Cor pulmonale

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Abstract

Cor pulmonale is defined as enlargement of the right ventricle secondary to abnormality of the lung, thorax, pulmonary vasculature, or circulation. This leads to right ventricular failure, with elevation of transmural right ventricular end-diastolic pressure. It may be acute, e.g., in pulmonary thromboembolism; or chronic, as in stable severe chronic obstructive pulmonary disease (COPD); or acute-on-chronic as in COPD with superimposed infection and intensification of hypoxia.

20% of hospital admissions of heart failure are due to right heart failure associated with cor pulmonale. This is high where COPD incidence is high.

Key words : COPD, Cor pulmonale, Right heart failure.

Cor pulmonale is the alteration of right ventricular structure or function that is due to pulmonary hypertension caused by diseases affecting the lung or its vasculature. Right-sided heart disease from primary disease of the left side of the heart or congenital heart disease is not considered.

Most of the conditions that cause cor pulmonale are chronic and slowly progressive, patients may also present with acute and life-threatening symptoms. Such abrupt decompensation occurs when the right ventricle is unable to compensate for the imposition of sudden additional demands, resulting either from progression of the underlying disease or a superimposed acute process.

Aetiology

Cor pulmonale is a state of cardiopulmonary dysfunction that may result from several different aetiologies and pathophysiologic mechanisms (table I):

- Pulmonary vasoconstriction (secondary to alveolar hypoxia or blood acidosis).
- Anatomic reduction of the pulmonary vascular bed (emphysema, pulmonary emboli, etc.)
- Increased blood viscosity (polycythaemia, sickle-cell disease, etc.)
- Increased pulmonary blood flow.

The most frequent cause of cor pulmonale is chronic obstructive pulmonary disease (COPD) due to chronic bronchitis or emphysema. In patients with COPD, an increased incidence of right ventricular involvement may correlate with increasing severity of lung dysfunction. As an example, right ventricular hypertrophy is present in 40 percent of patients with an FEV1 < 1.0 L and in 70 percent of those with an FEV1 < 0.6 L. However, the presence of hypoxaemia, hypercapnia, and polycythaemia also independently predict the development of right ventricular hypertrophy in COPD, although not as strongly as abnormal pulmonary mechanics.

Table I : Major causes of cor pulmonale.

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<tr>
<th>Lung disease</th>
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<td>Chronic obstructive pulmonary disease</td>
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<td>Cystic fibrosis</td>
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<td>Interstitial lung diseases</td>
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<th>Disorders of the pulmonary circulation</th>
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<td>Pulmonary thromboembolism</td>
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<td>Primary pulmonary hypertension</td>
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<td>Tumour emboli</td>
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<td>Sickle cell anaemia</td>
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<td>Schistosomiasis</td>
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<td>Pulmonary veno-occlusive disease</td>
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<th>Neuromuscular diseases</th>
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<td>Amyotrophic lateral sclerosis</td>
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<td>Myasthenia gravis</td>
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<td>Poliomyelitis</td>
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<td>Guillain-Barre syndrome</td>
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<td>Spinal cord lesions</td>
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<td>Bilateral diaphragmatic paralysis</td>
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<th>Thoracic cage deformities</th>
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<td>Kyphoscoliosis</td>
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<th>Disorders of ventilatory control</th>
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<td>Primary central hypoventilation</td>
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<td>Sleep apnoea syndromes</td>
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Prognosis

Development of cor pulmonale associated with pulmonary hypertension often has important prognostic implications. In COPD, for example, the development of pulmonary hypertension and peripheral oedema heralds a poor prognosis. Patients who develop peripheral oedema have a five year survival of only approximately 30 percent, and those whose pulmonary vascular resistance exceeds 550 dynes-sec/cm² rarely survive for more than 3 years\(^1\)\(^2\).

However, rather than having a substantial direct effect on mortality, the development of cor pulmonale in COPD may just reflect the severity of the underlying obstructive disease and its effect on mortality. Even in severe COPD, for example, it is uncommon to observe mean pulmonary artery pressures above 40 mmHg; such levels are far below those found in many patients with primary pulmonary hypertension or chronic unresolved pulmonary emboli.

Clinical characteristics

Clinical detection and assessment of cor pulmonale are difficult due to the subtle and often non-specific signs and symptoms. The development of peripheral oedema in COPD is not necessarily a reliable marker of pulmonary hypertension.

Symptoms: There are, however, symptoms directly attributable to pulmonary hypertension, including dyspnoea on exertion, fatigue, lethargy, chest pain, and syncope with exertion.

- Fatigue, lethargy, and exertional syncope reflect an inability to increase cardiac output during stress because of vascular obstruction in the pulmonary arterioles.

- Typical exertional angina may occur. The mechanism by which angina occurs is unclear, as both pulmonary artery stretching and right ventricular ischaemia have been proposed. The importance of right ventricular ischaemia induced by hypoxaemia during exertion was suggested in a case report in which angina was associated with electrocardiographic changes of right ventricular strain and was relieved with long-term oxygen therapy.

Less common symptoms related to pulmonary arterial hypertension: cough, haemoptysis, hoarseness (compression of the left recurrent laryngeal nerve by dilated main pulmonary artery).

Severe right ventricular failure leading to passive hepatic congestion may lead to complaints such as anorexia and right upper quadrant discomfort.

Physical findings: Should detect findings characteristic of pulmonary hypertension and right ventricular hypertrophy, sometimes accompanied by right ventricular failure.

- The initial physical finding of pulmonary artery hypertension is increased intensity of the pulmonic component of the second heart sound, may even become palpable. Second heart sound may also be narrowly split, a change that will not be present if right ventricular depolarisation is delayed because of concurrent right bundle branch block. Auscultation of the heart may reveal a systolic ejection murmur, in more severe disease, a diastolic pulmonary regurgitation murmur.

- Right ventricular hypertrophy is characterised by a prominent A wave in the jugular venous pulse, associated with a right-sided fourth heart sound and either a left parasternal heave or a downward sub-xiphoid thrust.

- Right ventricular failure leads to systemic venous hypertension. This can produce a variety of findings, such as elevated jugular venous pressure with a prominent V wave, a right ventricular third heart sound, and a high-pitched tricuspid regurgitant murmur.

The right-sided murmurs and gallops are augmented with inspiration, but may be obscured, depending upon the aetiology of the hypertension. In severe emphysema, the increased antero-posterior (AP) diameter of the chest makes auscultation difficult and changes the position of the right ventricular impulse.

Although ascites is uncommon, even in severe cor pulmonale, extra-cardiac changes that may be seen include hepatomegaly, a pulsatile liver (if tricuspid regurgitation is
prominent), and peripheral oedema, which may develop or be exacerbated during a course of steroid therapy\(^1,2\).

**Oedema:** Although some patients with severe COPD develop edema in association with clear evidence of right heart failure, other patients with oedema have no haemodynamic signs of right ventricular failure, and pulmonary artery pressure and arterial blood gases are stable\(^3\). The pathogenesis of oedema in such patients is not well understood: the cardiac output and glomerular filtration rate are usually normal or near normal, both in the resting state and with exercise. Oedema seems to occur primarily in patients with hypercapnia, suggesting that the high PCO\(_2\) rather than cardiac dysfunction may be responsible for the sodium retention in cor pulmonale. Hypercapnia is associated with an appropriate increase in proximal bicarbonate reabsorption, which serves to minimise the fall in arterial pH, but also can contribute to oedema formation, since it also promotes the passive reabsorption of NaCl and H\(_2\)O.

Another contributing factor to sodium retention may be hypoxaemia. Hypoxaemia can cause renal vasoconstriction, leading to a reduction in urinary sodium excretion.

**Evaluation**

Because of the non-specificity of symptoms and signs, ancillary evaluation may be useful, including the following techniques\(^4\):

- **Chest radiography**
- **Electrocardiography**
- **Two dimensional and Doppler echocardiography** (which can provide an indirect measurement of pulmonary artery pressure when tricuspid regurgitation is present)
- **Pulmonary function tests**
- **Radionuclide ventriculography**
- **Magnetic resonance imaging**
- **Right heart catheterisation**
- **Lung biopsy**

**Chest radiograph:** The characteristic chest X-ray in pulmonary arterial hypertension shows enlargement of the central pulmonary arteries (Fig. 1). In 95% of patients with COPD and pulmonary hypertension, the diameter of the descending branch of the right pulmonary artery is greater than 20 mm in width. Peripheral vessels are attenuated, leading to oligoemic lung fields.

Right ventricular failure may result in right ventricular and right atrial dilatation on chest radiography. Right ventricular enlargement can also lead to a decrease in the retrosternal space. However, these findings may be obscured in the presence of kyphoscoliosis, hyperinflated lungs, left ventricular enlargement, or interstitial lung disease.

**Electrocardiogram:** May demonstrate signs of right ventricular hypertrophy or strain (Fig. 2). Findings that may be seen in chronic right ventricular overload include:

- Right axis deviation and R/S ratio greater than 1 in lead V1.
- Increased P wave amplitude in lead II (P pulmonale) due to right atrial enlargement (figure 3, 4).
- Incomplete or complete right bundle branch block.

In acute cor pulmonale, such as occurs with acute pulmonary embolism, a classic pattern of an S wave in lead I with a Q and inverted T wave in lead III may be seen.
Most electrocardiographic criteria show a high specificity (i.e., the findings are absent in patients without the disease) but a low sensitivity (i.e., the findings are present in patients with the disease) for the detection of RVH. The sensitivity of the electrocardiogram is even worse in patients with bi-ventricular hypertrophy or COPD, but the presence of electrocardiographic changes of cor pulmonale in these settings connotes a poor prognosis.

Two-dimensional echocardiography: Most patients with pulmonary arterial hypertension have two-dimensional echocardiographic signs of chronic right ventricular pressure overload (Fig. 5, echocardiogram 1, 2, 3, and 4). The elevation in pressure leads to increased thickness of the right ventricle with paradoxical bulging of the septum into the left ventricle during systole (Fig. 6). At a later stage, right ventricular dilatation occurs, and the septum shows abnormal diastolic flattening.

Stress on the right heart initially produces hyperkinesis. However, this is eventually followed by right ventricular hypokinesis, associated with right atrial dilatation and tricuspid regurgitation. The latter is not due to an intrinsic abnormality of the tricuspid valve; it is a secondary manifestation of dilatation of the tricuspid annulus and right ventricle.
Doppler echocardiography: It is the most reliable non-invasive estimation of the pulmonary artery pressure. This technique takes advantage of the functional tricuspid insufficiency usually present in PAH. The maximum tricuspid regurgitant jet velocity is recorded, and the pulmonary artery pressure (PAP) is then calculated by the modified Bernoulli equation:

\[ \text{PAP systolic} = (4 \times \text{tricuspid jet velocity squared}) + \text{RAP} \]

where RAP is the right atrial pressure estimated from the inferior vena cava. Other findings associated with pulmonary hypertension are pulmonic insufficiency and mid-systolic closure of the pulmonic valve.

The efficacy of Doppler echocardiography may be limited by the ability to identify an adequate tricuspid regurgitant jet. It may also be less sensitive because of alterations induced by the underlying disease. For example, acoustic windows in patients with COPD may be limited by the increased antero-posterior diameter of the chest.

Despite these potential problems, Doppler estimation using tricuspid regurgitation is far more sensitive than the clinical examination and can make an accurate diagnosis in the majority of patients. This is illustrated by the following observations:

- The accuracy was even higher in patients with more severe disease (PA systolic pressure above 50 mmHg). Tricuspid regurgitation was detected in 95 percent of these patients, and there was a 97 percent correlation with the pressure measured by catheterisation.

- Echocardiographic cor pulmonale was said to be present when the right ventricular free wall thickness was > 0.6 cm in the sub-xiphoid view, PA systolic pressure was greater than 40 mmHg by tricuspid jet Doppler with saline contrast, and the RV/LV ratio was increased. Clinical criteria included right ventricular hypertrophy on the electrocardiogram, enlarged pulmonary arteries on the chest X-ray, and physical findings such as a loud pulmonic heart sound, parasternal heave, jugular venous distension, oedema, and hepatomegaly. Cor pulmonale was identified by clinical criteria in only 39% of patients versus 75% with echocardiography. The use of saline contrast significantly enhanced the sensitivity of Doppler ultrasound in detecting tricuspid regurgitation.

**Pulmonary function tests:** Pulmonary function tests should be performed in patients with a suggestive history of underlying lung disease and in those with normal cardiac function. It is important to appreciate that only severe interstitial lung disease (with lung volume below 50 percent of normal) produces secondary pulmonary hypertension, while a mild restrictive defect can be produced by pulmonary arterial hypertension itself. Thus, the latter finding is not indicative of interstitial lung disease as a cause of secondary pulmonary arterial hypertension.

**Right-sided cardiac catheterisation:** Catheterisation of the right heart is the gold standard for the diagnosis, quantification, and characterisation of pulmonary arterial hypertension. This procedure is indicated only when the necessary information cannot be obtained with Doppler echocardiography. Current indications include:

- When echocardiography does not permit
measurement of a tricuspid regurgitant jet, which does not exclude significant pulmonary artery hypertension.

- When symptoms are exertional, and simultaneous measurement of left-sided pressures during exercise is also indicated.

- When therapy will be determined by precise measurement of pulmonary vascular resistance and the response to vasodilators.

- When left heart catheterisation is also required, for example, in the patient over 40 years of age or with risk factors for coronary disease.

Right heart catheterisation can also be used to determine the potential reversibility of pulmonary arterial hypertension with vasodilators, such as sustained release calcium channel blockers.

Lung biopsy: Pathologic assessment of pulmonary artery hypertension requires lung biopsy. Historically, pathologic examination has been used intra-operatively to look for evidence of irreversible pulmonary artery pathology. Right heart catheterisation assessments of pulmonary vascular resistance and vasodilator response are usually adequate to guide therapeutic decisions.

Treatment
The medical management of patients with cor pulmonale has centred upon attempts to improve oxygenation (with hypoxaemic patients) or right ventricular contractility, as well as attempts to decrease pulmonary vascular resistance and vasoconstriction (primarily via vasodilators). This section will discuss the management of patients with cor pulmonale, focusing primarily on the treatment of those with cor pulmonale and COPD.

**Oxygen therapy:** Long-term oxygen therapy improves the survival of hypoxaemic patients with COPD; however, the mechanisms have not been fully elucidated. Two major (and not mutually exclusive) hypotheses may explain the survival benefit of oxygen therapy:

- Oxygen therapy relieves pulmonary vasoconstriction, thereby decreasing pulmonary vascular resistance; as a result, the right ventricle increases stroke volume and cardiac output. Renal vasoconstriction also may be relieved, resulting in an increase in urinary sodium excretion.

- Oxygen therapy improves arterial oxygen content, providing enhanced delivery to the heart, brain, and other vital organs.

**Diuretics:** If right ventricular filling volume is markedly increased, diuretics may be helpful in reducing cardiac chamber sizes and decreasing symptoms of congestion. The use of diuretics in the treatment of cor pulmonale depends on the degree of right ventricular dysfunction and the presence of pulmonary hypertension.

**Fig. 5 (Echocardiography 1): Pulmonary hypertension:** The four chamber view from a 2–D echocardiogram shows marked enlargement of the right atrium and ventricle which is also hypokineti as a result of elevated pressure due to pulmonary hypertension.

**Fig. 5 (Echocardiography 2): Pulmonary hypertension:** The short axis view from a 2–D echocardiogram shows significant right ventricular hypertrophy as a result of pulmonary hypertension.

**Fig. 5 (Echocardiography 3): Tricuspid regurgitation:** Subcostal view from a 2–D echocardiograms shows significant dilatation of the hepatic veins as a result of significant tricuspid regurgitation.
since a drop in cardiac output may result if right ventricular filling volume and pressure are reduced too dramatically in pulmonary hypertension. A simple method to assess volume status is to monitor the BUN and plasma creatinine concentration. As long as these parameters remain stable, it could be assumed that renal perfusion and therefore flow to other organs are being maintained. On the other hand, further fluid removal should cease if there is an otherwise unexplained elevation in these tests.

Another potentially important complication of diuretic therapy in cor pulmonale is the development of metabolic alkalosis. Alkalosis suppresses ventilation, which can have important implications in severe lung disease, e.g., leading to difficulty in weaning from a ventilator.

**Digoxin:** Except in cases of co-existent left ventricular failure, clinical studies do not support the use of digitalis in patients with cor pulmonale. Specifically, the use of digoxin in COPD patients with normal left ventricular function does not improve right ventricular ejection fraction at rest or during exercise, nor does it increase maximal exercise performance.

**Vasodilators:** Several vasodilator agents (including hydralazine, nitrates, nifedipine, verapamil, and ACE inhibitors) have been utilised in an attempt to ameliorate pulmonary hypertension. In some studies, short-term but modest reductions in pulmonary artery pressure have been documented. However, vasodilators generally do not result in sustained or significant improvement and may be associated with adverse side effects:

- Short-term studies usually fail to document an improvement in exercise capacity or functional status, probably resulting from the fact that these patients are limited more by lung mechanics than by the degree of pulmonary hypertension.
- Evidence of sustained efficacy (beyond three to six months) is relatively uncommon.
- The use of vasodilators in patients with COPD can be associated with worsening of arterial oxygenation and/or systemic hypotension, although these effects usually are not severe.

Overall, therefore, the use of vasodilator medications...
for patients with COPD has generally dropped from routine clinical practice. Nevertheless, patients with severe and persistent pulmonary hypertension despite oxygen and bronchodilator therapy may be candidates for a trial of vasodilator therapy. In this setting, right heart catheterisation is recommended during the initial administration of the vasodilator; either sustained release nifedipine (30 to 240 mg/d orally, sustained release) or diltiazem (120 to 720 mg/d orally, sustained release) is recommended in order to objectively assess efficacy and detect possible adverse haemodynamic consequences. A reduction in pulmonary vascular resistance of more than 20% (provided that cardiac output does not decrease and pulmonary artery pressure does not increase) is a reasonable criterion that has been suggested as evidence of efficacy.

**Theophylline and sympathomimetic amines:**
Theophylline and sympathomimetic amines (terbutaline) may have salutary effects not related to bronchodilation. These agents may:

- Improve myocardial contractility
- Provide some degree of pulmonary vasodilation
- Enhance diaphragm endurance

Such effects may explain why some patients treated with theophylline, for example, experience a reduction in dyspnoea (as documented in at least one double-blind trial) even without a reduction in airflow obstruction. It is reasonable to consider the use of theophylline as adjunctive therapy in the management of chronic or decompensated cor pulmonale in patients with COPD, at least until further evidence either supporting or refuting this approach is available.

**Almitrine:** The well documented ability of almitrine to improve arterial PO2 in patients with COPD led to initial enthusiasm regarding the potential clinical utility of this agent. Almitrine appears to improve gas exchange largely by enhancing hypoxic pulmonary vasoconstriction, thereby worsening pulmonary hypertension, especially during exercise. This may account for the dyspnoea experienced by some patients receiving this agent, despite enhanced arterial oxygenation. The use of almitrine in the management of COPD is not currently recommended.

**Phlebotomy:** In patients with severe polycythaemia (haematocrit above 55 percent), phlebotomy (to achieve a haematocrit of about 50 percent) is associated with a decrease in mean pulmonary artery pressure and pulmonary vascular resistance, and an improvement in exercise performance. However, the application of continuous oxygen therapy in appropriately selected patients should reduce the number of COPD patients who become severely polycythaemic. Use of phlebotomy should generally be reserved as adjunctive therapy in acute management of the markedly polycythaemic patient who has an acute decompensation of cor pulmonale, or for the rare patient who remains significantly polycythaemic despite appropriate long-term oxygen therapy.

**References**