Pulmonary Vascular Disease: Pulmonary Hypertension and Pulmonary Embolism

Selim M. Arcasoy, M.D.
Professor of Clinical Medicine
Medical Program Director
Lung Transplantation Program
Columbia University
College of Physicians and Surgeons

Pulmonary Vasculature

- Elastic pulmonary arteries (> 1-2 mm diameter)
- Muscular pulmonary arteries (100 μm-1 mm)
- Pulmonary arterioles (< 30-100 μm) -- no muscle
- 7 times more compliant than systemic vasculature
  - Pulmonary VR is one tenth of systemic VR
  - Pulmonary VR stays low due to “recruitment” and/or “distention” of capillary network

Control of Pulmonary Circulation

- Hypoxia
  - To match regional perfusion/ventilation
- Nervous system
  - Parasympathetic, sympathetic, NANC fibers, neurohormones
- Passive mechanisms
  - Anatomy, gravity, lung volume, alveolar pressure

Hemodynamic Physiology of Pulmonary Hypertension

Back to Physics-Modified Ohm’s Law

- Change in pressure = Flow x Resistance
  - \( P_{pa} - P_{pv} = Q \times PVR \)
  - \( P_{pa} = (Q \times PVR) + P_{pv} \)
  - \( PVR = \frac{(P_{pa} - P_{pv})}{Q} = 100 \text{ dynes/s/cm}^5 \)

- Alterations in PVR, Q and Ppv raise \( P_{pa} \)
  - PVR: occlusive vasculopathy of small arteries / arterioles (PAH), decreased area of pulmonary vascular bed (PE, ILD), hypoxic vasoconstriction (COPD, high altitude)
  - Q: Left to right shunt due to congenital heart disease, liver cirrhosis
  - Ppv: Left heart and valvular disease, constrictive pericarditis

- Increase in PVR is the primary cause of PH

Pulmonary Hypertension

Hemodynamic Definition

- Increased pulmonary vascular pressure
  - Isolated increase in pulmonary arterial pressure or increase in both pulmonary arterial and venous pressures
- Pulmonary arterial hypertension
  - Mean PAP >25 mm Hg at rest or >30 mm Hg with exercise
  - Normal pulmonary capillary wedge pressure (< 15 mm Hg)
  - PVR > 3 Wood units (or >200 dynes/s/cm²)
Pulmonary Hypertension

**WHO Classification**

- Five major categories based on pathophysiology, diagnostic findings and treatment response

I. Pulmonary arterial hypertension
- Idiopathic
- Familial
- Associated with:
  - Drugs/Anorexigen use (“Fen-phen”, cocaine, metham)
  - Collagen vascular disease
  - HIV infection
  - Portal hypertension
  - Congenital systemic-to-pulmonary cardiac shunts
  - Other (glycogen storage disease, HHT, splenectomy, hemoglobinopathy, myeloproliferative dis, thyroid)
- Associated with significant venous or capillary involvement (PVOD, PCH)

II. Pulmonary hypertension with left heart disease
- Atrial
- Ventricular
- Valvular

III. Pulmonary hypertension associated with lung diseases and/or hypoxemia
- COPD
- ILD
- Sleep-disordered breathing
- Alveolar hypoventilation
- High altitude exposure
- Developmental abnormality

IV. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
- Proximal
- Distal
- Other (tumor, parasite, foreign)

V. Miscellaneous
- Sarcoidosis, Langerhans-cell histiocytosis, vascular compression

Pulmonary Arterial Hypertension

**Pathology (I)**

- Endothelial thickening
- Smooth muscle hypertrophy

**Pathology (II)**

- Plexiform lesions
- In situ thrombosis
Pulmonary Arterial Hypertension

- Caused by an array of metabolic abnormalities that result in obliterator remodeling of pulmonary circulation
- Characterized by lumenal occlusion in medium-sized and small pulmonary arteries due to:
  - Excessive cellular proliferation in vascular wall and in situ thrombosis
  - Loss of microvessels and capillaries
- Leads to increase in right ventricular afterload, right ventricular failure and death

Emerging Concepts in PAH

- Proliferative and antiapoptotic environment in vascular wall share common features with neoplasia
- Loss of endothelial cells and microvessels has features of a degenerative disease
- Circulating and vascular inflammatory cells and mediators suggest a systemic inflammatory disease

Genetics and Pathobiology of PAH

- Loss-of-function mutations in gene encoding bone morphogenetic protein receptor type 2 (BMPR2)
  - Detected in 70% of familial PAH and 10-40% of idiopathic PAH
  - Only 20% of BMPR2 mutation carriers develop PAH
- BMPR2 is TGF-β family receptor involved in regulation of apoptosis and growth
  - Decrease in BMPR2 signaling leads to PAH
- "Second hits"
  - Endogenous -other- genetic abnormalities (serotonin pathway), flow change or exogenous stimuli (drugs, viral)
  - Dysregulated inflammation (collagen vascular disease, HIV)

Pathogenesis of Pulmonary Arterial Hypertension

Multiple-Hit Hypothesis

Primary Genetic Background

Environmental Trigger

Modifier Genes

Pulmonary Arterial Hypertension

Modified from Farber. NEJM 2004;351:1655

Imbalance of Vascular Effectors in PAH

- Likely exists because of endothelial-cell dysfunction or injury leading to
  - Vasoconstriction
  - Smooth-muscle cell and endothelial-cell proliferation
  - Thrombosis
Mediators of Pulmonary Vascular Responses in Pulmonary Arterial Hypertension

- Vasoconstriction
- Cell Proliferation
- Thrombosis

Epidemiology of PAH

- Prospective registries in the U.S., France and Scotland
- Prevalence of PAH 15 to 26 cases per 1 million adults
  - Half idiopathic and half associated with other conditions
- ~80% of patients referred to specialized centers are in NYHA class III or IV
- Mean age at diagnosis 36 to 50 years

Pulmonary Hypertension

**Clinical Presentation**

- Symptoms
  - Dyspnea “out of shape”
  - Fatigue
  - Palpitations
  - Chest pain
  - Lightheadedness
  - Syncope
  - Edema
  - Abdominal fullness, anorexia
  - Cough, hemoptysis, hoarseness (Ortner’s syndrome) less common
- Delay in diagnosis of >2 years

**Signs**

- Jugular venous distension with large a and v waves
- Loud P2
- Early systolic click
- TR murmur
- Diastolic murmur
- RV heave
- S2 and S4 gallop
- Hepatojugular reflux
- Hepatomegaly
- Pulsatile liver
- Ascites
- Edema
- Hypoperfusion

Diagnosis of Pulmonary Hypertension

- Initial routine evaluation for dyspnea and other symptoms of PH
  - CXR, EKG, pulmonary function testing, arterial blood gas, cardiopulmonary exercise study
- Doppler echocardiography
- Right heart catheterization
  - To confirm diagnosis
  - To characterize hemodynamics
Chest Radiograph

- Enlarged main pulmonary arteries
  - Attenuation of peripheral pulmonary vascular markings (pruning)
- Right ventricular enlargement
- Exclusion of parenchymal lung disease

Electrocardiography

- Right ventricular hypertrophy, right axis deviation, right atrial enlargement

Doppler Echocardiography in PH

- Tricuspid regurgitation
- Right a/v dilatation
- Right ventricular hypertrophy
- Right ventricular dysfunction
- Pulmonic insufficiency
- Intracardiac shunt
- Congenital heart ds
- Left heart size/fx
- Valvular morphology
- Pericardial effusion

Doppler Echocardiography

- Intracardiac shunt
- Congenital heart ds
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Right Heart Catheterization

- To diagnose CHARACTERIZE pulmonary hypertension
  - Mean pulmonary artery pressure
  - Pulmonary capillary wedge pressure
  - Mean right atrial pressure
  - Cardiac index
  - PVR calculation
- To assess severity of pulmonary hypertension
- To evaluate acute vasoreactivity (vasodilator response)

Right Heart Catheterization

- RA-4 mm Hg
- PA- 90/60 mm Hg
- PCWP- 8 mm Hg
- CI- 2.4 L/min
- PVR ~ 2066 dynes/cm²

- RA-12 mm Hg
- PA- 50/25 mm Hg
- PCWP- 8 mm Hg
- CI- 1.0 L/min
- PVR ~ 2000 dynes/cm²
Detailed Evaluation After Diagnosis of PH

- Medical history
  - PMH: VTE, heart, lung, and blood disorders, HIV
  - Family history
  - Exposures: weight loss medications
  - Drugs: cocaine, methamphetamine

- Diagnostic tests
  - Serologic evaluation for autoimmune disease and HIV
  - Pulmonary function tests
  - Radiologic tests
    - Exclude thromboembolic disease, obstructive and restrictive pulmonary disease
    - Sleep study and nocturnal oxymetry

Radiologic Evaluation

- Ventilation perfusion scan***
  - Pulmonary angiography may be needed to diagnose and characterize CTEPH

- High resolution computed tomography
- Cardiac MRI

Ventilation Perfusion Scan

- To exclude chronic thromboembolic PH

Chest Computed Tomography

- Pulmonary Capillary Hemangiomatosis

Therapies for Pulmonary Arterial Hypertension

- Preventative care
- Anticoagulation
- Supplemental oxygen
- Diuretics
- Inotropes
- Calcium channel blockers
- Prostacyclin analogues
- Endothelin-1 receptor antagonists
- PDE-5 inhibitors
- Cardiopulmonary rehabilitation
- Atrial septostomy
- Lung transplantation
Preventive Measures

Do's and Don’ts

- Cautious, graduated physical activity
- Supplemental oxygen to keep saturation ≥ 92%
- Avoid
  - Heavy physical activity
  - Bending over, rising quickly
  - Hot baths and showers
  - Excessive sodium intake
  - Air travel (use supplemental O2)
  - High altitude >1800 m above sea level (use supplemental O2)
  - Pregnancy
  - Concomitant medications, herbal preparations
  - Invasive procedures
- Immunization against influenza and pneumococcus

General Measures

- Anticoagulation
  - INR goal 1.5 to 2.5
  - Controversial in diseases other than iPAH
- Supplemental oxygen
- Diuretics and inotropic medications
  - Right ventricular failure
  - Monitor electrolytes and renal function
- Digitalis
  - Right ventricular failure and arrhythmia

Survival by Use of Chronic Anticoagulation

![Survival Curve](image)

- Warfarin: 78 64 49 14 7
- No Warfarin: 57 21 14 7

(Fuster, Circulation, 1984)

Vasodilator Testing and Calcium Channel Blockers

- Vasodilator testing during RHC
  - IV adenosine, epoprostenol or inhaled nitric oxide
- Definition of vasodilator responsiveness
  - Decrease of > 10 mm Hg in mean PAP to ≤ 40 mm Hg with an increase in or no change in cardiac output
  - Uncommon, occurring in 10% of patients with iPAH, less common with other subtypes
- iPAH with acute response to vasodilators may have improved survival with long-term use of CCB’s
  - Close follow-up for continued benefit essential as only 50% of patients maintain long-term benefit

Targets for Therapies in PAH

- Downregulation of prostacyclin axis
  - Reversed by exogenous prostacyclin analogues
- Downregulation of NO/cGMP axis
  - Reversed by inhaled NO and PDE5 inhibition
- Upregulation of endothelin axis
  - Reversed by endothelin receptor antagonists

(Targets for Therapy in PH

- Downregulation of prostacyclin axis
  - Reversed by exogenous prostacyclin analogues
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  - Reversed by endothelin receptor antagonists

Prostanoids

- Underproduction of prostacycline in PAH
  
  - Prostacycline promotes vasodilatation, inhibits vascular proliferation and platelet aggregation

- Epoprostenol (IV)
- Beraprost (PO)
- Treprostinil (SC or IV)
- Iloprost (inhalation)

- Improvement in hemodynamics, exercise capacity and symptoms and survival (with epoprostenol)

**Endothelin-Receptor Antagonists**

- 2 endothelin-receptor isoforms
  
  - ETA: vasoconstriction, proliferation of VSMC
  - ETB: Endothelin clearance and vasodilatation

- Dual ETA and ETB-receptor antagonist
  
  - Bosentan

- Selective ETA-receptor antagonists
  
  - Ambrisentan
  - Sitaxsentan

- Improvement in exercise capacity and hemodynamics in 12- to 16-wk clinical trials

**Phosphodiesterase-5 Inhibitors**

- Inhibition of cGMP-specific phosphodiesterase
  
  - Pulmonary arterial vasodilatation and inhibition of smooth muscle cell growth by enhancing effects of locally produced NO via its second messenger cGMP

- Sildenafil

- Improvement in symptoms, exercise capacity and hemodynamics in short-term studies

**Atrial Septostomy and Lung Transplantation**

- Atrial septostomy
  
  - Creation of right-to-left interatrial shunt for right ventricular decompression
  
  - Palliative or as bridge to lung transplantation

- Lung transplantation
  
  - Early referral
  - Close monitoring for response to therapy
  - Perform lung transplantation before advanced right heart failure and poor performance status
**Pulmonary Arterial Hypertension Treatment Algorithm**

**General therapy**
- Oxygen, anticoagulation, diuretics

**Acute vasoreactivity?**
- **YES**
- Sildenafil
- **NO**
  - FC-II FC-III FC-IV
  - Sildenafil Treprostinil
  - Bosentan Iloprost Epoprostenol

**Sustained response**
- Yes
- **Combination Rx?** Atrial Septostomy Lung Tx
- No improvement or worsening

**Modified from Badesch. Chest 2007;131:1917**

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**Survival in Idiopathic Pulmonary Arterial Hypertension**

<table>
<thead>
<tr>
<th>Location</th>
<th>1st Year Survival</th>
<th>2nd Year Survival</th>
<th>3rd Year Survival</th>
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<tbody>
<tr>
<td>NIH¹</td>
<td>68%</td>
<td>~58%</td>
<td>48%</td>
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<tr>
<td>New York²</td>
<td>87%</td>
<td>77%</td>
<td>75%</td>
</tr>
<tr>
<td>Chicago³</td>
<td>88%</td>
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<tr>
<td>Nashville⁴</td>
<td>85%</td>
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<tr>
<td>Philadelphia⁵</td>
<td>84%</td>
<td>71%</td>
<td>71%</td>
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<tr>
<td>Clamart⁶</td>
<td>85%</td>
<td>70%</td>
<td>63%</td>
</tr>
<tr>
<td>Germany⁷</td>
<td>68%</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

¹D’Alonzo, Ann Int Med, 1991
²Kawut, AJC, 2005
³McLaughlin, Circ, 2002
⁴Kuhn, AJRCCM, 2003
⁵Kawut, Chest, 2003
⁶Sitbon, JACC, 2002
⁷Wensel, Circ, 2002

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**Prognosis**
- Median survival in untreated PAH < 3 yrs
- Contemporary registries reveal improved survival
  - 65-75% survival at 3 years
  - 47-55% at 5 years in epoprostenol treated patients
- Right heart failure = lower survival rates
  - Elevated RAP, low CI, low MVO₂, poor exercise capacity, pericardial effusion, high BNP
- Close monitoring to evaluate treatment response, plan additional therapy and for lung transplantation

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**Future Directions**
- Discovery of novel mechanistic pathways and translational application into clinical practice
- Stem cell replacement/transplant with endothelial progenitor cells

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**Pulmonary Embolism**

*...no wonder you’re having trouble breathing... your cartoonist forgot to draw you nostrils!!*
**Epidemiology of Pulmonary Embolism**

- Estimated to occur in ~600,000 patients annually in the U.S.
- Causes or contributes to ~50,000 to 200,000 deaths
  - Accounts for 15% of in-hospital mortality
- Incidence of acute PE in hospitals ranges from 0.05 to 1%
- Diagnosis is missed in 50-70% of patients antemortem
- Wide spectrum of severity with short-term mortality figures between 2.5% and >50%

**Pathophysiology of Pulmonary Embolism**

- Sources of PE
  - Iliofemoral veins***
  - Pelvic, upper extremity, renal, right heart
- ~50% of iliofemoral DVT result in PE
  - 50-80% of iliofemoral DVT originate in calf veins
- Virchow’s triad
  - Endothelial injury, stasis, hypercoagulability

**Severity and Outcomes in Pulmonary Embolism**

Modified from Wood. Chest 2002;121:877-905

**Gas Exchange Physiology After PE**

- Acute vascular obstruction and vasoconstriction
- Increased alveolar dead space
  - Reflex bronchoconstriction to minimize dead space—**Trivial
  - Hyperventilation due to dead space
- Mechanisms of arterial hypoxemia
  - Shunt (flow through atelectatic regions, opening of latent pulmonary A-V anastomoses due high PAP or intracardiac)
  - VQ inequality (increased flow to low V areas without emboli due to increased PA pressure)
  - Diffusion impairment (high flow with reduced transit time)
  - Increased A-V O₂ difference from RV strain and decreased CO

**Pathophysiologic Response to PE (I)**

- **Without pre-existing cardiopulmonary disease**
  - Clinical and physiologic findings are related to embolism size
  - mPAP increases with 25-30% obstruction of vascular bed
  - RAP rises with 35-40% obstruction of vascular bed
  - mPAP remains under 40 mm Hg even if there is >50% obstruction (maximal pressure that a normal right ventricle can generate)
  - Cardiac output decreases when obstruction exceeds 50%

**Pathophysiologic Response to PE (II)**

- **With pre-existing cardiopulmonary disease**
  - Significant hemodynamic instability is common with lesser degree of pulmonary vascular obstruction
  - mPAP is much more elevated and cardiac output decreased with no consistent relationship between cardiovascular instability and magnitude of obstruction
Pathophysiology of Major PE

- PA pressure
- RV afterload
- RV dilatation
- RV dysfunction
- RV ischemia
- RV O2 demand
- RV O2 supply
- Hypotension
- LV preload
- LV output
- RV cardiac output
- Septal shift towards LV
- Vicious Cycle
- Coronary perfusion
- Risk Factors for Venous Thromboembolism
  - Acquired Factors
    - Reduced mobility
    - Advanced age
    - Cancer and chemotherapy
    - Acute medical illness
    - Major surgery and trauma
    - Spinal cord injury
    - Pregnancy/postpartum
    - Oral contraceptives
    - Hormone replacement Rx
    - Central venous catheter
    - Polycythemia vera
  - Hereditary factors
    - Factor V Leiden
    - Activated protein C resistance without F V L
    - Antithrombin deficiency
    - Protein C and S deficiency
    - Prothrombin gene mutation
    - Dysfibrinogenemia
    - Plasminogen deficiency
  - Probable factors
    - Elevated lipoprotein(a)
    - Elevated homocysteine, factors VIII, IX, XI, fibrinogen

Clinical Findings of PE

- Symptoms and signs
  - Dyspnea, chest pain, wheezing, cough, apprehension, leg pain and swelling, syncope, hemoptysis, fever
  - Tachycardia, tachypnea, accentuated P2, rales, JVD, DVT
- Chest radiograph
  - Atelectasis, pleural effusion, pleural-based opacity, cardiomegaly, diaphragmatic elevation, prominent central PA, Westermark sign
- ECG
  - Anterior T-wave inversions, ST-T segment changes, RBBB, S1Q3T3
- Arterial blood gas
  - Hypoxemia and hypocapnia

Diagnostic Evaluation

- Develop an estimate of pretest clinical probability based on symptoms, signs and risk factors
  - High (very likely), low (unlikely) or intermediate (possible/probable)
  - Clinical prediction scores (Wells or Geneva)
- Evaluation must be RAPID since majority of deaths occur within 6 hours of presentation
- Concomitant diagnosis, treatment, and resuscitation if needed
  - Start anticoagulation if PE is highly suspected and there are no contraindications

Estimation of Pretest Clinical Probability

- High (very likely)
  - Symptoms compatible with PE, not explained otherwise
  - Sudden-onset dyspnea, tachypnea, pleuritic pain, syncope
  - CXR, ECG, ABG findings compatible with PE, not explained otherwise
  - Presence of risk factors for venous thromboembolism
- Low (unlikely)
  - Symptoms incompatible with PE or compatible symptoms explained by alternative diagnoses (eg. pneumothorax, pneumonia)
  - No CXR, ECG findings of PE or findings that can be explained otherwise
  - Absence of risk factors for venous thromboembolism
- Intermediate (possible/probable)

Quantitative Clinical Assessment for PE

<table>
<thead>
<tr>
<th>Modified Wells Criteria</th>
<th>Probability Score</th>
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<tbody>
<tr>
<td>Clinical symptoms of DVT (leg swelling, pain)</td>
<td>3.0</td>
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<tr>
<td>Other diagnosis less likely than PE</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate &gt;100</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization (≥3 days) or surgery within last 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT/PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
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<tr>
<td>Malignancy</td>
<td>1.0</td>
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<tr>
<td>Probability</td>
<td>Score</td>
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<td>Traditional clinical probability assessment</td>
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</tr>
<tr>
<td>High</td>
<td>&gt;6.0</td>
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<tr>
<td>Moderate</td>
<td>2.0 to 6.0</td>
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<tr>
<td>Low</td>
<td>&lt;2.0</td>
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<tr>
<td>Simplified clinical probability assessment</td>
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<td>PE likely</td>
<td>≥4.0</td>
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<tr>
<td>PE unlikely</td>
<td>≤4.0</td>
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</tbody>
</table>
Diagnostic Tests For Major PE

- Chest radiograph and EKG
- VQ scan
- CT pulmonary angiography (CTPA)
- Duplex ultrasonography
- Laboratory markers
  - D-dimer, cardiac troponins, NT-pro-BNP and BNP
- Echocardiography
  - Findings compatible with or diagnostic of PE
  - Excludes alternative diagnoses in major PE
    - Acute MI, pericardial tamponade, aortic dissection
- Pulmonary angiography

Pulmonary Embolism


Diagnostic Algorithm Using Wells Criteria for Suspected Pulmonary Embolism

- Clinical Probability Score

  - Low (<2) or intermediate score (2-6)
  - High score (>6)

  - D-Dimer assay (highly sensitive)
    - Positive
      - CTA or VQ scan
    - Negative
      - No PE
      - PE confirmed

  - Do not treat

*Konstantinides. NEJM 2008;359:2804*

Treatment of Acute Pulmonary Embolism

- Anticoagulation with heparin products
  - Reach therapeutic levels quickly
  - Transition to oral anticoagulation
- Inferior vena cava filter placement
  - Anticoagulation contraindicated
  - DVT present along with severe PE
- Thrombolytic therapy
  - Hemodynamic instability
- Surgical embolectomy
  - Major PE unresponsive to anticoagulation, thrombolysis or contraindications to medical Rx

*Whoo—way too much information!"*