Lung Failure.....How Do We Achieve Success

David A. Hormuth, MD, MBA, FACS
Cardiothoracic Transplant Surgeon
Advanced Cardiothoracic Consultants, LLC

The Coalition of Advance Practice Nurses of Indiana (CAPNI) 2017 Conference
Indianapolis, IN.
February 24, 2017

• Overview Acute v. Chronic
• Chronic Clinical Conditions
• Pathophysiology
• Therapeutics
• Surgical Management
• "The End Game"
Lung Failure.....How Do We Achieve Success

“Acute Lung Failure”

Acute v. Chronic Lung Failure

Respiratory failure exists when the respiratory system cannot maintain gas exchange, causing dysfunction in other organs or threatening life.

- Oxygenation (hypoxemia)
- Ventilation (hypercapnia and respiratory acidosis)

Pathophysiology of Acute Ventilatory Failure

Pump Failure v. Drive Failure

Distinct Clinical Presentations

- ventilatory pump failure: are dyspneic and tachypneic with other signs of distress
- ventilatory drive failure: are not short of breath and typically demonstrate bradypnea or apnea
Clinical Classification of Ventilatory Failure by Site

Ventilatory drive
- Drug overdose: opioids, sedatives, alcohol; general anesthesia
- Cardiorespiratory accident: resuspension, cardiorespiratory reanimation

Spinal cord
- Cerebrovascular accident: Vascular accidents
- Trauma: Primary or metastatic
- Other: Polymyalgia, Amyotrophic lateral sclerosis
- Myopathy/micturition: Acute idiopathic demyelinating polyneuropathy
- Guillain-Barre Syndrome

Peripheral nerves
- Neuromuscular junction
- Neuromuscular junction: Pharmacologic: Neuromuscular blocking agents
- Autoimmune: Myasthenia gravis
- Infection/toxins: Botulism, tetanus, tick paralysis

Neuromuscular junction
- Neuromuscular junction: Pharmacologic: Neuromuscular blocking agents
- Autoimmune: Myasthenia gravis
- Infection/toxins: Botulism, tetanus, tick paralysis

Ventilatory muscles
- Congenital: Muscular dystrophy
- Autoimmune: Polymyositis; dermatomyositis
- Acquired: Hypophosphatemia, hypokalemia, hypomagnesemia

Vertebrae and rib cage
- Kyphoscoliosis; tight casts or bandages; ankylosing spondylitis
- Flail chest

Airways
- Epiglottitis, foreign body, tumor, vocal cord paralysis, tracheomalacia
- Obstruction: COPD, acute severe asthma

Parenchyma
- Increased dead space and very high V/Q ratio
- COPD very low V/Q ratio: General ARDS

Pulmonary circulation
- Pulmonary hypoperfusion: hypovolemia, congestive heart failure
- Pulmonary hypertension: Pulmonary thromboembolism, venous air embolism

Other
- Increased CO production (Inflammation, hypermetabolism, muscle activity: fever, burns, severe trauma, shivering, tetany, seizures, malignant hyperthermia
- Exogenous CO inhalation: Laboratory or industrial accident, therapeutic use, rebreathing

Acute Hypoxemic Respiratory Failure and ARDS

Hypoxemic respiratory failure
- Arterial PO2 < 60 mm Hg

Classification of Hypoxemia
- Pathophysiologic Mechanisms:
  - Decreased Inspired PO2
  - Hypoventilation
  - Increased diffusion
  - Inadequate perfusion (V/Q)
  - Intrathoracic: Right-to-left shunt
Lung Protective Mechanical Ventilatory Strategy

Ventilator settings are thus selected to provide at least this level of gas exchange (pH levels as low as 7.15 to 7.20 and Po2 values as low as 55 mm Hg) support while meeting three mechanical goals:

1. provision of enough PEEP to recruit the "recruitable" alveoli
2. avoidance of a PEEP-tidal volume combination that unnecessarily overdistends lung regions at end-inspiration
3. limiting tidal volumes to the physiologic range

Lung Failure.....How Do We Achieve Success

"Chronic Challenges"

Interstitial Lung Disease

Interstitial Lung Disease (ILD), in general, implies the clinical manifestation of inflammatory-fibrotic infiltration of the alveolar walls (septa) resulting in profound effects on the capillary endothelium and the alveolar epithelial lining cells.
Interstitial Lung Diseases

- The hallmarks of an ILD are progressive dyspnea and cough, an abnormal chest radiograph, and impaired pulmonary function tests.
- Exercise testing, which stresses the cardiopulmonary system and measures gas exchange, may unmask abnormalities in the dyspneic patients with or without abnormal chest radiographs and normal PFTs.
- High-resolution computed tomography (HRCT) scans and BAL can detect abnormalities in the presence of normal radiographs and physiologic tests in patients at high risk for development of ILD.

Clinical Classification of Interstitial Lung Diseases (ILDs)

**Idiopathic Fibrotic Disorders**
- Acute interstitial pneumonitis (Hamman-Rich syndrome)
- Idiopathic pulmonary fibrosis/usual interstitial pneumonia
- Familial pulmonary fibrosis
- Respiratory bronchiolitis / desquamative interstitial pneumonitis

**Connective Tissue Disease-Associated ILDs**
- Scleroderma
- Polymyositis-dermatomyositis
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Mixed connective tissue disease

**Treatment-Related or Drug-Induced ILDs**
- Antibiotics (nitrofurantoin, sulfasalazine, cephalosporins, minocycline, ethambutol)
- Antiarrhythmics (amiodarone)
- Antiinflammatories
- Anticonvulsants
- Chemotherapeutic agents
- Radiation

**Hereditary ILDs**
- Gaucher disease
- Niemann-Pick disease
- Hermansky-Pudlak syndrome
- Neurofibromatosis

**Other Causes of ILD**
- Aspiration
- Exogenous lipoid pneumonia
- Lymphangitic carcinomatosis
- Adenocarcinoma with lepidic pattern or mucinous type (formerly called bronchoalveolar carcinoma)
- Pulmonary lymphoma

**Primary (Unclassified) ILDs**
- Sarcoidosis
- Pulmonary Langerhans cell histiocytosis (eosinophilic granuloma)
- Amyloidosis
- Pulmonary vasculitis
- Lymphangioleiomyomatosis (with or without tuberous sclerosis)
- Acute respiratory distress syndrome
Histologic Patterns in Interstitial Lung Diseases and Their Disease Associations

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual Interstitial pneumonia</td>
<td>Connective tissue disease, adenosine, hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>pulmonary fibrosis, chronic radiation pneumonitis,</td>
</tr>
<tr>
<td></td>
<td>manifestations</td>
</tr>
<tr>
<td>Nonspecific Interstitial pneumonia</td>
<td>Connective tissue disease, drugs, hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>pulmonary fibrosis, resolving diffuse alveolar damage, AIDS,</td>
</tr>
<tr>
<td></td>
<td>infections</td>
</tr>
<tr>
<td>Diffuse alveolar damage</td>
<td>Respiratory syncytial pneumonia, drugs (tyrosine kinase</td>
</tr>
<tr>
<td></td>
<td>inhibitors, heroin, cocaine, tobacco (ethchlorvynol,</td>
</tr>
<tr>
<td></td>
<td>aspirin), radiation therapy, oxygen toxicity, connective</td>
</tr>
<tr>
<td></td>
<td>tissue disease, infections</td>
</tr>
<tr>
<td>Organizing pneumonia</td>
<td>Cryptogenic organizing pneumonia, organizing stage of</td>
</tr>
<tr>
<td></td>
<td>diffuse alveolar damage, infections (e.g., influenza) as</td>
</tr>
<tr>
<td></td>
<td>part of diffuse alveolar hemorrhage, drugs (amiodarone,</td>
</tr>
<tr>
<td></td>
<td>cocaine); infections, connective tissue disease,</td>
</tr>
<tr>
<td></td>
<td>hypersensitivity pulmonary fibrosis, eosinophilic pneumonia,</td>
</tr>
<tr>
<td></td>
<td>granulomatosis with polyangiitis (Wegener)</td>
</tr>
</tbody>
</table>

Interstitial Lung Diseases (Symptoms)

- Dyspnea
- Chough
- Wheezing
- Chest Pain
- Hemoptysis

Interstitial Lung Diseases (History)

<table>
<thead>
<tr>
<th>Category</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past History</td>
<td>Established connective tissue disease</td>
</tr>
<tr>
<td>Occupational and Environmental</td>
<td>Long latency period may occasionally exist between exposure and the</td>
</tr>
<tr>
<td>History</td>
<td>appearance of clinical impairment and disability</td>
</tr>
<tr>
<td>Drug History</td>
<td>A review of the medications used in the recent and distant past is</td>
</tr>
<tr>
<td></td>
<td>important. Uncommonly, lung disease may appear weeks to years after the</td>
</tr>
<tr>
<td></td>
<td>drug has been discontinued</td>
</tr>
<tr>
<td>Smoking History</td>
<td>Tobacco use also appears to enhance the development of interstitial</td>
</tr>
<tr>
<td></td>
<td>fibrosis in an asbestos-exposed population. The risk of asbestos-exposed</td>
</tr>
<tr>
<td></td>
<td>smokers was 13 times that in a nonsmoking asbestos-exposed cohort.</td>
</tr>
<tr>
<td>Family History</td>
<td>Familial associations (with an autosomal dominant pattern) have been</td>
</tr>
<tr>
<td></td>
<td>identified in cases of IPF, sarcoidosis, tuberculosis, and</td>
</tr>
<tr>
<td></td>
<td>neurofibromatosis.</td>
</tr>
<tr>
<td>Gender</td>
<td>Lymphangioleiomyomatosis arises almost exclusively in women. In addition,</td>
</tr>
<tr>
<td></td>
<td>many connective tissue diseases more commonly affect women. Occupational</td>
</tr>
<tr>
<td></td>
<td>causes are more likely in men.</td>
</tr>
</tbody>
</table>
**Interstitial Lung Diseases (Physical)**

- The most typical physical finding is bibasilar inspiratory crackles. Bilateral inspiratory crackles may also be present in a symptomatic patient with a negative chest radiograph.
- Clubbing of the digits, which in most cases indicates advanced fibrotic disease, is a common finding in patients with the idiopathic or familial forms of pulmonary fibrosis.
- With advanced fibrosis causing chronic hypoxemia, clinical signs of pulmonary hypertension and cor pulmonale appear.
- Attention to potential extrapulmonary physical findings or other manifestations may reveal a specific diagnosis.

---

**Interstitial Lung Diseases**

*Frontal chest radiograph in a patient with idiopathic pulmonary fibrosis.*

Peripheral basal predominant reticulation is seen consistent with fibrotic lung disease. Note diminished lung volumes.

---

**Interstitial Lung Diseases**

*Frontal chest radiograph showing characteristic features of honeycomb lung.*

A network of 2- to 3-mm cystic spaces is distributed throughout the lung fields. This patient with end-stage idiopathic pulmonary fibrosis also had pulmonary hypertension and was receiving oxygen through a transtracheal catheter.
Interstitial Lung Diseases

Advanced idiopathic pulmonary fibrosis

High-resolution CT image shows extensive honeycomb changes.

Interstitial Lung Diseases

Lymphangioleiomyomatosis

High-resolution CT image shows characteristic thin-walled cysts throughout the parenchyma

LAM
Lung Failure.....How Do We Achieve Success

“Pathophysiology”

Pulmonary Fibrosis

- Increase in elastic resistance (or decreased compliance)
- TLC, functional residual capacity, and residual volume are generally reduced

Schematic flow-volume Curves

Lung volume is reduced in the restrictive disorder, and maximum expiratory flow rates are low because they are achieved at low lung volumes.

Flow rates are higher than expected at low lung volumes because the driving pressure (lung elastic recoil) is increased
Pulmonary Fibrosis

• Most common form of IIP and accounts for 25% to 30% of ILDs
• Patients between 50 and 70 years of age
• Insidious onset of exertional breathlessness and a nonproductive cough
• Dyspnea with exertion as the disease progresses
• Most patients have these symptoms for months to years before definitive evaluation, (12 to 18 months)

Median survival after diagnosis, with or without treatment, is 2 to 3 years

Pulmonary Fibrosis (HRCT)

• Marked peripheral (subpleural) distribution of the interstitial opacities
• The involvement is patchy, with areas of reticulation intermingled with areas of normal tissue, often associated with cystic spaces 2 to 4 mm in diameter
• One of the key findings indicating the diagnosis of IPF is the presence of honeycomb cysts in a basilar subpleural distribution
Pulmonary hypertension due to IPF (PH-IPF) is relatively common and may contribute substantially to functional status, quality of life, morbidity, and mortality.

Prevalence of PH complicating the course of patients with IPF has been reported in between 32% and 85% of patients.
Pulmonary Fibrosis (Pathologic vascular findings)

- Adventitial thickening around the pulmonary vessels reflects an increase of connective tissue
- Smooth muscle cells hypertrophy and proliferate, and collagen and elastin accumulate in the media of the small muscular pulmonary arteries
- Distal pulmonary arterioles become muscularized

Histologic appearance of normal and abnormal pulmonary arterioles

A. Normal pulmonary arteriole: Characteristic features include a large lumen relative to wall thickness, a single elastic lamina and the absence of medial smooth muscle

D. Pulmonary arteriole from a patient with pulmonary hypertension from COPD showing medial hypertrophy and concentric laminar intimal fibrosis

F. Pulmonary arteriole from a patient with pulmonary hypertension from IPF showing muscularization of a small pulmonary arteriole
Lung Failure.....How Do We Achieve Success

“Therapeutics”

Pulmonary Fibrosis (Management)

• The response to corticosteroid treatment in IPF has been almost uniformly poor (No current indication)
• "antifibrotic" drugs, [immunomodulatory agents] but none thus far has shown significant improvements in outcome
• N-Acetylcysteine: no support its use for the preservation of FVC
• Cyclophosphamide: does not improve survival

Pulmonary Fibrosis (NEW Options for Therapy)

• Pirfenidone is a novel antifibrotic and anti-inflammatory agent that inhibits the progression of fibrosis in animal models
• Nintedanib is a tyrosine kinase inhibitor that targets the platelet-derived growth factor receptor, vascular endothelial growth factor receptors, and fibroblast growth factor receptors
• Interferon (IFN) γ-1b noted no difference in the primary end point (progression-free survival) or in most secondary end points
• Bosentan is a dual ET-1 receptor antagonist (ET A and ET B) that has been shown to be effective in the treatment of idiopathic PAH
Pulmonary Fibrosis
(Management - PAH)

- Supplemental oxygen
- Endothelin-1 (ET-1) receptor antagonists have been useful in patients with other types of pulmonary hypertension, mostly in primary PAH or PAH associated with connective tissue disease
- Prostacyclin (prostaglandin I\(_2\) [PGI\(_2\)]) analogues used via inhalation could maintain (or even improve) ventilation-perfusion matching and could have a beneficial effect targeting PH
- Sildenafil, a phosphodiesterase-5 inhibitor, promotes vasodilation and decreases smooth muscle proliferation and vascular remodeling

Pulmonary Fibrosis

Median survival after diagnosis, with or without treatment, is 2 to 3 years

Lung Failure.....How Do We Achieve Success

“More Chronic Challenges”
Pulmonary Hypertension

• The presence of PH-IPF is associated with worsening symptoms, functional impairment, and increased morbidity and mortality.

• Median survival of those with estimated PASP of greater than 50 mm Hg by echocardiography was less than 1 year (P = 0.009) compared to 4.8 years for patients without PH (PASP < 35 mm Hg), and 4.1 years for patients with mild PH (PASP 36 to 50 mm Hg).

• Those listed for lung transplantation with PH were 1.6 times more likely to die after being listed for transplantation compared to those without PH.

NIH/WHO Functional Classification for PAH

Class I: No limitation of physical activity. Ordinary physical activity does not cause undue dyspnea, fatigue, chest pain, or syncope.

Class II: Slight limitation of physical activity. Ordinary activity causes undue dyspnea, fatigue, chest pain, or syncope.

Class III: Marked limitation of physical activity. Ordinary activity causes severe dyspnea, fatigue, chest pain, or syncope.

Class IV: Inability to perform any physical activity without symptoms. Even in a resting state, dyspnea, fatigue, or chest pain may be present.

Dysfunctional pulmonary artery endothelial cells (blue) have decreased production of prostacyclin and endogenous nitric oxide, with an increased production of endothelin-1—a condition promoting vasoconstriction and proliferation of smooth muscle cells in the pulmonary arteries (red).
Evidence-based treatment algorithm

Restricted to patients in NYHA functional class III or IV because they represent the largest population included in controlled clinical trials.

NYHA class I or II, very few data are available.

Due to the complexity of the acute vasoreactivity tests and of the treatment options available, it is strongly recommended that consideration be given to referral of patients with PAH to a specialized center.

Acute vasoreactivity test should be performed in all patients with PAH even if the greater incidence of positive response is achieved in patients with IPAH and PAH associated with anorexigen use.

A positive acute response to vasodilators is defined as a fall in mean pulmonary artery pressure of at least 20 mm Hg up to 40 mm Hg, with an increased or unchanged cardiac output during acute challenge with inhaled NO, iv epoprostenol, or iv adenosine.

Sustained response to CCB is defined as patients being in NYHA functional class I or II with near-normal hemodynamics after several months of treatment.
Acute Vasoreactivity Test for PAH
Calcium Channel Blockers (CCB)

- Acute vasoreactive response =
  Reduction of mean PAP ≥ 10 mm Hg to reach a mean PAP ≤ 40 mm Hg with a normalized or increased CO with acute pulmonary vasodilator challenge with either inhaled NO or IV epoprostenol
- Positive response in < 10% of patients with IPAH
- Moderate recommendation based on scientific evidence

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>20 – 30 mg/day</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>180 – 240 mg/day</td>
</tr>
<tr>
<td>Dilazep</td>
<td>720 – 960 mg/day</td>
</tr>
</tbody>
</table>

Pulmonary Hypertension

Evidence-based treatment algorithm

In patients in NYHA functional class III, first-line therapy may include oral endothelin receptor antagonists, chronic IV epoprostenol, or prostanoid analogues.

Most experts consider that NYHA functional class IV patients in unstable condition should be treated with IV epoprostenol (survival improvement, worldwide experience, and rapidity of action).

Agents for the Treatment of PAH

- Prostaglandin analogs (PA)
  - Epoprostenol
  - Trecopril
  - Remodil
- Endothelin-receptor antagonists (ERA)
  - Bosentan
  - Iloprost
- Phosphodiesterase-5 inhibitors (PDE-5)
  - Sildenafil
  - Tadalafil
Pulmonary Hypertension

NIH Survival

- NYHA / WHO functional class
  - Simple, reliable assessment of disease severity
  - Encourages exercise tolerance, clinical symptoms, presence of syncope, and quality of life parameters
  - Clinical evidence of RV failure
  - Strong predictor of patient survival

<table>
<thead>
<tr>
<th>Class</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>6 years</td>
</tr>
<tr>
<td>Class II</td>
<td>6 years</td>
</tr>
<tr>
<td>Class III</td>
<td>2.5 years</td>
</tr>
<tr>
<td>Class IV</td>
<td>6 months</td>
</tr>
</tbody>
</table>


Lung Failure.....How Do We Achieve Success

“Surgical Options”
Surgical Options

**Acute:**
- ECMO
- Pulmonary Embolectomy

**Chronic:**
- Lung Transplantation
- Chronic Pulmonary Artery Thromboendarterectomy

---

**ECMO – “The Bridge”**

Extracorporeal membrane oxygenation (ECMO) is a technique of life support that consists of diverting a fraction of the patient’s blood flow (BF) through an artificial lung for gas exchange (oxygenation and carbon dioxide [CO₂] removal) and then returning it to the patient.

Indication for VV-ECMO is hypoxemic respiratory failure in patients with a high risk of mortality.

ECMO is indicated in patients with arterial Po₂ (Pao₂) /FiO₂ less than 80 mm Hg with FiO₂ greater than 90%.
**ECMO - “The Bridge”**

The primary indication for AV-ECMO is hypercarbia in patients with respiratory failure and adequate cardiac function.

**ECMO**

- Hypercapnic failure
- Hypoxic failure
  - Hemodynamic status stable
  - Hemodynamic status unstable
  - PH (severe RV dysfunction)
    - Support level A (Arteriovenous (pumpless))
    - Support level C (Veno-Arterial (pump-driven))
    - Support level B (Veno-Venous (pump-driven))

**Pulmonary Embolectomy**

The relationship of severity and mortality in patients with MPPE:

- Sudden Death
- Cardiac Arrest
- Shock
- Mortality by RV dysfunction

Embolism Size vs. Cardiopulmonary Status
Acute Massive Pulmonary Embolus

Pulmonary Embolectomy

Lung Transplantation

Timing of Referral for Transplantation
Lung Transplantation

Lung transplantation is a therapeutic option for a broad spectrum of chronic debilitating pulmonary disorders of the airways, parenchyma, and vasculature.

Leading indications include:

- Chronic obstructive pulmonary disease (COPD; 28% of cases)
- Idiopathic pulmonary fibrosis (IPF; 29% of cases)
- Cystic fibrosis (CF; 15% of cases)

Lung Transplantation (IPF)

Histologic or radiographic evidence of UIP and any of the following:

- \( \text{Dl CO} < 39\% \text{ predicted} \)
- \( \geq 10\% \text{ decrement in FVC during 6 months of follow-up} \)
- Decrease in pulse oximetry to < 88% during a 6MWT
- Honeycombing on HRCT (fibrosis score > 2)
Lung Transplantation (PAH)

- Persistent NYHA class III or IV on maximal medical therapy
- Low (350 m) or declining 6MWT
- Failing therapy with intravenous epoprostenol or equivalent
- Cardiac index < 2 L/min/m²
- Right atrial pressure > 15 mm Hg

Chronic Pulmonary Thromboembolic Disease

- Chronic thromboembolic disease develops in only 3.8% of patients with a clinically recognized acute pulmonary embolism
- Initial thromboembolism to the pulmonary arterial tree that does not resolve
- 5-year survival rate of 30% among patients with a mean pulmonary artery pressure greater than 40 mm Hg at the time of diagnosis and 10% in those whose pressure exceeded 50 mm Hg
Chronic Pulmonary Thromboembolic Disease

Lung Failure.....How Do We Achieve Success

“The End Game...or How do you take care of your patients”
Pulmonary Hypertension

PAH Determinants of Patient Risk
ACC / AHA Expert Consensus

References