Risk Factors and Pathophysiology of Chronic Obstructive Pulmonary Disease (COPD)

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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory disease of the lung characterized by chronic bronchitis, airway thickening and emphysema. Being the third largest cause of worldwide mortality and showing a steeply rising trend in global prevalence, COPD is likely to emerge as the most important disease for the physicians to manage.¹² Understanding the basic pathophysiology of COPD will be of great assistance in diagnosing and treating the disease in circumstances where new mechanisms, diagnostic tests and drug therapies are emerging at a rapid pace. The pathophysiology of the disease is complicated and largely undiscovered. However, with the advent of new technology and widespread advances in research the thick cloud cover over the pathophysiology of COPD is rapidly unveiling.

Risk factors

Smoking has traditionally been known to be the most important cause for COPD amounting to almost 85% of the COPD cases (50% smokers develop COPD),³⁵ the rest being classified as non-smoking COPD (15%).¹² These estimates were, however, based on the data generated from limited number of studies conducted only in developed countries. Subsequent large scale epidemiology studies have shattered the world not only with the finding of unusually high prevalence in the developing countries but also with the realization that the most important risk factor for COPD could be indoor-air pollution arising from the use of biomass fuel.₅⁷ In developing countries such as India COPD due to non-smoking causes account to 30-50% of all COPD cases.⁵ Burning biomass fuel such as wood, cow-dung and crop-residues leads to release of air pollutants like SO₂, CO, NO₂, formaldehyde and particulate matters smaller than 10 micron in size (PM10) in the ambient indoor air.₆₇ Chronic exposure to these pollutants has been shown to lead to COPD. This is especially worrisome considering the fact that more than 70% of Indian households rely on biomass fuel for domestic purposes such as cooking and heating. Recent unpublished data from our institute suggests that the inflammatory load in COPD caused by exposure to biomass fuel is similar to that caused by exposure to tobacco smoke.⁶₇

Another important risk factor for non-smoking COPD is the prolonged exposure to occupational smoke/dust. More than 10 occupations have been associated with the development of COPD (Table 1), the list of which is further increasing every year. Tuberculosis is increasingly getting recognized as a risk factor for COPD.¹²⁶ It has been seen that tuberculosis patients, even after adequate anti-Koch’s therapy are 2-6 times more prone to develop airway obstruction suggested by spirometry and symptoms suggestive of COPD in due course of time.¹²⁶ Recurrent respiratory infections in childhood have also been shown to be associated with development of COPD in adult age.¹²⁶ Even poorly treated asthma is considered to be a risk factor for development of irreversible airway obstruction, characteristic of COPD. Poverty is an important surrogate of COPD.¹²⁶ Physiological lung function decline induced by ageing can also predispose to COPD.¹

Genetics

There has been substantial stride however with negligible impact in understanding COPD genetics in last 50 years that primarily arose from epidemiological query that why only a fraction of smokers develop COPD while others with similar amount of smoking history do not develop the disease. Till date the only well-established genetic risk factor identified for COPD is SERPINA1 gene which codes for serine protease inhibitor, alfa-1 antitrypsin (AAT).²³ Perturbation in SERPINA1 gene leads to deficiency of AAT-1, causing uninhibited action of proteases and culminating in development of emphysema.⁸ The M allele is associated with normal AAT while Z alleles constitute AAT deficiency. However, only 1-2% of the population exhibits anomaly in SERPINA1, suggesting that many other genetic variations would be responsible for development of COPD.²³ Current understanding is that COPD is a polygenic disease involving complex interactions between various gene

<table>
<thead>
<tr>
<th>Table 1 : Risk factors for COPD</th>
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<tr>
<td><strong>Genes</strong></td>
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<td>Exposure to particles:</td>
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<td>Tobacco smoke (10 pack Years; 50% smokers develop COPD)</td>
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<tr>
<td>Indoor air pollution from heating and cooking with Biomass fuel in poorly ventilated homes (at least 25 years of exposures)</td>
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<tr>
<td>Occupational dusts, organic and inorganic: (attributable Risk 15% in American population)</td>
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<tr>
<td>a. Automobile-drivers, vehicular mechanics, fertilizer manufacturing, chlorinated organic compounds dyes, explosives, rubber products, metal etching, plastics, ammonia exposure in refrigeration and petroleum refining, grain dust and funguses in farmers, textile mill manufacturing, leather manufacturing, food products manufacturing and sales, beauty care workers and welders in automotive industries.</td>
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<tr>
<td>b. Exposures to crystalline silica: cement industry, brick manufacturing, pottery and ceramic work, silica sand, granite and diatomaceous earth industries, gold mining, and iron and steel founding</td>
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<td>Outdoor air pollution</td>
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<td>Reduced Lung volumes:</td>
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<tr>
<td>1. Lung growth and development</td>
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<td>2. Previous Tuberculosis (28-68% cases of post-treated TB; 2.9-6.6 folds increase risk)</td>
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<td>3. Early childhood Recurrent Lower Respiratory infections (2-3 fold risk)</td>
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<td>4. Poor Nutrition</td>
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<td>Female Gender (reason not known)</td>
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<td>Old Age (physiological obstruction)</td>
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<td>Low-Socioeconomic status (Multi component)</td>
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polymorphisms. Many genes have been associated with COPD (Table 2). However, the picture is likely to become less hazy once the results of presently ongoing genome-wide association studies (GWAS) are out.\(^9,10\)

### Molecular mechanisms in pathogenesis of COPD

COPD is a progressive chronic inflammatory disease of the airways primarily affecting the small airways and alveoli. Two important and mutually non-exclusive mechanisms implicated in the pathogenesis of COPD are the presence of perpetual inflammation and oxidant-antioxidant imbalance leading to oxidative stress. Unlike asthma inflammation which primarily involves steroid-responsive eosinophils and mast cells, the inflammatory cells in COPD refuse to respond to steroids. The cells primarily involved in COPD inflammation are neutrophils, macrophages and lymphocytes. These inflammatory cells further release a battery of inflammatory mediators like cytokines, chemokines and chemotractants which perpetuate the inflammation leading to an uncontrolled cascade. Neutrophils by releasing chemotactants like interleukin-8 (IL-8) and leukotrien B4 (LTB4) further attract neutrophils to the site.\(^11\) Proteolytic enzymes such as elastase, proteinase-3, cathepsin G, cathepsin B and matrix metalloproteinases (MMP) released by neutrophils cause damage to elastic lung tissue (Figure 1).\(^11\)

Macrophages release cytokines and chemokines such as IL-8, IL-6, IL10 TNFα, LTB4 etc and reactive oxygen species which attract and activate various inflammatory cells, and series of proteases, particularly MMPs such as MMP-2, MMP-9, MMP-12, MMP-14, with tremendous elastolytic potential and elastinolytic cysteine proteinases such as cathepsin K, L and S.\(^12\) CD8+ lymphocytes release destructive enzymes such as perforin and granzyme B which have the ability to induce apoptosis of the alveolar epithelial cells and CD4 lymphocytes induce autoimmune response to the lung tissue.\(^15\) A series of COPD related pathological changes have also been attributed to oxidative stress such as oxidative inactivation of antiproteases and surfactants, mucus hypersecretion, membrane lipid per-oxidation, alveolar epithelial injury, remodelling of extracellular matrix, and apoptosis, reduction in elastin collagen synthesis and fragmentation of these skeletal proteins and steroid-unresponsiveness (Figure 1).\(^14\)

### Pathophysiology of COPD

The pathological consequences of the COPD inflammation induce series of physiological changes which eventually impact the quality of life and survival in the natural progress of COPD. Firstly elastin proteolysis results in reduction in elastic recoil pressures in the lungs, also since the integrity and movement of air in the bronchioles are primarily reliant on elastic recoil pressures induced by surrounding elastic tissue, the damage to the elastin in COPD results in significant airway narrowing with reduction in air-flow in the bronchioles and air-trapping in lungs; secondly, fibrotic remodelling of the airways results in fixed airway narrowing causing increased airway resistance which does not fully revert even with bronchodilators; thirdly extensive alveolar and bronchiolar epithelial cells and pulmonary capillary apoptosis in histological feature such as emphysema and physiological feature such as decreased surface area of alveoli for gaseous exchange and ventilation- circulation mismatch (V/Q). Emphysema also reduces lung elastic recoil pressure which leads to a reduced driving pressure for expiratory flow through narrowed and poorly supported airways in which airflow resistance is significantly increased (Figures 1, 3).\(^15,17\)

Fixed airway obstruction is cardinal to COPD diagnosis and severity grading which depicts intensity of small airway inflammation (mucosal edema, airway fibrotic remodeling and mucous impaction) and possibly increased cholinergic airway smooth muscle tone. Due to reduced airway caliber and increased airway resistance there is reduced airflow particularly during expiration which prolongs the removal of air from the lungs. This physiological feature of COPD is usually detected with forced spirometric maneuvers using spirometric lung volume ratio of volume of air removed in first second (FEV1) and total volume of air removed (FVC) during forceful expiration after maximal inhalation as less than 0.7 (FEV1/FVC <0.7). Reduction in FEV1 is hallmark of airflow obstruction, and in COPD there is usually a progressive decline of 30-60 ml in FEV1 every year versus 20-30 ml in normal healthy adults (Figure 2).\(^18\)

Lung hyperinflation or air-trapping is hallmark of COPD pathophysiology. Most patients with COPD have some degree of underlying hyperinflation that needs detailed physiologic analysis for detection, and which usually remains undiagnosed.
in routine clinical practice. Hyperinflation is primary cause of dyspnoea, poor quality of life and adverse disease prognosis associated with COPD. Damage to elastin and narrowing of airways are major causes for air-trapping in COPD. The barrel shaped chest in COPD is attributed to hyperinflation of the lungs. The inward lung elastic recoil pressures are the primary forces which drive air out of the small airways and alveoli during tidal expiration for which it has to counteract outward recoil pressures generated by thoracic wall. During end tidal expiration both these forces equally balance each other causing relative airflow stasis and relaxed lung state. The volume of air trapped in the lungs at this equi-pressure stage is physiologically termed as functional residual capacity (FRC). In COPD pathologically weakening of elastic tissue generates inadequate inward lung elastic recoil pressures to cause movement of air out of the lungs. Therefore to counteract the outward recoil pressures of thoracic cage, the reduced elastic recoil of the lungs generates equi-presures states with larger FRC resulting in state of hyperinflation.\(^{15,16}\) This pushes the equi-pressure point further away from the alveoli. Body-plethysmography can measure the extent of hyperinflation by measuring FRC. It is believed that the symptomatic improvement produced by bronchodilators is majorly by reduction in lung hyperinflation rather than actual bronchodilation (Figure 3).\(^{19}\)

The hyperinflation is dynamic in nature and is present in all stages of the disease, which is usually manifested in hyperventilation states which are outcome of expiratory flow limitations, anxiety and ventilation perfusion mismatches related to COPD exacerbations or any activity which increases oxygen demand. In hyperventilation during each breath, inhalation commences before full exhalation is achieved, this results in air-trapping which enhances with each successive breath. With every breath FRC increases and capacity to inspire (Inspiratory capacity) reduces. When the rising FRC encroaches inspiratory reserve volumes further increase in inspiratory muscle activation produce little or no additional ventilation (Figure 4). Also, FRC no longer occurs at the passive point of equilibrium between chest wall and lung recoil, but occurs at a positive end-expiratory pressure (PEEP) before exhalation has achieved the relaxation volume.\(^{17}\) The outcome of this neuromechanical dissociation when an increasing level of ventilatory drive is associated with a reduced capacity of the respiratory muscles to develop force and effective ventilation is the principal mechanism of breathlessness in COPD patients. The increasing intrinsic-PEEP during dynamic hyperinflation places diaphragm in a mechanical disadvantaged position shortens its operating length and alters the mechanical linkage between its various parts. This progressively diminishes the tension and resulting transdiaphragmatic pressure generated by diaphragmatic contraction.\(^{19}\) These altered actions of diaphragm can potentially cause disability and impending respiratory failure during COPD exacerbations. Therefore the physiotherapy paradigms in COPD management should especially aim to improve diaphragmatic strength and contractility. Hyperinflated lungs in COPD patients...
vascular resistance which predisposes PAH. Increased thickenings, plexiform lesions, endothelial dysfunctions and can induce pulmonary capillary muscularization, intimal-wall secondary polycythemias and lung and systemic inflammation as hypoxia, hyperinflation, emphysema, hypoxia-induced resistance. Pathophysiological consequences of COPD such pressure plus product of cardiac-output and pulmonary—of COPD exacerbation increases pulmonary arterial pressure by known independent prognostic marker of COPD. Each episode a rare accompaniment of mild-moderate COPD cases. PAH is a from poorly ventilated alveoli. Therefore aggressive correction in the pulmonary capillaries which redirects the blood away arteries and the aortic arch. Hypoxia also causes vasoconstriction in the pulmonary capillaries which redirects the blood away from poorly ventilated alveoli. Therefore aggressive correction of hypoxia with high-flow oxygen in COPD especially during exacerbations reduces physiological respiratory drive in COPD patients which could be catastrophic, and therefore needs judicious management.

**Changes in Respiratory Drive**

The destruction of alveoli and pulmonary vasculature in COPD reduces the surface area for air-diffusion causing chronic hypercapnic and hypoxic states. The chronic CO2 retention reduces sensitivity of CO2 brainstem chemo-receptor apparatus which no longer contributes as the primary mechanism of respiratory drive in COPD. The respiration in this disease is driven by hypoxia through receptors located in the carotid arteries and the aortic arch. Hypoxia also causes vasoconstriction in the pulmonary capillaries which redirects the blood away from poorly ventilated alveoli. Therefore aggressive correction of hypoxia with high-flow oxygen in COPD especially during exacerbations reduces physiological respiratory drive in COPD patients which could be catastrophic, and therefore needs judicious management.

**Pulmonary Artery Hypertension (PAH)**

Structural changes in COPD initiate instability in pulmonary hemodynamics. Most moderate-to-severe COPD patients develop some degree of mild PAH (25-35 mmHg) over the course of time, and rarely severe PAH (>45mmHg), however, it may be a rare accompaniment of mild-moderate COPD cases. PAH is a known independent prognostic marker of COPD. Each episode of COPD exacerbation increases pulmonary arterial pressure by 20mmHg which can develop into full fledged PAH on recurrent episodes. PAH primarily depends on pulmonary artery wedge pressure plus product of cardiac-output and pulmonary-resistance. Pathophysiological consequences of COPD such as hypoxia, hyperinflation, emphysema, hypoxia-induced secondary polycythemas and lung and systemic inflammation can induce pulmonary capillary muscularization, intimal-wall thickening, plexiform lesions, endothelial dysfunctions and apoptosis which can potentially generate enhanced pulmonary vascular resistance which predisposes PAH. Increased intrathoracic pressures in emphysema induce positive pressures on right ventricle resulting in increased pulmonary artery wedge pressure. Left ventricular diastolic dysfunction secondary to cardiovascular morbidity in COPD can also cause back pressure changes in pulmonary vasculature and right ventricles. Chronic severe pulmonary hypertension increases right ventricular afterload and eventually leads to the clinical syndrome of right heart failure with systemic congestion and inability to adapt right ventricular output to peripheral vascular demands (Figure 5).

**COPD is a Disease of Systemic Inflammation**

COPD has been recently recognized as a multicomponent disorder associated with systemic inflammation. The origin of systemic inflammation has been hypothesised to inflammatory spill from the lungs into the blood through the thin layered pulmonary vasculature that can potentially predispose inflammatory affects to other organs of the body (Figure 6). However, research to identify haplotype of inflammatory genes which predisposes to systemic inflammation in COPD is currently underway. Various studies have shown enhanced levels of acute phase proteins like C-reactive protein (CRP) and pro-inflammatory cytokines such as tumour necrosis factor (TNF)-alpha and IL6 in blood of many COPD patients.

The major systemic co-morbid conditions associated with COPD are cardiovascular diseases. Cardiovascular disease (CVD) is an important cause of mortality in COPD. Studies have shown raised level of myocardial-biomarkers such as NT pro BNP, troponin-T and platelet-monocyte aggregates in COPD patients during COPD exacerbations when burden of systemic inflammation is at peak. Also, the pressure swings induced by phenomenon such as air-trapping affect the end diastolic pressures in the heart and interact with both right and left ventricular contractility in complex pattern and can stimulate cardio-vascular events.

Second most important systemic manifestations of COPD is skeletal muscle dysfunction and wasting especially muscles of thighs and upper arms. The early fatigue of skeletal mass has been regarded as one of the causes of increasing dyspnoea amongst the COPD patients. The biopsy studies have shown reduction in type I fibers and a relative increase in type II fibers, accelerated apoptosis, increased oxidative stress and inflammatory changes in the muscle mass of the COPD patients. There is also emerging evidence to show insulin resistance in COPD patients which is related to systemic inflammation effects. Recently an association with diabetes and COPD has been demonstrated. COPD has also been linked to metabolic syndrome as it predisposes patients to increased cardiovascular morbidity and diabetes mellitus. Amongst the other systemic...
manifestations studies have shown nearly 70% of COPD have underlying osteoporosis and many COPD suffer with depression.27

Conclusions

With every passing day the understanding about the pathophysiology of COPD is improving and simultaneously becoming more complex. The increasing life expectancy all over the world suggests that COPD would emerge as the most important disease for the physicians to manage. Understanding its pathophysiology would just be the right step in that direction.

References

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