RESPIRATORY DISEASES AND CORONARY ARTERY DISEASES

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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

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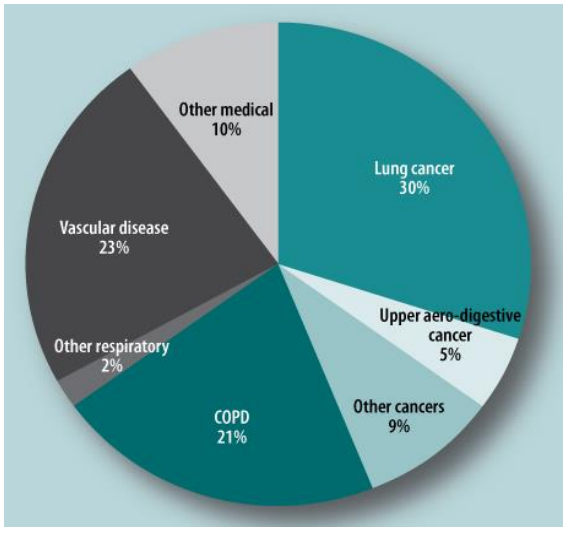
like VCAM1 (Vascular Endothelial Adhesion Molecule). Further release of cytokines leads to entry and accumulation of monocytes and macrophages transforming into foam cells.Th1 cells release interferon ɣ, TNFα and IL 1 which will further augment inflammation. Other types of cells like Th2 and NKT cells 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):

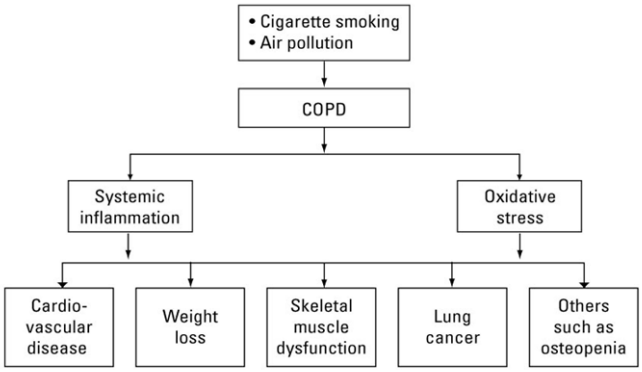
Smoking is a common etiological factor for both CAD and COPD. So it can be expected that both the diseases to coexist often. Smoking accounted for 36% of MI cases worldwide in INTERHEART study [2]. It increases the risk of coronary artery disease by 2-4 times. COPD is a leading chronic respiratory disease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

Fig 1: Deaths due to Smoking



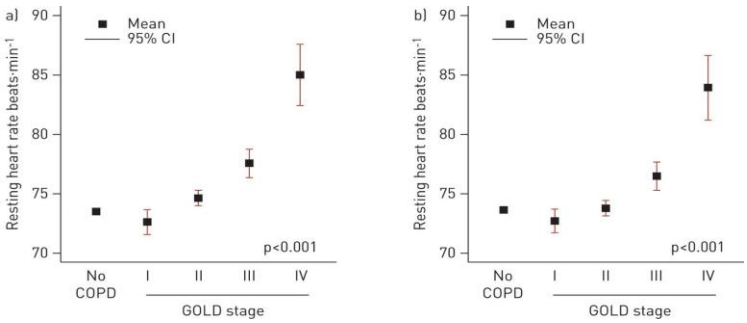
CAD prevalence was high in COPD patients in a VA study [4] amounting to 33.6%. Nearly 60% of patients of COPD patients had angiographically proven, significant coronary artery disease [5]. Delayed presentation to medical care was observed in MI patients with COPD than those without COPD [6]. High fibrinogen, 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. Inspite 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].

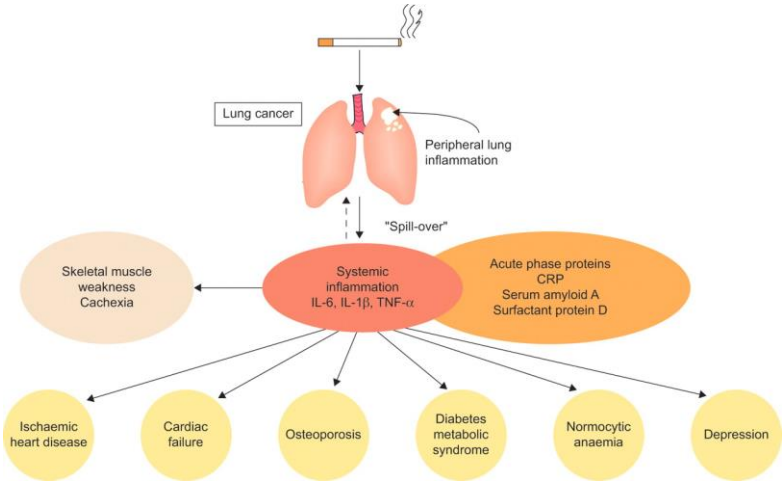
Diagnosis is itself challenging in these patients as chest pain ECG changes and biomarkers may be seen in acute exacerbations also [12]. An algorithmic approach like COPD CoRi [13] is useful in these situations.

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, 1year 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-1β 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 CORONARYARTERY 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].

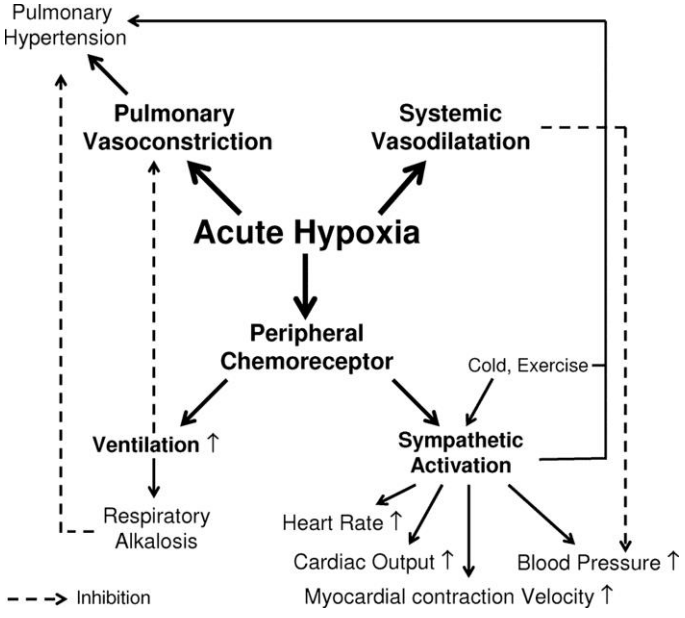
Basic mechanisms of pathogenesis in IPF and CAD like increased inflammation, epithelial mesenchymal transformation, aberrant wound healing leading to hypoxia. Increased levels of IL8, TNF alpha were observed in IPF [55]. Increased Tissue Factor levels in IPF are observed which may indicate extrinsic 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].

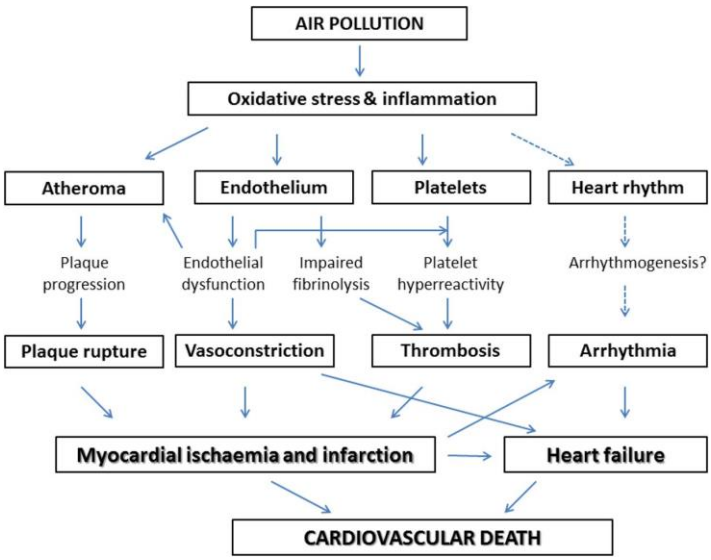
BRONCHIECTASIS:

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 wither 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



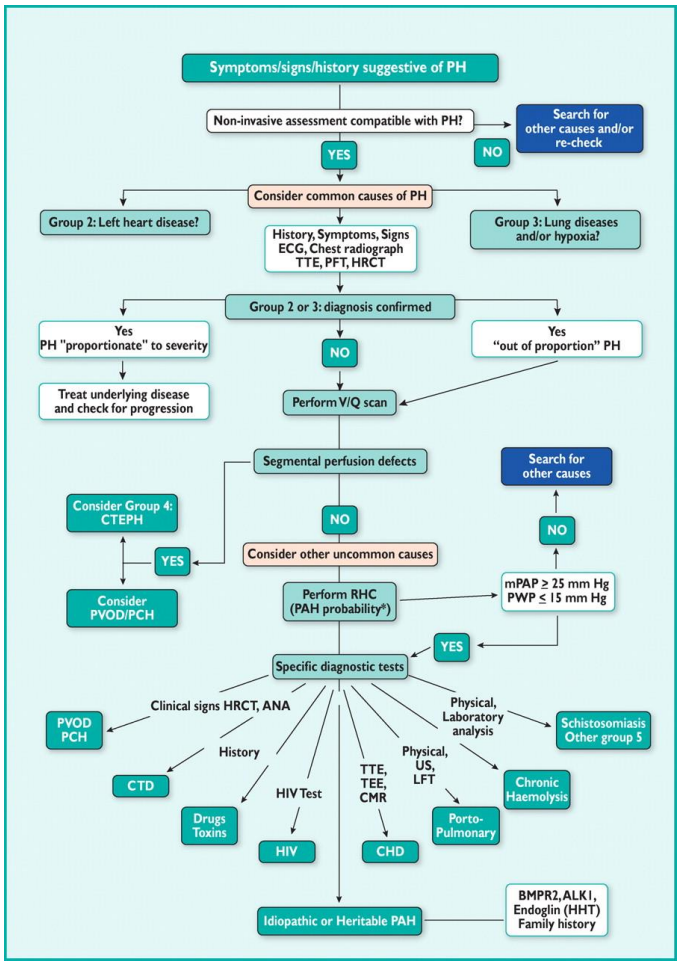
EOSINOPHILIC DISEASES:

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 study15 % 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**.**

REFERENCES:

1. WHO,Fact sheet September 2016

2. Yusuf, S., et al. "Investigators IS. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study." Lancet 364.9438 (2004): 937-52.

3. WHO fact sheet COPD September 2016.

4. Mapel, Douglas W., David Dedrick, and Kourtney Davis. "Trends and cardiovascular co- morbidities of COPD patients in the Veterans Administration Medical System, 1991–1999." COPD: Journal of Chronic Obstructive Pulmonary Disease 2.1 (2005): 35-41.

5. Reed, Robert M., et al. "Coronary artery disease is under-diagnosed and under-treated in advanced lung disease." The American journal of medicine125.12 (2012): 1228-e13.

6. Rasputina, Lesia, et al. "Chronic obstructive pulmonary disease and myocardial infarction: Special aspects of clinical course in comorbid conditions." European Respiratory Journal 44.Suppl 58 (2014): P3616.

7. Ross, Russell. "The pathogenesis of atherosclerosis: a perspective for the 1990s." (1993):801-809.

8. Hansson, Göran K. "Inflammation, atherosclerosis, and coronary artery disease." NewEngland Journal of Medicine 352.16 (2005): 1685-1695.

9. Falk, Jeremy A., et al. "Cardiac disease in chronic obstructive pulmonary disease." Proceedings of the American Thoracic Society 5.4 (2008): 543-548.

10. Majewski S, Slomka S, Zielinska-Wyderkiewicz E, Ciebiada M, Gorski P. Heart Rate-lowering efficacy and respiratory safety of ivabradine in patients with obstructive airway disease: a randomized, double-blind, placebo-controlled, crossover study. Am J Cardiovasc Drugs. 2012 Jun 1;12(3):179-88. doi:10.2165/11597400-000000000-00000. PubMed PMID: 22409211

11. Mortensen, Eric M., et al. "Impact of statins and ACE inhibitors on mortality after COPDexacerbations." Respiratory research 10.1 (2009): 1.

12. Harvey, Martyn G. and Robert J. Hancox. "Elevation of cardiac troponins in exacerbation of chronic obstructive pulmonary disease." Emergency Medicine 16.3 (2004): 212-215.

13. Cazzola, Mario, et al. "Chronic obstructive pulmonary disease and coronary disease: COPDCoRi, a simple and effective algorithm for predicting the risk of coronary artery disease in COPD patients." Respiratory medicine 109.8 (2015): 1019-1025.

14. Salpeter, S. R., et al. "Cardioselective beta-blockers for chronic obstructive pulmonary disease: a meta-analysis." Respiratory medicine 97.10 (2003): 1094-1101

15. Rutten, Frans H., et al. "β-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease." Archives of Internal Medicine 170.10 (2010): 880-887.

16. Dransfield, Mark T., et al. "Use of β blockers and the risk of death in hospitalized patients with acute exacerbations of COPD." Thorax 63.4 (2008): 301-305.

17. Albouaini K, Egred M, Alahmar A, Wright DJ. Cardiopulmonary exercise testing and its application. Postgrad Med J. 2007 Nov; 83(985):675-82. Review. PubMedPMID: 17989266; PubMed Central PMCID: PMC2734442.

18. Kotlyar, Eugene, et al. "Tolerability of carvedilol in patients with heart failure and concomitant chronic obstructive pulmonary disease or asthma." The Journal of heart and lung transplantation 21.12 (2002): 1290-1295.

19. Suissa, ST. Assimes, and P. Ernst."Inhaled short acting β agonist use in COPD and the risk of acute myocardial infarction." Thorax 58.1 (2003): 43-46.

20. Aljaafareh A, Valle JR, Lin YL, Kuo YF, Sharma G. Risk of cardiovascular events after initiation of long-acting bronchodilators in patients with chronic obstructive lung disease: A population-based study. SAGE Open Med. 2016 Oct4; 4:2050312116671337. PubMed PMID: 27757229; PubMed Central PMCID: PMC5052927.

21. Calverley, Peter MA, et al. "Cardiovascular events in patients with COPD: TORCH study results." Thorax 65.8 (2010): 719-725.

22. Lee TA, Pickard AS, Au DH, Bartle B, Weiss KB. Risk for Death Associated with Medications for Recently Diagnosed Chronic Obstructive Pulmonary Disease. Ann Intern Med. 2008;149:380-390. doi: 10.7326/0003-4819-149-6-200809160-00004

23. Singh, Sonal, Yoon K. Loke, and Curt D. Furberg. "Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis." Jama 300.12 (2008): 1439-1450.

24. Celli, Bartolome, et al. "Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with the chronic obstructive pulmonary disease." American journal of respiratory and critical care medicine 180.10 (2009): 948-955.

25. Andell, Pontus, et al. "Impact of chronic obstructive pulmonary disease on morbidity and mortality after myocardial infarction." Open heart 1.1 (2014): e000002.

26. D'Urzo AD, Kerwin EM, Chapman KR, et al. Safety of inhaled glycopyrronium in patients with COPD: a comprehensive analysis of clinical studies and post-marketing data.Int J Chron Obstruct Pulmon Dis 2015; 10: 1599–612.

27. Gelb, Arthur F., et al. "Long-term safety and efficacy of twice-daily aclidinium bromide in patients with COPD." Respiratory medicine 107.12 (2013): 1957-1965.

28. Gershon, Andrea, et al. "Cardiovascular safety of inhaled long-acting bronchodilators in individuals with

chronic obstructive pulmonary disease." JAMA internal medicine 173.13 (2013): 1175-1185.

29. White WB, Cooke GE, Kowey PR, Calverley PM, Bredenbröker D, Goehring UM, Zhu

H, Lakkis H, Mosberg H, Rowe P, Rabe KF. Cardiovascular safety in patients receiving roflumilast for the treatment of COPD. Chest. 2013 Sep;144(3):758-65. doi: 10.1378/chest.12-2332. PubMed PMID: 23412642.

30. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA Jr, Criner GJ, CurtisJL, Dransfield MT, Han MK, Lazarus SC, Make B, Marchetti N, Martinez FJ, Madinger NE, McEvoy C, Niewoehner DE, Porsasz J, Price CS, Reilly J, Scanlon PD, Sciurba FC, Scharf SM, Washko GR, Woodruff PG, Anthonisen NR; COPD Clinical Research Network.. Azithromycin for prevention of exacerbations of COPD. N Engl J Med.2011Aug 25;365(8):689-98. doi: 10.1056/NEJMoa1104623. Erratum in: N Engl J Med. 2012 Apr 5;366(14):1356. PubMed PMID: 21864166; PubMed Central PMCID: PMC3220999.

31. Beasley, Richard, et al. "Prevalence and etiology of asthma." Journal of Allergy and Clinical Immunology 105.2 (2000): S466-S472.

32. Kiss, D. et al. "Bronchial asthma causing symptoms suggestive of angina pectoris." European Respiratory Journal 21.3 (2003): 473-477.

33. Soriano JB, Roche N, Cockcroft JR, Rabe KF, Kearney M, Brusselle G, et al. Prevalence and under-diagnosis of airflow limitation and other lung function abnormalities in patients with ischaemic heart disease: an interim analysis of the ALICE study. Eur Respir J 2012;40(Suppl 56):P450.

34. Tattersall, Matthew C., et al. "Asthma Predicts Cardiovascular Disease Events The Multi- Ethnic Study of Atherosclerosis." Arteriosclerosis, thrombosis, and vascular biology 35.6 (2015): 1520-1525.

35. Iribarren C, Tolstykh IV, Miller MK, Sobel E, Eisner MD. Adult asthma and riskof coronary heart disease, cerebrovascular disease, and heart failure: aprospective study of 2 matched cohorts. Am J Epidemiol. 2012 Dec1;176(11):1014-24. doi:10.1093/aje/kws181. PubMed PMID: 23139248.

36. Onufrak, Stephen J., et al. "Relation of adult-onset asthma to coronary heart disease and stroke." The American journal of cardiology 101.9 (2008): 1247-1252.

37. Torén K, Lindholm NB. Do patients with severe asthma run an increased risk from ischaemic heart disease? Int J Epidemiol. 1996 Jun;25(3):617-20. PubMedPMID: 8671564.

38. Tattersall, Matthew C., et al. "Late-Onset Asthma Predicts Cardiovascular DiseaseEvents: The Wisconsin Sleep Cohort." Journal of the American Heart Association 5.9(2016): e003448.

39. Saito, Nayuta, et al. "Asthmatic Attack Complicated with Takotsubo Cardiomyopathy after Frequent Inhalation of Inhaled Corticosteroids/Long-Acting Beta2-Adrenoceptor Agonists." Internal Medicine 55.12 (2016): 1615-1620.

40. Lee, Hwa Mu, Steven T. Truong, and Nathan D. Wong. "Association of adult-onset asthma with specific cardiovascular conditions." Respiratory medicine106.7 (2012): 948- 953.

41. Suissa, Samy, et al. "Bronchodilators and acute cardiac death." American journal of respiratory and critical care medicine 154.6 (1996): 1598-1602.

42. C. Iribarren,I. V. Tolstykh, and MD. Eisner, "Are patients with asthma at increased risk of coronary heart disease?" International Journal of Epidemiology, vol. 33, no 4, p 743–748,2004.

43. Suissa S, Assimes T, Brassard P, Ernst P. Inhaled corticosteroid use in asthma and the prevention of

myocardial infarction. Am J Med. 2003 Oct 1;115(5):377-81. PubMed PMID: 14553873,

44. Zeki AA, Oldham J, Wilson M, et al. BMJ Open 2013; 3:e003314. doi:10.1136/bmjopen-2013-003314

45. FRAN LOWRY. Statins Can Make Asthma Worse. Medscape. Nov 14, 2011.

46. Ali, Ayad K., and Abraham G. Hartzema. "Assessing the association between omalizumab and arteriothrombotic events through spontaneous adverse event reporting." J Asthma Allergy 5.1 (2012): 1-9.

47. De Torres-Alba, Fernando, et al. "Obstructive sleep apnea and coronary artery disease:from pathophysiology to clinical implications." Pulmonary medicine 2013 (2013).

48. Schäfer H, Koehler U, Ewig S, Hasper E, Tasci S, Lüderitz B. Obstructive sleep apnea as a risk marker in coronary artery disease. Cardiology. 1999;92(2):79-84. PubMed PMID: 10702648.

49. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, Mediano O, Chen R, Drager LF, Liu Z, Chen G, Du B, McArdle N, Mukherjee S, Tripathi M, Billot L, Li Q,Lorenzi- Filho G, Barbe F, Redline S, Wang J, Arima H, Neal B, White DP, Grunstein RR, Zhong N, Anderson CS; SAVE Investigators and Coordinators.. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. N Engl J Med.2016 Sep 8; 375(10):919-31. doi: 10.1056/NEJMoa1606599. PubMed PMID: 27571

50. Kizer JR, Zisman DA, Blumenthal NP, Kotloff RM, Kimmel SE, Strieter RM,Arcasoy SM, Ferrari VA, Hansen-Flaschen J. Association between pulmonary fibrosis and coronary artery disease. Arch Intern Med. 2004 Mar 8;164(5):551-6. PubMed PMID:

51. Izbicki, Gabriel, et al. "The prevalence of coronary artery disease in end-stage pulmonary disease: is pulmonary fibrosis a risk factor?." Respiratory medicine 103.9 (2009): 1346-1349.

52. Hubbard, Richard B., et al. "The association between idiopathic pulmonary fibrosis and vascular disease: a population-based study." American journal of respiratory and critical care medicine 178.12 (2008): 1257-

53. Cicchitto, Gaetano, et al. "Idiopathic pulmonary fibrosis and coronary artery disease." Multidisciplinary respiratory medicine 9.1 (2014):..

54. Nathan, Steven D. et al. "Prevalence and impact of coronary artery disease in idiopathic pulmonary fibrosis." Respiratory medicine 104.7 (2010): 1035-1041.

55. Agrawal, Abhinav et al. "Cardiac manifestations of idiopathic pulmonary fibrosis." Intractable & rare diseases research 5.2 (2016): 70.

56. Imokawa, Shiro, et al. "Tissue factor expression and fibrin deposition in the lungs of patients with idiopathic pulmonary fibrosis and systemic sclerosis." American journal of respiratory and critical care medicine 156.2 (1997): 631-636.

57. Fujii, Masato, et al. "Relevance of tissue factor and tissue factor pathway inhibitor for hypercoagulable state in the lungs of patients with idiopathic pulmonary fibrosis." Thrombosis research 99.2 (2000): 111-117.

58. Sprunger, David B., et al. "Idiopathic pulmonary fibrosis co-morbidity: thromboembolic disease and coronary artery disease." Current Respiratory Care Reports 2.4 (2013): 241-247.

59. Madjid M, Miller CC, Zarubaev VV, Marinich IG, Kiselev OI, Lobzin YV, FilippovAE, Casscells SW 3rd. Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8

years of autopsies in 34,892 subjects. Eur Heart J. 2007May;28(10):1205-10. PubMed PMID: 17440221.

60. Meier CR, Jick SS, Derby LE, Vasilakis C, Jick H. Acute respiratory-tract infections and risk of first-time acute myocardial infarction. Lancet 1998;351:1467–1471.Corrales- Medina, Vicente F., Mohammad Madjid, and Daniel M. Musher. "Role of acute infection in triggering acute coronary syndromes." The Lancet infectious diseases 10.2 (2010): 83- 92.

61. Warren-Gash, Charlotte, Liam Smeeth, and Andrew C. Hayward. "Influenza as a trigger for acute myocardial infarctionor death from cardiovascular disease: a systematic review." The Lancet infectious diseases 9.10 (2009): 601-610.

62. Ciszewski, Andrzej, et al. "Influenza vaccination in secondary prevention from coronary ischaemic events in coronary artery disease: FLUCAD study." European heart journal (2008).

63. Barnes, Michelle, et al. "Acute myocardial infarction and influenza: a meta-analysis of case–control studies." Heart 101.21 (2015): 1738-1747.

64. Shebl, R. Eman, and Mohamed Salah Hamouda. "Outcome of community-acquired pneumonia with cardiac complications." Egyptian Journal of Chest Diseasesand Tuberculosis 64.3 (2015): 633-638.

65. Musher, Daniel M., et al. "The association between pneumococcal pneumonia and acute cardiac events." Clinical Infectious Diseases 45.2 (2007): 158-165.

66. Chung, W-S., et al. "Mycoplasma pneumonia increases the risk of acute coronary syndrome: a nationwide population-based cohort study." QJM(2015): hcv015.

67. Griffin, Allen T.Timothy L. Wiemken,and Forest W. Arnold. "Risk factors for cardiovascular event in hospitalized patients with community-acquired pneumonia." International Journal of Infectious Diseases 17.12 (2013): e1125-e1129.

68. Vila-Corcoles, Angel, et al. "Clinical effectiveness of pneumococcal vaccination against acute myocardial infarction and stroke in people over 60 years: the CAPAMIS study, one-year follow-up." BMC Public Health 12.1 (2012): 1.

69. Eurich, Dean T., et al. "Pneumococcal vaccination and risk of acute coronary syndromes in patients with pneumonia: population-based cohort study." Heart 98.14 (2012): 1072-1077.

70. Chung, Wei-Sheng, et al. "Tuberculosis increases the subsequent risk of acute coronary syndrome: a nationwide population-based cohort study." The International Journal of Tuberculosis and Lung Disease 18.1 (2014): 79-83.

71. Huaman, Moises A., et al. "Tuberculosis and cardiovascular disease: linking the epidemics." Tropical diseases, travel medicine and vaccines 1.1 (2015): 1.

72. Navaratnam, Vidya, et al. "Bronchiectasis and the risk of cardiovascular disease: a population-based study." Thorax (2016): thoraxjnl-2015.

73. Chalmers, James D., et al. "The bronchiectasis severity index. An international derivation and validation study." American journal of respiratory and critical care medicine 189.5 (2014): 576-585.

74. Oda, Takeshi, et al. "Coronary Artery Bypass Grafting in a Patient with Unstable Angina Pectoris and Bronchiectasis." Annals of Thoracic and Cardiovascular Surgery 20.Supplement (2014): 761-764.

75. Bury, Roger W., Jerzy Wojciuk, and Grahame K. Goode. "Multiple coronary artery fistulae associated with bronchiectasis: rarity or recognized phenomenon?." Texas Heart Institute Journal 37.3 (2010): 380.

76. Landen, Deborah D., et al. "Coal dust exposure and mortality from ischemic heart disease among a cohort of US coal miners." American journal of industrial medicine 54.10 (2011): 727-733.

77. Liu, Yuewei, et al. "Long-term exposure to crystalline silica and risk of heart disease mortality." Epidemiology 25.5 (2014): 689-696.

78. Rong, Yi, et al. "Occupational exposure to asbestos and cardiovascular related diseases: A meta-analysis." Preventive medicine reports 2 (2015): 920-926.

79. Torén, Kjell, et al. "Occupational exposure to particulate air pollution and mortality due to ischaemic heart disease and cerebrovascular disease." Occupational and environmental medicine 64.8 (2007): 515-519.

80. Sjögren, B., J. Weiner, and K. Larsson. "Ischaemic heart disease among livestock and agricultural workers." Occupational and environmental medicine 60.8 (2003): e1-e1.

81. Mukherjee, Sutapa, et al. "Chest pain in asbestos-exposed individuals with benign pleural and parenchymal disease." American journal of respiratory and critical care medicine 162.5 (2000): 1807-1811.

82. Ogbogu, Princess U., Douglas R. Rosing, and McDonald K. Horne. "Cardiovascular manifestations of hyper eosinophilic syndromes." Immunology and allergy clinics of North America 27.3 (2007): 457-475.

IMAGES REFERENCES:

1. Wen Q. Gan, MD, MSc, S.F. Paul Man; Systemic effects and mortality in chronic obstructive pulmonary disease; BCMJ, Vol. 50, No. 3, April 2008, page(s) 148-151.

2. Magnus Thorsten Jensen, Jacob L. Marott et al; Resting heart rate is a predictor of mortality in COPD; European RespiratoryJournal 2013 42: 341-349; DOI:

10.1183/09031936.00072212.

3. P. J. Barnes, and B. R. Celli Eur Respir J 2009;33:1165-1185

4. Peter Bärtsch, J. Simon R. Gibbs, Effect of Altitude on the Heart and the Lungs; Circulation. 2007;116:2191-2202.

5.David E. Newby, Pier M. Mannucci, Grethe S. Tell et al; Expert position paper on air pollution and cardiovascular disease; Eur Heart J (2014) 36 (2): 83-93.