Pulmonary edema, pulmonary embolism, cor pulmonale – pulmonary hypertension

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Pulmonary edema

• **Definition**: A condition characterized by fluid accumulation in lung caused by extravasation of fluid from pulmonary vasculature into the interstitium and alveoli of the lungs.

• **Physiology of fluid movement**: Accumulation of fluid depends on the balance of hydrostatic and oncotic forces within the pulmonary capillaries and in the surrounding tissues:
  - Hydrostatic pressure favors movement of fluid from the capillary in the interstitium
  - Oncotic pressure favors movements of fluid into the vessel
  - Lymphatic in the tissue carry away the small amounts of protein that may leak out
  - Tight junction of endothelium are impermeable for proteins

• **Epidemiology**: The incidence of PE increases with the age and may affect about 10% of population over the age of 75 years.
Pathophysiology of pulmonary edema

• Imbalance in starling force
  • Increased pulmonary capillary pressure (LVF, volume overload)
  • Decreased oncotic pressure (hypalbuminemia)

• Increased negativity of interstitial pressure
  • Rapid removal of pneumothorax with large applied negative pressures

• Damage to alveolar-capillary barrier
  • Inhaled toxins, hypersensitivity pneumonitis, drugs, DIC, aspiration, acute hemorrhagic pancreatitis

• Lymphatic obstruction
  • After lung transplantation, lymphangitis carcinomatous

• Disruption of endothelial barrier

• Incompletely understood
  • High altitude, neurogenic, pulmonary embolism, etc.
Classification of pulmonary edema based on the underlying cause

- **Cardiogenic**
  - Due to increased hydrostatic pressure in the pulmonary venous and pulmonary capillaries because of cardiac abnormalities

- **Non-cardiogenic**
  - Evidence of alveolar fluid accumulation without hemodynamic evidence that suggest a cardiogenic etiology
    - Hydrostatic pressure is normal
    - Leakage of protein and other molecule into the tissue. Associated with dysfunction of surfactant lining alveoli, increased surface force and a propensity for the alveoli to collapse at low volume
<table>
<thead>
<tr>
<th>Causes of cardiogenic and non-cardiogenic PE</th>
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</thead>
<tbody>
<tr>
<td><strong>Cardiogenic PE</strong></td>
</tr>
<tr>
<td>• LV volume overload</td>
</tr>
<tr>
<td>• Dysrhythmia</td>
</tr>
<tr>
<td>• LV hypertrophy and cardiomyopathy</td>
</tr>
<tr>
<td>• Myocardial infarction</td>
</tr>
<tr>
<td>• Left ventricular outflow obstruction</td>
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<tr>
<td><strong>Non-cardiogenic PE</strong></td>
</tr>
<tr>
<td>• Direct lung injury</td>
</tr>
<tr>
<td>• Pneumonia, lung contusion, aspiration, pulmonary embolism with reperfusion</td>
</tr>
<tr>
<td>• Hematogenous injury of the lung</td>
</tr>
<tr>
<td>• Sepsis, pancreatitis, non-thoracic trauma, multiple blood transfusion, intravenous drug use, etc.</td>
</tr>
<tr>
<td>• Possible lung injury with increased hydrostatic pressure</td>
</tr>
<tr>
<td>• High altitude, neurogenic, etc.</td>
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</tbody>
</table>
Staging of pulmonary edema based on fluid accumulation

- Stage 1: All excess fluid can still be cleared by lymphatic drainage
- Stage 2: Characterized by the presence of interstitial edema
- Stage 3: Characterized by alveolar edema due to altered alveolo-capillary permeability
Symptoms of acute pulmonary edema and chronic congestive failure of the heart

**Acute**
- Shortness of breath
- A feeling of suffocating
- Anxiety, restlessness
- Cough-frothy sputum that may be tinged with blood
- Excessive sweating
- Pale skin
- Chest pain
- Palpitation

**Long-term (chronic)**
- Paroxysmal nocturnal dyspnea
- Orthopnea
- Rapid weight gain
- Loss of appetite
- Fatigue
- Ankle and leg swelling
Signs of pulmonary edema

- Tachycardia
- Tachypnea
- Confusion
- Agitation
- Anxious
- Diaphoric
- Hypertension
- Cool extremities
- Rhonchi, rales, wheezing
- S3, accentuated of pulmonic component of S2, distension of jugular vein
Continuous sounds are generated in the bronchi
- long in duration
- musical character
- occur when air flows rapidly through bronchi that are narrowed nearly to the point of closure
  - **Wheeze**: high-pitched, hissing (whistle)
  - **Rhonchi**: low-pitched, snoring (organ pipe)
  - **Stridor**: very coarse inspiratory sound, that represents flow through a narrowed upper airway (goiter, croup). Audible without the stethoscope.

**Pleural rub**: coarse, loud, grating sound, indicates inflamed pleural surfaces rubbing against each other. Appears close under the stethoscope.
Investigations in patients with pulmonary edema

• Chest radiography
  • Cardiomegaly, pleural effusion, Kerley lines, cephalization suggest cardiogenic origin. The infiltration in cardiogenic cases perihilar alveolar, in non-cardiogenic cases uniform alveolar

• Echocardiography

• Laboratory examinations

• Pulmonary artery catheterization
  • The cause is uncertain or/and in therapy refractory cases. Pulmonary capillary wedge pressure more than 20 Hgmm suggests cardiogenic cause.
Adult (acute) respiratory distress syndrome – acute lung injury, shock lung syndrome, diffuse alveolar damage

• Imbalance between proinflammatory and anti-inflammatory cytokines
  • Activation of NF-kB (transcription factor controlling expression of pro-inflammatory genes. Increased production of pro-inflammatory cytokines (IL-1, IL-8, TNF, thrombin), compared to production of anti-inflammatory cytokines, like IL-10

  Endothelium necrosis
  Type 1 alveolar cell necrosis
  Waxy hyalin membrane
  (necrotic debris from epithelial cells + edema)
  Fibrin
  Edema
  Type 2 alveolar cell necrosis – loss of surfactant - atelectasis
Causes of ARDS

- Infections (SARS- Coronavirus)
- Sepsis
- Head injury
- Gastric aspiration
- Pancreatitis
- Burns
- Trauma
- Fractures with fat embolism
Clinical features of ARDS

• Acute respiratory difficulty
• Gasping for breath
• Severe hypoxemia unresponsive to oxygen
• Bilateral infiltrates on chest radiography
• Absence of signs of LVF
• 40% mortality
• Healing may result in interstitial fibrosis
Treatment of pulmonary edema

- Support of oxygenation and ventilation
  - Oxygen therapy
  - Positive pressure ventilation
- Reduction of preload
  - Loop diuretics
  - Nitrate
  - Morphine
- Reduction of afterload
- Inotrop support
- Conditions that complicate PE must be corrected
  - Infection
  - Renal failure
  - Anemia
Pulmonary embolism

• **Definition:** Is a blockage of the main artery of the lung or one of its branches by a substance that has travelled from elsewhere in the body through the bloodstream

• **The main cause** of pulmonary embolism is venous thromboembolus. Up to 40% of patients with deep vein thrombosis without pulmonary embolism symptoms will have a pulmonary embolism by angiography.
  • A small portion of cases are caused by the embolization of air, fat, or talc in drugs of intravenous drug users

• **Epidemiology:**
  • 1/1000 people per year (500 000 PE/year in USA, 50 000 individuals die from pulmonary embolism each year)
  • More common in older people
  • Pulmonary embolism is a major health problem that is highly treatable when diagnosed, but carries high risk for morbidity and mortality – 30%, depends on the severity – is undiagnosed.

BaHamman A: Pulmonary embolism.Lecture
Venous thrombosis

• Source of pulmonary embolism:
  • Deep vein thrombosis of lower extremities (90%)
  • Pelvic veins

• Risk factors for venous thrombosis (Virchow’s triad)
  • Stasis (immobilization, obesity, hospitalization)
  • Vessel injury (infections, implant, hypertension, atherosclerosis)
  • Alterations in the coagulation-fibrinolytic system (estrogens, pregnancy, cancers, surgery)
### Risk factors for pulmonary embolism

<table>
<thead>
<tr>
<th>Acquired</th>
<th>Inherited thrombophilia</th>
</tr>
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<tbody>
<tr>
<td>Surgery, (especially orthopedic)</td>
<td>Factor V Leiden mutation</td>
</tr>
<tr>
<td>Immobilization</td>
<td>Prothrombin gene mutation</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Protein C and protein S deficiency</td>
</tr>
<tr>
<td>Oral contraceptives (+smoking)</td>
<td>Antithrombin deficiency</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>Dysfibrinogenemia</td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
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<tr>
<td>Congestive failure</td>
<td></td>
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<tr>
<td>Myeloproliferative disorders</td>
<td></td>
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<tr>
<td>Inflammatory bowel disease</td>
<td></td>
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<tr>
<td>Obesity</td>
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</table>
Provoked or unprovoked DVT or PE

• **Provoked deep vein thrombosis (DVT) or pulmonary embolism (PE)** in a patient with
  • an antecedent (within 3 months) and transient major clinical risk factor for VTE – for example surgery, trauma, significant immobility (bedbound, unable to walk unaided or likely to spend a substantial proportion of the day in bed or in a chair), pregnancy or puerperium – or in a patient who is having hormonal therapy (oral contraceptive or hormone replacement therapy).

• **Unprovoked DVT or PE** in a patient with:
  • no antecedent major clinical risk factor for VTE (see ‘Provoked deep vein thrombosis or pulmonary embolism’ above) who is not having hormonal therapy (oral contraceptive or hormone replacement therapy) or
  • active cancer, thrombophilia or a family history of VTE, because these are underlying risks that remain constant in the patient.

http://guidance.nice.org.uk/CG144
Types of pulmonary embolus (PE)

• Acute
  • Massive: Blood pressure < 90/40 Hgmm > 15 min)
  • Sub-massive: Does not meet above definition (Embolus in a terminal vessel)

• Chronic

• Saddle pulmonary embolism
  • Embolus lodges at the main pulmonary artery bifurcation
Clinical features of pulmonary embolism

**Symptoms**
- Dypnoe at rest or with exertion (73%)
- Pleuritic pain (44%)
- Calf or thigh pain (44%)
- Calf or thigh swelling (41%)
- Cough (34%)
- Orthopnea (28%)
- Wheezing (21%)

**Signs**
- Tachypnea (54%)
- Tachycardia (24%)
- Crackles (18%)
- Decreased breath sounds (17%)
- Loud S2 (15%)
- Raised JVP (14%)

Cardiac effects of pulmonary embolism

Embolic clot size and location determines presentation

Cardiac Effects:
- Clot obstructs RV outflow
- Sudden increased RV dilatation and pressures
- RV pressure can reduce left ventricle functions
- R to L shunt can occur
- Vasoconstriction of pulmonary vasculature:
  - Increased pulmonary vascular resistance
  - Release of neural/humoral mediators which increase pulmonary vasculature resistance

**DECREASED cardiac output, VQ mismatch - Sudden, unpredictable cardiovascular collapse**

Michele M. Nypaver, MD, 2011
Laboratory investigations in pulmonary embolism

• D-dimer (fibrin degradation product)
  • Non-specific, but high negative predictive value

• ABGs
  • Hypoxemia
  • Hypocapnia
  • Respiratory alkalosis
  • In case of massive embolization hypercapnia, respiratory and metabolic acidosis)
ECG in pulmonary embolism

• Sinus tachycardia
• Non-specific ST/T abnormalities
• Classical findings (uncommon)
  • S1Q3T3
  • RV strain
  • New incomplete RBBB
Radiological procedures in pulmonary embolism

• Chest X-ray
  • Atelectasis due to collapse of non perfused alveoli, which then don’t make surfactant, elevated hemidiaphragm, pleural effusion, cardiomegaly
  • Westermark’s sign: Dilatation of the pulmonary vessels proximal to the embolism along with collapse of distal vessels
  • Hampton’s hump: a triangular pleural-based infiltrate with the apex toward the hilum

• Ventilation-perfusion lung scintigraphy
  • Normal VQ excludes the possibility of embolization
  • The result is interpreted as probability
  • Diagnosis of pulmonary embolism requires integration of pretest probability

• Angio-CT
  • Rapid, highly specific for main, lobar and segmental vessels
  • Less sensitive for detection of subsegmental vessels

• Pulmonary angiography (gold-standard, but never)
  • Mortality 0.5%, major complications 1%, minor complications 5% (worsening shotrness of breath, artery perforation)
## Well’s score to assess probability of pulmonary embolism

<table>
<thead>
<tr>
<th>Factor</th>
<th>Points</th>
</tr>
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<tbody>
<tr>
<td>Clinically suspected DVT</td>
<td>3</td>
</tr>
<tr>
<td>Alternative diagnosis is less likely than PE</td>
<td>3</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization/surgery in the previous four weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>History of DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy (treatment in preceding 6 months)</td>
<td>1</td>
</tr>
</tbody>
</table>

**Interpretation of the Well’s score:**

0-4 = PE unlikely, > 4 = PE likely

* pneumonia, acute coronary syndrome, pneumothorax, aortic dissection, cardiac tamponade
Diagnostic strategy used in patients with suspected pulmonary embolism

Determine pretest probability (Unlikely or likely)

PE unlikely

D-dimer

normal

PE excluded

elevated

PE unlikely

CT pulmonary angiogram

negativ

PE improbable (Doppler US of legs, d-dimer)

positive

PE confirmed

PE likely

Van Belle et al JAMA 2006;295:172, modified
Management of pulmonary embolism

- Anticoagulation (Acute)
  - Thrombolysis
  - Unfractionated heparin (iv., target PTT 1.5-2.5x the control aPTT)
  - Low Molecular Weight Heparin (does not require monitoring)
  - Fondaparinux (10a inhibitor)

- Anticoagulation (Chronic)
  - Warfarin (started after administration of heparin, adjusted dose to INR 2-3)

- New agents
  - Dabigatran (thrombin inhibitor, does not require monitoring)
  - Rivaroxaban (Factor Xa inhibitor, does not require monitoring)
Indication of thrombolytic therapy in pulmonary embolism

- **Massive PE with hemodynamic instability**
  - Hypoxia on 100 % oxygen
  - Right ventricular dysfunction by echocardiography
  - RV thrombus in transit
  - Saddle embolus

Absolute contraindication: active bleeding
Relative contraindications: HT, cerebrovascular event, infectious endocarditis, etc.

- Approved thrombolytic in pulmonary embolism
  - Streptokinase
  - Urokinase
  - Recombinant tissue plasminogen activator
Further investigation in patients with unprovoked DVT or PE who are not known to have cancer

- Full medical history and physical examination and
  - Blood test (blood cell count, serum calcium, liver function tests etc.)
  - Urine analysis
  - Chest X-ray
- No signs or symptoms of cancer based on initial investigation, but over 40 years old:
  - PSA in men,
  - mammography in women to look for underlying malignancy
  - Consider abdominal-pelvic CT and colonoscopy if any suspicion
- Thrombophilia testing
  - Consider for patients with unprovoked DVT or PE if it is planned to stop anticoagulation treatment

http://guidance.nice.org.uk/CG144
Cor pulmonale

• Cor pulmonale means: „pulmonary heart”

• **Definition:** Cor pulmonale is a disease of the right ventricle characterized by hypertrophy and dilatation that results from diseases directly affecting the lung parenchyma or lung vasculature.
  - „Lungs cause the heart to fail”

• Right heart failure need not be present in cor pulmonale.

• **Epidemiology:**
  - 10% of all causes of heart failure
  - 5-year mortality 70-80%

• Cor pulmonale can be either acute or chronic in development
  - Acute:
    - result of a sudden increase in right ventricular pressure (massive pulmonary embolism, ARDS)
  - Chronic:
    - Hypoxic subtype (the cause in 50% COPD)
    - Vascular obliterans subtype: pulmonary thromboembolic disease
Pathophysiology of cor pulmonale

• The right ventricle is thin walled and able to accommodate considerable changes in volume without large changes in pressure

• The initial event in the development of cor pulmonale is elevation of the pulmonary vascular resistance

• Because of the elevated resistance the pulmonary arterial pressure rises, right ventricular work increases, right ventricular hypertrophy (thickening and dilatation)

• Right ventricular failure occurs when compensation through dilatation and hypertrophy are exhausted.

• Any process that results in pulmonary hypertension can cause cor pulmonale
• **Definition:** When pulmonary pressure reaches 1/4th of systemic levels (usually not more than 1/8 of systemic)
  - Pulmonary arterial hypertension
  - PH with left heart failure
  - PH with lung disease
  - PH with chronic thrombotic or embolic disease
Pathophysiology of pulmonary hypertension

- Hypoxic vasoconstriction - acute vasocontraction optimizes ventilation-perfusion relationship - and arterial occlusion are the major causes
- Reduced blood flow with increased vascular resistance
- Chronic hypoxemia leading chronic vasoconstriction – smooth muscle cells proliferation in small pulmonary arteries – increased resistance and pressure.
- Architectural changes may promote platelet aggregation – thrombi formation – further increases the pulmonary vascular resistance and hypertension
- Decreased production of nitric-oxide, increased production of endothelin-1 and platelet derived growth factors – impaired smooth muscle cell relaxation
- PDGFs results in pulmonary vascular remodeling – increases the vascular resistance and pressure
Common morphological changes in pulmonary hypertension

• Medial hypertrophy affecting muscular and elastic arteries
• Atheromas of large pulmonary elastic artery
Etiological factors:
• COPD or interstitial lung disease
• Congenital heart disease (L-R shunt-VSD)
• Recurrent thromboembolism (in small vessels)
• Connective tissue disease
• Obstructive sleep apnea
• Idiopathic (rare, young women with recurrent dyspnea and syncope. BMPR2 locus mutation)
Symptoms and signs of pulmonary hypertension and cor pulmonale

**Symptoms**
- Fatigability
- Dyspnea on exertion
- Syncope
- Chest pain
- Palpitation
- Abdominal distension/edema
- Lower extremity edema

**Signs**
- Accentuated A wave of the jugular venous pulsations
- Accentuated pulmonary component of the second heart sound
- Right sided S4
- Murmurs of tricuspid and pulmonic insufficiency
- Peripheral edema and hepatomegaly
Treatment of cor pulmonale

• Non pharmacological
  • Oxygen therapy - improves the survival of patients with COPD
  • Phlebotomy– may provide symptomatic relief in patients with polycythemia (Ht>0,60)
  • Non invasive positive pressure ventilation –for patients with acute COPD exacerbations

• Pharmacological
  • Diuretics – decreases the water retention, improves alveolar ventilation
  • Anticoagulant therapy- in patients with cor pulmonale resulting from thrombo-occlusive pulmonary disease
  • Vasodilatators –improve cardiac output
  • Endothelin receptor antagonist (Bosentan) – produces pulmonary vasodilatation and attenuates ventricular remodeling. Improves survival on chronic use