Understanding the Relation between COPD and Coronary Artery Disease

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Abstract: Coronary artery disease (CAD) is one of the leading causes of mortality in chronic obstructive pulmonary disease (COPD). Right ventricular hypertrophy and ischemia are known to occur in COPD due to secondary pulmonary hypertension, but there is a significant link between COPD & CAD, regarding etiology, pathophysiology and precipitating factors. There is a definite role of smoking, respiratory muscle strength and lung function (independent of the effect of smoking) and inflammatory markers, which predisposes the patient of COPD to CAD. Even precipitating factors for acute exacerbation of COPD like infections, hyperglycemia or enzyme matrix metalloproteinase (MMP) have a role to play in acute coronary syndrome. Steroids given for COPD in long term can contribute to CAD and statins have a beneficial role to play in COPD also. We should look for CAD in patients of COPD before severe left ventricular dysfunction sets in.

Keywords: MMP (Matrix Metalloproteinase); PFT (Pulmonary Function Test); FEV\textsubscript{1} ( Forced Expiratory Volume in 1 second).

Introduction

In hospital admissions, a patient being admitted with acute exacerbation of COPD is a regular feature. Reynolds found that 50 percent of patients with COPD past the age of 50 years had CAD, hypertension, or heart failure\textsuperscript{1}. Also in SPRINT study, a series of 5800 patients with acute myocardial infarction, the incidence of COPD was roughly 50 percent higher than in the general population\textsuperscript{2}. In many such known patients of COPD usual presentation is congestive cardiac failure. However, a sizeable number presents with biventricular failure or pure left ventricular failure. Breathlessness in such patients may be due to underlying CAD. Traditional paradigm is that COPD patients die from progressive respiratory failure but actual fact is CAD is one of the leading causes of mortality in COPD cases. We should try to probe the following in relation to COPD.

- Proportion of cardiac patients having concomitant COPD.
- Cause of acute breathlessness- mainly respiratory, or cardiac or difficult to differentiate?
- Standard line of drugs we prescribe for COPD patients and their safety in underlying CAD.
- How frequently we go for Spirometry and interpret it in COPD and CAD (acute LVF).

It is surprising that a measure of respiratory function hasn't been included in health assessment programmes. Significantly, still many don't perceive respiratory functions having direct relation with underlying cardiac status.

Role of Spirometry: This is underused. A severe obstructive or restrictive pattern would point to a respiratory cause. In borderline cases echocardiography can clinch the diagnosis. Similar symptoms of dyspnoea, chest pain, due to right ventricular ischemia or secondary pulmonary hypertension in COPD. raised JVP, crepitations, rhonchi, and signs of cardiac failure, may not give clear picture many times. Non-specific ECG changes in COPD; mild rise in troponins: unequivocal echocardiographic study may understandably mask underlying CAD. Two conditions do masquerade as COPD with pulmonary hypertension. Important is a curable condition of chronic constrictive pericarditis, here echocardiography using superior vena cava Doppler can assist in differentiation. The other condition, albeit historical, is reverse Bernheim's disease. Here a thickened interventricular septum of severe pulmonary hypertension bulges into left ventricle compromising left ventricular function. Both cases may be construed to arise from CAD. Our article will focus on the definite association between COPD & CAD, so as to highlight the fact that COPD is now a strong risk factor for CAD and timely diagnosis of CAD will positively affect the prognosis of COPD patients.

We will try to analyze each and every known possible link between COPD and CAD one by one.
A. Smoking:
Undoubtedly, it is significantly related to causation of chronic bronchitis and emphysema and also is a major risk factor for CAD. Possible link is due to poor lung function and low FEV\textsubscript{1} which has a dose response relationship to the intensity of cigarette smoking - expressed as pack years. Low FEV\textsubscript{1} has a direct effect on CAD as explained below.\textsuperscript{5}

Smoking deranges lipid profile which becomes more atherogenic, induces changes in platelet function, and causes endothelial dysfunction by the mechanism of free radical injury, increases sICAM-1 (soluble intracellular adhesion molecule-1), fibrinogen, monocytes and CRP, which is the platform for atherogenesis.\textsuperscript{4} Cessation of smoking has been shown to alter lipid profile favorably and accelerate regression of plaque in vessels.

B. Right Ventricular Ischemia:
Long standing COPD causes secondary pulmonary hypertension which leads to right ventricular hypertrophy (RVH). RVH along with hypoxemia in COPD leads to supply demand mismatch and can cause angina due to RV ischemia.\textsuperscript{5,6} Right ventricular myocardial infarction is also seen in patients of COPD more due to these factors.\textsuperscript{7}

C. Inflammatory Markers:
COPD is a state of systemic inflammation and high level of inflammatory markers are associated with severity of airflow obstruction and cardiac injury. Inflammatory process in airway parenchyma and pulmonary vasculature may spillover into systemic circulation promoting a generalized inflammatory reaction i.e., process of reverse causation. This inflammation was seen in COPD persons who were non current smokers and once COPD develops cessation of smoking may not fully attenuate the inflammatory process associated with this condition. Inflammatory markers set the stage not only for COPD but also for atherosclerosis and thus CAD. Apart from leucocytosis, CRP, fibrinogen, α1 antitrypsin, haptoglobin, ceruloplasmin and orosomucoid were found to be associated with low FVC and increased chances of cardiovascular death. These inflammatory sensitive proteins (ISP) play a detrimental role in atherosclerosis.\textsuperscript{8} These inflammatory markers not only predispose COPD patients to CAD but also to osteoporosis, muscle wasting and malignancy.\textsuperscript{8,9,10,11} Notably all these complications are observed in COPD (along with CVA/ischemic stroke). Fibrinogen\textsuperscript{14,15}, TNF α\textsuperscript{16}, CRP\textsuperscript{17} and leucocytes\textsuperscript{18} were shown to be associated with decreased FEV\textsubscript{1} and FEV\textsubscript{1}/FVC ratio. Interlukin-6 ELISA assay was found to be positively correlated with low lung functions and complications of COPD\textsuperscript{19}. This relation was found even in non-current smokers showing that once COPD develops cessation of smoking may not fully attenuate the inflammatory process. COPD is characterized by intense inflammation of airways, parenchyma and lung vasculature. It is possible that there is an inflammatory spillover into the systemic circulation causing this to be a generalized process.\textsuperscript{20,21} It is possible that common genetic and constitutional factors may predispose individuals with COPD to systemic and pulmonary inflammation. So COPD is responsible for systemic inflammation along with possibility of reverse causation i.e., systemic inflammation causing injury to airways. Inflammatory markers cause accelerated decline in lung function, repeated hospital admissions and acute coronary events\textsuperscript{22} as airflow limitation doubles the risk of cardiovascular mortality independent of smoking.\textsuperscript{13,23}

D. Lung function in COPD and cardiovascular risk:
Poor lung function is associated with risk of developing diabetes and high BP, fatal stroke and cardiovascular disease.\textsuperscript{24} Poor lung functions FEV\textsubscript{1}, FEV\textsubscript{1}/FVC ratio, PO\textsubscript{2}, PaCO\textsubscript{2} levels, respiratory muscle strength all have been shown to have strong association with CAD independent of effect of smoking and atherogenic lipid profile. Adverse effect of lung function on CAD was found more marked in women.\textsuperscript{26,27} Lung function is strongly related with height and gender. Low FEV\textsubscript{1} is related to CAD and is independent of the confounding effect of smoking as findings were found to be consistent among never, current and former smokers. Stronger relation among women was found to be either due to an artifact or the consequence of residual confounding, a chance finding or may be due to unknown biological effect on lung function which is different in men and women.\textsuperscript{28} Low FEV\textsubscript{1} apart from increased levels of inflammatory markers is associated with ventilation perfusion mismatch, low PaO\textsubscript{2} and high PaCO\textsubscript{2} which in turn lead to higher pulmonary artery pressures and poor left ventricular function.

E. Respiratory Muscle Strength:
It is also related to CAD.\textsuperscript{29,30} Maximal inspiratory pressure (MIP) is a measure of diaphragm muscle strength and reduced MIP is a risk factor for respiratory and total mortality. A low MIP is a marker of generalized poor health. Inflammation, malnutrition, mechanical stress, metabolic stress, oxidative stress and drugs are all related to low MIP and poor health. Thus, low MIP is associated with decreased FEV\textsubscript{1}, FVC and PEF and cardiovascular morbidity and mortality\textsuperscript{11,32} The effect of MIP on CAD is similar to that of decreased FVC. Inclusion of FVC (modestly) attenuated the effect of MIP on outcome. Interestingly markers of inflammation donot appear to explain the effect of MIP on...
CAD and also decreased MIP doesn't appear to be a risk factor for incident CHF although in prevalent CHF, decreased MIP was an independent predictor of prognosis.35

F. Risk of CAD in bronchial Asthma:
On the similar above mentioned risk factors like inflammatory markers, decreased lung function, not only COPD but also bronchial asthma is associated with modest but statistically significant increased risk of CAD among women especially. This association was seen both in never and in ever smoking younger and older women. By contrast, asthma was not found to be significantly associated with CAD among men.

G. Precipitating factors for Acute Exacerbation of COPD & ACS:
There is a definite link between AECOPD (Acute Exacerbation of COPD) and ACS at the level of precipitating factors especially infections, hyperglycemia and raised levels of MMPS (matrix metalloproteinases).

a. Hyperglycemia: It is known to be associated with poor outcomes.35,36 Tight blood sugar control is advised in AECOPD, in ACS and post cardiothoracic surgery.37 Administration of insulin benefits the patients due to its anti-inflammatory and anabolic properties and promotes better utilization of glucose as a metabolic fuel which generates more molecules of ATP per molecule of oxygen than free fatty acids with observed potential benefits for ischemic tissue.37 The damaging effect of hyperglycemia is due to glucose toxicity as seen in autopsy study of surgical patients in whom mitochondrial damage was limited to tissues characterized by expression of glucose transporter GLUT-1 & 3 but not GLUT-4.38 GLUT-1 & 3 are cell membrane transport protein that allow equilibrium of intra- and extra-cellular glucose independently of insulin. Increased blood sugar causes many potentially damaging events like production of ROS (reactive oxygen species), super oxide and peroxinitrites, glycosylation of proteins, impairment of leucocyte functions, activation of pro-inflammatory genes through transcription factors like NF-κB (nuclear factor kappa B) and AP-1 (activator protein-1). Hyperglycemia causes deranged lipid metabolism, altered membrane function and endotoxin scavenging. Raised level of these endotoxins in tissues and bronchial aspirates leads to proliferation of bacteria (staphylococcus sp.), along with poor bacterial clearance and poor host response which can be effectively countered to some extent by insulin infusion. So the target of blood sugar should be below 8 mmol/1 in acutely in patients, even in those who are non diabetics.49 Hyperglycemia in COPD (>11 mmol/l) on admission predicts failure of noninvasive ventilation and infection complications in ICU.42 Blood sugar is high in acutely ill patients due to raised catecholamine concentration, oral steroids given in COPD, raised glucocorticoid hormone concentration and increased peripheral insulin resistance.43,44

b. Role of MMPS in AECOPD and ACS: Several MMPS are involved in the pathogenesis of COPD. MMPS are a family of metalloproteinases that contain a zinc atom at their active site and are able to degrade matrix molecules including collagen, elastin and laminin.45,46 In addition to their ability to degrade extra cellular matrix components, some MMPS also cleave cytokines and antiproteolytic molecules.48 MMPS especially MMP-9 & 12 are found in mice and play a crucial role in development of emphysema and were found in high concentration in alveolar macrophages.49 MMP-12 knock out mice were found to be protected from emphysema. MMPS not only have a direct effect on extra-cellular matrix but also cause inactivation of α1 antitrypsin by MMP-12 mediated recruitment of neutrophils. Molet and colleagues found high level of MMP-12 in BAL (bronchoalveolar lavage) fluid by western blot analysis of bronchial biopsy tissues than in controls.50,51 Thus in early stages of COPD, MMP-12 can be an important biomarker of the disease activity. The mechanism by which MMP-12 is induced in COPD may be due to local deficiency of TGF β1 or rise in IL-13 or γ-IFN which lead to the overproduction of MMP-12.52,53 Grumelli showed that in human subjects, lung macrophages release MMP-12 in response to infection, inducible protein-10 and monokine induced by interferon- 2 chemokines that are secreted by lung macrophages and lymphocytes from patients with emphysema. MMPS are not only secreted from alveolar macrophages but also from bronchial epithelial cells in response to cigarette smoking and the secretion is mediated by chemokine receptor-3 (CXCR3) on macrophages in emphysema. In mice, potent inhibitor of both human and murine MMP-12 (RS-113456) prevented progression of emphysema in smoke exposed animals.55 MMPS thus have a role in acute exacerbation of COPD and also in ACS (Plaque instability).

c. Infections: They are very important precipitating factors for acute exacerbation of COPD and some of them like Chlamydia pneumoniae, Helicobacter pylori and Cytomegalovirus (especially in post-transplant patients) can accelerate atherosclerosis and precipitate acute coronary syndrome by causing plaque instability.56,57 AECOPD (acute exacerbation of COPD) is known to be precipitated by bacterial infection (Hemophilus influenzae, Streptococcus pneumonia, Moraxella catarrhalis, Hemophilus parainfluenza, Pseudomonas aeruginosa and other
gram negative bacteria^{58,59}. Viruses such as rhinovirus, influenza, parainfluenza, coronavirus, adenovirus, Respiratory syncytial virus, Picorna virus are shown to cause AECOPD in 40% cases by PCR^{60}. Atypical organisms like Mycoplasma and Chlamydiae, environmental pollutants, change of temperature are also important causes. All these factors increase inflammatory markers, increase MPO (myeloperoxidase) in sputum and increase interleukin-8(CXCL8), leukotriene (LTB4), tumour necrosis factor-α (TNFα). Inflammatory environment causes decrease in FEV\textsubscript{1}. So infections are a common precipitating factor for AECOPD and ACS. AECOPD can also affect ventricular functions by reducing preload, high pulmonary artery pressures, hypoxemia, V/Q mismatch increased right ventricular after load. LV diastolic functions are adversely affected due to ventricular interdependence, although systolic functions remain normal except in AECOPD where due to increased LV after load as a consequence of increased transmural pressure gradient, LV systolic performance is impaired^{61}.

d. **Drugs, COPD and ACS**: Oxygen inhalation plays a beneficial role in COPD and ACS if used judiciously. Oral steroids given for COPD for long terms have shown to cause hyperglycemia which is a negative factor for both COPD and ACS. β2 agonists, theophyllines and anticholinergics given in COPD with cardiac dysfunction may have negative effect as they cause tachycardia and arrhythmia. Dofloxifen is safer for cardiac patients instead of theophyllines. However, inhalers have to a large extent reduced the risk of beta-agonists and bronchodilators. Statins are known to decrease mortality not only in ACS but also in COPD by improving endothelial functions^{62}.

**I. Comorbidity in COPD**: is defined as disease coexisting with primary disease of interest. In COPD, they are cardiovascular diseases, lung carcinoma and osteoporosis - link is systemic inflammatory pathway^{63}.

**Conclusion**

Long duration of COPD is a major risk factor for CAD. Almost like diabetes, COPD is a major risk factor for CAD and common link of inflammation and poor respiratory function mainly explains this association. We should try to rule out ACS or LV dysfunction in AECOPD and in ACS patients, look for the presence of COPD also, as only combined approach of treatment including drugs will have an effect on outcome. Apart from traditional investigations, echocardiography is now in increasing use.

In COPD patients we should unmask the presence of underlying CAD and target them before patient lands in ACS.

**References**


