Pulmonary Hypertension

Daniel L. Maxwell, D.O., FACOI

Alpena Regional Medical Center
Alpena, MI

Clinical Presentation

- Due to RV insufficiency
- Exertional Dyspnea
- Lethargy
- Fatigue

Progress

- Peripheral Edema
- Chest Pain
  - Typical cardiac
    - Subendocardial ischemia
    - (L) main coronary compression (by PA)
    - PA dilation
- Exertional syncope

Classification

World Health Organization

Group 1 (PAH)

- Idiopathic (sporadic, heritable)
- Disease Localized to Small PAs
  - Connective Tissue Dx, Portal Hypertension, HIV, VenoOcclusive Dx, Drug/Toxins
- Incidence: 5-10 / 10^6

Classification (PH)

- Group 2: Left Heart Disease
- Group 3: Hypoxemia / (R) Heart Disease
  - COPD, Interstitial Lung Disease,
  - Sleep Apnea, Alveolar Hypoventilation
- Group 4: Chronic V TE Disease
- Group 5: Multifactorial / Other
  - Hematological Dx, Sarcoid, Metabolic
- Incidence: Not clear

Pathophysiology

- Vasoconstriction
  - Endothelial Vasodilators
    - Prostacyclin, Nitric Oxide (NO), Serotonin
  - Endothelial Vasoconstrictors
    - Endothelin-1, Thromboxane A2
- Vascular Remodeling
  - Vascular Smooth Muscle Hypertrophy
    - Intimal hyperplasia / fibrosis
    - Medial hypertrophy
  - Endothelial Cell Proliferation
- Platelet Aggregation
  - In situ Thrombosis

Pathophysiology

- Pulmonary Hypoxic Vasoconstriction
  - Regional / Short-term
    - Redistributes flow to aerated alveoli
    - Reversible with restoration of oxygenation
  - Chronic Global Hypoxia
    - Less Reversible

Pulmonary Hypoxic Vasoconstriction

- Decreased NO
  - Decreased Production
  - Increased Hb binding/inactivation
- K^+/Ca^{2+} Channel Inhibition
  - Increased Intracellular Ca^{2+}
  - Smooth Muscle Contraction
- Increased Arachadonic Acid Release
  - Increased Phospholipase A2 activity
    - Increased Prostaglandins, Leukotrienes, Thromboxane

Severity

- New York Heart Association Functional Classification
  - I No limitation in normal activity
  - II Slight limitation of ordinary activity
  - III Symptoms with less than ordinary activity
    - Comfortable only at rest
  - IV Symptoms at rest

Natural History (PAH)

- Progressive / Inexorable
  - Symptomatic (NYHA II – III)
    - Median Survival: 3 years
      - Worse with systemic disease
      - Worse with (R) Heart Failure / Cor Pulmonale

Diagnosis

- Physical Examination
  - Increased P2
  - Fixed Split P2
  - Prominent A wave
  - RV S4
  - Peripheral Edema
  - HepatoJugular Reflux

Diagnosis

- Testing required to confirm clinical suspicion
  - Echocardiogram
    - Suggests Pulmonary Hypertension
    - (R) Ventricular Structure and Function
    - Atrial size
    - (L) Heart / Valvular Heart Disease

    - RVSP (Right Ventricular Systolic Pressure)
    - TRV (Tricuspid Regurgitant Velocity)
- Right Heart Catheterization Required
  - Mean PAP > 25 mmHg

Echocardiography

- Likely
  - RVSP > 50 / TRV > 3.4
- Unlikely
  - RVSP <= 36 / TRV <=2.8
- Indeterminate

So What

- Until Recently
  - No effective therapy
  - No safe therapy
- Now
  - Improved understanding of pathophysiology
  - Selective pulmonary vasodilators
    - New classes of drugs
    - Improved methods of administration
    - Newly identified uses of other agents

Diagnostic Evaluation

- Screening Echocardiogram
- ECG
- PFT / 6 Minute Walk Test
- CXR / Venous Doppler / V/Q scan / CT Pulmonary Angiogram
- Polysomnography
- Serology
  - HIV
  - ANA, RF, ANCA
  - AntiCentromere, Antitopoisomerase (Anti SCL-70)
  - Anti-RNA polymerase III, Anti U3-RNP

Diagnostic Evaluation

- Vasoreactivity Testing
  - Group 1
  - Candidates for Calcium Channel Blocker Therapy
- Agents
  - Prostacyclin
  - Adenosine
  - Nitric Oxide

Treatment

- Underlying Cause
  - Group 4 (VTE Dx) Surgical Evaluation
    - Pulmonary Endarterectomy
- Oxygen
- Anticoagulation
  - Warfarin (INR ~2.0)
  - Newer Agents
- Digoxin
  - Improve RVEF
  - Control HR (SVT)

Treatment

- Exercise Training (Pulmonary Rehabilitation)
  - Improved 6 MWT distance
  - Improved NYHA / WHO Functional Class
  - Improved VO_2 max
  - Improvements exceed any pharmacotherapy
  - No improvement in RVSP

Treatment

- Pulmonary Vasodilator Therapy
  - Calcium Channel Blockers
  - Prostanoids
    - Epoprostanol (IV infusion)
    - Treprostanil (IV / SQ infusion)
    - Iloprost (inhalation)
  - Endothelin Receptor Antagonists
    - Nonselective (Bosentan)
    - Selective (Ambrisentan)
  - Phosphodiesterase 5 Inhibitors
    - Sildenafil
    - Tadalafil
  - Combinations
- Lung Transplantation

Treatment

- Literature
  - Group 1
    - Clear evidence for treatment
  - Group 2
    - Pulmonary vasodilator therapy contraindicated
  - Group 4
    - Medical Therapy is adjunct to surgery
  - Group 3 / 5
    - No data / support
    - Protocol / Tertiary Center

Treatment

- Rural Medicine
  - Distance from Tertiary Centers
  - Patient Population
  - Limited Tertiary Center Interest

Treatment

- Tertiary Center
  - Young Patients
  - Idiopathic / Hereditary PAH
  - Group 4 (VTEdx) -- Surgical
- Local
  - Severely Symptomatic (NYHA III-IV)
  - Unwilling / Unable to travel
  - Group 1, 3, 5

Treatment

- Persistent & Severely Symptomatic
- Underlying Disease Maximally Treated
- Diuretics, Digoxin, Anticoagulation
- Pulmonary Rehabilitation
- Hypoxia corrected
- Compliant with CPAP
- Absent Significant (L) Heart or Valvular Disease

Treatment

- Right Heart Catheterization
  - Vasoreactivity Challenge
    - Prostacyclin (vice NO/Adenosine)
    - Slower protocol
    - Initiate oral therapy with hemodynamic monitoring

Treatment

- PDE5 Inhibitors
  - Sildenafil
  - Tadalafil
- Prostacyclin Analogs
  - Inhaled Iloprost
- No Calcium Channel Blockers
- No Endothelin Receptor Antagonists
  - Increased edema

Monitoring

- Quarterly
  - Clinical evaluation
  - 6 MWT
- Annually
  - Echocardiogram
  - +/- (R) Heart Catheterization

Conclusions

- Nonprimary Pulmonary Hypertension is common and associated with significant symptomatology
- Symptoms may not be relieved by treatment of the underlying process(es)

Conclusions

- Very symptomatic patients may benefit from treatment with selective pulmonary vasodilators

- Treatment can be managed locally
  - Selected Group 1, 3, 4 (post-op) and 5 patients
  - Unwilling / unable to travel

Questions?