Ischemic heart disease and chronic obstructive pulmonary disease

Zubiashvili M.[1]

Abstract

Abstract

Ischemic heart disease (IHD) has steadily occupied the leading position among cardio-vascular diseases (CVD) in terms of patient referrals, disability and mortality in economically developed countries. According to statistics, 17 million people die from CVD every year and among them 7 million deaths are caused by IHD. It is expected that the number of deaths from ischemic disease will be even increased overtime.

The major problem represents poly-morbidity (the combination of various diseases with one patient). Poly-morbidity is mainly characteristic to the patients of elderly age group, who are over 60 years old. The course, therapy and prevention of the disease mainly depends on the concomitant diseases, against the bakground of which the IHD has developed

IHD and chronic obstructive pulmonary disease (COPD) very often represent the comorbid diseases. According to the researches of various authors, COPD has been identified to be concomitant with IHD in 62% cases of patients with COPD.

Nowadays, in terms of mortality COPD occupies the fourth place worldwide with the possible perspective of progression in respect of its incidence as well as mortality in the nearest decade. According to World Health Organization (WHO), in 2020 COPD was ranked 5th for the economic damage inflicted by the diseases at the global scale.

In the epidemiologic researches on morbidity and mortality the due assessment of the extent of damage caused by COPD is not frequently conducted, because it is not diagnosed prior to the onset of severe clinical stage of the disease.

Social factors for the prevalence of CVD and COPD represent the violation of urbanization and ecological balance of the population. These processes are accompanied by the sedentary lifestyle, smoking, malnutrition, which, as a rule, are risk-factors for COPD and CVD.

(TCM-GMJ February 2022; 7 (1):P45-P49)

Keywords: Chronic obstructive pulmonary disease, Cardiovascular disease, Comorbidity.

Introduction

COPD represents one of the key problems in people over 40. Today, it ranks the forth in terms of mortality, however, the disease is expected to gradually move to the third position in the future. COPD and CVD are often closely linked to each other. They have the common risk-factors, patho- physiological peculiarities and symptoms and lead to the similar negative predictive diagnostics

According to the viewpoint of epidemiologists, the patients suffering from COPD are especially vulnerable to cardiovascular diseases. Actually, the mortality rate in the patients with CVD, who suffer from the moderate severity of COPD, is far higher than in the people whose death is related to respiratory insufficiency.

As it was mentioned above, COPD and CVD carry common risk-factors, patho- physiological processes and clinical signs and symptoms. (1-3) Pulmonary hypertension, right ventricular dysfunction, arrhythmia and coronary ischemic disease represent the well-known outcomes of COPD progression. (4) It was revealed that the patients who have diagnosed COPD and are detected the right ventricular dysfunction, demonstrate the low degree of tolerance for physical activities that is conditioned by the decrease in CO diffusion and right ventricular insufficiency. (5) Occasioned by the aforesaid, the physical loads limitation, which is caused by all the above mentioned pathology, restricts the quality of life.(6)

The increased risk of cardio - vascular syndrome is identified even in general population after experiencing acute respiratory infection .(7) The same may concern COPD exacerbation, (8) whose frequency was in direct relation to higher incidence of developing myocardial infarction. (9) In addition, the cardiac markers, such as C

From the [1]K. Eristavi National Center of Surgery, Iv.Javakhishvili Tbilisi state University;
Received December 08, 2021; accepted January 21 , 2022.
Address requests to: Zubiashvili Maria
E-mail: mariazubiashvili2@gmail.com

reactive protein (CRP), fibrinogen, natriuretic peptide, troponin, vascular endothelial growth factor (VEGF) are higher in patients with COPD exacerbation and they are associated with the independent risk-factors for fatality. (10)

The established traditional fear of using beta -2- agonists in IHD patients as well as the use of beta blocker in patients with COPD lead to the non-optimal consequences of the treatment of both conditions, when they coexist. The current guidelines clearly highlight that the control of comorbidities gain the obvious advantage over potential risks of using the above mentioned medications and the confirmed evidences reflecting any menace does not exist. (1-3, 6, 11)

On the other hand, the integrated study on the positive impact of aggressive therapy for COPD and CVD patients has not been thoroughly conducted in terms of mortality improvement.(12) CVD encompass the wide range of conditions with a variety of patho-physiology, prognosis and treatment.

The leading cause of COPD development is Tabaco smoke and the effect of diverse particles of toxic gases, which, due to the obstruction and emphysema of airways, result in the reduction of oxygen flow as well as the formation of systemic inflammatory process finally leading to airways smooth muscle dysfunction, the peripheral circulatory failure and diminished flow. (13-15)

The paradigm is expressed in therapy with beta blockers administered to COPD patients and the use of beta2 agonists for patients with respiratory diseases. (3, 16, 17)

Left and right ventricular systolic as well as diastolic dysfunction is encountered in the patients with COPD. (4, 18) The direct cause of right ventricle failure is the destruction of lung parenchyma and hypoxic vasoconstriction, which condition the increase in the pulmonary vascular resistance. (4, 18) Right ventricular dilation and its hypertrophy, as the consequence of elevated pulmonary artery hypertension, may cause the translocation of septum towards the left ventricle, abnormal right ventricular diastolic filling, the impairment of stroke volume (SV) and heart rate. (19, 20)

Hypoxia is the cause of systemic arteries dilation as well as the vasodilation in pulmonary vascular bed. (21) However, the hemodynamic pulmonary responses to hypoxia vary from each other. (21)

Some researches suggest that the moderate impairment of Forced Expiratory Volume per second (FEV1) represents the independent risk- factor for CVD and is associated with the elevated incidence of heart failure among middle-aged(22) and elderly people (23, 24). In comparatively young individuals pulmonary pathology precedes the right ventricular dysfunction (25) and the direct link has been explored between FEV1/FVC (Forced Vital Capacity) reduction and the increase in emphysema, left ventricular ultimate diastolic volume, SV and cardiac output. (26, 27)

Chronic inflammatory changes developed during the course of COPD is related to innate as well as adaptive immunity and is more manifested in bronchial walls.28 In case of COPD this inflammatory process is characterized by the pronounced inhomogeneity. This leads to emphysema with parenchymal impairment as well as chronic bronchitis, which mainly damages the small airways. (28) Previously existing studies revealed the persistent chronic inflammatory processes in 16% of COPD patients, which was related to the worst prognosis and 6-fold more mortality compared to the patients with less pronounced inflammatory processes.(29) After the manifestation of COPD inflammatory processes, the condition becomes persistent and progressive overtime, despite giving up smoking and liquidating other harmful factors. (30) Although the factors causing inflammation in the course of COPD are not identified, the role of smoking, bacterial infectious processes and other damaging effects are clearly revealed. (31)

Under the impact of both innate (microphages, neutrophils) and adaptive immune system (CD4; CD8 B- lymphocytes), the inflammatory process conditions the increase in bronchial tissue volume on the expense of infiltration of the wall through the formation of lymphatic follicles. In case of COPD, the major factor of inflammatory generation is the auto- immune system. Emphysema is an auto-immune disease, which is characterized by anti-elastin anti-bodes and T-Helper (Th1) response, which are in direct correlation with the degree of severity in emphysema. (32, 33)

The most prevailed bacterium identified in the patients with COPD, represent atypical bacterium Haemophilus influenza (NTHi). The animal model showed, that NTHi causes changes in the presence of COPD. (34) The new strains are also related to COPD exacerbation. (35) It was also indicated that this agent activates pulmonary T- cells and causes the expression of active forms of proteases and oxygen in COPD patients. (36) The infection-inflammatory vicious circle conditions the intensification of exacerbation

The concomitant elevation of CRP, fibrinogen and leucocytes represents the probability of increased risk in patients with stable COPD. Compared to patients with the normal level of these inflammatory markers, the individuals, who were detected 3-fold elevated indicators of inflammatory markers, carry 4-fold higher risk of frequent exacerbations in the first year of observation. It is still uncertain, if this can reflect the basic process of bacterial colonization or the stable latent virus infection. (37)

Several biomarkers were determined from the clinical viewpoint:

CRP represents the potential biomarker of atherosclerosis and low- grade systemic inflammation in COPD. The reduction in FEV1/FVC and FEV1 is in correlation with the elevation of high sensitivity CRP, in addition, the risk of heart ischemic disease is higher in the patients with moderate and severe obstruction during CRP elevation. (38, 39)

Fibrinogen - is acute phase protein, which was described as the marker determining the COPD activity. The high indicator of this marker represents the predictor of severity and risk of COPD exacerbation. (40, 41)

Brain-type natriuretic peptide (BNP) and N- terminal pro-BNP (NT-proBNP) are the earlier and sensitive biomarkers diagnosing heart failure (HF), which is associated with the reduction of left ventricle ejection fraction, left ventricle hypertrophy, the increase in ventricular pressure, acute myocardial infarction and other types of ischemia. (38, 42, 43) They are also increased in the patients with pulmonary diseases – right ventricular dysfunction, pulmonary hypertension and cor pulmonare. The increase of BNP and NT-proBNP in proportion to the severity of right ventricular dysfunction is identified in COPD patients. (38, 42, 43) BNP is also elevated in the stable COPD patients, who do not suffer from Pulmonary hypertension. In addition, the close links exist between BNP significance and left ventricular ejection fraction as well as pulmonary artery systolic pressure. (38, 42, 43). Finally, BNP was in relation to mortality in COPD patients as well. (38, 42, 43)

Troponini is elevated in 81-27% of hospitalized patients with COPD exacerbation and represents the independent predictor of mortality in the acute phase as well as in long-term prospect. (44 -48, 51)

VEGF (Vascular Endothelial Growth Factor) represents the significant predictor biomarker of cardio-vascular diseases. VEGF regulates angiogenesis, induce the endothelial cell migration and proliferation, increases the vascular wall permeability and lead to modulating thrombogenesis. Acute COPD patients have increasingly circulating VEGF. (39)

Surfactant Protein D (SO-D) is synthesized by the bronchial and alveolar epithelial cells and may be explored in human plasma. It performs the key role in the processes of inflammatory and immune regulation. It is also expressed in coronary ventricles showing its anti-inflammatory effect

The assessment methods of COPD and adjacent vascular diseases

The patients suffering from COPD and concomitant vascular diseases should be conducted the assessment of pulmonary and cardiac functions. In addition, it is necessary to determine systemic inflammatory status. These assessments should be conducted in different manners considering whether a patient suffers from COPD exacerbation or its chronic course.

The clinical and functional assessment of stable COPD patients encompasses:

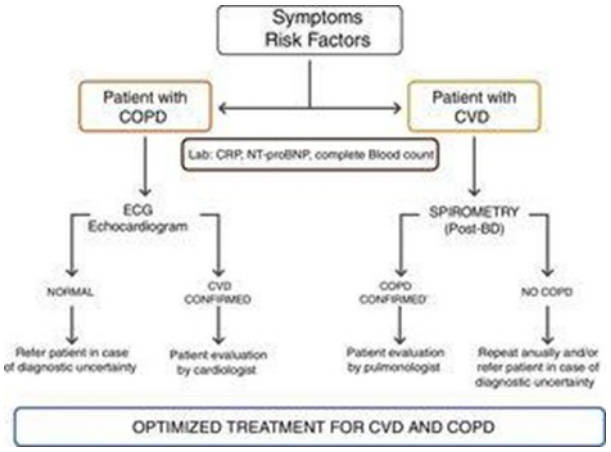
Laboratory assessment including complete blood count, arterial blood gas analysis, CRP, NT-proBNP and BNP

Spirometry, chest x-ray

12-lead electrocardiogram, and further echocardiogram investigation, if necessary.

The patients with known concomitant heart ischemic disease or other heart diseases must be necessarily conducted the assessment according to the guidelines provided (Figure 1)

It is necessary to conduct the active study of COPD in patients with heart diseases as well as COPD symptoms and risk-factors, hence, apart from the specific investigations characteristic to cardiac diseases, it is essential to carry out spirometry.



The proposed assessment algorithm for CVD in case of stable COPD

The radiological changes characteristic to COPD may be identified in the patients, who are performed CT coronary angiogram to investigate cardiac diseases. In patients with COPD, who are performed chest computer tomography, coronary calcification or cardiomegaly indicating the basic cardiac disease may be revealed. (49)

For the patients with acute COPD:

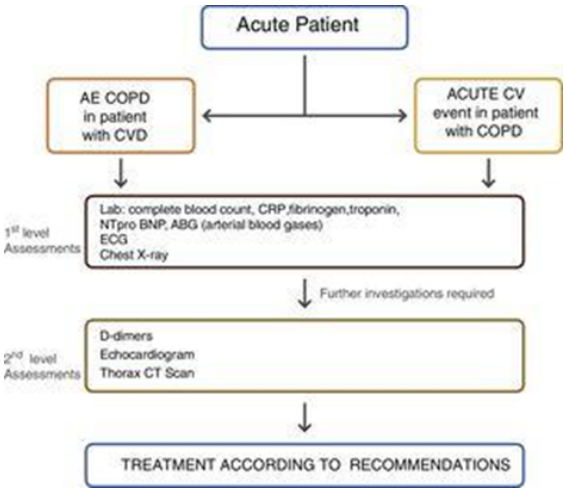
The complete clinical history and physical examination

Laboratory assessment encompassing complete blood count, leucocytes and thrombocytes count, determination CRP and fibrinogen, arterial blood gas analysis, the assessment of NT-proBNP or BNP and troponin.

Chest X-ray

12-lead electrocardiogram,

The therapeutic approach should be determined by the diagnosis, which is linked to acute clinical decompensation. The treatment to such patients may be extremely difficult, especially at the acute stage. Actually, despite the fact, that the cause of decompensation may be cardiovascular or respiratory genesis, the management of both conditions should be performed simultaneously due to the constant bilateral interaction of dysfunctional mechanisms.



The proposed assessment algorithm in the acute state

The pharmacological therapy of COPD and cardiovascular diseases

The course of COPD treatment should not be affected by the existence of comorbidities and the comorbidities should be cured according to the usual standards, notwithstanding the presence of COPD. (12)

Cardiovascular medications for patients with COPD

The study was conducted on the safety and effectiveness of medications, which are necessary for the treatment of cardiovascular and respiratory diseases in COPD patients with the concomitant CVD. The medications, such as antiplatelet, anticoagulants, inhibitors of angiotensin - converting enzyme (ACE inhibitors), angiotensin receptor blockers, beta blockers represent the most frequently prescribed medicines in CV patients. (50)

The patients with the coexisting pathology of COPD and CVD have far worse prognosis than the common denominator of independent manifestation of the same diseases, however, in case of a certain patient or a group of patients, it is difficult to determine the priori risk ratio due to the complicated etiology and patho- physiological interaction network of both diseases. (11,52)

Based on the literature data, one might say, that in COPD cases the risk ratio of developing cardiovascular comorbidities 2-3 fold exceeds the risks related to smoking.(53) COPD is linked with the considerable cardiovascular modifications. (54) It can be also affected by Tabaco addiction and cholesterol metabolism.5(4) In case of COPD, the depression of pulmonary function is associated with the increased incidence of mortality, which is conditioned by all the cardiovascular comorbidity – related reasons, myocardial infarction and arrhythmias. (55) In COPD patients the mortality occasioned by CVD remain the most frequent cause of mortality. (56)

Conclusion

In conclusion, the therapy of cardiac pathology accompanying COPD represents the considerably important process, as the prognosis of COPD is mainly determined by the coexistence of IHD or heart failure. Due to the strong patho-physiological interrelation between IHD and COPD, the investigation of possible concomitant CVD must be necessarily conducted in all COPD patients (during its chronic course as well as at the acute stage)

Referenes

1. Baum C, Ojeda FM, Wild PS, Rzayeva N, Zeller T, Sinning CR, Pfeiffer N, Beutel M, Blettner M, Lackner KJ, Blankenberg S. Subclinical impairment of lung function is related to mild cardiac dysfunction and manifest heart failure in the general population. International journal of cardiology. 2016 Sep 1;218:298-304.
2. Lipworth B, Skinner D, Devereux G, Thomas V, Jie JL, Martin J, Carter V, Price DB. Underuse of β-blockers in heart failure and chronic obstructive pulmonary disease. Heart. 2016 Dec 1;102(23):1909-14.
3. Vestbo J, Anderson JA, Brook RD, Calverley PM, Celli BR, Crim C, Martinez F, Yates J, Newby DE, Summit Investigators. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. The Lancet. 2016 Apr 30;387(10030):1817-26.
4. Falk JA, Kadiev S, Criner GJ, Scharf SM, Minai OA, Diaz P. Cardiac disease in chronic obstructive pulmonary disease. Proceedings of the American thoracic society. 2008 May 1;5(4):543-8.
5. Mesquita R, Franssen FM, Houben-Wilke S, Uszko-Lencer NH, Vanfleteren LE, Goërtz YM, Pitta F, Wouters EF, Spruit MA. What is the impact of impaired left ventricular ejection fraction in COPD after adjusting for confounders?. International Journal of Cardiology. 2016 Dec 15;225:365-70.
6. Watz H, Mailänder C, Baier M, Kirsten A. Effects of indacaterol/glycopyrronium (QVA149) on lung hyperinflation and physical activity in patients with moderate to severe COPD: a randomised, placebo-controlled, crossover study (The MOVE Study). BMC pulmonary medicine. 2016 Dec;16(1):1-0.
7. Clayton TC, Thompson M, Meade TW. Recent respiratory infection and risk of cardiovascular disease: case-control study through a general practice database. European heart journal. 2008 Jan 1;29(1):96-103.
8. Sullivan P, Stephens D, Ansari T, Costello J, Jeffery P. Variation in the measurements of basement membrane thickness and inflammatory cell number in bronchial biopsies. European Respiratory Journal. 1998 Oct 1;12(4):811-5.
9. McAllister DA, Maclay JD, Mills NL, Leitch A, Reid P, Carruthers R, O'Connor J, McAlpine L, Chalmers G, Newby DE, Clark E. Diagnosis of myocardial infarction following hospitalisation for exacerbation of COPD. European Respiratory Journal. 2012 May 1;39(5):1097-103.
10. Chang CL, Robinson SC, Mills GD, Sullivan GD, Karalus NC, McLachlan JD, Hancox RJ. Biochemical markers of cardiac dysfunction predict mortality in acute exacerbations of COPD. Thorax. 2011 Sep 1;66(9):764-8.
11. Bateman ED, Ferguson GT, Barnes N, Gallagher N, Green Y, Henley M, Banerji D. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. European Respiratory Journal. 2013 Dec 1;42(6):1484-94.
12. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. In. 2018.
13. A. Laizo. [Chronic obstructive pulmonary disease - a review]. Rev Port Pneumol., 15 (2009), pp. 1157-1166 . Medline
14. Antonio C, Gonçalves AP, Tavares A. Pulmonary obstructive chronic disease and physical exercise. Revista portuguesa de pneumologia. 2010 Jul 1;16(4):649-58.
15. Pereira ÂM, Santa-Clara H, Pereira E, Simões S, Remédios Í, Cardoso J, Brito J, Cabri J, Fernhall B. Impact of combined exercise on chronic obstructive pulmonary patients' state of health. Revista Portuguesa de Pneumologia (English Edition). 2010 Sep 1;16(5):737-57.
16. Farland MZ, Peters CJ, Williams JD, Bielak KM, Heidel RE, Ray SM. β-Blocker use and incidence of chronic obstructive pulmonary disease exacerbations. Annals of Pharmacotherapy. 2013 May;47(5):651-6.
17. Mentz RJ, Wojdyla D, Fiuzat M, Chiswell K, Fonarow GC, O'Connor CM. Association of beta-blocker use and selectivity with outcomes in patients with heart failure and chronic obstructive pulmonary disease (from OPTIMIZE-HF). The American journal of cardiology. 2013 Feb 15;111(4):582-7.
18. Stone IS, Barnes NC, James WY, Midwinter D, Boubertakh R, Follows R, John L, Petersen SE. Lung deflation and cardiovascular structure and function in chronic obstructive pulmonary disease. A randomized controlled trial. American journal of respiratory and critical care medicine. 2016 Apr 1;193(7):717-26.
19. MacNee W. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. Part One. American journal of respiratory and critical care medicine. 1994 Sep;150(3):833-52.
20. Vonk-Noordegraaf A. The shrinking heart in chronic obstructive pulmonary disease. New England Journal of Medicine. 2010 Jan 21;362(3):267-8.
21. Forfia PR, Vaidya A, Wiegers SE. Pulmonary heart disease: The heart-lung interaction and its impact on patient phenotypes. Pulmonary circulation. 2013 Jan;3 (1):5-19.
22. Engström G, Melander O, Hedblad B. Population-based study of lung function and incidence of heart failure hospitalisations. Thorax. 2010 Jul 1;65(7):633-8.
23. Georgiopoulou VV, Kalogeropoulos AP, Psaty BM, Rodondi N, Bauer DC, Butler AB, Koster A, Smith AL, Harris TB, Newman AB, Kritchevsky SB. Lung function and risk for heart failure among older adults: the Health ABC Study. The American journal of medicine. 2011 Apr 1;124(4):334-41.
24. Agarwal SK, Heiss G, Barr RG, Chang PP, Loehr LR, Chambless LE, Shahar E, Kitzman DW, Rosamond WD. Airflow obstruction, lung function, and risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) study. European journal of heart failure. 2012 Apr;14(4):414-22.
25. Cuttica MJ, Colangelo LA, Shah SJ, Lima J, Kishi S, Arynchyn A, Jacobs Jr DR, Thyagarajan B, Liu K, Lloyd-Jones D, Kalhan R. Loss of lung health from young adulthood and cardiac phenotypes in middle age. American journal of respiratory and critical care medicine. 2015 Jul 1;192(1):76-85.
26. Barr RG, Bluemke DA, Ahmed FS, Carr JJ, Enright PL, Hoffman EA, Jiang R, Kawut SM, Kronmal RA, Lima JA, Shahar E. Percent emphysema, airflow obstruction, and impaired left ventricular filling. New England Journal of Medicine. 2010 Jan 21;362(3):217-27.
27. Watz H, Waschki B, Meyer T, Kretschmar G, Kirsten A, Claussen M, Magnussen H. Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation. Chest. 2010 Jul 1;138(1):32-8.
28. Choudhury G, MacNee W. Role of inflammation and oxidative stress in the pathology of ageing in COPD: potential therapeutic interventions. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2017 Jan 2;14(1):122-35.
29. Agustí A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE, Vestbo J, Lomas DA, Calverley PM, Wouters E, Crim C. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. PloS one. 2012 May 18;7(5):e37483.

30. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, Cherniack RM, Rogers RM, Sciurba FC, Coxson HO, Paré PD. The nature of small-airway obstruction in chronic obstructive pulmonary disease. New England Journal of Medicine. 2004 Jun 24;350(26):2645-53.
31. Cosio MG, Saetta M, Agusti A. Immunologic aspects of chronic obstructive pulmonary disease. New England Journal of Medicine. 2009 Jun 4;360(23):2445-54.
32. Lee SH, Goswami S, Grudo A, Song LZ, Bandi V, Goodnight-White S, Green L, Hacken-Bitar J, Huh J, Bakaeen F, Coxson HO. Antielastin autoimmunity in tobacco smoking–induced emphysema. Nature medicine. 2007 May;13(5):567-9.
33. Agusti A, MacNee W, Donaldson K, Cosio M. Hypothesis: does COPD have an autoimmune component?. Thorax. 2003 Oct 1;58(10):832-4.
34. Moghaddam SJ, Clement CG, De la Garza MM, Zou X, Travis EL, Young HW, Evans CM, Tuvim MJ, Dickey BF. Haemophilus influenza e Lysate Induces Aspects of the Chronic Obstructive Pulmonary Disease Phenotype. American journal of respiratory cell and molecular biology. 2008 Jun;38(6):629-38.
35. N.R. Anthonisen. Bacteria and exacerbations of chronic obstructive pulmonary disease. N Engl J Med., 347 (2002), pp. 526-527 .
36. King PT, Lim S, Pick A, Ngui J, Prodanovic Z, Downey W, Choong C, Kelman A, Baranyai E, Francis M, Moshinsky R. Lung T-cell responses to nontypeable Haemophilus influenzae in patients with chronic obstructive pulmonary disease. Journal of allergy and clinical immunology. 2013 May 1;131(5):1314-21.
37. Thomsen M, Ingebrigtsen TS, Marott JL, Dahl M, Lange P, Vestbo J, Nordestgaard BG. Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. Jama. 2013 Jun 12;309(22):2353-61.
38. de Miguel Díez J, Morgan JC, García RJ. The association between COPD and heart failure risk: a review. International journal of chronic obstructive pulmonary disease. 2013;8:305.
39. Ghoorah K, De Soyza A, Kunadian V. Increased cardiovascular risk in patients with chronic obstructive pulmonary disease and the potential mechanisms linking the two conditions: a review. Cardiology in review. 2013 Jul 1;21(4):196-202.
40. Duvoix A, Dickens J, Haq I, Mannino D, Miller B, Tal-Singer R, Lomas DA. Blood fibrinogen as a biomarker of chronic obstructive pulmonary disease. Thorax. 2013 Jul 1;68(7):670-6.
41. Mannino DM, Ford ES, Redd SC. Obstructive and restrictive lung disease and markers of inflammation: data from the Third National Health and Nutrition Examination. The American journal of medicine. 2003 Jun 15;114(9):758-62.
42. Kessler R, Partridge MR, Miravitlles M, Cazzola M, Vogelmeier C, Leynaud D, Ostinelli J. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. European Respiratory Journal. 2011 Feb 1;37(2):264-72.
43. Cazzola M, Rogliani P, Matera MG. Cardiovascular disease in patients with COPD. The Lancet Respiratory Medicine. 2015 Aug 1;3(8):593-5.
44. Puente-Maestu L, Álvarez-Sala LA, de Miguel-Díez J. Beta-blockers in patients with chronic obstructive disease and coexistent cardiac illnesses. COPD Research and Practice. 2015 Dec;1(1):1-0.
45. Brekke PH, Omland T, Holmedal SH, Smith P, Søyseth V. Determinants of cardiac troponin T elevation in COPD exacerbation–a cross-sectional study. BMC Pulmonary Medicine. 2009 Dec;9(1):1-8.
46. Brekke PH, Omland T, Holmedal SH, Smith P, Søyseth V. Troponin T elevation and long-term mortality after chronic obstructive pulmonary disease exacerbation. European Respiratory Journal. 2008 Mar 1;31(3):563-70.
47. Baillard C, Boussarsar M, Fosse JP, Girou E, Le Toumelin P, Cracco C, Jaber S, Cohen Y, Brochard L. Cardiac troponin I in patients with severe exacerbation of chronic obstructive pulmonary disease. Intensive care medicine. 2003 Apr;29 (4):584-9.
48. Brodde OE. β1-and β2-Adrenoceptor polymorphisms and cardiovascular diseases. Fundamental & clinical pharmacology. 2008 Apr;22(2):107-25.
49. Washko GR. The role and potential of imaging in COPD. Medical Clinics. 2012 Jul 1;96(4):729-43.
50. Campo G, Pavasini R, Biscaglia S, Contoli M, Ceconi C. Overview of the pharmacological challenges facing physicians in the management of patients with concomitant cardiovascular disease and chronic obstructive pulmonary disease. European Heart Journal-Cardiovascular Pharmacotherapy. 2015 Jul 1;1(3):205-11.
51. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, Conway WA, Enright PL, Kanner RE, O'hara P, Owens GR. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1: the Lung Health Study. Jama. 1994 Nov 16;272(19):1497-505.
52. Mapel DW, Dedrick D, Davis K. Trends and cardiovascular co-morbidities of COPD patients in the Veterans Administration Medical System, 1991–1999. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2005 Jan 1;2(1):35-41.
53. Cazzola M, Calzetta L, Bettoncelli G, Cricelli C, Romeo F, Matera MG, Rogliani P. Cardiovascular disease in asthma and COPD: a population-based retrospective cross-sectional study. Respiratory medicine. 2012 Feb 1;106(2):249-56.
54. e Silva PG, Califf RM, Sun JL, McMurray JJ, Holman R, Haffner S, Thomas L, Lopes RD. Chronic obstructive pulmonary disease and cardiovascular risk: Insights from the NAVIGATOR trial. International journal of cardiology. 2014 Oct 20;176(3):1126-8.
55. Corlateanu A, Covantev S, Mathioudakis AG, Botnaru V, Siafakas N. Prevalence and burden of comorbidities in chronic obstructive pulmonary disease. Respiratory investigation. 2016 Nov 1;54(6):387-96.
56. Agarwal S, Rokadia H, Senn T, Menon V. Burden of cardiovascular disease in chronic obstructive pulmonary disease. American journal of preventive medicine. 2014 Aug 1;47(2):105-14.