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# CORRELATION OF CRP AND AIRFLOW OBSTRUCTION IN PREDICTING CARDIAC DYSFUNCTION WITH UTILIZATION OF ECHOCARDIOGRAPHY IN COPD: PROSPECTIVE OBSERVATIONAL STUDY IN TERTIARY CARE SETTING IN INDIA

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**ABSTRACT**

**BACKGROUND-** COPD will become 3rd leading cause of mortality and 5th leading cause of DALY (disability adjusted life years) worldwide by 2020. Cardiovascular alterations are among the most frequently observed and constitute majority of this morbidity and mortality.

**METHODS-** This is prospective observational study conducted during November 2012 to February 2014, had 50 patients of COPD from the outpatient and indoor of Pulmonary Medicine and Internal Medicine, MIMSR Medical college, Latur India. These patients belonging in majority to moderate (II) and severe (III) GOLD (Global Initiative on obstructive Lung Disease) stages were analyzed by blood profile, BMI, Resting oxygen saturation, CX Ray, Spirometry, ECG and Echocardiography. Main objective was to observe cardiovascular effects in these COPD patients. The statistical analysis was done using Chi Square and Students't' test.

**RESULTS:-** Maximum patients had Emphysema predominant on CX ray, BMI was low, CRP was raised and were hypoxic, belonged to MMRC grade II and III with low Hemoglobin and Hematocrit. The chief cardiovascular alterations were LVDD (56%), Pulmonary hypertension (48%), Right Ventricular enlargement (46%) and Right atrial enlargement (32%) while LVSD (18%), LA enlargement (10%), LVH (10%) and Cor pulmonale (18%).These changes were significantly associated with the stage of COPD and increasing MMRC grades of dyspnea.

**CONCLUSIONS:-** CRP has definite correlation with airflow obstruction which will be easily assessed by simple spirometry test. Both the parameters will help in predicting cardiac dysfunction by applying electrocardiography and echocardiography, and have positive correlation with it

**KEYWORDS :** Left heart dysfunction, right heart dysfunction, COPD, Pulmonary hypertension

## INTRODUCTION:

COPD is a leading cause of morbidity and mortality worldwide, much of it comes from its cardiovascular alterations which may be its systemic effects or comorbidity. The systemic inflammation in COPD as measured by CRP<1, 1-3, >3mg/litre is associated with lower, moderate and higher ***cardiovascular*** risks respectively.[1] For every 10% decrease in FEV1 all cause related mortality increases by 14%, cardiovascular mortality by 28% and non fatal coronary events by 20%,[2] 20% COPD patients have overt or impending CHF.

Patients with COPD are 2-3 times more at risk of Cardiovascular mortality which accounts for about 50% of total deaths in these patients. [3,4] Established spectrum of cardiovascular disease includes right ventricular dysfunction, pulmonary hypertension, coronary artery disease and arrhythmias[5], besides left ventricular dysfunction also seems to be common but under-recognised. The goal of this study was to identify the left ventricular dysfunctions apart from the right side derangements.

It has been hypothesized that pulmonary venous hypertension and LVDD can occur independently of the right sided effects due to hypoxia, extravascular fluid overload, dynamic hyperinflation in lungs and ventricular interdependence mainly via IVS of the patients of COPD.[6] There are a number of causes of impaired LV filling in patients with COPD and other obstructive airways diseases. Patients with airflow obstruction may generate large negative inspiratory swings in intrathoracic pressure, especially during exercise. Such swings increase venous return during inspiration, further dilating the RV and leading to greater diastolic interdependence. In addition, patients with COPD often demonstrate pulmonary hyperinflation. By direct mechanical heart–lung interactions, an increased volume of the lower lobes of the lung can hinder LV filling. Finally, hypoxemia itself can impair LV relaxation. In addition, there are factors contributing to possible LV systolic dysfunction. Large decreases in intrathoracic pressure, especially if sustained, can impair LV ejection (i.e., increase LV afterload). If intrathoracic pressure decreases more than aortic pressure during inspiration, then LV systolic transmural pressure, one measure of LV wall stress or afterload, may increase. Finally, many patients with COPD have concomitant coronary artery, valvular, or hypertensive heart disease. These conditions certainly affect LV function and contribute to further deterioration of RV function through the mechanism of backward series interaction.[7]

The essential feature of left ventricular dysfunction is an increase in left atrial pressure and pulmonary venous congestion leading to a fluid flux across the pulmonary microvasculature. Small acute increase (<10mmHg: as may occur in AECOD) in left atrial pressure enhance the extravascular fluid volume in the airways and activate the rapidly adapting receptors (RAR). With larger increases in the left atrial pressure (-25mmHg) both the RAR and C-fiber receptors in the airways and the alveoli are activated. Activation of RAR causes a reflex increase in respiratory rate, tracheal tone and mucus secretion from the airways, and reflex diuresis mediated by activation of neuronal nitric oxide synthase in the renal medulla (Krishnan Ravi et al[8], Funk G C et al[9]).

Shrinking heart (Lt. Ventricle) occurs due to gross emphysema Anton Von et al [10]. Impaired left ventricular filling reduced stroke volume, and lower cardiac output without changes in Ejection fraction correlated with percent emphysema and airflow obstruction, a 10% points increase in emphysema was associated with a 4.1ml decrement in left ventricular end diastolic volume, a 2.7ml decrement in stroke volume and a decrement of 0.19 litre/min in cardiac output, which was less associated with FEV1, Barr Graham.[11]

## MATERIALS AND METHODS:

This is prospective observational study conducted during November 2012 to February 2014, had 50 patients of COPD from the outpatient and indoor of Pulmonary Medicine and Internal Medicine, MIMSR Medical college, Latur India. Patients of all ages, either from the outdoor or the indoor of our hospital who presented with signs, symptoms and history suggestive of COPD and willing to participate in the study were enrolled after proper counseling. The protocol was explained to the patient/care provider before enrolment and informed consent was taken.

### Criteria of inclusion of cases under study

1. Pt. having chronic cough (any pattern) with or without sputum for more than 3 months each year for last two years
2. Progressive, persistent dyspnoea over time which increases with exercise
3. History of risk factors like smoke, biofuel, occupational etc
4. Chest x ray showing marks of either hyperinflation or chronic bronchitis or both.
5. COPD diagnosed and staged according to GOLD by spirometry.

### Criteria of exclusion of cases under study

1. Systemic hypertension or other previously known/diagnosed primary cardiac disease.
2. Chronic lung disease other than COPD. Other Systemic diseases

which may have pulmonary and cardiac manifestations (CVD, portal hypertension, HIV, drugs, toxins, Veno occlusive disease etc).

3. Acute Exacerbation of COPD cases were excluded from study.

After a detailed clinical history and thorough physical examination, the patient underwent a battery of tests, comprising; CBC, Liver and kidney function tests, Serum uric acid, Lipid profile, Serum Ca+2, C-reactive protein, Blood sugar, Skiagram chest both P.A and Rt. Lateral view, Electocardiography, Echocardiography, Sputum smear for AFB, Serum total proteins, albumin and globulin, Resting Spo2 and Spirometry. As alpha 1 antitrypsin level in serum detection facility was not available in our setting, no patient were subjected to this testing to rule out familial cause of COPD.

**Statistical Analysis**

Statistical analysis was done mainly by Chi square test when comparing many variables whilst student't' test was used to compare two variables. P value was considered significant if it was below 0.05 and highly significant in case <0.001.

## RESULTS

The study done in 2010-2011 had 50 COPD patients, of whom most were 51- 65 year old males. Average smoking history was 40 pack years and mostly presented in grade II or III of MMRC dyspnea scale. Average BMI was in the range of 19-20 (44% being underweight; BMI <18) and the most common presenting features were SOB and cough (100%) with or without sputum production along with Rhonchii (58%) and crepitations on chest exam . Pedal edema (38%) was the most common general sign representing the Cardiac involvement or anemia and hypoproteinemia. Orthopnea (12%) was the chief left sided cardiac sign and Engorged neck veins (22%) and Hepatomegaly (16%) were the most common right sided cardiac sign.

On chest x ray PA and lateral views, Hyperinflated lung fields (84%) was the most common finding followed by Increased BV markings (68%), many patients had mixed findings. Cardiomegaly (18%) and LVH (6%) were also evident on X ray besides increased retrosternal air column (36%).

The CRP levels were increased in 56% of patients representing the systemic inflammation.

Most patients were in GOLD stages II (32%) and III (38%) besides I (16%) and IV (14%).

**Table 1: Patient distribution according to CRP (C-reactive protein); A marker of systemic inflammation**

| CRP (µgm/ml) | No. of Cases | Percentage |
|---|---|---|
| <6 | 22 | 44% |
| >6 | 28 | 56% |
| **Total** | 50 | 100% |

Increased CRP titres are seen in systemic inflammatory states like COPD more so with increased degree of inflammation. (table 1)

**Table 2 Correlations of CRP with patient variables**

| CRP Titre | Resting SPO2% | BMI | MMRC grade |
|---|---|---|---|
| < 6 ug/ml (n=22) | 91.09±3.14 | 22.04±2.72 | I-3,II-9,III-7,IV-3,V-0 |
| >6 µg/ml (n=28) | 88.42±3.14 | 18.2±2.46 | I-1,II-8,III-11,IV-5,V-3 |
| Total | 89.60±3.41 | 19.89±3.21 | I-4,II-17,III-18,IV-8,V-3 |

With inflammatory titres of CRP (>6µg/ml) the patient's SPO2 and BMI tend to fall and the MMRC grade of dyspnea increases. (table 2)

On applying student t test
CRP/sPO2- P value <0.001 -Highly significant
CRP/BMI – P value <0.001 – Highly significant
CRP/ MMRC grade of dyspnea – P value <0.05 significant. (table 2)
Systemic inflammation as assessed by the CRP titres incapacitates the patient gradually. (Table 2)

**Table 3: Correlation of CRP with patients GOLD stage and smoking pack years taken in this study**

| CRP titre | Spirometry grade | Smoking pack years |
|---|---|---|
| < 6µg/ml (n=22) | I-7,II-6,III-7,IV-2 | I-1,II-7,III-10 IV-2,V-2, VI-0 |
| >6ug/ml (n=28) | I-1,II-10,III-12,IV-5 | I-2,II-5,III-5 IV-6,V-7,VI-1 |

CRP titres tend to increase with increasing spirometric grade of COPD and smoking pack years. (table 3)
On applying Chi Square test
CRP/Smoking pack years; X2 =9.6, P value <0.05= significant
CRP/GOLD stage; X2 =7.48, P value <0.05 = significant

Systemic inflammation as assessed by the CRP titres increases significantly with the Stage of COPD and Patients with increased titres of CRP have a more pack year history. (table 3)

**Table 4: Correlation of CRP titres with Right sided cardiac findings in ECHO**

| CRP titre | PH mild | PH moderate | PH severe | PHT | RAE | RVE | CP |
|---|---|---|---|---|---|---|---|
| <6 (n=22) | 5 (22.3%) | 3 (13.6%) | - | 8 (36.4) | 2 (9%) | 5 (22.7%) | 2 (9%) |
| >6 (n=28) | 6 (21.4%) | 8 (28.6%) | 2 (7%) | 16 (57%) | 14 (50%) | 18 (64.3%) | 7 (25%) |

All right sided derangements of cardiac function tend to increase significantly with raised titres of CRP. Strongest association is with Right atrial enlargement (RAE) followed by increased frequencies of RVE and Cor pulmonale at par. Pulmonary hypertension was normal in many patients with raised CRP; ie intermittent rises of PHTN (like in sleep or exercise) did not reflect in this observation but CRP was raised. Yet frequency of Severe and Moderate PH increases with the raised titres of CRP. (table 4)

**Table 5: Correlation of CRP titres with Left sided cardiac findings in ECHO**

| CRP titre | LVDD | LVSD | LVH | LVEF | LVmass | LA dim | E/A ratio |
|---|---|---|---|---|---|---|---|
| <6 N=22 | 12 | 4 | 2 | 56.81± 9.37 | 111.3± 26.7 | 32.13± 6.5 | 0.81± 0.20 |
| >6 N=28 | 15 | 4 | 4 | 56.17± 9.77 | 106.2± 20.3 | 30.95± 6.9 | 0.83± 0.29 |

The left sided cardiac effects occur without significant association of CRP titres ie some other factors like static/dynamic hyperinflation in the pathogenesis of left sided effects play a more important role. (table 5)

Normal patients in <6ug/ml CRP cohort = 8
Normal patients in >6ug/ml CRP cohort =2
This implies more cardiac involvement is seen in Cohort of CRP >6ug/ml then <6ug/ml cohort. But no significant association occurred in particular with any individual parameter (table 5)

## DISCUSSION:

Raised CRP titres have been observed in patients with more severe disease and the BMI is below normal, representing systemic inflammation and cachexia. The raised CRP level is associated significantly with lower SPO2, low BMI and increasing MMRC grade of dyspnea. Increased CRP is also seen with increased pack years of smoking and all the right sided cardiac dysfunctions including Pulmonary hypertension. No correlation was established in raised CRP and Left sided cardiac function. Similar findings were documented by various previous studies (Funk G C , N K Gupta, Boussuges , Malerba and various other workers ) [9,12,13,14,15,16,17]

LVDD in COPD without Right sided heart involvement (Funk G C , N K Gupta, Boussuges , Malerba and various other workers ) [9,12,13,14,15,16,17.]

LVDD in COPD and other pulmonary diseases may be caused by-

1. Long term hypoxia leading to recurrent episodes of subclinical myocardial ischemia
2. IVS bowing/shifting
3. Nocturnal increases in Blood pressure and Sympathetic nervous system activity
4. Futile inspiratory efforts ( Elevated Negative intrathoracic pressures leading to increase in LV transmural pressure and enhanced Left ventricular afterload which affects.
5. LV filling; it can be reversed by positive pressure ventilation and LTOT
6. In patients with DM, hypertension and aortic stenosis.
7. In OSA and obesity hypoventilation syndromes.
8. Intrinsic mechanisms in LV myocardium.
9. Undefined mechanisms.
10. Increased sPAP in case of right heart involvement [12,13]

Reason 5and 6 were ruled out in this study Reason 1,3 ,4 and 9 most pertinent to the cohort in this study.

LVDD characterized by increased Isovolumiec Relaxation Time (IVRT) and decrease compliance and filling pressures in the left atrium, Grade I by increase in IVRT only and Grade II and Grade III with alteration in the compliance and filling pressures of the left atria. The findings are in accordance with various studies which mention the occurrence of subclinical LVDD in COPD even in Mild disease [9,15,16,and17.]

LVEF decreased with the severity of disease, but generally was maintained within normal limits leading to Heart failure with normal Ejection Fraction (HFNEF) which is an early finding prior to overt LVSD and overt Heart failure. The occurrence of LVSD was 18% (reported range is 10-46% in various studies).[18]

Factors favouring diagnosis of left ventricular diastolic dysfunction in the presence of pulmonary hypertension as assessed by Doppler echocardiography.[19]

**1. Clinical features-** Age >65, Elevated systolic BP, Elevated pulse pressure, Obesity, metabolic syndrome, Hypertension, Coronary artery disease, Diabetes mellitus, Atrial fibrillation

**2. Echocardiography-** Left atrial enlargement, concentric remodelling of the LV (relative wall thickness .0.45), LV hypertrophy, Presence of echocardiographic indicators of elevated LV filling pressure

**Interim evaluation (after echocardiography)**
Symptomatic response to diuretics, Exaggerated increase in systolic blood pressure with exercise, Re-evaluation of chest radiograph consistent with heart failure.(ESC task force Task Force for Diagnosis and Treatment of , Acute and Chronic Heart Failure 2008 of European Society of Cardiology.[19]

**Pathogenetic Mechanisms working in COPD [20,21]**
**(**I) Hypoxic pulmonary vasoconstriction
(II) Pulmonary endothelial remodeling
(III) Lung hyperinflation
(IV) Arterial oxygen desaturation during exercise and/or sleep (V) Renal and Hormonal Abnormalities
(VI) Sympathetic activation
(VII) Activation of the renin-angiotensin aldosterone system
(VIII) Increased vasopressin levels

Hypoxic vasoconstriction and hypoxia induced pulmonary vessels remodeling have been considered the main causal factors

**Diagnostic Difficulties [22]**
Recognising HF in the presence of COPD and *vice versa* is made difficult by similarities in symptoms and physical findings in the two conditions. Compounding the difficulties are the several similarities between cor-pulmomale and HF and the possibility of a biventricular failure. Hence, a high index of clinical suspicion is required along with a judicious use of specialized investigations. Coexistent COPD and HF often modifies classical findings in several of the investigations. In recent years, it has been increasingly recognized that LV diastolic dysfunction can also result in signs and symptoms of HF which is difficult to assess on the basis of clinical examination alone.

The well known ECG features of right heart enlargement including a right axis deviation, P-pulmonale, prominent R waves in right sided chest leads and prominent S waves in left-sided chest leads may mask LV changes. On the other hand, left-sided chamber hypertrophy and enlargement may alter or cancel out the above signs of right-sided enlargement. Hence, presence of mixed signs (for example, P-pulmonale with left axis deviation, P-pulmonale with left bundle branch block) or absence of the classical combination of features should arouse a suspicion on coexistent diseases. An ECG, however, provides little information on diastolic failure.

**CONCLUSION:**
CRP has definite correlation with airflow obstruction which will be easily assessed by simple spirometry test. Both the parameters will help in predicting cardiac dysfunction by applying electrocardiography and echocardiography, and have positive correlation with it.

The cardiovascular alterations in COPD are far too common especially LVDD, which remains grossly unmanaged. Diastolic dysfunction should be sought actively in COPD besides the right sided changes and pulmonary hypertension. Both can give rise to clinical worsening and exacerbation in COPD. Most correctable factor is Hypoxia. Treatment of condition is rewarding. So all patients of COPD especially of Moderate and Severe stages should have thorough cardiovascular checkup and Holistic management.

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