RESPIRATORY DISEASES AND CORONARY ARTERY DISEASES

G.K.Paramjyothi

INTRODUCTION:

Cardiovascular diseases are the leading cause of death worldwide. They accounted for 31% of total global deaths in 2012 and 42% of them were due to coronary vascular diseases [1]. Respiratory diseases like pneumonia, Chronic Obstructive Pulmonary Disease (COPD) are also leading causes of mortality and morbidity. COPD is the likely third most common cause of death by 2030.

Tissue oxygenation in human body is carried by coordinated action of cardiovascular system and respiratory system. Pulmonary diseases are characterized by hypoxia which not only increases the burden on the heart to compensate but also make it vulnerable target to undergo decompensating when baseline function is suboptimal.

Anatomical, physiological closeness of both these structures makes them to share several diseases and clinical manifestations. Distribution of sympathetic and cholinergic receptors on both systems Presence of beta 2 receptors in alveoli, beta1 receptors in airway smooth muscle, cardiac muscles, cholinergic M1, 2,3, receptors on bronchial smooth muscle, mucous glands, epithelium lead to invariable desired and undesired effects due to medications. Palpitations, bronchospasm and precipitation of coronary events are expected in those patients using beta blockers or agonists.

Common respiratory diseases include upper and lower respiratory infections including influenza illness, pneumonia, obstructive airway diseases including bronchial asthma, Chronic Obstructive Pulmonary Disease (COPD), fibrosing conditions like idiopathic

Pulmonary Fibrosis (IPF), obstructive sleep apnea, obesity hypoventilation syndrome (OSA/OHS). Recent COPD as asystemic disease with needed comprehensive care including cardiovascular, musculoskeletal aspects of care. Similarly, cardiovascular impact of OSA and OHS are well noted and require careful attention. With this background, no respiratory diseases should be considered as an isolated one and pragmatic approach is necessary to a chief complete care of the patient.

Coronary artery diseases (CAD) is a spectrum of disorders ranging from stabling in a to acute coronary syndromes (ACS) like unstable angina, NSTEMI (Non ST Elevation Myocardial Infarction), STEMI (ST Elevation Myocardial Infarction). Pathophysiology includes mismatch between blood supply to demand because of progressive restenosis of coronaries or atherosclerotic plaque rupture leading to acute coronary syndromes.

Hypercholesterolemia and hypertension were the initial foci of the pathogenesis of coronary artery disease. Development of therapeutic interventions, however, couldn't eliminate the disease completely leading to speculation of other mechanisms and further research has focused on inflammation as the important one in this aspect.

Atherosclerotic plaque is the main culprit lesion in the pathogenesis of CAD. It's formed in the intima of coronary vessels with the interaction of inflammatory and immune cells along with structural cells like endothelial cells, lipids, ECM (Extracellular matrix), chemokines and cytokines. Rupture of atheroma plaque and endothelial erosion are two mechanisms predispose to acute coronary syndromes. Inflammation has been shown to have an impact on all these processes leading to the speculation of targeting this process therapeutically. LDL undergoes oxidation or enzymatic activation leading to endothelial activation, platelet attachment, leukocyte attachment to adhesion molecules

like VCAM1 (Vascular Endothelial Adhesion Molecule). Further release of cytokines leads to entry and accumulation of monocytes and macrophages transforming into foam cells. Th1 cells release interferon γ , TNF α and IL 1 which will further augment inflammation. Other types of cells like Th2 and NKT cells CD 8 cells will also participate to a smaller extent. On the other side are protective mechanisms like TGF β and IL 10, B cells producing antibodies try to contain these processes.

COPD (CHRONIC OBSTRUCTIVE PULMONARY DISEASE):

Smoking is a common etiological factor for both CAD and COPD. So it can be expected that both the diseases to coexist often. Smoking accounted for 36% of MI cases worldwide in INTERHEART study [2]. It increases the risk of coronary artery disease by 2-4 times. COPD is a leading chronic respiratory disease worldwide also caused by smoking & accounting for 6% of total deaths [3] (Fig 1).

Fig 1: Deaths due to Smoking

CAD prevalence was high in COPD patients in a VA study [4] amounting to 33.6%. Nearly 60% of patients of COPD patients had angiographically proven, significant coronary artery disease [5]. Delayed presentation to medical care was observed in MI patients with COPD than those without COPD [6]. High fibrinogen, leukocytosis, elevated CRP is raised in both diseases.[7, 8, 9].COPD is characterized by exacerbations

and these pose a special threat on both respiratory and cardiac functions (Fig 2).

Fig 2: Systemic effects of chronic obstructive pulmonary disease.

More than 55% of patients have associated cardiovascular disease and decompensated heart disease can itself be a cause of exacerbation in significant number of patients. 8-25% patients had elevated troponin and ECG changes that can fulfill the diagnostic criteria of ACS in COPD patients. Mechanisms include hypoxia, tachycardia, increased afterload due to vascular stiffness, pulmonary hypertension leading to right ventricular strain and associated left ventricular dysfunction, impaired biventricular filling because of dynamic hyperinflation of lungs, increased systemic inflammatory markers leading to prothrombotic condition and persistent autonomic dysfunction (Fig 3).

Fig 3: Resting heart rate is a predictor of mortality in COPD.

Cardio selective beta blockers have been shown to be beneficial in terms of mortality in stable COPD patients. Beta blockers reduce mortality and exacerbations but prospective studies are needed to prove these beneficial

effects. In spite of these benefits of beta blockers they are grossly underutilized in COPD. Ivabradine appears to be a promising drug for heart rate control [10], statins reduced mortality but not exacerbations, Angiotensin Converting Enzyme Inhibitors (ACE I) and Angiotensin Receptor Blockers (ARB) roles have to be established in controlled trials [11].

Diagnosis is itself challenging in these patients as chest pain ECG changes and biomarkers may be seen in acute exacerbations also [12]. An algorithmic approach like COPD CoRi [13] is useful in these situations.

In stable COPD patients, cardio selective beta blockers are shown to be safe [14]. They are shown to reduce mortality and risk of exacerbation in these patients [15,16]. Non selective beta blockers also can be used in mild to moderate COPD without reversible airway obstruction component [17]. Carvedilol has been shown to be well tolerated in COPD patients while asthmatics could not tolerate it [18].

On the other side impact of cardiovascular medications have an impact on CAD are widely documented. Beta 2 agonists cause tachycardia so that theoretically can precipitate ACS. Safety of SABA has been established in some studies [19]. A retrospective cohort of patients with COPD risk of cardiovascular events is significantly higher in patients with preexisting cardiovascular disease and cardiovascular medications [20]. TORCH (Towards a Revolution in COPD Health) trial [21] showed no increase in cardiovascular mortality with salmeterol, fluticasone or combination. Ipratropium was associated with risk of increased mortality in COPD patients and ICS are associated with lower risk of death [22]. Although initial studies of tiotropium have shown increased cardiovascular mortality [23] further studies and analyses [24] showed decreased mortality. In a group of MI patients with prior history of COPD, 1 year mortality and new onset heart failure were significantly higher [25].

COPD is known to be associated with other comorbid conditions along with other systemic effects (Fig 3). Peripheral lung inflammation may cause a "spill-over" of cytokines, such as interleukin (IL)-6, IL-1 β and tumor necrosis factor (TNF)- α , into the systemic circulation, which may increase acute-phase proteins such as C-

reactive protein (CRP). Systemic inflammation may then lead to skeletal muscle atrophy and cachexia and may initiate and worsen comorbid conditions. Systemic inflammation may also accelerate lung cancer. An alternative view is that systemic inflammation causes several inflammatory diseases, including COPD.

Fig 4: Systemic effects and comorbidities of chronic obstructive pulmonary disease (COPD).Curtsey of P. J. Barnes.

Newer anticholinergic like glycopyrronium [26] has good safety profile except for small risk of atrial fibrillation. Similarly, studies of umeclidinium, aclidinium [27] were safe with respect to cardiovascular diseases.

Results of drug safety trials of COPD are hampered by so called "COPD trial paradox". It's due to exclusion of major cardiovascular diseases in studies whom the actual general population represent with multiple comorbidities. Clinical trials have assured safety while observational studies have shown increased risk of newly started long acting beta agonists (LABA) [28].

Theophyllines, Roflumilast [29] and, Azithromycin [30] which are used in COPD patients have not shown significant cardiovascular mortality except slight increase in atrial fibrillation.

BRONCHIAL ASTHMA:

Bronchial asthma is a chronic inflammatory reversible obstructive disease of airways with a prevalence of 1.6%

- 36.8% [31]. Inflammation, bronchospasm leads to reversible obstruction of airways followed by airway remodeling leading to fixed airways obstruction. Because of its complex pathogenic mechanisms, several phenotypes have been described. Medications useful are inhalational steroids, beta 2 agonists, anticholinergics, biologicals like omalizumab in selected cases.

In a study by Kiss et al, 20% patients who had symptoms suggestive of angina and negative stress echo had actually bronchial asthma that was undiagnosed previously [32]. In Airflow Limitation in Cardiovascular patients in European patients (ALICE) study [33] airflow obstruction was observed in 30% patients of CAD. Of them, 70% didn't have a spirometric diagnosis of asthma indicating under-recognition of this condition in CAD patients. Asthma association with cardiovascular disease was not constantly shown in studies. Study by Schanen has not shown positive relation between asthma and CVD. In other studies persistent asthmatics [34] women asthmatics were at more risk for CAD than men [35, 36, 37]. Late onset asthma has been shown to be a risk factor for cardiovascular events [38].

Medications are expected to have significant effects. Repeated usage of salbutamol was suspected as a cause for Takotsubo cardiomyopathy in some cases [39]. Mode of delivery of beta agonists can have impact. More incidence of MI/IHD was observed in patients with nebulized or oral beta agonists rather than MDI (Metered Dose Inhalers) [40, 41, 42]. As inflammation has considerable role in the pathogenesis of asthma and CAD there is a theoretical possibility of reduced risk of coronary events in asthmatics patients who use ICS. Usage of ICS has shown to decrease the risk of MI in asthmatics in previous studies whereas in recent studies such protection against nonfatal MI could not be demonstrated [43]. Statins are frequently used in CAD patients, some studies have their beneficial effect [44] in severe asthmatics whereas some recent studies reported worsening allergic asthma [45] due to shifting of Th2. Omalizumab an IgE antibody has shown increased risk of MI [46]. Finally, all these drugs need to be used carefully in patients with preexisting cardiovascular diseases with regular monitoring in the initial stages of starting beta agonists. Development of an algorithmic approach is the need of hour in these patients.

Cardio selective beta blockers in asthma are better tolerated in asthma but not completely risk-free. These effects can be minimized by starting from low doses and treating bronchospasm with beta agonists.

OSA (OBSTRUCTIVE SLEEP APNEA) AND CORONARY ARTERY DISEASE:

OSA is grossly under-recognized condition characterized by repetitive obstruction of the upper airway during sleep leading to hypoxia, fluctuating sympathetic surges, sleep fragmentation, daytime sleepiness and various consequences. Repetitive obstruction of the upper airway leads to hypoxia and re-oxygenation increase oxidative stress. This oxidative stress leads to endothelial dysfunction, lipid peroxidation. Endothelial dysfunction also leads to reduced smooth muscle relaxation leading to ideal site of atheromatous plaque formation. Severe OSA patients have higher atherosclerotic plaque volume, non-calcified and mixed plaques. OSA also is a condition of chronic low grade inflammation as evidenced by several studies [47]. Sympathetic fluctuation can lead to imbalances of blood flow and increased cardiac oxygen demands leading to ischemia in patients with baseline coronary disease.

Prevalence of OSA in angiographically proven CAD was 30% and AHI (Apnea Hypopnea Index) and BMI (Body Mass Index) was significantly more in these patients when compared to controls. AHI more than 20 was an independent risk factor for myocardial infarction [48]. Although initial CPAP (Continuous Positive Airway Pressure) intervention was exciting and showed a decrease in cardiovascular mortality recent SAVE study (Sleep Apnea cardio Vascular Endpoints) has shown that CPAP has not improved cardiovascular outcomes [49] in non-sleepy patients didn't have a significant reduction in long term cardiovascular outcomes.

IPF (IDIOPATHIC PULMONARY FIBROSIS) AND CAD:

IPF is a chronic progressive fibrotic lung disease characterized by hypoxia and its complications. Prevalence of angiographically proven CAD in non-granulomatous fibrotic lung disease was high (OR 2.18) in patients planned for lung transplantation [50].

In another study the prevalence of angiographically proven CAD was more in fibrosis (28.6%) patients when compared to emphysema (9.8%) even after adjusting the smoking rates [51]. Not only prevalence but incident CAD was also more in IPF patients [52]. IHD can be a significant cause of clinical deterioration in these patients (9.5%), although respiratory failure is the most common cause. Cardiopulmonary exercise testing will be a valuable investigation in this subset where symptoms of both diseases overlap [53]. Unsuspected significant CAD is also higher in IPF patients (18%) and results in worse outcomes [54].

Basic mechanisms of pathogenesis in IPF and CAD like increased inflammation, epithelial mesenchymal transformation, aberrant wound healing leading to hypoxia. Increased levels of IL8, TNF alpha were observed in IPF [55]. Increased Tissue Factor levels in IPF are observed which may indicate extrinsic coagulation pathway activation and procoagulant state [56, 57]. Altered state of fibrinolysis was also observed in several studies, as indicated by reduced levels of u-PA, PAI and increased levels of antiplasmin. The overall changes are more favorable towards to procoagulant state and increased acute coronary syndrome risk [58].

RESPIRATORY INFECTIONS – CAD:

Influenza is one of the most common causes of respiratory infections worldwide. The increase in cardiovascular and respiratory mortality has been a consistent observation since longtime. Although influenza is the dominant organism other viruses like RSV and human metapneumo viruses are also reported to cause epidemics. Mohd Majidi [59] reported 30% increase in autopsy confirmed MI during flu epidemics. Risk of MI was 3 times higher in the first 5 days of acute respiratory infections [60]. Main pathogenesis includes inflammation as evidenced by acute leukocytosis, cytokine response and these can result in atheroma instability. Vaccination for influenza has been beneficial in reducing incidence of MI and death [61, 62]. In a meta-analysis of case cohort studies influenza infection was significantly associated with AMI and vaccination was effective in reducing AMI related mortality. The interesting point is the effectiveness was equivalent to medications in

preventing secondary CAD [63]. Inconsistencies of vaccine effectiveness are thought to be due to individual's ability to elicit the immune response and variations in the potencies of vaccines.

Community acquired pneumonia is a common cause of hospitalization and mortality in elderly patients. This can be complicated by cardiac complications like CHF, arrhythmias and MI. The incidence of MI varied from 3%-10% in various studies [64]. Association was observed between not only pneumococcal organism [65] but also with atypical infections like mycoplasma [66]. Risk factors for developing cardiac complications in a pneumonia patient include severe pneumonia, hyperlipidemia, staphylococci, Klebsiella [67]. More vigilance is required in these patients for possible complications and early treatment. Cardiac complications are risk factors for increased mortality and worse outcomes [64]. Hypoxia, tachycardia results in higher myocardial oxygen demands (Fig 4), reduced diastole thereby reducing coronary perfusion, increased systemic inflammation leading to procoagulant state, inflammatory activity in the atherosclerotic plaque lead to the myocardial ischemia and precipitation of coronary events. PPV (Pneumococcal Polysaccharide Vaccine) was shown to reduce these complications in several studies [68, 69]. Vaccination is mandatory in those people at risk for pneumonia.

Fig 5: Effects of hypoxia on systemic and pulmonary circulation.

Tuberculosis is a common infection worldwide, more in developing countries. Nearly 2 billion patients are infected with it and 2 million die each year. In a cohort study by Chung [70] risk of ACS was 40% higher in PTB patients than the general population. Even latent TB is also associated with higher inflammatory markers and increased CAD risk [71].

BRONCHIECTASIS:

Bronchiectasis is a common disease with diverse etiologies. Characterized by dilated bronchi, mucous stasis leading to recurrent infections and hypoxia. Inflammatory markers are significantly high in bronchiectasis patients. Combined with hypoxia and inflammation, expected cardiovascular mortality is high in these patients. In a population-based study prevalence of CAD was 33% higher and more severe in bronchiectasis patients and incident CAD was also high [72]. Arterial stiffness is one finding observed with prevalence in bronchiectasis patients which may predispose to CAD. Original Chalmers validation study [73] for bronchiectasis severity index has 25 % mortality due to cardiovascular diseases. As these patients are under risk of massive hemoptysis due to coronary bronchial artery fistulas, patients undergoing procedures like CABG, it may be necessary to do arterial embolization and close these communications [74, 75].

OCCUPATIONAL LUNG DISEASE:

Lungs are especially at risk of occupational lung disease in view of its constant exposure. Pneumoconiosis like coal work pneumoconiosis [76], silicosis [77], asbestosis [78], particulate matter from air pollution, diesel exhaust [79] and agricultural and livestock exposures [80]. Asbestosis may pose a clinical challenge as some patients may have angina chest pain [81] (Fig 6).

Fig 6: Mechanism of air pollution producing cardiovascular disease

EOSINOPHILIC DISEASES:

Although eosinophilic disorders commonly involve lungs, HES (Hypereosinophilic Syndrome) main manifestation is heart failure and valvular disease, thrombin left ventricle. Coronary involvement is less common; in one study 15 % patients had myocardial necrosis with thrombin small coronaries [82]. Finally, there is a need for further research in finding precise therapeutic targets with minimal side effects and specifically algorithms for evaluating comorbidities and management of patients with comprehensive care.

CHRONIC LUNG DISEASE AND PAH

All the chronic lung diseases are known to have an effect on heart by increasing the pulmonary arterial hypertension. The Fig. 6 gives flow chart to how to evaluate a PAH patients secondary to the lung disease.

Fig 7: PAH evaluation

CONCLUSION:

In conclusion, there are the common risk factors for the lung and heart diseases like smoking and air pollution which can be a predisposing factor for COPD as well as CAD. Other than as a common risk factor there are different pathophysiological ways by which CAD incidence increases in lung disease patients which is discussed in length under the headlines of different lung diseases.

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