

Pulmonary Vascular Disease

Arthur Jones, EdD, RRT

This Presentation is Approved for
1 CRCE Credit Hour

Learning Objectives

- Explain the etiologies, manifestations, diagnostic techniques, & current management strategies for pulmonary thromboembolism & pulmonary hypertension

Pulmonary Thromboembolism

Definitions

- **Thrombus:** stationary blood clot, such as in deep veins of legs (DVT)
- **Embolus:** blockage of an artery by matter, such as a blood clot - thromboembolism

Acute PE Epidemiology

- Incidence (US) - 650,000/yr
- Mortality > 15% for first 3 months after diagnosis
- In 25% PE patients, first sign is sudden death
- Third most common cause of death
- Leading cause of maternal death

Acute PE Epidemiology

- Missed diagnosis of PE > 400,000/yr
- About 100,000 patients die who would have survived with the proper diagnosis & treatment
- Autopsies find much greater incidence of PE among patient deaths than are diagnosed
- PE among hospital patients considered a public health crisis in the UK

Types of Emboli

- Thromboemboli: blood clots
- Fat (lipid embolus) - fractured bones
- Air
 - ❖ Decompression illness
 - ❖ Parenteral injection

Types of Emboli

- Amniotic - significant cause of maternal death
- Septic
 - ❖ Thrombophlebitis
 - ❖ IV drug abuse
- Foreign substances - IV drug abuse (fillers, e.g. talc)
- Worms, e.g. schistosomiasis

See links below to view schistosoma mansoni in mesenteric veins & schistosoma masoni life cycle

Sites for Embolism

- Brain: cerebrovascular accident (CVA)
- Joints: sickle cell crisis
- Pulmonary arteries: pulmonary thromboembolism (our focus)

Risk Factors

- Inherited predisposition - thrombophilia
 - ❖ Younger patients
 - ❖ Family members with history
- Deep venous thrombi (DVT)
 - ❖ Stasis (immobility)
 - ❖ Surgery
 - ❖ Trauma
- Malignancy

Risk Factors

- Obesity
- Myocardial infarction
- Pulmonary disease (smoking)
- Polycythemia
- Pregnancy
- Trauma
- Vascular catheters

PE Pathophysiology

Perfusion of the Lung

- > Pulmonary circulation
 - ❖ Pulmonary arteries to alveolar capillaries
 - ❖ Perfuses alveoli for gas exchange

See links below to view pulmonary circulation

Perfusion of the Lung

- > Bronchial circulation
 - ❖ Thoracic aorta to terminal bronchioles
 - ❖ Perfuses
 - Esophagus
 - Trachea
 - Visceral pleura
 - Airways to terminal bronchioles

Perfusion of the Lung

- > Anastomoses between pulmonary & bronchial circulations
 - ❖ Bronchioles to pulmonary capillary beds
 - ❖ Bronchial circulation increases flow through anastomoses to compensate for pulmonary embolism

See links below to view peripheral bronchial & pulmonary circulation & a diagram of bronchial-pulmonary anastomoses

Perfusion of the Lung

- > Pulmonary infarction results from embolization of medium-size pulmonary artery; compensatory bronchial circulation causes reperfusion injury, hemorrhage

See links below to view pulmonary infarction & hemorrhagic pulmonary infarction

Development of Thrombi

- > Blood clots in deep vein
 - ❖ Calf
 - ❖ Thigh
 - ❖ Pelvis - frequently fatal
 - ❖ Axillary, subclavian - frequently fatal

Development of Thrombi

- > Blood clots in deep vein
 - ❖ Calf
 - ❖ Thigh
 - ❖ Pelvis - frequently fatal
 - ❖ Axillary, subclavian - frequently fatal
- > Clotting predisposed by
 - ❖ Hemostasis
 - ❖ Coagulopathy
- > Clot breaks off, flows to lung

See links below to view DVT & pulmonary embolism

PE Pathophysiology

- > Hemodynamics - severity depends on size of embolus
 - ❖ Physical obstruction
 - ❖ Release of vasoconstrictors
 - ❖ Hypoxemia of distal lung causes vasoconstriction
 - ❖ Acute pulmonary hypertension

PE Pathophysiology

- > Hemodynamics
 - ❖ Acute pulmonary hypertension
 - ❖ Increased right ventricular afterload
 - Ventricular dilatation
 - Interseptal bulging to left
 - Left ventricular impairment
 - Right ventricular infarction - release of troponin, brain natriuretic peptide (BNP)

PE Pathophysiology

- > Gas exchange O₂
 - ❖ Non-perfused lung - increased VQ (dead space units)
 - ❖ Blood directed to other units decreases their VQ (shunt)
 - ❖ Overall, mixed VQ defects
 - ❖ Alveolar hemorrhage & atelectasis may contribute to hypoxemia
 - ❖ If patent foramen ovale, then right-to-left shunt (severe hypoxemia)

PE Pathophysiology

- > Gas exchange - CO₂
 - ❖ Tachypnea - arterial hypocapnea
 - ❖ Alveolar dead space - alveolar hypocapnea, with increased P(a - E)CO₂
 - ❖ If hypercapnea →
 - Massive embolus
 - Comorbidity, e.g. emphysema

FYI see links below for article on acute PE

PE Manifestations

Symptoms

- > Anxiety
- > Chest pain
- > Chest wall tenderness (important)
- > Syncope
- > Shortness of breath
- > Back pain
- > Wheezing

Physical Signs

- Tachypnea
- New onset wheezes
- Crackles (usually with infarction)
- Tachycardia
- Fever
- Diaphoresis
- Cyanosis
- Hemoptysis
- Thrombophlebitis

Massive PE

- Dyspnea
- Cyanosis
- Altered mental status
- Cardiogenic shock
- Cardiac arrest

Chest Radiograph

- May be normal
- Used to rule out alternatives
- Reduced distal vascular markings
- Dilated pulmonary arteries
- Atelectasis - common with infarction
- Wedge-shaped density - infarction
- Pleural effusion - 1/3 of PE patients
 - ❖ Small
 - ❖ Unilateral
 - ❖ Likely to loculate

Electrocardiograph

- May be unchanged from baseline
- May suggest alternatives, e.g. MI
- Most common with PE
 - ❖ Sinus tachycardia
 - ❖ Right axis deviation
 - ❖ Right bundle branch block

Blood Gases

- Nonspecific for PE
 - ❖ Hypocapnia
 - ❖ Mild-severe hypoxemia
- Severe hypoxemia with patent foramen ovale - worsens with PEEP
- End-tidal CO₂ & ABG used to measure V₀/V_T

PE Diagnosis

Goals for Diagnostic Techniques

- > Rule in/out PE
- > Risk stratification to select treatment
 - ❖ Risk-benefits for drugs, interventions
 - ❖ Avoid costly procedures, e.g. imaging

Bases for Diagnosis

- > History
- > Physical findings
- > Laboratory tests
- > Imaging

Clinical Probability for PE

- > Wells score - parameters
 - ❖ Clinically suspected DVT
 - ❖ Alternative diagnosis is less likely than PE
 - ❖ Tachycardia
 - ❖ Immobilization/surgery in previous four weeks
 - ❖ History of DVT or PE
 - ❖ Hemoptysis
 - ❖ Malignancy (palliative treatment within 6 months)

Clinical Probability for PE

- > Wells score interpretations
 - ❖ Traditional interpretation
 - Score > 6.0 - High
 - Score 2.0 to 6.0 - Moderate
 - Score < 2.0 - Low
 - ❖ Alternate interpretation
 - Score > 4 - PE likely → diagnostic imaging
 - Score 4 or less - PE unlikely → D-dimer to rule out PE

Laboratory Studies

- > D-dimer - formed by lysis of fibrin (clot)
- > Increased by
 - ❖ Aging
 - ❖ Inflammation
 - ❖ Malignancy
 - ❖ Embolism
- > Negative predictive value
- > Combined with Wells score - strong negative predictive value

Laboratory Studies

- > Potential markers for PE - need additional study
 - ❖ C-reactive protein
 - ❖ Myeloperoxidase

Laboratory Studies

- > Troponin I - prognostic indicator
 - ❖ Marker for myocardial injury
 - ❖ Elevation suggests right ventricular overload
 - ❖ Peaks 4 hours after suspected PE
 - ❖ May predict adverse outcome for PE
 - ❖ May be used to select aggressive treatment

Laboratory Studies

- > Brain natriuretic peptide (BNP) - prognostic marker
 - ❖ Elevated with right ventricular dysfunction
 - ❖ Elevation is proportional to severity of embolism

Pulmonary Testing

- > Dead space measurement
 - ❖ PE increases alveolar dead space & V_D/V_T
 - ❖ Measurement requires $ETCO_2$ & $PaCO_2$
 - ❖ Combined with negative D-dimer has strong negative predictive value
 - ❖ Research needed to standardize techniques & parameters for PE evaluation

Imaging

- > Computed tomographic pulmonary angiography (helical, spiral)
 - ❖ Agrees with VQ scan for exclusion
 - ❖ Detects PE not found by VQ scan
 - ❖ Useful in detecting alternative diagnoses

See links below for algorithm of PE diagnosis with CT angiography

Imaging

- > Magnetic resonance imaging (MRI)
 - ❖ Similar accuracy to CT scanning
 - ❖ Also detects alternative diagnoses
 - ❖ No ionizing radiation - safer for pregnant patients, esp. females
 - ❖ Technology is advancing

Imaging

- > Pulmonary angiography
 - ❖ Criterion standard for PE
 - ❖ Adverse effects - cannot be done on sickest patients
 - ❖ Expensive

See links below to view PE on angiogram

Imaging

- Ventilation-perfusion (VQ) scan
 - ❖ Former, usual test for PE
 - ❖ If normal, excludes PE
 - ❖ Significant number of abnormal scans do not have PE
 - ❖ High probability scan - confirms PE

See links below to view VQ scan with PE

Imaging

- Ultrasonography
 - ❖ Detection of DVT
 - ❖ Positive test → evidence of PE
 - ❖ Negative result suggests decreased risk for recurrence of PE
 - ❖ Safe - no ionizing radiation

Imaging

- Echocardiography
 - ❖ Not a routine test for PE
 - ❖ May visualize central emboli
 - ❖ Identifies cardiac dysfunction & alternative causes of hemodynamic compromise
 - ❖ Detects shunting through patent foramen ovale

PE Management & Prevention

Respiratory Care

- Oxygen - all PE patients
- Ventilation - PEEP may open foramen ovale by increasing pulmonary vascular resistance
- ETCO₂ particularly useful - observe for changes in P(a - E)CO₂

Anticoagulants

- Reduce risk of additional clots
- Slow clot progression
- Do not dissolve clots
- Low molecular weight heparin
 - ❖ Enoxaparin (Lovenox)
 - ❖ Ardeparin (Normiflo)
 - ❖ Dalteparin (Fragmin)

Thrombolytics

- Dissolve clots
- Definite for massive PE
 - ❖ Clinical ventricular dysfunction
 - ❖ Hypotension
 - ❖ Severe hypoxemia
- Controversial for submassive PE

Thrombolytics

- Considered for all patients with PE & without contraindications, e.g.
 - ❖ Previous hemorrhagic stroke at any time
 - ❖ Active internal bleeding
 - ❖ Suspected aortic dissection
 - ❖ Acute pericarditis
- Decrease mortality, morbidity, recurrence

Thrombolytics

- Agents
 - ❖ Tissue plasminogen activators (TPA)
 - Alteplase (Activase®)
 - Retaplast (Retavase®)
 - Tenecteplase (TNK-tPA)
 - ❖ Streptokinase (Eminase®)
 - ❖ Urokinase (Abbokinase®)

Invasive Interventions

- Percutaneous methods
 - ❖ Catheter-directed thrombolysis
 - ❖ Embolectomy
- Pulmonary endarterectomy
 - ❖ Circulatory arrest
 - ❖ Hypothermia
 - ❖ Serious postoperative complications
- Embolectomy via thoracotomy

FYI see links below for article on invasive interventions for PE

Prevention

- Anticoagulants
 - ❖ Heparin
 - ❖ Warfarin (Coumadin)
- Compression stockings
- Pneumatic compression
- Physical activity

Prevention

- Air travel - longer flights, greater risk for PE
- Prevention
 - ❖ Fluids
 - ❖ Avoidance of alcohol & smoking
 - ❖ Loose clothing
 - ❖ Elastic support stockings
 - ❖ Avoidance of leg crossing
 - ❖ Physical activity

FYI see links below for article on air travel & PE

Prevention

- Vena cava (Greenfield) filter
 - ❖ Especially for patients with contraindications to anticoagulation
 - ❖ Percutaneous insertion
 - ❖ Outpatient procedure
 - ❖ Temporary, retrievable filters are available

See links below to view retrievable vena cava filter

Pulmonary Hypertension

Pulmonary Arterial Hypertension (PAH)

- Elevated pulmonary artery pressure
- Normal = 13 mm Hg (mean)
- Hypertension = 25 mm Hg (mean) at rest

PAH WHO Classifications

- Group I - Pulmonary arterial hypertension (PAH)
 - ❖ Idiopathic: unknown etiology
 - ❖ Familial
 - ❖ Persistent pulmonary hypertension of newborns (PPHN)
 - ❖ Associated with
 - Portal hypertension
 - Collagen dx
 - HIV
 - Toxins, e.g. Fen-Phen (litigation)

PAH WHO Classifications

- Group II - Pulmonary hypertension associated with left heart disease
 - ❖ Left-sided atrial or ventricular disease
 - ❖ Left-sided valvular disease

PAH WHO Classifications

- Group III - Pulmonary hypertension associated with lung diseases &/or hypoxemia
 - ❖ COPD
 - ❖ Interstitial lung disease
 - ❖ Sleep-disordered breathing
 - ❖ Chronic high-altitude exposure

PAH WHO Classifications

- > Group IV - Pulmonary hypertension due to chronic thrombotic &/or embolic disease
- > Group V - Miscellaneous
 - ❖ Sarcoidosis
 - ❖ Histiocytosis
 - ❖ Compression of pulmonary vessels (neoplasms)

Acute PAH & Cardiac Interventions

- > Reperfusion injury: return of blood flow to ischemic myocardium - 'stunned myocardium'
- > Definition: prolonged post-ischemic dysfunction of viable tissue salvaged by reperfusion

FYI see links below for AHA article on reperfusion therapy

Acute PAH & Cardiac Interventions

- > Reperfusion injury
- > Occurs after
 - ❖ Coronary thrombolysis
 - ❖ Percutaneous coronary interventions
 - ❖ Coronary artery bypass
 - ❖ Heart transplantation

NYHA Functional Classifications

- > Class I - no limitation of physical activity - ordinary physical activity
- > Class II - slight limitation of physical activity
 - ❖ Comfortable at rest
 - ❖ Ordinary physical activity - undue dyspnea or fatigue, chest pain, etc.

NYHA Functional Classifications

- > Class III - marked limitation of physical activity
 - ❖ Comfortable at rest
 - ❖ Minimal activity causes dyspnea, fatigue, chest pain
- > Class IV - inability to perform physical activity without symptoms
 - ❖ Right heart failure
 - ❖ Dyspnea &/or fatigue at rest
 - ❖ Discomfort with any physical activity

PAH Manifestations

Manifestations

- Increased pulmonary artery pressure
 - ❖ Echocardiography - noninvasive
 - ❖ Right heart catheterization (definitive)
- RV hypertrophy
- Severe hypoxemia, esp. in presence of anatomic shunt (cyanosis)

Manifestations

- Dyspnea, fatigue
- Syncope
- Chest pressure or pain
- Edema: pedal edema, ascites
- Tachycardia, palpitations
- Can mimic asthma, especially in young persons

PAH Management

PAH General Management (First Line)

- Oxygen: reverses hypoxemic vasoconstriction
- Anticoagulants
- Diuretics
- Potassium
- Inotropic agents

See links below for PAH treatment algorithm

Calcium Channel Blockers

- Amlodipine (Norvasc)
- Nifedipine (Procardia)
- Diltiazem (Cardizem)
- Verapamil (Isoptan)

Endothelin Antagonist

- Bosentan (Tracleer)
 - ❖ Oral administration
 - ❖ Likely to cause birth defects
 - ❖ Potential for hepatotoxicity

FYI see links below for article on endothelin antagonists for PAH

Phosphodiesterase Inhibitors

- > Sildenafil (Viagra)
- > Vardenafil (Levitra)
- > Tadalafil (Cialis)
- > Milrinone (Primacor): nebulized for PAH from reperfusion injury

FYI see links below for info on phosphodiesterase inhibitors

Nitric Oxide Gas

- > Selectively dilates pulmonary vessels, because it is rapidly taken up by hemoglobin & neutralized
- > Effects
 - ❖ Decreases pulmonary vascular resistance
 - ❖ Improves V/Q matching by increasing blood flow to ventilated alveoli

Nitric Oxide Gas Delivery

- > Disadvantages of NO
 - ❖ Additional equipment: iNOvent, monitors
 - ❖ Additional training
 - ❖ Rebound PAH with cessation of delivery
 - ❖ Bottom line: very costly

Prostacycline

- > Endogenous vasodilators
- > Prostaglandin i2 analogs (synthetic)
- > Non-acute indications
 - ❖ WHO Group I
 - ❖ NYHA Class III - IV severity
 - ❖ Failure of other medications

Prostacyclins

- > iloprost (Ventavis) - prostaglandin i2 analog
 - ❖ Potency \geq nitric oxide
 - ❖ Effect duration = 120 min
 - ❖ Aerosol 2.5 or 5.0 mcg 6 - 9 times daily
 - ❖ Unit doses 2.5 or 5.0 mcg
 - ❖ Specific nebulizers required

See links below to view nebulizers for Ventavis

Epoprostenal (Flolan)

- > Short-acting PGI-2
- > Less expensive than iNO
- > Duration of action 3 - 5 min
- > Delivery
 - ❖ Continuous infusion: acute or non-acute care
 - ❖ Continuous aerosol: acute care alternative to nitric oxide

FYI see links below for additional Flolan information

Epoprostenal (Flolan)

- Delivery by infusion
 - ❖ Same indications as Ventavis for non-acute setting
 - ❖ Cost > \$100,000/year
 - ❖ Home care setting: patient has infusion pumps

Flolan Acute Care Aerosol Delivery

- Indications - severe PAH, refractory to standard therapy
 - ❖ Reperfusion injury, e.g. post-cardiopulmonary bypass
 - ❖ Portal-pulmonary hypertension
 - ❖ Independent or single-lung ventilation
 - ❖ ARDS
 - ❖ PPHN
 - ❖ RV failure
 - ❖ Septic shock

Flolan Acute Care Aerosol Delivery

- Precautions/contraindications
 - ❖ Interruption of delivery can result in rebound, death
 - ❖ May cause systemic hypotension (unlikely)
 - ❖ May cause hemorrhage
 - ❖ Flolan is photosensitive, so must be shielded from light

Treprostinil (Remodulin)

- Formulated for IV or SC injection
- Four hour duration of action
- Pilot studies of aerosolized treprostinil found sustained vasodilation (> 3 H) with dosage delivered in a single breath
- Additional study required for aerosol route

Summary & Review

Summary & Review

- Pulmonary embolism epidemiology & importance
- Types & sites for embolism
- Risk factors for thromboembolism
- PE pathophysiology
 - ❖ Hemodynamics
 - ❖ Gas exchange

Summary & Review

- PE manifestations
 - ❖ Symptoms & signs
 - ❖ Radiograph
 - ❖ ECG
 - ❖ Blood gases
- PE diagnosis
 - ❖ Clinical probability - Wells score
 - ❖ Laboratory studies - PE markers vs. prognostic indicators
 - ❖ Imaging

Summary & Review

- PE management
 - ❖ Respiratory care
 - ❖ Anticoagulants
 - ❖ Thrombolytics
 - ❖ Invasive interventions
- PE prevention
 - ❖ Anticoagulants
 - ❖ Thromboembolic deterrent (TED) stockings
 - ❖ Vena cava filters

Summary & Review

- PAH classifications (WHO groups)
- PAH functional classifications (NYHA classes)
- Manifestations

Summary & Review

- General management: O₂, etc.
- Calcium channel blockers
- Endothelin antagonist
- Phosphodiesterase inhibitors
- Nitric oxide gas
- Prostacyclins
 - ❖ Flolan
 - ❖ Ventavis
 - ❖ Remodulin

References

- Baglin T. Venous thromboembolism in hospitalised patients: a public health crisis? *Br J Haematol.* 2008 Jun;141(6):764-70. Epub 2008 Apr 10.
- Frazier AA, et al. From the Archives of the AFIP : Pulmonary Vasculature: Hypertension and Infarction. *RadioGraphics* 2000 20: 491-524.
- Goldhaber SZ, Elliott CG. Acute pulmonary embolism: part I: epidemiology, pathophysiology, and diagnosis. *Circulation.* 2003;108(22):2726-9.
- Stein PD, Henry JW. Clinical characteristics of patients with acute pulmonary embolism stratified according to their presenting syndromes. *Chest* 1997;112:974-79.
- Wells PS. Derivation of a Simple Clinical Model to Categorize Patients Probability of Pulmonary Embolism: Increasing the Models Utility with the SimpliRED D-dimer. *Thrombosis and Haemostasis* 2000 83 3: 416-420.
- Kearon C. Diagnosis of pulmonary embolism. *CMAJ* 2003;168:183-194.

References

- Dresang LT, Fontaine P, Leeman L, King VJ. Venous thromboembolism during pregnancy. *Am Fam Physician.* 2008 Jun 15;77(12):1709-16.
- Becattini C, Vedovati MC, Agnelli G. Diagnosis and prognosis of acute pulmonary embolism: focus on serum troponins. *Expert Rev Mol Diagn.* 2008 May;8(3):339-49.
- Klok FA, Mos IC, Huisman MV. Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: a systematic review and meta-analysis. *Am J Respir Crit Care Med.* 2008 Aug 15;178(4):425-30.
- Porcel JM, Light RW. Pleural effusions due to pulmonary embolism. *Curr Opin Pulm Med.* 2008 Jul;14(4):337-42.
- Anderson DR, et al. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. *JAMA.* 2007;298:2743-53.

References

- > Ghaye B, Dondelinger RF. When to perform CTA in patients suspected of PE? *Eur Radiol.* 2008 Mar;18(3):500-9.
- > Mitchell AM. Tandem measurement of D-dimer and myeloperoxidase and C-reactive protein to effectively screen for pulmonary embolism in the emergency room. *Acad Emer Med.* 2008;15:800-805.
- > Horlander KT, Leeper KV. Troponin levels as a guide to treatment of pulmonary embolism. *Curr Opin Pulm Med.* 2003;9:374-77.
- > Klok FA, Mos IC, Huisman MV. Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: a systematic review and meta-analysis. *Am J Respir Crit Care Med.* 2008 Aug 15;178(4):425-30.
- > Kline JA, et al. Diagnostic accuracy of a bedside D-dimer assay and alveolar dead space measurement for rapid exclusion of pulmonary embolism. *JAMA.* 2001;285:76168

References

- > Eriksson L, et al. Diagnosis of pulmonary embolism based upon alveolar dead space analysis. *Chest.* 1989;96:357-62.
- > Konstantinides SV. Massive pulmonary embolism: what level of aggression? *Semin Respir Crit Care Med.* 2008; 29(1):47-55.
- > Uflacker R, Schönholz C. Percutaneous interventions for pulmonary embolism. *J Cardiovasc Surg.* 2008 Feb;49(1):3-18.
- > Roscoe A, Klein A. Pulmonary endarterectomy. *Curr Opin Anaesthesiol.* 2008 Feb;21(1):16-20.
- > Douma RA, Kamphuisen PW. Thrombolysis for pulmonary embolism and venous thrombosis: is it worthwhile? *Semin Thromb Hemost.* 2007 Nov;33(8):8218.
- > Young T, Tang H, Aukes J, Hughes R. Vena caval filters for the prevention of pulmonary embolism. *Cochrane Database Syst Rev.* 2007 Oct 17;(4):CD006212.

References

- > Haraldsson A, Kieler-Jensen N, Ricksten SE. The Additive Pulmonary Vasodilatory Effects of Inhaled Prostacyclin and Inhaled Milrinone in Postcardiac Surgical Patients with Pulmonary Hypertension. *Anesth Analg* 2001 93: 1439-1445
- > Siobal M, Kallet H, et al. Description of a delivery system for aerosolized prostacyclin. *Resp Care* 2003;48(8):742753.
- > Siobal M. Pulmonary vasodilators. *Resp Care* 2007;52(7):885-899.
- > Siobal M. Aerosolized prostacyclin. *Resp Care* 2004;49(6):640-652.
- > Sandifer BL, Brigham KL, Lawrence EC, et al. Potent effects of aerosol compared with intravenous treprostinil on the pulmonary circulation *J Appl Physiol* 99: 23632368, 2005

References

- > Kassiani T, et al. Inhaled iloprost controls pulmonary hypertension after cardiopulmonary bypass. *Can J Anesth* 2002;49(9):963-967.
- > Komai H, et al. Increased plasma levels of endothelin-1 after cardiopulmonary bypass in patients with pulmonary hypertension and congenital heart disease. *J Thor Cardio Surg* 1993;106:473-478.
- > Olchewski H, et al. Aerosolized Prostacyclin and Iloprost in Severe Pulmonary Hypertension. *Ann Intern Med* 1996; 820-824
- > Eichelbrönnner O ; Reinelt H ; Wiedeck H ; Mezödy M ; Rossaint R ; Georgieff M ; Radermacher PAerosolized prostacyclin and inhaled nitric oxide in septic shock-different effects on splanchnic oxygenation? *Intensive Care Med.* 1996; 22(9):880-7 (ISSN: 0342-4642).

References

- > Lamarche, Y., Malo, O., Thorin, E., Denault, A., Carrier, M., Roy, J., Perrault, L.P. Inhaled but not intravenous milrinone prevents pulmonary endothelial dysfunction after cardiopulmonary bypass *J Thorac Cardiovasc Surg* 2005 130: 83-92
- > Sablotzki, Armin, Starzmann, Wolfgang, Scheubel, Robert, Grond, Stefan, Czeslick, Elke G. Selective pulmonary vasodilation with inhaled aerosolized milrinone in heart transplant candidate. *Can J Anesth* 2005 52: 1076-1082