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A COMPARATIVE STUDY OF PRE AND POST TREATMENT ECHOCARDIOGRAPIC FINDINGS IN ACUTE EXCERBATION OF COPD PATIENTS

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Tahir Ashraf Kar	Post Graduate, Department of Internal and Pulmonary Medicine, SKIMS Soura
Syed Mudasir Qadri	Associate Professor, Department of Internal and Pulmonary Medicine, SKIMS Soura
Umar Hafiz Khan	Associate Professor, Department of Geriatric Medicine, SKIMS Soura
Imran Hafeez	Associate Professor, Department of Cardiology, SKIMS Soura
Anjum Afshan	Research Scholar, Centre of Research for Development, University of Kashmir
Aamir shafi*	Research Scholar, Centre of Research for Development, University of Kashmir*Corresponding Author

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Abstract

COPD is currently the 4th leading cause of death in the world and is projected to increase in coming years and presents as serious global health problem all over the world. It is a preventable and treatable disease characterised by progressive airflow limitation. It has significant extra pulmonary effects amongst which cardiovascular involvement is most important. Pulmonary artery hypertension is common in COPD. This study was conducted to assess the changes in echocardiographic parameters in pre and post exacerbation of COPD. A total of 118 patients presenting as AECOPD were included in the study. A detailed clinical and laboratory evaluation was done along with echocardiography. These patients were followed up after 6 weeks for repeat echocardiography to assess the changes in echocardiographic parameters. Mean age of patients was 68±11.12 years, most of which belonged to rural areas. Majority of our patients belonged to GOLD 3 (52.5%) and GOLD 2 (31.4%) and group C (44.9%) and group D (52.5%) categories. During AE, 20.7% patients had mild PAH, 45.9% had moderate PAH and 33.3% had severe PAH and on follow up 64% of patients had mild PAH, 31.55% had moderate PAH and only 4.5% had severe PAH with an overall notable reduction in mean RVSP on follow up ($p<0.05$), signifying increase in PAH during AECOPD. We also found a direct correlation between severity of PAH and pCO2. As per our results, we found mean pCO2 of 46.2 in mild PAH category, 47.4 in moderate PAH category and 51.3 in severe PAH category during acute exacerbation with an overall p value of 0.004. 85 patients (72%) in our study also had evidence of right ventricular failure during acute exacerbation. Cor pulmonale (evidence of RV dysfunction) was found in 72% (n=85) of our patients. The study showed that COPD exacerbations have a negative impact on RV function and pulmonary artery pressures.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. It is currently the fourth leading cause of death in the world1 but is projected to be the 3rd leading cause of death by 2020.COPD is defined as a disease state characterized by airflow limitation that is not fully reversible. COPD is a powerful and independent risk factor for cardiovascular morbidity and mortality which includes right ventricular (RV) dysfunction and cor pulmonale secondary to pulmonary arterial hypertension (PAH), left ventricular dysfunction. The presence of pulmonary hypertension (PH) and Cor pulmonale increases mortality and predicts hospital readmission for exacerbations in patients with COPD[2].

Pulmonary manifestations of COPD might be one aspect of expression of a systemic inflammation with several other organic manifestations. Cardiovascular disease accounts for approximately 50% of all hospitalization and nearly one third of all deaths, usually when forced expiratory volume in one second (FEV 1) <50% of predicted3. Pulmonary arterial hypertension develops late in the course of COPD with the development of hyperaemia (PaO2 <60 mmHg) and hypercapnia. It is the major cardiovascular complication of COPD and is associated with the development of Right ventricular hypertrophy/dilatation (cor pulmonale) and with time to right heart failure and is associated with poor prognosis. 2 D echocardiography can be used to assess right ventricular dimensions, wall thickness and right ventricular volume overload in patients with COPD and also the presence of pulmonary artery hypertension[4,5].

COPD exacerbation is defined as an acute worsening of respiratory symptoms that results in additional therapy[6,7]. These exacerbations are key drivers of morbidity and mortality. Pulmonary hypertension that is frequently seen in COPD patients, may drastically increase during exacerbation that may result in right ventricular (RV) dysfunction and systemic congestion by increasing RV afterload. These exacerbations impair RV function even when there is no clinical evidence of LV dysfunction.

Echocardiography provides a rapid, non-invasive portable and relatively accurate method to evaluate the right ventricle function, right ventricular filling pressure, tricuspid regurgitation, left ventricular function and valvular function. The present study was aimed at ascertaining changes in pulmonary artery hypertension before and after treatment of acute exacerbation of COPD.

MATERIALS AND METHODS

This study was conducted in the department of internal and pulmonary medicine over a period of two years from Sep 2018 to Sep 2020. All the patients of COPD admitted with Symptoms and/or Signs suggestive of acute exacerbation were selected as subjects. Total 118 patients were initially enrolled in the study, out of which 7 patients expired and remaining 111 patients were followed up after 6 weeks with repeat echocardiography.

INCLUSION CRITERIA

- Patients aged more than 40 years, males as well as females
- Patients who are diagnosed as cases of COPD
- Patients who present with symptoms and/or signs suggestive of

acute exacerbation

EXCLUSION CRITERIA

- Patients aged less than 40 years
- Patients with congenital heart diseases and history of coronary artery diseases
- Patients with pulmonary pathologies like tuberculosis, bronchiectasis, interstitial lung diseases, pneumoconiosis
- Patients with psychiatric illness

Before commencement of the study, ethical clearance was sought from IEC and Informed consent was taken from the participants before collection of data on preformed proforma. Patients were categorised on the basis of severity of exacerbation into mild, moderate or severe. Cardiac evaluation was done during hospitalisation by cardiologist with echocardiography to assess parameters; valvular anatomy and function, right and left chamber size, ejection fraction, cardiac function and pulmonary artery pressure and other related parameters. Right ventricular systolic pressure was estimated based on the modified Bernoulli equation and was considered to be equal to the systolic pulmonary artery pressure (sPAP) in the absence of right ventricular outflow obstruction: sPAP (mmHg) = right ventricular systolic pressure (RVSP) = trans-tricuspid pressure gradient (TTPG) + right atrial pressure (RAP), where trans-tricuspid gradient is 4V2 (V = peak velocity of tricuspid regurgitation, m/s) 8,9,10. RAP was estimated to be 5, 10, or 15 mmHg based on the variation in the size of inferior vena cava with inspiration, complete collapse: RAP = 5 mmHg; partial collapse: RAP = 10 mmHg; and no collapse: RAP = 15 mmHg11. Parameters were defined as:

- Pulmonary artery hypertension (PAH) was defined as Resting PAP ≥ 30 mmHg and was further classified into mild, moderate and severe category as resting PAP 30-50, 50-70, >70 mmHg, respectively [12,13].
- RVH or cor pulmonale was defined if right ventricular free wall thickness exceeded 0.4 cm.
- RV failure : Tricuspid regurgitation and dilatation of IVC and hepatic veins
- E/A = Diastolic filling of left ventricles usually classified on the basis of the peak mitral flow velocity of the early rapid filling wave (E) and peak velocity of the late filling wave caused by atrial contraction (A). In normal subjects, LV elastic recoil is vigorous because of normal myocardial relaxation, therefore more filling is completed during early diastolic, so LV diastolic dysfunction (LVDD) is said to be present when E/A is <1.3 (age group 40-49 years), <1.2 (age group 50-59 years), <1.0 (age group 60-69 years), and <0.8 (age group ≥70 years)[14].
- The presence of RV dilation, RVH, or RV failure is taken as evidence of corpulmonale[15].

Patients enrolled in the study were managed according to standard GOLD guidelines. After settling of event of exacerbation, these patients were followed with repeat echocardiography after 6 weeks to reassess any change in cardiac status and pulmonary artery pressure.

Statistical Analysis

The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean ±SD and categorical variables were summarized as frequencies and percentages. Graphically the data was presented by bar and pie diagrams. Pre and post treatment comparison of continuous and categorical variables was done by employing paired t-test and McNemar chi-square test respectively. Chi-square test was applied for assessing correlation between severity of PAH and GOLD staging. A p-value of less than 0.05 was considered statistically significant. All p-values were two tailed.

Results

A total of 118 patients were enrolled in our study over a period of 2 years, of which 111 patients were followed up for repeat echocardiography and 7 patients expired during study. The mean age of our study patients was 68.5±11.12 years (40-92) with male population of 46.6% and female population of 53.4%. Most of the patients in our study population were residents of rural areas (91 patients, 77.1%). Other clinical characteristics of our study population are depicted in figure 1, 2 and 3.

Echocardiographic parameters:

In our study (Table 1), there was a direct correlation between severity of PAH and PCO2. As per our results, we found mean pCO2 of 46.2 in mild PAH category, 47.4 in moderate PAH category and 51.3 in severe PAH category during acute exacerbation with an overall p value of 0.004.

With regard to severity of PAH, out of total 118 patients enrolled initially for echocardiography during acute exacerbation, 24 patients (20.33%) were found to have mild PAH with a mean RVSP of 41.4 mmHg, 54 patients (45.76%) had moderate PAH with mean RVSP of 56 mmHg and rest of 40 patients (33.9%) had severe PAH with mean RVSP of 75.1 mmHg. All COPD patients on reassessment echo after 6 weeks had changes as (Table 2 &5): 24 patients (20.33%) were in mild PAH category initially and on follow up echo these patients were still in mild PAH category but with decrease in mean RVSP (n=23, 19.5%) and 1 patient among this category expired. 53 patients (44.91%) were in moderate PAH category initially and on follow up echo, only 3 patients(2.54%) were in moderate category , 48 patients (40.6%) were in mild PAH category and 2 patients (1.69%) had expired among this group. 41 patients (34.74%) were initially in severe PAH category and on follow up echo, only 5 patients (4.23%) were in severe PAH category, 32 patients (27.1%) were in moderate PAH group and 4 patients (3.38%) had expired among this group. So on follow up, we had total of 71 patients (64%) with mild PAH, 35 patients (31.5%) with moderate PAH and 5 patients (4.5%) with severe PAH with a p value of < 0.001. The mean RVSP of mild PAH category during exacerbation was 41.4 mmHg (SD 3.12) and on follow up mean RVSP of 39.6mmHg (SD 3.37) with a difference of 1.8 and p value of 0.007. In moderate PAH category mean RVSP during exacerbation was 56.5mmHg (SD 4.09) and on follow up with mean RVSP of 42.7mmHg (SD 3.36) and the analysis showed reduction of RVSP by 13.8mmHg with p value of <0.001 along with improvement in quality of life and symptoms. In severe PAH Category mean RVSP during exacerbation was 75.1 mmHg (SD 5.21) and on follow up mean RVSP of 56.8mmHg (SD 6.65) with reduction of RVSP by 18.3mmHg and a p value of <0.001. The overall mean RVSP pre and post exacerbation were 59.6mm Hg (SD 13.15) and 46.7 mmHg (SD 8.57) respectively with an overall reduction of RVSP of 12.9mm Hg and a p value of <0.001 (Table 2).

This initial PAH of patients was correlated with severity of airflow limitation in terms of GOLD staging. Among these patients, in mild PAH category, 12 patients (50%) were of GOLD 2, in moderate PAH Category 33 patients (61.1%) were of GOLD 3 and in severe PAH Category 22 patients (55%) were of GOLD 4 with a p value of <0.001(statistically significant) and Chi square of 42.743, signifies the strong correlation between severity of airflow limitation and severity of PAH (Table 4).

We also documented left ventricular diastolic dysfunction (LVDD) in our study subjects (Table 6). In moderate PAH category, 12 patients (10.8%) were found to have LVDD, in severe PAH category, 21 patients (18.9%) had LVDD during exacerbation. On follow up only 3 patients (2.7%) had LVDD in moderate PAH category with a p value of 0.012 and in 17 patients (15.3%) in severe PAH category with a p value of 0.352. Overall a total of 33 patients (29.7%) had LVDD during exacerbation and on follow up only 20 patients (18%) had LVDD with a p value of 0.041.

Table 1: Correlation of pCO2 with severity of PAH

PAH STATUS	PCO2		P-value
	MEAN	SD	0.004
MILD PAH	46.2	5.96	

MODERATE PAH	47.4	6.64	
SEVERE PAH	51.3	6.02	

Table 2: Pre and Post Treatment PASP (mmHg)

PAH Status	Pre treatment		Post treatment		Difference	P-value
	Mean	SD	Mean	SD		
Mild PAH	41.4	3.12	39.6	3.37	1.8	0.007*
Moderate PAH	56.5	4.09	42.7	3.36	13.8	<0.001*
Severe PAH	75.1	5.21	56.8	6.65	18.3	<0.001*
Overall	59.6	13.15	46.7	8.57	12.9	<0.001*

Table 3: Pre and Post Treatment Change of Severity Category of PAH

	PRE TREATMENT		POST TREATMENT							
	NO.	%	MILD		MODERATE		SEVERE		EXPIRED/NOT FOLLOWED UP	
			NO.	%	NO.	%	NO.	%	NO.	%
MILD	24	20.33	23	19.5	0	0	0	0	1	0.84
MODERATE	53	44.91	48	40.6	3	2.54	0	0	2	1.69
SEVERE	41	34.74	0	0	32	27.1	5	4.23	4	3.38
TOTAL	118	100	71	60.1	35	29.66	5	4.23	7	5.93
		118(100%) = (111/94% Followed UP + 7/6% Expired/ Not followed UP)								

Table 4: Correlation between Severity of PAH and GOLD Staging

GOLD Staging	Mild PAH		Moderate PAH		Severe PAH	
	No.	%age	No.	%age	No.	%age
GOLD 1	3	12.5	3	5.6	0	0.0
GOLD 2	12	50.0	14	25.9	7	17.5
GOLD 3	7	29.2	33	61.1	11	27.5
GOLD 4	2	8.3	4	7.4	22	55.0
Total	24	100	54	100	40	100
Chi-square=42.743; P-value<0.001 (Statistically Significant)						

Table 5: Pre and Post Treatment Severity of PAH

Severity of PAH	Pre treatment		Post treatment		P-value
	No.	%age	No.	%age	
Mild	23	20.7	71	64.0	<0.001*
Moderate	51	45.9	35	31.5	
Severe	37	33.3	5	4.5	
Total	111	100	111	100	

Table 6: Pre and Post Treatment LVDD

Severity of PAH	Pre treatment		Post treatment		P-value
	No.	%age	No.	%age	
Mild	0	0.0	0	0.0	-
Moderate	12	10.8	3	2.7	0.012*
Severe	21	18.9	17	15.3	0.352
Overall	33	29.7	20	18.0	0.041*

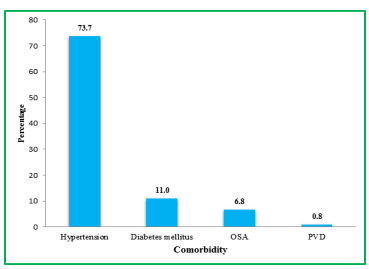

Figure 1: Comorbidities of study patients.

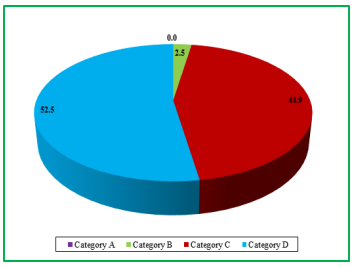

Figure 2: Distribution as Per Risk of Exacerbation

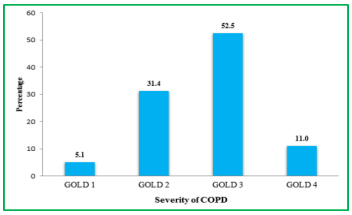

Figure 3: Severity of COPD (Gold Stages)

Discussion

COPD is a multicomponent disease characterized by an inflammatory response of the lungs to noxious particles, and extra pulmonary effects, including cardiovascular system abnormalities that contribute to disease severity[16-19]. The spectrum of cardiovascular disease includes right ventricular (RV) dysfunction, pulmonary hypertension (PH), coronary artery disease (CAD), and arrhythmias[20]. Pulmonary vascular disease associated with COPD increases morbidity and worsens survival [2,21,22-26]. Hypoxia plays a role in the pathogenesis of PH in COPD by inducing vascular remodelling. Hypoxic vasoconstriction may become increasingly significant during exercise, exacerbation due to decreased mixed venous partial pressure of oxygen. Hypoxic pulmonary vasoconstriction reduces blood flow in small pulmonary arteries, arterioles, capillaries, and venules. In addition, acute hypoxia causes increase in pulmonary vascular resistance reaching a peak in 2 hours. After a period of several hours of hypoxia, the response to acute hypoxia is enhanced, and there is further increase in PVR[27].

Our study clearly documents increased pulmonary pressures during exacerbation and improvement in the same on follow up and highlights the negative impact of acute COPD exacerbations on RV function and pulmonary hypertension which in turn has a negative impact on the symptoms, functional capacity, prognosis, morbidity, and mortality rates of COPD patients. There are only few studies on comparison of echocardiographic finding during and after exacerbation of COPD. Our results are in consistent with another study conducted by Muthukumaran et al in 2016[28], wherein they found similar rates of reduction in mean RVSP of patients during and after COPD exacerbation in all three groups of mild, moderate and severe PAH category patients. Ozben BE et al[29] conducted a study in 2015 on impairment of right ventricular function during acute exacerbation of COPD and reported that during exacerbation periods, COPD patients had significantly increased pulmonary artery systolic pressure measures, which might cause increased RV afterload and impair RV function.. Recently, Akcay et al[30] conducted a similar study and reported that treatment of patients with acute COPD exacerbation according to guidelines improved not only pulmonary function, but also RV function and PAH.

As discussed in our results, we found severity of PAH to be directly correlated with severity of airflow limitation. Muthhukumaran et al[28] conducted a similar study and observed that 51.13% among their mild PAH category were GOLD 3, in moderate PAH category 64.70% were of GOLD 4 and in severe PAH category all of their patients belonged to GOLD 4 stage. Similar studies conducted by Chaouat A et al[31] and Scharf SM et al[32] which also showed severity of pulmonary

hypertension directly proportional to severity of airflow limitation. Acute exacerbation periods may impair RV function in COPD patients, even when there is no clinical evidence of RV dysfunction. RV dysfunction has a negative impact on the symptoms, functional capacity, prognosis, morbidity, and mortality rates of COPD patients. The prevalence of RV failure secondary to COPD is estimated to be 10-30%[32]. There is evidence that RV dysfunction is present in the early stages of the disease, even before systemic venous congestion develops. It is important to identify patients with RV dysfunction, as it further worsens the prognosis of COPD patients who are already suffering from ventilator insufficiency[21,33,34]. We found Cor pulmonale (evidence of RV dysfunction) in 72% of our patients . Burgess et al[21] showed that RV diameter was an independent predictor of survival in COPD patients, and found that the COPD patients had a larger RV during acute exacerbation compared to measures obtained after recovery.

Acute COPD exacerbation is characterized by the release of inflammatory cytokines. This cytokine burden is known to affect cardiac function[35-39]. There is worsening of right ventricular systolic as well diastolic functions and increase in PAH during exacerbations**.** Elevation of systolic pulmonary artery pressure induces a dilatation of the right heart chambers, which shift the interventricular septum and decreases left ventricular filling. The result is a restriction in early LV filling and a prolonged isovolumetric relaxation time[40]**.** Ackay et al[30] found that systolic function of the RV improved and that pulmonary artery pressures decreased after treatment. RV and LV functions during diastole were also improved after the therapy but did not reach the level of the control group. Mahmoud et al[41] studied the assessment of Left Ventricular function in COPD patients. They grouped their study patients into 2 categories, group 1 included patients with AECOPD with evidence of Right Ventricular Failure and another group 2 included patients with AECOPD without evidence of Right Ventricular Failure. In their study, 77% of group 1 patients had LVDD and in group 2, 50% patients had LVDD.

Conclusion

COPD is one of the leading cause of morbidity and mortality worldwide. Cardiovascular diseases is recognised as one of the important predictor of in hospital and long term mortality following AECOPD. COPD exacerbations have a negative impact on RV function and Pulmonary artery pressures. Echocardiography is a simple tool for evaluation of cardiac functions in patients with COPD during acute exacerbation as well on follow up to know their actual PAP and thus help in identifying individuals likely to suffer increased mortality and morbidity warranting close monitoring and intense treatment.

References

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, AlMazroa MA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The lancet. 2012 Dec 15;380 (9859):2095-128.
2. Oswald-Mammosser M, Weitzenblum E, Quoix E, Moser G, Chaouat A, Oswald Charpentier C, Kessler R. Prognostic factors in COPD patients receiving long-term oxygen therapy: importance of pulmonary artery pressure. Chest. 1995 May 1;107(5):1193-8.
3. Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. New England Journal of Medicine. 1995 Jul 27;333(4):214-21.
4. France AJ, Prescott RJ, Biernacki W, Muir AL, MacNee W. Does right ventricular function predict survival in patients with chronic obstructive lung disease?. Thorax. 1988 Aug 1;43(8):621-6.
5. Higenbottam T. Pulmonary hypertension and chronic obstructive pulmonary disease: a case for treatment. Proceedings of the American Thoracic Society. 2005 Apr;2(1):12-9.
6. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. The Lancet. 2007 Sep 1;370(9589):786-96.
7. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 1998 May 1;157(5):1418-22.
8. Currie PJ, Seward JB, Chan KL, Fyfe DA, Hagler DJ, Mair DD, Reeder GS, Nishimura RA, Tajik AJ. Continuous wave Doppler determination of right ventricular pressure: a simultaneous Doppler-catheterization study in 127 patients. Journal of the American College of Cardiology. 1985 Oct 1;6(4):750-6.
9. Chan KL, Currie PJ, Seward JB, Hagler DJ, Mair DD, Tajik AJ. Comparison of three Doppler ultrasound methods in the prediction of pulmonary artery pressure. Journal of the American College of Cardiology. 1987 Mar 1;9(3):549-54.
10. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation. 1984 Oct;70(4):657-62.
11. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. European Respiratory Journal. 2006 Sep 1;28(3):523-32.
12. Rycroft CE, Heyes A, Lanza L, Becker K. Epidemiology of chronic obstructive pulmonary disease: a literature review. International journal of chronic obstructive pulmonary disease. 2012;7:457.
13. Salvi S. COPD : The neglected epidemic. IN: Jindal SK, editor. Textbook of pulmonary and critical care medicine. 1st edition. New Delhi: Jay Pee Publications, 2011; 971-4.
14. Salcedo EE. The right atrium and the right ventricle. Atlas of Echocardiography. 2nd ed. Ch. 14. Philadelphia, PA: W. B. Saunders Company; 1985. p. 281-92.
15. Plibby P, Bonow RO, Zipes DP, Mann DL, editors. Braunwald's Heart Disease. 8th ed. Philadelphia, PA: Saunders; 2008. p. 251
16. Wouters E. Chronic obstructive pulmonary disease 5: Systemic effects of COPD. Thorax. 2002 Dec;57(12):1067.
17. Agusti AG. COPD, a multicomponent disease: implications for management. Respiratory medicine. 2005 Jun 1;99(6):670-82.
18. Oudijk ED, Lammers JJ, Koenderman L. Systemic inflammation in chronic obstructive pulmonary disease. European Respiratory Journal. 2003 Nov 2;22(46 suppl):5s-13s.
19. Agusti AG, Noguera A, Sauleda J, Sala E, Pons J, Busquets X. Systemic effects of chronic obstructive pulmonary disease. European Respiratory Journal. 2003 Feb 1;21(2):347-60.
20. Hunninghake DB. Cardiovascular disease in chronic obstructive pulmonary disease. Proceedings of the American Thoracic Society. 2005 Apr;2(1):44-9.
21. Burgess MI, Mogulkoc N, Bright-Thomas RJ, Bishop P, Egan JJ, Ray SG. Comparison of echocardiographic markers of right ventricular function in determining prognosis in chronic pulmonary disease. Journal of the American Society of Echocardiography. 2002 Jun 1;15(6):633-9.
22. Burrows B, Kettel LJ, Niden AH, Rabinowitz M, Diener CF. Patterns of cardiovascular dysfunction in chronic obstructive lung disease. New England Journal of Medicine. 1972 Apr 27;286(17):912-8.
23. Weitzenblum E, Hirth C, Ducolone A, Mirhom R, Rasaholinjanahary J, Ehrhart M. Prognostic value of pulmonary artery pressure in chronic obstructive pulmonary disease.Thorax. 1981 Oct 1;36(10):752-8.
24. Traver GA, Cline MG, Burrows B. Predictors of mortality in chronic obstructive pulmonary disease: a 15-year follow-up study. American review of respiratory disease. 1979 Jun;119(6):895-902.
25. Incalzi RA, Fuso L, De Rosa M, Di Napoli A, Basso S, Pagliari G, Pistelli R. Electrocardiographic signs of chronic cor pulmonale: a negative prognostic finding in chronic obstructive pulmonary disease. Circulation. 1999 Mar 30;99(12):1600-5.
26. Leuchte HH, Baumgartner RA, Nounou ME, Vogeser M, Neurohr C, Trautnitz M, Behr J. Brain natriuretic peptide is a prognostic parameter in chronic lung disease. American journal of respiratory and critical care medicine. 2006 Apr 1;173(7):744-50.
27. Smith TG, Balanos GM, Croft QP, Talbot NP, Dorrington KL, Ratcliffe PJ, Robbins PA. The increase in pulmonary arterial pressure caused by hypoxia depends on iron status. The Journal of physiology. 2008 Dec 15;586(24):5999-6005.
28. Muthukumaran L, Manu MK, Tom D, Mohapatra AK, Ashok, Kumar YG. A comparitive study of pre and post treatment ecg and echo findings in acute exacerbation of copd patients.European journal. of pharmaceutical and medical research. 2016; 3(1): 190-212.
29. Ozben BE, Eryuksel EM, Tanrikulu AM, Papila NU, Ozyigit TO, Celikel TU, Basaran Y. Acute exacerbation impairs right ventricular function in COPD patients. Hellenic journal of cardiology. 2015;56:324-31.
30. Akcay M, Yeter E, Durmaz T, Keles T, Akar Bayram N, Uyar M, Davutoglu V, Yüksel I, Kurt M, Bozkurt E. Treatment of acute chronic obstructive pulmonary disease exacerbation improves right ventricle function. European Journal of Echocardiography. 2010 Jul 1;11(6):530-6.
31. Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. European Respiratory Journal. 2008 Nov 1;32(5):1371-85.
32. Scharf SM, Iqbal M, Keller C, Criner G, Lee S, Fessler HE. Hemodynamic characterization of patients with severe emphysema. American journal of respiratory and critical care medicine. 2002 Aug 1;166(3):314-22.
33. Sekhar CG, Sammaiah P, Bookya K, Balaji B. Study of cardiovascular complications in chronic obstructive pulmonary disease with reference to ECG and 2D echocardiography findings. Am J Pharm Health Res. 2016;4(1):97-111.
34. Naeije R. Pulmonary hypertension and right heart failure in chronic obstructive pulmonary disease. Proceedings of the American Thoracic Society. 2005 Apr;2(1):20-2.
35. Munger MA, Johnson B, Amber IJ, Callahan KS, Gilbert EM. Circulating concentrations of proinflammatory cytolcines in mild or moderate heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. The American journal of cardiology. 1996 Apr 1;77(9):723-7.
36. Yokoyama T, Vaca L, Rossen RD, Durante W, Hazarika P, Mann DL. Cellular basis for the negative inotropic effects of tumor necrosis factor-alpha in the adult mammalian heart. The Journal of clinical investigation. 1993 Nov 1;92(5):2303-12.
37. Finkel MS, Oddis CV, Jacob TD, Watkins SC, Hattler BG, Simmons RL. Negative inotropic effects of cytokines on the heart mediated by nitric oxide. Science. 1992 Jul 17;257(5068):387-9.
38. Finkel MS, Hoffman RA, Shen L, Oddis CV, Simmons RL, Hattlen BG. Interleukin-6 (IL-6) as a mediator of stunned myocardium. Am J Cardiol 1993;71:1231–2.
39. Gulick TS, Chung MK, Pieper SJ, Lange LC, Schreiner CF. Interleukin I and tumor necrosis factor inhibit cardiac myocyte contractility detects immune factor-mediated inhibition of b-adrenergic responses. Circulation 1991;84: 313–21.
40. Louie EK, Rich S, Levitsky S, Brundage BH. Doppler echocardiographic demonstration of the differential effects of right ventricular pressure and volume overload on left ventricular geometry and filling. Journal of the American College of Cardiology. 1992 Jan 1;19(1):84-90.
41. Mahmoud M, Shalan IM, Kawtshy H, Azeem HA. Assessment of left ventricular function in chronic obstructive pulmonary disease echocardiographic study. Al-Azhar Assiut Medical Journal. 2015 Apr;13(2).