

CHRONIC OBSTRUCTIVE PULMONARY DISEASE - RECENT TRENDS

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Chronic obstructive pulmonary disease (COPD) which includes chronic bronchitis and emphysema is a major cause of morbidity and mortality in industrialised countries. An increasing prevalence of the disease has been observed in our country as well. Chronic bronchitis, emphysema and bronchial asthma are the major causes of obstruction to airflow from the lungs. Unlike Bronchial asthma, the airflow limitation in COPD is persistent. A CIBA symposium in 1959 defined chronic bronchitis, as a condition of subjects with chronic or recurrent excessive mucous secretions in the bronchial site without a demonstrable cause, either local or general occurring most on most of the days for at least three months in the year during last two years. National Heart lung and Blood Institute in Intermittent positive pressure Breathing trial defined emphysema morphologically as a condition of the lung characterised by abnormal permanent enlargement of the airspaces distal to the terminal bronchioles accompanied by destructive changes of the alveolar walls and without obvious fibrosis

Pathogenesis

In 1964, Erikson showed that congenital deficiency of Alpha 1 antitrypsin (AAT) would lead to emphysema especially in severe deficiency state associated with a protease inhibitor phenotype z z (PI Z). The AAT level in PI Z disease is less than 11 μ mol. Even though, the serum antiprotease levels in common heterozygous for AAT deficiency (PI MZ Phenotype) is low, compared to normal PI MM Phenotype, subjects with PI MZ Phenotype do not appear to be at increase risk of developing COPD. This led to the protease – antiprotease theory of pathogenesis of emphysema. Tobacco-smoking is the most important risk factor associated with COPD. Tobacco smoke attracts alveolar macrophage (AM) and they cluster around the terminal bronchioles. Alveolar macrophages activated by tobacco smoke release neutrophil chemotactic factors such as leukotriene

B_4 (LTB_4), complement components ($C5_a$) and neutrophil chemotactic factor. Thus circulating neutrophils from the blood stream are attracted to the site where AM have already clustered around the terminal bronchioles. Tobacco smoke causes activation of neutrophils resulting in release of Human Neutrophil Elastase (HNE). HNE is capable of lysing elastin, collagen, proteoglycans, fibronectin and laminin which form the interstitium of lung. In a healthy individual, HNE is inactivated by alpha 1 - PI which is Produced in the liver. The molecular weight of alpha-1 PI is 52000 kilodalton (KD) and this molecular size enables alpha-1 PI to migrate to epithelial lining fluid of lung from blood. The binding of alpha-1 PI with HNE results in inactivation of HNE.

An active methionine residue present in alpha- PI molecule is essential for neutralisation of HNE. Oxidants present in smoke oxidises methionine, thus preventing the binding and inactivation of HNE. In addition oxidants released by activated neutrophils are also capable of oxidising alpha 1 - PI. Thus tobacco smoke, in addition to increasing the HNE burden in the lower respiratory tract, causes inactivation of protein alpha - PI which is essential for body's defense against elastases. This results in unopposed action of HNE on lung tissue leading to destructive changes.

British investigators hypothesised that chronic airflow obstruction is a late stage of chronic bronchitis which results predominating from cigarette smoking and is referred to as "British hypothesis". However, Dutch investigators proposed that chronic bronchitis and emphysema were closely related to bronchial asthma. According to the Dutch hypothesis, airway narrowing developed as a primary abnormality in subjects who were over-reactive in a manner analogous to allergic asthma to a variety of allergic and other environmental stimulants.

Clinical features

Breathlessness on exertion, gradually progressing to breathlessness at rest is the most important presenting symptom in patients with emphysema. In chronic bronchitis, the predominant symptom is cough, often with episodes of persistent sputum especially in winter months but without haemoptysis. Often these patients may present with a history of wheeze. The breathlessness

is usually relatively constant from day to day unlike the day to day variability observed in bronchial asthma,

On physical examination, hyperinflation of the chest as evidenced by reduction in the cricosternal distance, bilateral respiratory indrawing of supraclavicular fossae and intercostal spaces over the lower portion of the chest, loss of absolute cardiac dullness to percussion and widening of the subcostal angles are important findings.

In order to describe two types of patients with chronic bronchitis and emphysema, two descriptive terms, pink puffer (Type A) and blue bloater (Type B) were used. Both blue bloaters and pink puffers have similar degrees of airway obstruction. However, blue bloaters have marked central cyanosis, secondary polycythemia, suffusion of conjunctivae and face, elevated jugular venous pressure, ankle oedema, distension of forearm veins and a full volume pulse. These patients have arterial hypoxemia and CO_2 retention with compensated respiratory acidosis. Their body weight tends to be higher than normal. Bird-flapping tremor (tremor of the outstretched hands) signifies acute CO_2 retention.

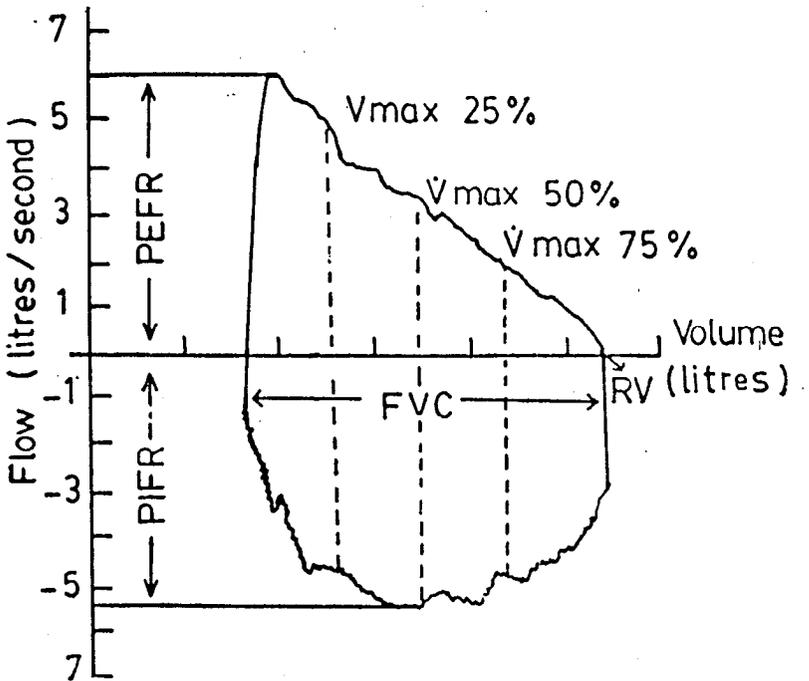
On the other hand, the pink-puffers are often thin with a body weight below average. These patients are very breathless. Central cyanosis is only minimal because profound arterial hypoxemia is rare. CO_2 retention, secondary polycythemia and cor pulmonale are also rare.

Respiratory function

The cardinal feature of the COPD is the demonstration of airflow obstruction as revealed by a low FEV1/FVC ratio and low Peak Expiratory Flow Rate (PEFR). In addition, all flow rates (VE max 25%, 50%, and 75%) are reduced in COPD. Typical flow volume curves from a south Indian non-smoking normal subject and from a patient with COPD are shown in figures 1 and 2.

FIGURE - I

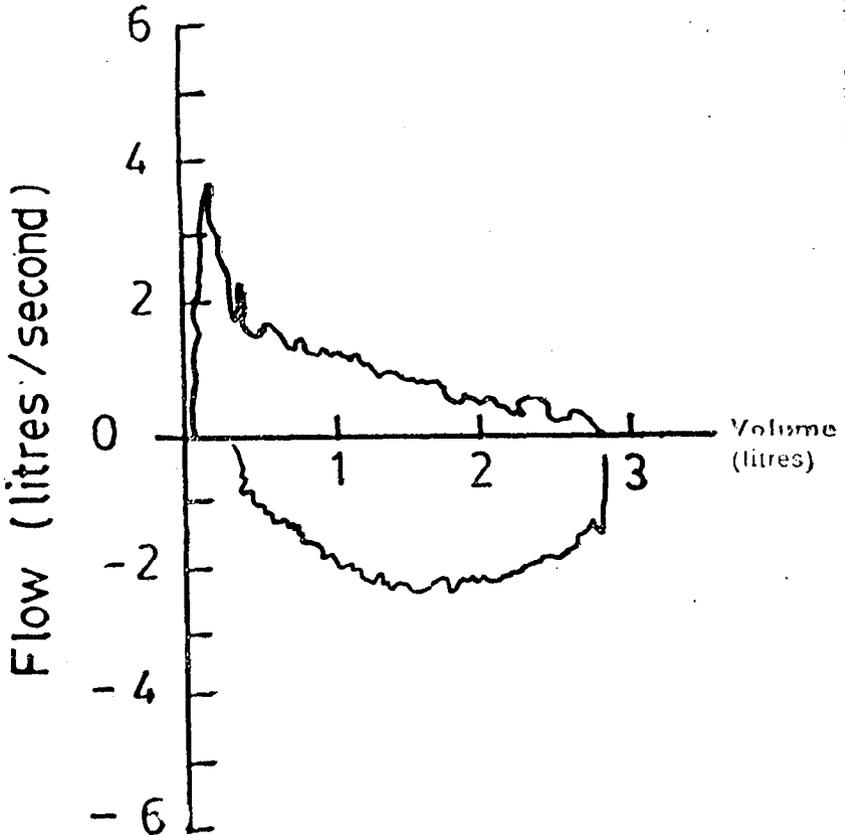
FLOW - VOLUME LOOP IN A NORMAL
NON - SMOKING S. INDIAN SUBJECT



- PEFR = Peak expiratory flow rate
 PIFR = Peak inspiratory flow rate
 FVC = Forced vital capacity
 RT = Residual volume

FIGURE - 2

FLOW VOLUME LOOP IN A PATIENT
WITH CHRONIC OBSTRUCTIVE AIRWAYS DISEASE



Lung volumes show hyperinflation as evidenced by an increase in total lung capacity (TLC) and the ratio of RV (Residual Volume) to TLC. The difference between the multiple breath TLC and single breath TLC will be more than 500ml, suggesting that airtrapping is a feature of COPD. Both diffusing

capacity (DLCO) and transfer coefficient (KCO) are reduced in emphysema. However, DLCO and KCO may be normal in chronic bronchitis, possibly due to secondary polycythemia.

Radiology

Chest radiographs may show flattened diaphragm, irregular radiolucency of the lungs. Lateral chest radiographs reveal an abnormal retrosternal space. These findings may not be of diagnostic value in COPD. Examination of the width of the right descending (inter - lobar) pulmonary artery on routine chest radiographs can detect pulmonary artery hypertension in COPD. Width of the descending branch of right pulmonary artery > 20 mm has been found to be an useful criterion for identifying patients with pulmonary hypertension.

The presence of localised areas of abnormally low attenuation without surrounding walls or with very thin (> 1 mm diameter) walls is the characteristic CT finding in emphysema. CT may show evidence of emphysema in patients with normal chest radiographs. Even though CT is currently the most accurate method of diagnosing emphysema in vivo, it has a very limited role in the clinical assessment of emphysema because of its cost. However, CT may be useful in assessing symptomatic patients with abnormal gas transfer without evidence of airway obstruction on pulmonary function. It is also useful in the pre-operative assessment of patients with large bullae being referred for bullectomy. CT may also be indicated in the assessment of patients with recurrent spontaneous pneumothorax.

Cardiovascular-Pulmonary interaction

The pulmonary vascular bed is a low pressure, low-resistance system, enabling it to accommodate marked increase in blood flow with minimal elevations in pressure. Three factors influence pulmonary vascular resistance:

Pulmonary vascular resistance (mm Hg / L / min) =

Pulmonary artery pressure (mmHg) / Left atrial or wedge pressure (mmHg)

Pulmonary blood flow (L/min).

In patients with COPD, loss of vascular surface and alveolar hypoxia induce pulmonary vasoconstriction that lead to augmented pulmonary vascular resistance and pulmonary vascular pressure. This results in an increase in the afterload on right ventricle both at rest and at exercise. Hypoxemia is the primary factor that leads to pulmonary hypertension. Acidemia acts synergistically with hypoxemia in elevating pulmonary artery pressure and vascular resistance. Elevated PaCO₂ exerts an indirect effect by reducing the PH. Untreated elevations in pulmonary vascular pressure in patients with COPD have important prognostic implications. Patients with hypoxemic pulmonary vasoconstriction and resting pulmonary hypertension with associated cor-pulmonale have poor prognosis.

The ejection fraction (EF) which is the mathematical ratio of stroke volume to end-diastolic volume may be reduced either due to a fall in stroke volume or an increase in diastolic filling.

$$\text{Ejection fraction} = \frac{\text{Stroke volume}}{\text{End-diastolic volume}}$$

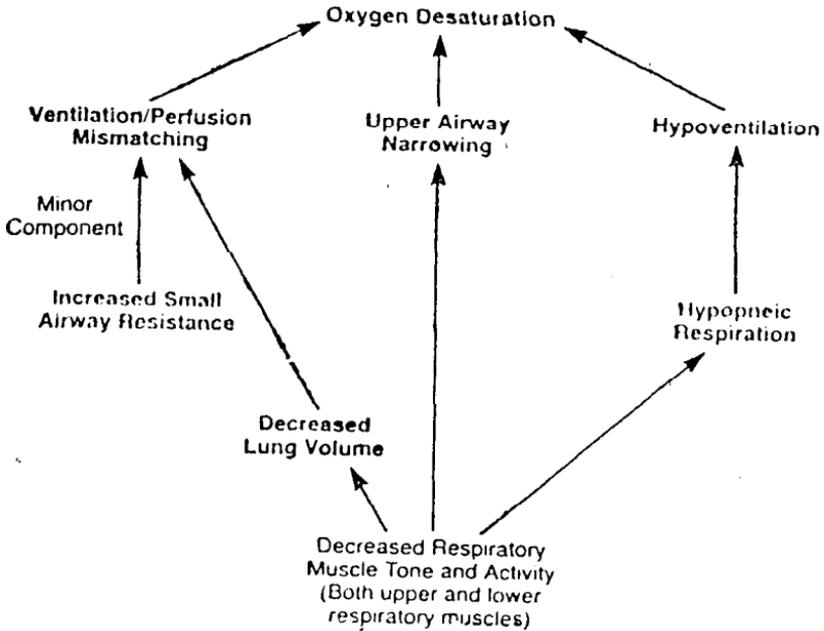
A reduced resting right ventricular EF can be utilised as a marker for the presence of hypoxemia and pulmonary hypertension in patients with COPD. A strong inverse correlation between right ventricular EF and two indices of afterload namely, peak pulmonary artery systolic pressure and pulmonary vascular resistance was observed in patients with COPD. Thus, reduction of EF in COPD patients can be considered as an early sign of cor-pulmonale. In conformity with this, it had been observed that in COPD patients with abnormal right ventricular EF, but without clinical signs of right heart failure, cor-pulmonale developed on follow up.

Sleep studies

Even though hypoxemia is thought to be responsible for severe sequelae such as cor-pulmonale in patients with COPD, some patients with COPD and right sided heart failure have only slightly abnormal awake arterial blood gases. However, these patients have severe intermittent nocturnal hypoxemia and this may be the initiating point for the development of pulmonary hypertension. The proposed mechanism of nocturnal oxygen

desaturation and a common pattern of oxygen desaturation over a night's sleep in patients with COPD are shown in figures 3 and 4.

PROPOSED MECHANISM OF NOCTURNAL OXYGEN DESATURATION IN COPD.



Treatment

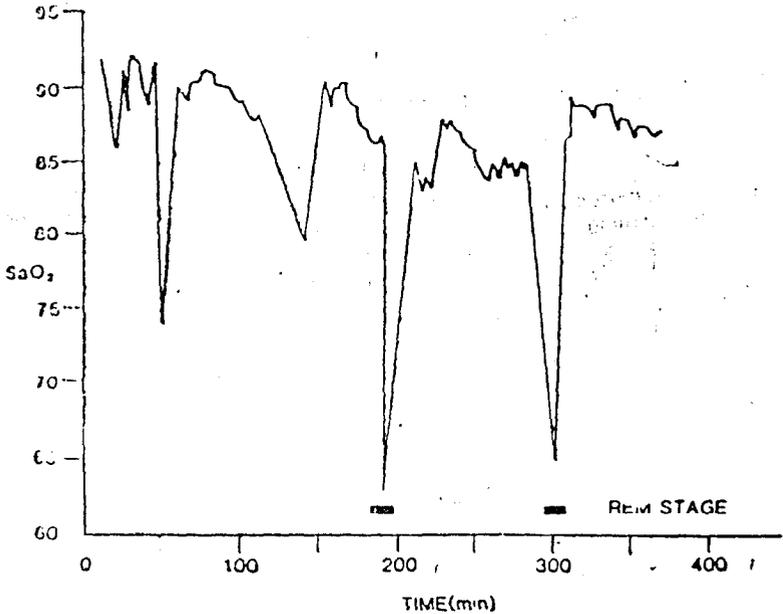
Long - term management of COPD involves the following :

1. Stopping smoking for life.

Cigarette smoking is the single most important preventable cause of COPD. Smoking cessation is therefore the most important component of a treatment programme. Smoking cessation can be tried either with drug treatment or with behavioral intervention. Drug therapy includes nicotine substitution with nicotine polacrilex gum or transdermal patches. Clonidine has also been shown to augment nicotine substitution in alleviating withdrawal symptoms.

FIGURE-4

A COMMON PATTERN OF OXYGEN DESATURATION OVER
A NIGHT'S SLEEP IN PATIENT WITH COPD.



2. Bronchodilators.

1. Theophylline
2. B₂ agonists (Terbutaline, Pirbuterol)
3. Anticholinergics (Ipratropium bromide)

Beta₂ agonists and anticholinergics may induce short-term improvement in FEV₁ after inhalation in patients with COPD. Even though the bronchodilator effect is very small, patients may have symptomatic benefit. Thus bronchodilator use may improve symptoms.

3. Corticosteroids.

The role of inhaled corticosteroids in the management

of COPD is controversial. Recent studies have suggested that addition of anti-inflammatory therapy to regular bronchodilators attenuates the decline of lung function in symptomatic patients with COPD. However, the ongoing European Multicentre Study (Euroscop) on inhaled corticosteroids in smokers with airflow obstruction will give an answer to the question of the role of corticosteroids in COPD.

4. Mucokinetic agents.

1 Water

2 I o d i d e

3 Oral expectorants (Guaifenesin)

4 Mucolytics (Acetylcysteine).

Although there is no clear evidence for therapeutic benefit from mucokinetic agents, the chronic use of acetylcysteine may protect the lungs from oxidant damage because of its antioxidant properties.

5. Treatment of infective exacerbations.

Empiric use of broad spectrum antibiotics is recommended for the acutely deteriorating patients with neutrophilic sputum despite no overt sign of pneumonia.

6 Alpha 1- antitrypsin replacement

a) Alpha 1 – antitrypsin (Injection, aerosol)

b) Danazol (200 mg three times a day)

More studies are required before these drugs can be prescribed for the treatment of COPD>

7. Pulmonary vasodilators

a). Alpha – adrenergic blockers
(Prazosin, urapidil)

b). Calcium channel blockers
(Nifedipine, Nitrendicine)

c). Angiotensin Converting Enzyme inhibitors
(Captopril, Enalapril)

d). Prostaglandins
1. E 1, E 2

2. Prostacycline (Prostaglandin 1_2)

An ideal pulmonary vasodilator drug is yet to be identified.

8. Almitrine bismesylate

Almitrine is reported to increase PaO_2 and reduce PaCO_2 in patients with COPD.

9. Diuretics

Diuretics may be required in congestive cardiac failure or cor pulmonale.

10. Digitalis

Digitalis is the drug of choice for left ventricular failure or Supraventricular tachyarrhythmias. However, digitalis has not been shown to improve right ventricular function either at rest or during exercise, except in the presence of concurrent left ventricular failure. The possibility that digoxin may have favourable effects when used in combination with other medications such as theophylline, vasodilators, selective B. – adrenergic agents and oxygen requires further study.

11. Phlebotomy

Phlebotomy should be reserved for use as an adjunctive therapy in the acute management of the markedly polycythemic patients who has an acute decompensation of cor pulmonale.

12. Prevention of influenza

Since patients with COPD are at increased risk from influenza and its sequelae including respiratory failure, they should be vaccinated with an inactivated influenza vaccine currently circulating.

13. Exercise training

Since fatigue of respiratory muscles is an important feature of COPD, inspiratory muscle training has been shown to improve exercise endurance and 12-minute walking distance.

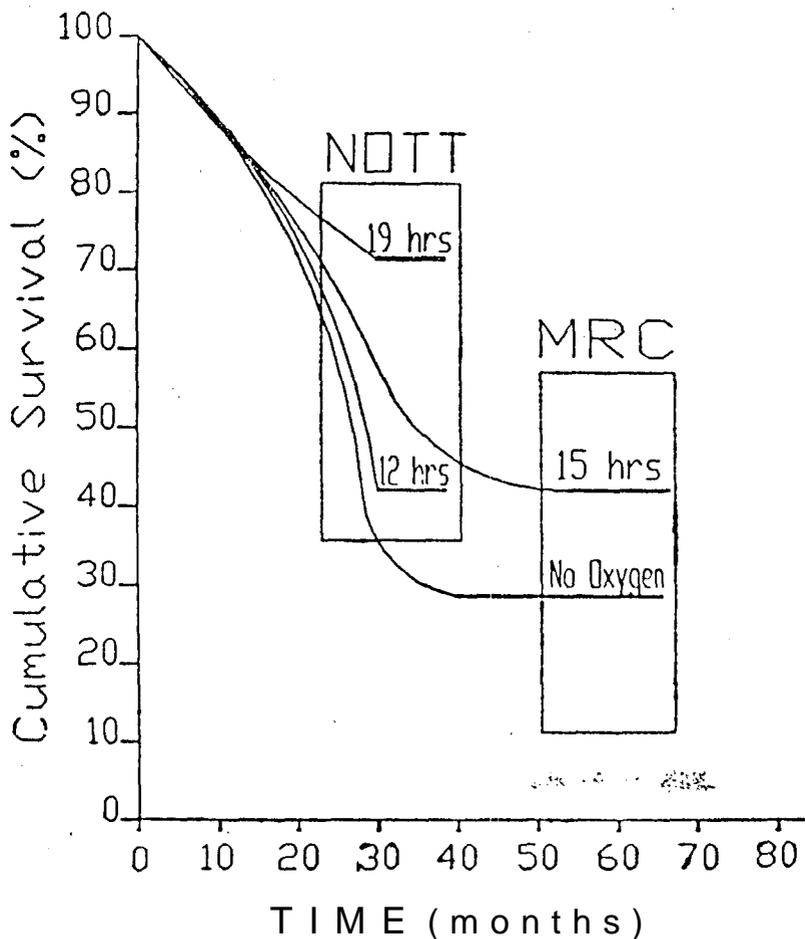
14. Nutritional therapy to reverse malnutrition in emphysematous patients.

15. Long-term home oxygen therapy

Two landmark studies, the National Heart, Lung and

Blood Institute's Nocturnal Oxygen Therapy Trial (NOTT) and the British Medical Research Council (BMRC) multicentre trial have demonstrated that oxygen improved survival in selected patients with advanced COPD. BMRC study compared 15 hours of continuous oxygen including hours of sleep with no oxygen in a randomly assigned patients. The NOTT study compared oxygen for 12 hours a day (nocturnal group) with 24 hours a day (continuous group) in patients with advanced COPD.

COMPOSITE GRAPH OF THE BMRC AND THE NHLBI NOTT STUDY.



The continuous oxygen therapy group actually received oxygen for an average of 19.4 hours a day. Both studies enrolled patients with advanced COPD with significant hypoxemia, who were in stable state and were otherwise receiving good treatment for airflow obstruction. In the BMRC study, the oxygen therapy group had improved survival, which became apparent in males after 500 days of the study had elapsed. In the NOTT trial, a clear survival benefit was observed in continuous oxygen therapy group compared to only nocturnal oxygen therapy group. The combined results of these studies are summarised in figure 5. Patients who received no oxygen had a survival of only 30% in five years. On the other hand, BMRC patients who had received oxygen therapy for 15 hours per day had similar survival compared to NOTT trial patients who had received nocturnal oxygen for 12 hours per day. The best results were in NOTT trial patients who received oxygen for approximately 19.4 hours per day. Thus, in COPD patients, no oxygen is bad, some oxygen is better and continuous oxygen is best. Guidelines for home oxygen for patients with advanced COPD is given in Table 1.

Table 1

**General Prescribing Guidelines for Home Oxygen
for Patients with Advanced COPD**

Patient Selection Criteria:

1. Stable course of disease on optimum indicated medical therapy, eg., bronchodilator, antibiotics, corticosteroids
2. At least two arterial blood gas determinations while breathing air for at least 20 minutes.
3. Room air PO_2 consistently 55, or consistently 55 - 59 + cor pulmonale clinically diagnosed or hematocrit 55%.
4. Normoxic patients in whom less dyspnea and increased exercise is demonstrated with oxygen.

Oxygen Dose :

1. Continuous flow by double or single nasal cannulae.
2. By demand system with demonstration of adequate

oxygen saturation.

3. Lowest liter flow to raise PO_2 to 60-65 or oxygen saturation to 88-94%.
 4. Increase baseline liter flow by 1 L during exercise and sleep.
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Oxygen systems

Oxygen is furnished in three forms : compressed gas oxygen, liquid oxygen and oxygen concentrator. Advantages and disadvantages of home oxygen systems are given in Table 2.

Table 2

Advantages and Disadvantages of Available Home Oxygen Systems

LIQUID PORTABLE	CONCENTRATORS	COMPRESSED GAS
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Advantages :

- | | | |
|--|----------------------------|--|
| 1. Light weight | 1. Lower cost | 1. Lower cost in general (cost may equal liquid in continuous use situations). |
| 2. Long range portable canister | 2. Convenient at home | 2. Widespread availability |
| 3. Most practical ambulatory system | 3. Attractive equipment | |
| 4. Valuable for pulmonary rehabilitation | 4. Widespread availability | |
| 5. 100% oxygen at all flow rates | | |

Disadvantages :

- | | | |
|---|-------------------------|--|
| 1. More expensive than concentrators used alone | 1. Electricity required | 1. Multiple tanks necessary for ambulation |
|---|-------------------------|--|

		unless transfilling can be done at home
2. Not available in small or rural communities	2. May need back-up tank system	2. Frequent deliveries needed
	3. Not portable: does not assist in ambulation or pulmonary rehabilitation	3. Heavy and unsightly tanks; not as effective in pulmonary rehabilitation
	4. Noise	

Several means of oxygen delivery have been available including nasal catheters, various permutations of masks, nasal cannulas and transtracheal catheters. Most patients on long - term oxygen therapy can be managed via continuous flow nasal cannulas. The most common flow setting is 2 L/min and this raises the FI_{O_2} of room air from 20.9% to about 27% which is sufficient to improve oxygen saturation to 90% or above in most patients with COPD. However, only a small portion of this continuously flowing oxygen is actually available for alveolar ventilation. To overcome this problem of oxygen: wastage, oxygen conserving devices ate developed. Three distinct categories of oxygen conserving devices are currently available: Transtracheal oxygen delivery, reservoir canulas (the oxymizer and oxymizer pendant) and Electronic - demand oxygen delivery devices.

16. Home ventilatory support

Home ventilatory support should be considered for those patients with frequent decompensation of respiratory failure to prevent a fatal episode, in those who fail to wean alter an acute exacerbation and where PaO_2 cannot be maintained over 7.0 Kpa (52 mmg) without excessive hypercapnia ($PaCO_2$ 10.0 Kpa or 75 mm Hg.) Respiratory muscle rest in the form of assisted ventilation would relieve chronic fatigue and produce a sustained correction of hypercapnia. The methods available are intermittent negative pressure ventilation and intermittent positive pressure ventilation. Negative pressure ventilation by tank respirator, cuirass shell or pneumosuit is cumbersome and

uncomfortable. It has been reported recently that nasal intermittent positive pressure ventilation can be used effectively at home during sleep in selected patients with COPD. Future studies comparing domiciliary ventilation with long - term oxygen therapy are required to clarify the role of domiciliary ventilation in the treatment of COPD.

Lung Transplantation

Lung transplantation has been found to be an effective modality for the management of end stage pulmonary disease. The most significant factor restricting the application of lung transplantation is donor availability. Donor selection and recipient criteria are given in Tables 3 and 4.

Table 3

General Donor Selection Guidelines

1. Age < 65 for lung; < 45 for heart-lung.
2. No severe chest trauma or infection.
3. Clear chest X-ray (exception may occur).
4. No prolonged cardiac arrest (heart-lung only).
5. Minimal pulmonary secretions.
6. Negative HIV screen.
7. ABO compatibility.
8. Similar total lung capacities

Table 4

General Recipient Guidelines

1. Untreatable end-stage pulmonary vascular disease of any aetiology.
2. No other significant medical. diseases.
3. Substantial limitation of daily activities.
4. Limited life expectancy,
5. Ambulatory with rehabilitation potential.
6. Acceptable nutritional status.
7. Satisfactory psychosocial profile and emotional support system.

Contraindications for lung transplantation are listed in Table 5.

Table 5

Contraindications for Lung Transplantation

1. Active extra pulmonary infection.
2. Significant disease of other organ systems.
3. Current cigarette smoking.
4. Poor nutritional status.
5. Post rehabilitation potential.
6. Significant psychosocial problems,
Substance abuse, or history of medical non-compliance

Lung Transplantation : Report of the ATS Workshop on Lung Transplantation Amer Rev Respir Dis : 1993; 147 : 772 – 76.

Transplant procedures available for COPD patients are Heart – Lung transplantation, Double lung and single lung Transplantations. Transplantation procedures that are applicable to disease states are provided in Table 6.

Table 6

Transplantation procedure by Disease state

Transplantation procedure	Disease state
Heart – Lung	Eisenmenger's syndrome with irreparable cardiac defect; pulmonary hypertension with Cor pulmonale; end-stage lung disease with concurrent severe cardiac disease,
Double Lung	Cystic fibrosis; generalised bronchiectasis some patients with COPD.
Single Lung	Restrictive fibrotic lung disease; Eisenmenger's syndrome with repairable cardiac anomaly; some patients with COPD; primary pulmonary hypertension.

Agency for Heart Care Policy and Research (USA) states. "lung transplantation has evolved a clinical procedure achieving a favourable risk – benefit ratio and acceptable 1 – and 2 – year survival rates"

Pulmonary Rehabilitation

Pulmonary rehabilitation was defined by the American College of Chest Physicians committee on Pulmonary Rehabilitation as an art of medical practice wherein an individually tailored, multidisciplinary programme is formulated which through accurate diagnosis, therapy, emotional support, and education, stabilizes or reverses both the physio–and psychopathology of pulmonary diseases and attempts to return the patient to the highest possible functional capacity allowed by his pulmonary handicap and overall life situation.

Components and benefits of pulmonary rehabilitation are listed in Tables 7 and 8.

Table 7

Components of Pulmonary Rehabilitation

General

1. Patient and family education
2. Proper nutrition including weight control
3. Avoidance of smoking and other inhaled irritants
4. Avoidance of infection (immunization, etc.)
5. Proper environment
6. Adequate hydration

Medications

1. Bronchodilators
2. Expectorants
3. Antimicrobials
4. Corticosteroids
5. Cromolyn sodium
6. Digitalis
7. Diuretics
8. Psychopharmacologic agents

Respiratory therapy techniques

1. Aerosol therapy

- 2. Oxygen therapy
 - 3. Home use of ventilators
 - Physical therapy modalities
 - 1. Relaxation training
 - 2. Breathing retraining
 - 3. Chest percussion and postural drainage
 - 4. Deliberate coughing and expectoration
 - Exercise conditioning
 - Occupational therapy
 - 1. Evaluate activities of daily living
 - 2. Outline energy-conserving maneuvers
 - Psychosocial rehabilitation
 - Vocational rehabilitation
-

Table 8

Demonstrated Benefits of Pulmonary Rehabilitation

- 1. Reduction in respiratory symptoms.
- 2. Reversal of anxiety and depression and improved ego strength.
- 3. Enhanced ability to carry out activities of daily living.
- 4. Increased exercise ability.
- 5. Better quality of life.
- 6. Reduction in hospital days required.
- 7. Prolongation of life in selected patients, i.e., use of continuous oxygen in patients with severe hypoxemia.

Prognosis

Factors related to survival are listed in Table 9.

Table 9

Factors related to survival

Factors Related Positively to Survival *

- 1. FEV₁
- 2. PaO₂

3. Reversibility of airflow obstruction following inhaled bronchodilator.
4. Exercise capacity.
5. Diffusing capacity.
6. Vital capacity.
7. Atopy.

Factors Related Negatively to Survival * *

1. Age
2. Decrease in FEV₁ on serial testing.
3. Resting heart rate.
4. PaCO₂
5. Pulmonary artery pressure/cor pulmonale.
6. Total lung capacity.
7. Perceived physical disability/dyspnea.
8. Continued smoking.
9. Malnutrition/weight loss.
10. Alpha – Antitrypsin deficiency.

* The higher the value or presence of the factor, the better the survival

** The higher the value or presence of the factor, the poorer the survival.

Further Reading

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4. Lung Transplantation : Report of the American Thoracic Society Workshop on Lung Transplantation. Am. Rev. Respir Dis 1993 ; 147 : 772 – 76.