Secondary pulmonary hypertension – diagnosis and management

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Abstract. – Secondary pulmonary hypertension (SPHtn) is generally attributable to abnormalities in structure or function of the heart or lung parenchyma. While often defined as a physiologic parameter, pulmonary hypertension (PHtn) can be a major contributor to death and disability in cardiopulmonary diseases. Both detection and management are a challenge. We will review the pathophysiology, diagnostic tools, and treatment strategies in SPHtn with an emphasis on cor pulmonale associated with chronic obstructive pulmonary disease (COPD), pulmonary vascularopathies, and pulmonary embolus.

The pathophysiology and common etiologies of SPHtn can be divided into three major categories: (1) elevated pulmonary venous pressure (LV failure and mitral valve disease), (2) pulmonary vascular occlusive disease with or without pulmonary parenchymal disease (pulmonary emboli, COPD, connective tissue diseases), and (3) hypoxemia (sleep apnea).

The echo-Doppler is a simple cost-effective tool for detecting PHtn, evaluating right ventricular function, and distinguishing common etiologies such as abnormal systolic and diastolic left ventricular function and mitral valve disease. The ventilation-perfusion radionuclide scan can be used to exclude thromboembolic PHtn, but a helical computer tomography with contrast or pulmonary angiography are necessary to distinguish patients that may benefit from a pulmonary thromboendarterectomy. The six minute walk oxygen saturation test is useful as a quantitative measure of functional capacity, prognosis, response to therapy, and oxygen requirement.

Treatment strategies in cor pulmonale are tailored to the specific diagnosis, but generally include proper nutrition, exercise, oxygen supplementation, medications such as digoxin, diuretics, anti-coagulation, and pulmonary vasodilator therapy in selected patients.

Key Words:
Pulmonary hypertension, Diagnosis, Cardiopulmonary testing, Therapy.

Abbreviation list
ASD = Atrial Septal Defect
CHF = Chronic Heart Failure
CO = Cardiac Output
COPD = Chronic Obstructive Pulmonary Disease
CPET = Cardiopulmonary Exercise Testing
CVP = Central Venous Pressure
CTEPHtn = Chronic Thromboembolic Pulmonary Hypertension
DLCO = Diffusion (capacity) of the Lung for CO
DVT = Deep Vein Thrombosis
IPVOD = Intrinsic Pulmonary Vascular Occlusive Disease
ILD = Interstitial Lung Diseases
LV = Left Ventricular
mPA = mean Pressure
MWT = Minute Walk Test
PAD = Diastolic Pressure
PAR = Pulmonary Arterial Resistance
PAs = Systolic Pressure
PCW = Pulmonary Capillary Wedge Pressure
PE = Pulmonary Embolus
PHtn = Pulmonary Hypertension
PPHtn = Primary Pulmonary Hypertension
PVR = Pulmonary Vascular Resistance
RV = Right Ventricular
RVSP = Right Ventricular Systolic Pressure
SLE = Systemic Lupus Erythematosus
SPHtn = Secondary Pulmonary Hypertension
TLC = Total Lung Capacity
VSD = Ventricular Septal Defect

Introduction

Pulmonary hypertension (PHtn) is defined as an increase in the pressure within the pulmonary artery and its branches, which can be detected at heart catheterization or estimated as right ventricular systolic pressure by echo-
Doppler. Pulmonary hypertension, which can be diagnosed by invasive and non-invasive techniques, needs to be defined in order to allow optimal targeted therapies. PHtn is an important contributor to death and disability in cardiopulmonary diseases, and therefore should be suspected in the right setup and if possible prevented. The ability of the right ventricle to compensate for increased pulmonary resistance and work load is a major determinant of prognosis in cor pulmonale in which right ventricular failure following valve and coronary bypass surgery is a major predictor of poor outcome.

Discussing PHtn it is important to mention the Primary pulmonary hypertension (PPHtn). This entity which is rare and nearly uniformly fatal, is defined an intrinsic pulmonary vasculature pathology in the absence of functional or structural abnormalities of the heart, lung parenchyma, and hypoxemia. While once considered idiopathic (e.g., primary), PPH is often associated with one or more triggers. In Pulmonary Hypertension Program registry of Ann Arbor, University of Michigan, out of eighty-five cases of PPH six are familial, and the remainder isolated or associated with one or more of the following: cirrhosis and portal hypertension (8), anorexigens (2), atrial septal defect (10), cocaine or heroin (4), HIV (4), HCV (8), Obesity (35), thyroid disease (15), and chronic anemia (4). The histologic changes in PPH include hypertrophy and fibrosis of the small pulmonary arterioles, in situ thrombi and obliterating plexiform lesions, each of which can be found in most forms of severe PHtn.

We will review the approach to diagnosis and management of the secondary forms of PHtn, with an emphasis on chronic obstructive pulmonary disease (COPD), chronic thromboembolic and connective tissue diseases.

### Pulmonary Vascular Physiology

Pulmonary artery pressure is determined by four major factors: (1) stroke volume, (2) the elasticity of the pulmonary artery and its proximal branches, (3) the capacitance of the resistance vessels and (4) pressure in the pre and post capillary bed. Abnormalities in one or more of these parameters can result in pulmonary hypertension (PHtn), which is defined as a systolic pressure (PAs) > 30 mmHg, diastolic pressure (PAD) > 12 mmHg, and a mean pressure (mPA) > 17 mmHg².

Soon after birth the right ventricular systolic pressure (RVSP) and pulmonary artery pressures drop to approximately one fifth of the left ventricular (LV) systolic pressure and systemic pressures. Pulmonary artery pressure is kept low throughout life, thanks to ~100,000 small resistance vessels (pre-capillary arterioles) which retain their vasodilator capacity until old age. During exercise, lung volume and blood volume (cardiac output) increase while mPA increases only modestly, due to recruitment and relaxation of pulmonary arterioles.

The main pulmonary artery and major branches are relatively thin walled compliant vessels, and generally are not affected by atherosclerosis. Small pulmonary arterioles’ walls are characterized by a functioning endothelium and up to two smooth muscle layers. This structure enables a change in the diameter of these vessels according to different endothelial and neurohumoral factors, flow velocity, oxygen tension and ventilation of adjacent air sacs.

Normal pulmonary artery pressures, vascular resistances and factors which influence each of them are reviewed in Table 1. The pulmonary vascular resistance (PVR) is measured in Wood units

\[
PVR = \frac{mPA - PCW}{CO}
\]

where
- \( mPA \) = mean pulmonary artery pressure,
- \( PCW \) = pulmonary capillary wedge pressure,
- \( CO \) = cardiac output

The normal PVR ranges from about 0.7 to less than 1.1 Wood units. An increase in the pulmonary flow without appropriate pulmonary vasodilator reserve results in an increase in PAs, PAD, and mPA. In contrast, isolated systolic pulmonary hypertension can result from a high stroke volume, such as with anemia, obesity and stress, or from stiffness of the pulmonary artery associated with age, atherosclerosis, and long standing heart failure.

Pulmonary vascular response to maximal exercise effort is up to a threefold increase in the cardiac output (pulmonary flow), a rise in the PAs to 45-60 mmHg and mPA to
20-25 mmHg, with no change in the PAd and usual decrease in PAR to 0.6-0.9 Wood units.

Pulmonary artery pressures and PVR can only be assessed by invasive hemodynamic measures, however the RVSP, which approximates the PAs, is readily estimated by assessing the tricuspid-valve flow velocity with echo-Doppler. In the presence of even small amounts of tricuspid regurgitation, the pressure gradient in mmHg across the tricuspid valve during systole is approximately 4 times the square of the Doppler flow velocity in meters per second. The RVSP is the tricuspid valve gradient in systole plus the estimated right atrial pressure or CVP (RVSP = 4V² + CVP).

The maximal normal tricuspid flow velocity is 2.5 m/s (4V² = 25 mmHg). The addition of 5 mmHg for the RA pressure results in the normal upper limit for the RVSP of 30 mmHg, identical to that measured invasively. In many echo laboratories the CVP is estimated at 10-14 mmHg, which results in an upper limit for the RVSP by echo-Doppler of 35-40 mmHg.

Clinical Classification of Pulmonary Hypertension

PHtn is defined as an increase in the mPA pressure > 20 mmHg or a PVR > 1.2 Wood units. The entity of abnormality is not well established, but the following criteria are useful for clinical estimation: borderline PHtn, mPA 17-20 mmHg or PVR 1.1-1.3 Wood units; mild PHtn, mPA 20-25 mmHg or PVR 1.3-3 Wood units; moderate PHtn, mPA 26-35 mmHg, PVR 3-6 Wood units; moderately severe PHtn, mPA 36-45 mmHg and PVR 6-10 Wood units; severe PHtn, mPA 45-60 mmHg and PVR > 10 Wood units. While mild pulmonary hypertension is relatively common in heart and lung disease, severe pulmonary hypertension suggests one of the following causes: a multifactor process, PPH either isolated or triggered, Scleroderma, CREST syndrome, SLE (Systemic Lupus Erythematous) or chronic thromboembolic pulmonary hypertension (CTEPHtn).

Several signs and symptoms characteristic of PHtn reflect an underlying systemic disease (e.g., COPD, CHF, Mitral Stenosis, Scle-
rderma), and the effect of abnormal pulmonary vasculature on the pulmonary pressures, right heart function and oxygen transport (Table II). Dyspnoea and fatigue are findings that may be found in modest and even occult PHtn, but evidence of right heart failure (increased jugular vein pressures, hepatomegaly, edema) is an unusual finding in the absence of severe PHtn.

**Secondary Pulmonary Hypertension**

A pathophysiologic and clinical classification of pulmonary hypertension is shown in Table III. Causes of secondary pulmonary hypertension can be divided into three major categories: (1) pulmonary venous pressure elevation, (2) pulmonary vascular occlusion with or without pulmonary parenchymal disease, and (3) hypoxemia. Often multiple factors are present at the same time (Ex. an obese hypertensive chronic smoker with both obstructive and restrictive pulmonary function patterns, hypoxemia, LV diastolic dysfunction, and sleep apnea).

**Table II.** Symptoms and signs of pulmonary hypertension.

<table>
<thead>
<tr>
<th>Common symptoms</th>
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<tbody>
<tr>
<td>Dyspnoea</td>
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<td>Fatigue</td>
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<tr>
<td>Angina</td>
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<tr>
<td>Pre-syncpe</td>
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<tr>
<td>Syncope</td>
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<tr>
<td>Weakness</td>
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<tr>
<td>Palpitations</td>
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<tr>
<td>Abdominal fullness</td>
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<tr>
<td>Leg swelling</td>
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<tr>
<td>Raynaud's phenomenon</td>
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<table>
<thead>
<tr>
<th>Common signs</th>
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</thead>
<tbody>
<tr>
<td>Normal to low blood pressure (occasionally hypertension)</td>
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<tr>
<td>Lung findings dependent upon parenchymal involvement</td>
</tr>
<tr>
<td>Jugular venous distention with prominent a and v waves</td>
</tr>
<tr>
<td>Increase split of S2 with increased P2</td>
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<tr>
<td>Systolic murmur at left 4th ICS increasing with inspiration (tricuspid insufficiency)</td>
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<tr>
<td>Soft diastolic decrescendo murmur of pulmonic regurgitation in left 3rd ICS</td>
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<tr>
<td>Pulmonic ejection click, systolic ejection murmur at left 2nd or 3rd ICS</td>
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<tr>
<td>RV lift, RV S4 and or RV S3</td>
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<tr>
<td>Hepatomegaly, pulsatile liver, ascites, peripheral edema, cyanosis, clubbing</td>
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**Table III.** Secondary forms of pulmonary hypertension.

<table>
<thead>
<tr>
<th>Resistance to pulmonary venous drainage</th>
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<tr>
<td>Left heart failure, mitral valve disease, left atrial myxoma, cor triatriatum pulmonary veno-occlusive disease due to drugs (bleomycin, mitomycin C, cyclophosphamide, etoposide), mediastinitis, radiation, and invasive malignant tumors (breast, lung, lymphoma)</td>
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<tr>
<th>Pulmonary vascular obliteration</th>
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<tr>
<td>Pulmonary obliterative without parenchymal lung disease</td>
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<tr>
<td>Pulmonary embolus-thrombus, sickle cell, tumors, schistosoma, vasculopathy-scleroderma, CREST, lupus, Takayasu's, polyarteritis, Wegener's, giant cell, ulcerative colitis, Eisenmenger's syndrome-PDA, VSD, truncus</td>
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<thead>
<tr>
<th>Pulmonary obliterative with parenchymal disease</th>
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<tbody>
<tr>
<td>Emphysema, interstitial lung disease, radiation, pneumococcosis, cystic fibrosis, granulomatosis, alveolar proteinosis, collagen disease</td>
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<thead>
<tr>
<th>Hypoxemia</th>
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<tbody>
<tr>
<td>Airways disease</td>
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<tr>
<td>Sleep apnea, extreme obesity, asthma, chronic upper airway obstruction, chronic lower airway obstruction, pulmonary, parenchymal lung disease, lung resection</td>
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<tr>
<th>Respiratory excursion disorders</th>
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<tr>
<td>Marked obesity, severe kyphoscoliosis, neuromuscular disorders, pleural fibrosis</td>
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<th>Ventilatory drive disorders</th>
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<td>CNS disorders</td>
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<tr>
<th>High altitude residence</th>
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<tr>
<td>Chronic mountain sickness</td>
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The later can result from associated pulmonary fibrosis (hemosiderosis or mitral lung), in situ thrombi, non-obliterative atherosclerosis, and morbid arteriolar hypertrophy.

Pulmonary venous hypertension without left ventricular failure or mitral disease (pulmonary veno-occlusive disease) is uncommon, but should be considered when dyspnea and hypoxemia occur with prominent pulmonary venous markings on chest x-ray, especially in patients with SLE, malignancies such as lymphoma or leukemia, following chemotherapy, and with mediastinal fibrosis.

**Pulmonary vascular obstruction:** The second most common cause of SPHtn, pulmonary vascular obstruction, may be associated with pulmonary parenchymal disease or hypoxemia (Table III). Intrinsic pulmonary vascular occlusive disease (IPVOD) associated with limited scleroderma or lupus can be fixed or reversible, depending on the degree of inflammation, fibrosis, in-situ thrombosis, plexiform lesions and the presence of a reversible vasoreactive component. PHtn is usually severe when patient is symptomatic. Scleroderma, particularly the CREST variant, and SLE can present initially with dyspnea, fatigue, and Raynaud’s phenomenon and mimic PPHtn. Various Interstitial lung diseases (ILD) and other parenchymal lung diseases can result in PHtn through perivascular inflammation, hypoxemia, and fibrosis, but rarely cause severe PHtn unless are associated with other factors.

Eisenmenger’s syndrome defines pulmonary hypertension associated with long standing high pressure left to right intracardiac shunting. It is the result of irreversible smooth muscle proliferation, which late in its course may contain plexiform lesions and in situ thrombi. The classic Eisenmenger’s syndrome is associated with a ventricular septal defect (VSD). In contrast, atrial septal defects (ASD), which are high flow-low pressure shunts, are not commonly associated with severe PHtn. When severe PHtn complicates a low pressure shunt, the pathophysiology should be related to PPH. Chronic high pulmonary blood flow is thought to results in endothelial injury and the formation of plexiform lesions, in genetically susceptible individuals.

Pulmonary emboli, particularly when large and central, less often when multiple, small and recurrent, can result in mild, moderate, and severe pulmonary hypertension and cor pulmonale. The pathogenic mechanism of PHtn involves flow resistance due to large and small vessel obliteration by occlusive thrombi, subsequent deposition of fibrotic material, as well as the presence of vasoactive factors.

**Hypoxemia:** Chronic hypoxemia is an important stimulus for vasoconstriction. It often results in a modest rise in mPA but rarely severe PHtn. While hypoxemia worsenes PHtn, it is not understood why isolated hypoxemia induces irreversible PHtn. Endothelial dysfunction and vasoconstriction, in situ thrombi, smooth muscle cell proliferation and hypertrophy, perivascular infiltration, and fibrosis are common factors contributing to the gradual loss of pulmonary vascular bed in hypoxic PHtn. Figure 1 depicts the pathophysiology of pulmonary hypertension associated with hypoxemia.

**The Role of Cardiac and Pulmonary Testing in Pulmonary Hypertension**

**Electrocardiogram** may highlight right atrial and ventricular hypertrophy, right axis deviation and strain.

**Echo-Doppler** is a simple cost-effective tool for detecting PHtn, evaluating right ventricular function, and distinguishing some common etiologies, e.g. abnormal systolic and diastolic left ventricular function and mitral valve disease. Several studies have correlated echographic findings with the outcome of patients affected with PHtn. Eysmann evaluated 41 echocardiographic variables by a univariate analysis and the following factors were found to be predictive: (1) heart rate > 87 beats/min, pulmonic flow acceleration time of < 62 ms, tricuspid early flow deceleration ≤ 300 cm²/s, and mitral early flow/ratio ≤ 1.0. Several years later Raymond assessed echocardiographic factors with an univariate analysis: predictive factors of survival were the presence of pericardial effusion and RA area index. Evaluation by a multivariate analysis proved that only pericardial effusion was a significant predictor of death. Tei and Yeo showed that a Doppler-derived RV index is a prognostic factor.
Chest x-ray: enlargement of the cardiac silhouette, prominence of the central arteries while the peripheral vessels become attenuated.

Ventilation-perfusion scanning can exclude thromboembolic PHtn.

Helical and high resolution computer tomography, employed when the ventilation-perfusion scanning is inconclusive for pulmonary emboli. This imaging modality allows to distinguish patients who may benefit pulmonary thromboendarterectomy.

Magnetic resonance angiography: a noninvasive technique helpful for (1) visualizing pulmonary artery thromboemboli, (2) evaluating right ventricular function. In contrast to helical CT, a contrast agent is not required.

Pulmonary angiography: is the gold standard in the diagnosis of pulmonary embolism, where the ventilation-perfusion scanning has failed.

Lung biopsy: can help to exclude subtle interstitial lung disease and/or vasculitis.

Right heart catheterization with a vasodilator trial is the gold standard in the study of PHtn; it allows a direct determination of pulmonary hemodynamics. Right heart catheterization with a vasodilator trial allows to recognize early hemodynamic changes (e.g., fall in systemic pressure, rise in heart rate, or failure of cardiac output to rise).

Arterial blood gases: arterial PO$_2$ < 55-50 mmHg are significant for the presence of PHtn.

Pulmonary function tests are employed to exclude an intrinsic lung disease. In PHtn, the pulmonary engorgement and enlarged heart reduce the total lung capacity (TLC) and the vital capacity, the FEV$_1$ and FVC decrease but the RV/TLC tends to increase. DLCO is low due to alteration of the alveolar-capillary membrane by chronic edema and interstitial fibrosis which brings to decreased alveolar volume.

Cardiopulmonary metabolic exercise testing analyzes the decreasing peak VO$_2$, peak work rate, the ratio of VO$_2$ increase to work rate increase, anaerobic threshold, peak oxygen pulse, and increase VE-VCO$_2$ slope. It is obvious that exercise limitation in PHtn is caused by V/Q mismatching, lactic acidosis at a low work rate, arterial hypoxemia, and inability to increase stroke volume and cardiac output.

Six minute walk test (6 MWT): a submaximal exercise test utilized to assess functional capacity in congestive heart failure. The utility of this test is variable according to different authors. We found this tool very useful in the evaluation and treatment of PHtn$^{8,9}$. The 6 MWT is commonly used for evaluating PHtn patients for the following reasons: (1) the ease of reproducibility, (2) it is in good correlation with maximal exercise testing (standard cycle ergometry, cardiopulmonary exercise testing [CPET], shuttle walk test, and treadmill walk time), which patients suffering from PHtn and RV failure may not be able to

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**Flow-chart. Pulmonary hypertension pathophysiology**

**Agonist factors**

Endothelin-1 (ET-1) and serotonin play an important role in pulmonary vasoconstriction in vivo:

ET-1 + serotonin $\rightarrow$ High plasma levels

$\downarrow$

Hypoxemia $\rightarrow$ Chronic hypoxemia

$\downarrow$

Vasoconstriction high

$\downarrow$

Remodelling in pulmonary arteries [hypertrophy and proliferation of pulmonary vascular smooth muscle cells and increasing of platelets (the latter only serotonin)]

$\downarrow$

Pulmonary vascular resistance high

$\downarrow$

Increasing of pulmonary hypertension

$\downarrow$

Major detrimental impact on the quality of life

$\downarrow$

Low exercise tolerance $\downarrow$

Overall morbidity $\downarrow$

Low prognosis $\downarrow$

**Antagonist factors**

1. O$_2$ therapy
2. Calcium antagonists
3. Inhaled Nitric Oxide
4. Prostaglandin infusion
5. Prostaglandin nebulization

*Figure 1.* Diagram of the pulmonary hypertension pathophysiology.
complete; (3) most patients reach the end-point. In patients suffering from heart failure, the distance walked in 6 minutes correlates with cardiovascular mortality and morbidity, particularly for those who perform in the lowest quartile (<300-370 meters). In contrast, Miyamoto demonstrated that the distance in 6 MWT was independently associated with survival. The short-distance group (<332 m) had a significantly lower survival rate than long-distance group (≥332 m). Lucas suggested that the 6-MWT was excessively influenced by muscle strength, and concluded that the VO₂ peak, measured by bicycle or treadmill exercise is the preferred study in advanced heart failure. Paciocco did not find the 6 MWT distance to be independently correlated with survival. This finding may be due to the protocol used, in which test is terminated if pulse oxymetry O₂ saturation decreased to values less than 86%. The protocol used in the latter, which was similar to that of Scurba, included application of the 6-MWT almost 2 hours after pulmonary function tests were performed. Patients walked rapidly for six minutes on a 42-meter long circular level. Oxygen saturation was measured by pulse oxymetry at baseline and during the exercise. The test was terminated at an O₂ saturation of less than 86%, except for patients with an atrial right to left shunt. The walk was repeated with calculated dose of supplementary oxygen in those patients with resting or exercise O₂ Sat < 90%.

Selected Forms of Secondary Pulmonary Hypertension: COPD and Cor Pulmonale

Cor pulmonale occurs in about 6%-7% of adults in the US. COPD is the most common etiology. The severity of PHtn closely correlates with survival in chronic lung disease. The median survival in COPD patients with cor pulmonale is approximately 7 years while, those without cor pulmonale survive a median of 13.5 years.

Hypertension, a common finding in different lung diseases, may be episodic or progressive depending on the reversibility of the underlying lung disease, the degree and duration of hypoxemia. There are several compensatory mechanisms in COPD: an increase in heart rate and cardiac output, both in resting and exercise, facilitates the oxygen transport and masks the early manifestations of both combined lung disease and PHtn. When the compensatory mechanisms fail, a sudden deterioration occurs with minimal change in lung function. When right ventricular failure develops, symptoms of dyspnoea and fatigue may appear, along with hepatic engorgement and peripheral edema.

Treatment in COPD with cor pulmonale; few treatments with scarce positive results are available. The main objective is to correct the underlying cause of the elevated pulmonary pressures. Continuous oxygen administration in order to maintain an arterial saturation of at least 90% increases the exercise performance, reduces episodic nocturnal and exertional hypoxemia, and may reduce the rate of progression of PHtn. Two liters per minute via nasal cannulae of supplemental oxygen is often adequate to correct a resting desaturation. Monitoring of cutaneous O₂ saturation during the exercise should be used to identify suitable rates and possibly forms of oxygen delivery.

A pulmonary rehabilitation program including patient education, exercise training, breathing retraining, psychosocial support and nutritional assessment should be considered when patients are malnourished (25% of these subjects) and have reduced respiratory muscle function capacity. It is important to bear in mind that obese COPD patients treated with appetite suppressants are prone to develop pulmonary hypertension due to these pharmaceuticals.

Non-selective vasodilator drugs have been used in SPHtn associated with parenchymal lung disease and COPD, but offer no long-term symptomatic improvement or survival advantage and may have adverse effects. Fishman reported that 30 mg of nifedipine daily did not reduce adequately the pulmonary artery pressure, neither was the vasodilatation of systemic vessels accompanied by adequate pulmonary vasodilatation. Furthermore, fatal hypotension was a common side effect. Vasodilating agents (calcium channel blocker's, nitroglycerin, hydralazine, ACE inhibitors, epoprostenol or PGI2, and nitric oxide) may worsen hypoxemia, by increasing the abnormal perfusion or under-
ventilated lung. In contrast to PPH, the response to calcium antagonists in COPD patients depends on mPA basal level (the higher the initial level of mPA the less effective the drug)\(^{16}\). To overcome the problems associated with a continuous intravenous infusion, and the lack of pulmonary selectivity of prostacyclin, the drug could be administered by inhalation or orally. Some advantages of this method are the pulmonary selectivity and the minimization of the ventilation-perfusion mismatch, as well as the ease of administration. Some disadvantages are the frequent doses that are still required and the cost of the treatment. An alternative to intravenous prostacyclin therapy is an orally active analogue of prostacyclin, the beraprost. Unfortunately, the half-life of beraprost is one hour and therefore necessitates multiple administrations. Inhaled nitric oxide (NO) offers an advantage in that it augments the arterial partial pressure of oxygen. By diffusing selectively to well ventilated regions of the lungs, ventilation-perfusion mismatching is prevented. In patients with COPD, nitric oxide reduces PAP, but PaO\(_2\) is improved only during the exercise. The effects of NO on the systemic circulation are short-lived and not severe. In a small study, inhaled nitric oxide with supplemental oxygen was safe and effective in COPD and pulmonary hypertension\(^{17}\). The principal disadvantage is the formation of potentially toxic products like methaemoglobin.

Dyspnoea, fatigue, and edema are the classic signs of RV failure and are treated similarly to left heart failure. Digitalis, which increases right-heart contractility, should be used cautiously since its toxic effects are more common in COPD associated cor pulmonale respectly to other forms of heart disease. Adequate diet is of paramount importance, should be high in protein, low in fat, and low in salt (\(\leq 2\) Gm sodium). Both loop and potassium sparing diuretics are effective. Caution is necessary to avoid dehydration and orthostatic hypotension, which may reflect hypovolemia and under filling of the left or right ventricle. Although the effects of anticoagulants in cor pulmonale have not been checked in a controlled study, the benefits of sodium warfarin in PPH are fairly well established. Endothelial dysfunction resulting from chronically elevated pulmonary artery pressures predisposes to in-situ thrombosis, which may be prevented by the anticoagulation\(^{16,19}\). Thus, in the absence of contraindications, oral anticoagulants may be indicated for the patients with moderate to several secondary forms of PHtn.

### Connective and Interstitial Lung Diseases

Two groups of restrictive diseases are often associated with pulmonary hypertension: (a) interstitial lung diseases (ILD), (b) connective-tissue diseases. The former are characterized by increased vascular resistance due to progressive fibrosis and remodeling of the pulmonary interstitium; in the latter vascular disease is caused by an impairment of the diffusion capacity due to a thickened alveolar-capillary membrane but without fibrosis. The most common ILDs which evolves to pulmonary hypertension are sarcoidosis, asbestosis, and radiation pneumonitis. Among the connective tissue diseases, of particular importance are SLE, scleroderma (and two of its variants: the CREST syndrome and the Overlap syndrome).

The incidence and the severity of PHtn are lower in chronic obstructive diseases than in interstitial lung diseases. A particular form of ILD, histiocytosis X, severe pulmonary hypertension is remarkable. It is possibly related to an intrinsic pulmonary vascular disease where the damage involves small airways with resultant parenchymal injury\(^{20}\).

**Treatment in connective and ILD:** a variety of agents including oxygen have been evaluated whether they can reduce the mPA and PVR, while maximizing oxygen delivery in patients from SPHtn. Several studies have suggested that prostacyclin analogues IV eprostenol, bosentan, inhaled prostacycline may have good therapeutic effects. Current therapeutic options for PHtn are limited by their variable efficacy and considerable adverse effects Aerosolized iloprost\(^{21}\) offers an improvement in the delivery of prostacyclins, and may overcome some of the risks and adverse effects typical of the parenteral forms. Endothelin-receptor antagonists such as bosentan have been proved to be efficacious, especially in patients with lung in-
volvement of systemic Scleroderma, in improving exercise capacity, pulmonary hemodynamics and the quality of life of PHtn patients. Spironolactone, a potassium sparing diuretic, is particularly effective liver congestion and can be effectively used in conjunction with loop diuretics. There is a theoretical possibility that small doses may reduce mPA and pulmonary vascular resistance. Considering the poor results of the current treatments, transplantation of single lung has become a treatment option for PHtn. The outcome of lung transplantation can be gauged by several end points: survival, physiologic function, quality of life, and cost-effectiveness. The 5-years survival rate is between 45% and 50%.

Figure 2. Pulmonary hypertension treatment.
Chronic Thromboembolic Pulmonary Hypertension (CTEPHtn)

Several studies have shown an impairment of the pulmonary vascular endothelium in patients with PPH or severe SPHtn. Some of the factors involved in the local thrombosis are: an increasing of thrombin activity and platelets activation, an elevated level of TxA2 (platelet-derived), the release of mediators such as PGI2 and NO by endothelial cells of pulmonary arteries. A correct understanding of the pathophysiology of PPH or chronic thromboembolic pulmonary hypertension (CTEPHtn) could avoid chronic lung damage. CTEPHtn generally results from incomplete lysis of a large organized thrombus in the main pulmonary artery and secondary branches, leading to obliterative pulmonary hypertension, disabling right heart failure, and finally death. In properly selected patients pulmonary thromboendarterectomy can be life saving, reduce the PHTn, and improve both the right-heart function and well being. The diagnosis should be suspected in all patients with symptoms suggestive of pulmonary hypertension, particularly when there is a past history of deep vein thrombosis (DVT) or pulmonary embolus (PE).

CTEPHtn is usually unrecognized and often confused with coronary artery disease, asthma, ILD, psychogenic dyspnea, and merely deconditioning. Unfortunately, the objective findings on physical examination, chest x-ray and electrocardiogram in the early phases of the disease are subtle or actually absent.

Diagnosing CTEPHtn: CTEPHtn should be considered in all patients with a history of PE, DVT, hypoxemia, symptoms and signs of pulmonary hypertension or RV failure, and unexplained PHtn or RV function abnormalities on echo-Doppler. The absence of a history of DVT and PE is common.

Ventilation perfusion (V/Q) scanning is an effective screening tool. At least one segmental (usually more) defect is present. In the absence of a history of PE or DVT, a normal or low probability of the V/Q scan in conjunction with normal lower extremity Doppler studies, nearly excludes a thromboembolic etiology for PHTn. If still suspected, central organized thrombi can be detected by helical (spiral) computer tomography or magnetic resonance angiography, but neither tool should be considered adequate to exclude CTEPHtn in a high risk population until better studied.

Pulmonary angiography is necessary to confirm the diagnosis and select candidates.

Figure 3. Pulmonary angiography before (A) and after left pulmonary artery thrombolysis (B) in a 60 year old man who developed cardiogenic shock due to acute pulmonary embolus following a prostatectomy.
for thromboendarterectomy. Rather than the classic cutoffs and filling defects of acute PE, the findings include grossly irregular central arteries (adherent thrombus) or subtle angiographic appearance of organized clots and recanalized vessels. Pulmonary angiography in CTEPHtn is safe when applied with appropriate precautions by an experienced angiographer accustomed to high risk angiography. Complete right-heart catheterization along with pulmonary angiography is necessary to evaluate the degree of pulmonary hypertension, the right-ventricular function, and the operative risks and benefits.

All patients with CTEPHtn should be screened for a pro-thrombotic diathesis by platelet count, PT, PTT, fibrinogen, protein C, S, anti-thrombin III, homocysteine, Factor V Leiden deficiency, and antiphospholipid antibody. A low titer of the latter in PPH and a high titer in CTEPHtn associated with lupus anticoagulant help to differentiate the two entities.

Treatment of CTEPH: surgical thromboendarterectomy, currently performed only in selected medical centers, has evolved over the past five to ten years. The procedure requires delicate entry into the sub-intimal space of the pulmonary artery and the removal of a “cast” of the chronic adherent thrombus from the central, primary and secondary pulmonary artery branches. Surgery is generally indicated in patients with greater than mild symptoms or exercise capacity less than 5-6 MET’s, and a PVR greater than 3 Wood units. Age, coronary artery disease, previous chest surgery, and markedly impaired RV function and tricuspid insufficiency increase the risk, but do not preclude surgery. The procedure requires a median sternotomy, a cardiopulmonary bypass and some periods of anoxic arrest. In experienced hands the average hospital stay is 7 to 10 days. The post-operative course is often complicated by right heart failure and transient post operative mental status changes. The patients also undergo the insertion of an inferior vena caval filter and life long anticoagulation. When performed in experienced centers, on appropriately selected patients, a perioperative mortality of less than 10% can be expected and more than 90% of survivors recover to NYHA Class I or II. An alternative to the surgical embolectomy is the thrombolytic therapy. Thrombolytic agents should be selected when multiple emboli stop the central sites on the left or on the right pulmonary arteries, causing hemodynamic instability or respiratory compromise (Figure 3).

In conclusion, pulmonary hypertension presents a challenge to practicing physicians both in establishing the specific cause and in the treatment. Echo-Doppler is a simple cost-effective tool in both detecting PHtn and evaluating RV function. Effective but non-specific therapies (digoxin, diuretics, anticoagulation) for pulmonary hypertension and right heart failure, achieve a degree of symptomatic improvement, and should be considered in patients with moderate to severe disease. Inhalations of nitric oxide combined with oxygen, offer good support to patients with COPD and pulmonary hypertension with non significant adverse effects. Similarly endothelin receptor antagonists and/or prostacyclin analogues can be helpful in the treatment of patients with secondary pulmonary hypertension associated with connective tissue diseases and ILD. Central thromboembolic PHtn should be considered in patients with dyspnea. Since the more severe forms of PHtn are not uncovered until late in their course, high level of suspicion is required when evaluating symptoms and risk factors consistent with pulmonary vascular disease.

References


