REVIEW ON PRIMARY AND ADVANCED THERAPIES FOR THE TREATMENT OF PULMONARY HYPERTENSION

March 10th, 2015

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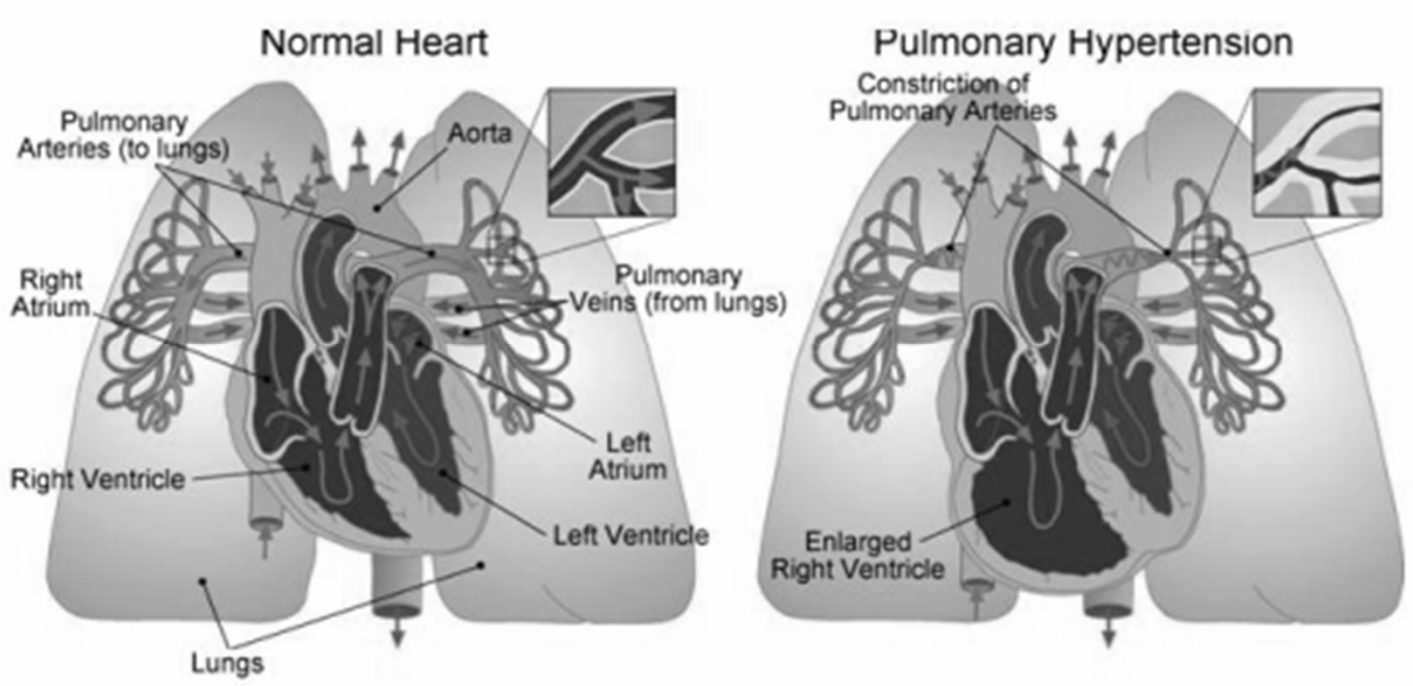
OBJECTIVES

- Define pulmonary hypertension (PH) and the pathophysiology behind the disease state
- Distinguish between the five different groups of pulmonary hypertension based upon etiology
- Identify universal treatment modalities for all groups of pulmonary hypertension
- Review the primary therapy recommended for each group of pulmonary hypertension
- Understand the utilization and caveats of advanced therapy for each group of pulmonary hypertension

PULMONARY HYPERTENSION



- Pressure in pulmonary artery ≥ 25 mm Hg at rest & PCWP ≤ 15 mm Hg

"What is Pulmonary Hypertension?"The American Heart Association. Last updated: 08/04/2014. Accessed on 03/06/2015.
<www.nationwidechildrens.org>

WHO CLASSIFICATIONS OF PH

- Group 1: Pulmonary arterial hypertension
  - Idiopathic, hereditary, or due to dz's that localize to pulmonary arterioles
  - Connective tissue dx, HIV, portal HTN, congenital heart dz, schistosomiasis, drug use
- Group 2: Pulmonary venous hypertension
  - Chronic left atrial or ventricular dz
  - Systolic dysfunction, diastolic dysfunction, valvular heart dz

Hopkins W, Rubin L, Mandel J, et al. "Treatment of pulmonary hypertension in adults". www.UptoDate.com Accessed March 3rd, 2015.

WHO CLASSIFICATIONS OF PH

- Group 3: Hypoxemia/lung dz
  - COPD, interstitial lung dz
  - Sleep-disordered breathing, alveolar hypoventilation disorders

- Group 4: Thrombo-embolic dz
  - TE obstruction of proximal/distal PA
  - Non-thrombotic PE

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WHO CLASSIFICATIONS OF PH

- Group 5: Miscellaneous
  - Uncommon, from multi-factorial mechanisms
  - Myeloproliferative disorders, chronic hemolytic anemia, sarcoidosis, glycogen storage dz

- Treatment:
  - Baseline assessment: functional status & hemodynamic disturbance
  - Primary therapy: targets underlying cause
  - Advanced therapy: directed at PH, itself

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UNIVERSAL TREATMENT OPTIONS

- Diuretics for fluid retention
  - Hepatic congestion/peripheral edema
- Oxygen therapy for hypoxemia
  - Goal: O_2 sat >90%
- Anticoagulation
  - DOC: warfarin w/INR goal ~ 2
  - Bleeding risk varies w/subtype of PH
- Exercise training/vaccinations

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GROUP 1: PAH

- Primary therapy: no real effective treatments
  - O_2 tx = no significant improvement in congenital HD
  - Anticoagulation data mostly from PAH
- Advanced therapy: widely accepted
  - Vasoreactivity test for agent selection
  - Positive = CCB
  - Negative = prostanoid, ERA, PDE-5 I's, or soluble guanyl cyclase stimulant

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GROUP 2: PVH

- Primary therapy: treat underlying heart dz
  - Systolic HF: ACEI/ARB, BB, diuretic, AA
  - Diastolic HF: CCB or BB, ACEI/ARB, diuretic, AA

- Advanced therapy: generally avoided
  - May be harmful
    - Epoprosentol + SOC in severe LVD = ↑ mortality
  - Could consider in persistent PH w/mitral valve dz & undergone MVR

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GROUP 3: HYPOXEMIA/LUNG DZ

- Primary therapy: treat underlying cause of hypoxemia
  - NOT trial: O_2 tx had mortality benefit in sub-population
    - Continuous tx (19 hrs/day) for COPD/ PaO_2 <55 mm Hg
    - Three yr mortality: 22% vs 42% (19 hrs vs 12 hrs)

- Advanced therapy: not approved in US
  - Considered for rare cases of severe, refractory dx
  - Administer cautiously: can worsen ventilation-perfusion mismatch
    - ↑ hypoxia w/epoprostenol in PF
    - ↑ hypoxia w/sildenafil in COPD

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GROUP 4: THROMBO-EMBOLIC DZ

- Primary therapy: anticoagulation
  - Prevention of recurrent PE (INR goal: 2-3)
    - Data behind this lacking
- Surgical option: thromboendarterectomy = curative
  - Reserved for TE obstruction of proximal PA
  - 3 months of anticoagulation required + severely incapacitated from PH
- Advanced therapy: riociguat (Adempas)
  - Soluble guanylate cyclase stimulant
  - Reserved for non-surgical candidates & refractory cases

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GROUP 5: MISCELLANEOUS

- Primary therapy: treat underlying dz
  - No real data
- Advanced therapy: unclear
  - Some promising data for epoprostenol in sarcoidosis
  - Very limited data

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ENDOTHELIN RECEPTOR ANTAGONISTS

- ET-1: potent vasoconstrictor & smooth muscle mitogen
  - Found to be ↑ in lungs of pts w/PAH
- Agents available:
  - ET-receptor A & B inhibitors: bosentan (Tracleer) & macitentan (Opsumit)
  - Selective ET-receptor A inhibitor: ambrisentan (Letairis)
- Improve exercise capacity, dyspnea, & hemodynamic measures
  - Better results for females & caucasians
- Recommended for WHO functional class II-III

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ENDOTHELIN RECEPTOR ANTAGONISTS

- Main AE's:
  - Teratogenic: double method contraception required for females
  - Peripheral edema: ~ 17% incidence (most common)
  - Hepatotoxicity: rate of LFTs ↑ < 6%
    - Monitor occasionally w/macitentan & ambrisentan

- Agent-specific caveats:
  - Ambrisentan: least hepatotoxic but concerns w/concurrent IPF
  - Bosentan: monitor LFTs monthly indefinitely*
  - Macitentan: < peripheral edema but > anemia & nasopharyngitis

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PHOSPHODIESTERASE 5 INHIBITORS

- Alterations in NO pathway in PH = ↑ vascular tone/proliferation
- PDE5 hydrolyzes cGMP from NO stimulation of GC
  - PDE5I's: Prolong vasodilatory effect of cGMP in lungs
- Agents available: -sildenafil (revatio) -tadalafil (adcirca)
  -vardenafil (staxyn): not FDA approved
- Improve exercise capacity, pulmonary hemodynamics, & prevent clinical deterioration
  - Recommended for WHO functional class II-III
- Generally well tolerated
  - Still concern w/concomitant nitrates, PH 2◦ to sickle cell, priapism, HA, hypotension

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GUANYLATE CYCLASE STIMULANT

- MOA: similar ultimate action of PDE5I's
  - ↑ sensitivity of sGC (NO receptor) to endogenous NO
  - Directly stimulate sGC
- Agent available: riociguat (adempas)
  - Preferred agent for inoperable Group 4 PH
  - Shown benefit in PAH
- Increase exercise capacity, improve sx, PVR, WHO class, & time to clinical worsening
  - Recommended for WHO functional class II-III
- Caveats of tx: DI's, pregnancy category X, hypotension*, concomitant nitrates, HA

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PROSTANOIDS

- MOA: prostaglandin that causes vasodilation of arterial vascular beds & inhibits platelet aggregation

- Agents available:
  - Epoprostenol (flolan)
  - Treprostonil (remodulin or tyvaso)
  - Iloprost (ventavis)

- Improves hemodynamic parameters & functional capacity
  - Improves survival in IPAH (epoprostenol)

- Recommended for WHO functional class III or IV
  - Agents most studied in severe forms of PH

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PROSTANOIDS

- Main issues:
  - Short half-lives
  - Mixed response to therapy
  - Flushing, HA, N/V, hypotension, jaw pain

- Agent-specific caveats:
  - Epoprostenol: 1st line for severe cases, delivered via permanently implanted CVC w/portable pump
    - Unique risks: life-threatening withdrawal, pump malfunction, CVC infection
  - Treprostinil: several routes available (SC= painful), longer $t_{1/2}$, no need for refrigeration, more flexibility
    - Inhalation form improves exercise capacity only
  - Iloprost: available as inhalation only, requires frequent administration
    - Given 6-9 times daily shown to improve WHO class & exercise capacity

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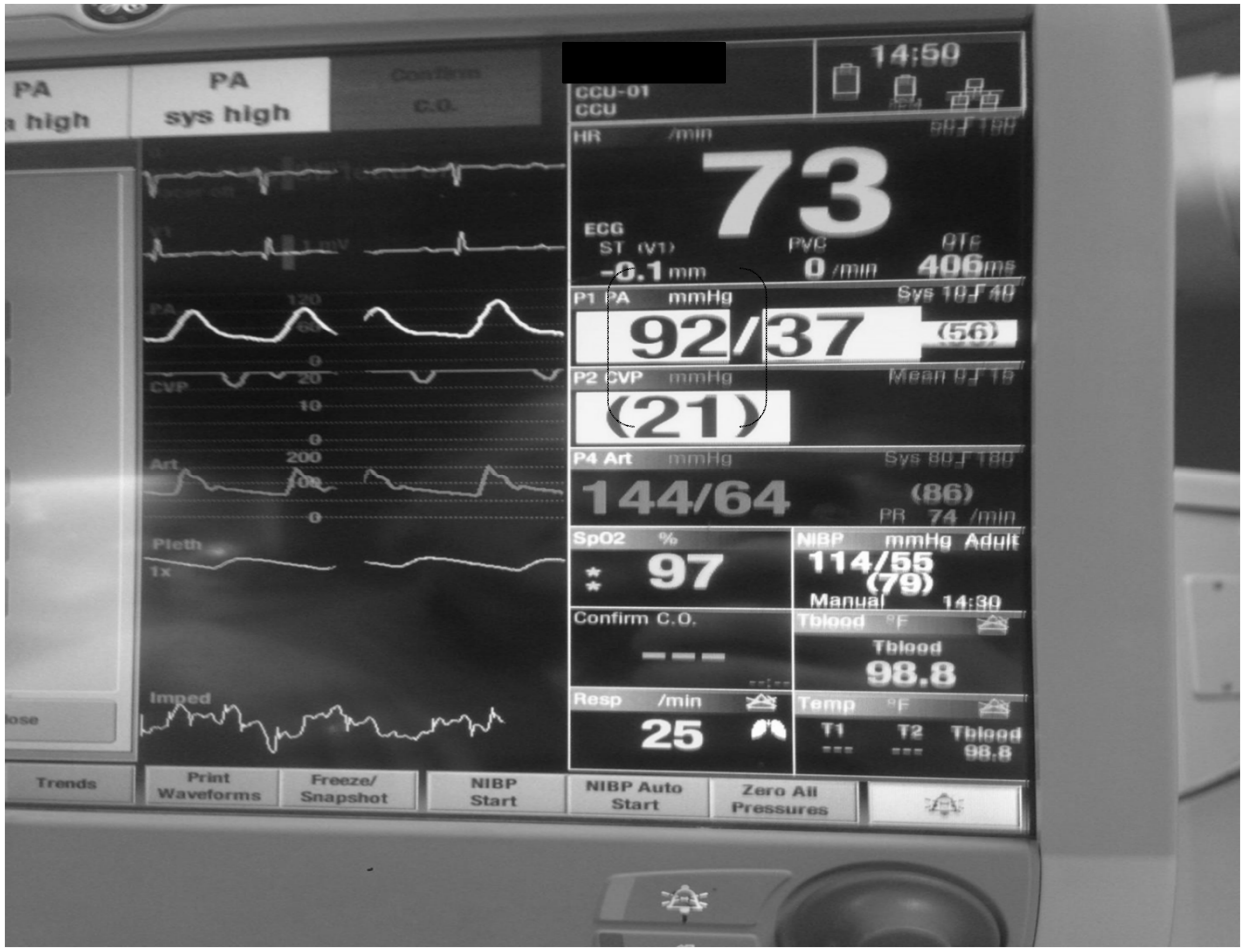
PATIENT CASE

- WH is a complicated 70 YO M presenting with acute respiratory failure & hypotension
- PMH: COPD requiring home O_2, OSA, obesity, T2DM, hypothyroidism, & diverticulosis
- Initially improved but had PEA & sent back to CCU
  - Believed to be secondary to respiratory arrest
- PE vs HF?
  - ECHO revealed severe RV enlargement
- Right heart cath revealed…

PATIENT CASE



PATIENT CASE

- After confirmation of PH, Revatio therapy started
- Pt eventually improved & was extubated again & sent to floor & later D/C'd

- What PH Group does WH belong to?

- What primary tx has shown proven mortality benefit in this group?

- If pt needed combination tx, what advance tx should not be used?

- If pt went on to develop severe WHO functional class IV PH what agent if the first line option?

PATIENT CASE

- **Answers:**

- WH belongs to Group 3: hypoxemia/lung dx- COPD/OSA

- Continuous oxygen therapy- NOT trial

- Riociguat (adempas) = contraindicated w/nitrate agents
  - Only real proven benefit in Group 1 & 4 PH

- Epoprostenol (flolan) = 1st line for **severe** PH
  - Mortality benefit

?QUESTIONS?

- ??