term outcomes</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Vasoreactivity</td>
<td>Improve vasoreactivity; sometimes raise PCWP due to inability to reduce LVEDP</td>
</tr>
<tr>
<td>Hydralazine/ isosorbide dinitrate</td>
<td>Clinical status</td>
<td>Improved endpoints (primarily from A-HeFT and observational series)</td>
</tr>
<tr>
<td>Bosentan</td>
<td>Clinical status</td>
<td>No change, some risk for anemia/edema and hepatotoxicity (not indicated), but did not restrict to pts with PH</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Exercise</td>
<td>Improved exercise, blunted HR; some acute hemodynamic improvement; additive benefits synergistic with nitrates and LVAD</td>
</tr>
</tbody>
</table>

Future: Increased Intra-cardiac Pressures Precede HF Hospitalizations

Adamson et al, J Am Coll Cardiol 2003
**Future: Chronicle® Offers Management to Patients with Advanced Signs & Symptoms of Heart Failure (COMPASS-HF)**

Baseline Evaluation

\[ (N=134) \]

Total Clinician Access Group

CHRONICLE

Implant Randomization

(N=140)

Blocked Clinician Access Group

CONTROL

1 Month Follow-up Weekly data transmission with surveillance calls

1 Month Follow-up

3 Month Follow-up

3 Month Follow-up

6 Month Follow-up

6 Month Follow-up

At 6 months Chronicle guided care enabled in all patients

Bourge et al. J Am Coll Cardiol 2008

**Future: COMPASS-HF HF-related Hospitalization**

All Patients

NYHA III Patients

\[ RR = 0.79 (95\% CI = 0.64 - 0.98) \]

\[ p = 0.029 \]

\[ RR = 0.76 (95\% CI = 0.60 - 0.97) \]

\[ p = 0.023 \]

\[ ↓21\% First HF-related Hospitalization (p = 0.029) \]

\[ ↓33\% Worsening HF by Symptom Score (p = 0.035) \]

Bourge et al. J Am Coll Cardiol 2008

**Future: Next-Generation Hemodynamic Sensors**

Rozeman et al., JACC 2007

Venket et al., JACC 2007
Conclusions

- Pulmonary hypertension is prevalent, clinically significant, but underappreciated in left heart failure
- “Find the lesion” is important: PH in left heart disease can be due to either pulmonary venous or pulmonary arterial hypertension (or both)
- Need to appreciate pros and cons of diagnostic tests
- RV dysfunction may alter pulmonary artery pressures and portends poor prognosis
- Potential interventions include valve surgery, heart failure drug titrations, mechanical assist devices ± transplant
- Limited treatment options, although vasodilators (especially nitric oxide donors) and PDE-V inhibitors are promising; PH drugs are of limited use.