Prevalence of cardiovascular diseases in patients hospitalized for acute exacerbation of COPD: prospective observational study

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ABSTRACT

Background: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) has considerable cardiovascular risk. Various cardiovascular diseases are common during exacerbations. Both diseases share several similarities such as older age of the patient, smoking as a common risk factor and symptoms of exertional dyspnea. Knowledge regarding the magnitude of underlying cardiovascular diseases during AECOPD is limited. Authors performed this study to assess the presence of different associated cardiovascular diseases (CVDs) in patients hospitalized for AECOPD and its effect on the outcome.

Methods: It was a prospective observational study involving 436 patients of AECOPD divided to Group 1 (AECOPD with CVD- 137 (31.4%) patients) and Group 2 (AECOPD without CVD 299 (68.6%) patients). All the patients were subjected to full history taking, clinical examination, chest X-ray, spirometry, ECG and echocardiography.

Results: COPD patients in exacerbation with CVD, were significantly more likely to have longer duration of hospital stay (p < 0.0001), high CRP level (p<0.001), more frequent mechanical ventilations (p < 0.001), two or more exacerbations per year (p <0.0001) and the mortality was (p<0.0001). Also, they have GOLD grade III/IV severe (43.5%) and very severe (19.5%) air flow limitation. The high percentage of them had (64.8%) pulmonary hypertension, (37.3%) systemic arterial hypertension, (31.5%) arrhythmia, (27.8%) ischemic heart diseases and (21.3%) heart failure.

Conclusions: The prevalence of cardiovascular diseases (CVD) in patients hospitalized for COPD was high. Age, sex and CVD trends, as well as life style changes, should be considered when prevention and control strategies are formulated.

Keywords: COPD, Cardiovascular diseases, Mechanical ventilation (MV), Pulmonary hypertension (PH)

INTRODUCTION

Long standing chronic obstructive pulmonary disease (COPD) characterized by a progressive decline in lung function associated with airway narrowing due to inflammation, fibrosis and mucus plugging, and parenchymal destruction.1,2 Cardiovascular disorders i.e. coronary artery disease (CAD), congestive cardiac failure (CCF), pulmonary artery hypertension (PAH), systemic hypertension (HTN) and peripheral vascular disease (PVD) are important comorbidities associated with COPD.3 Further, presence of respiratory impairment in COPD itself increases the risk of development of cardiovascular diseases (CVD).4 Acute insults either infectious (viral or bacterial), or environmental in nature in patients with COPD results in the clinical syndrome of...
acute exacerbation of COPD (AECOPD).\(^1\) AECOPD constitutes a major cause of morbidity and mortality in patients with COPD with a 50% mortality at 3.6 years, 75% mortality at 7.7 years, and 96% mortality at 17 years following the index hospitalization for AECOPD.\(^5\) Not infrequently, there is a cardiovascular trigger underlying this clinical presentation and this remains a challenge to identify.\(^6\)

During acute exacerbations, hypoxemia and stress associated with an increased work of breathing may promote sympathetic over-activity that increases myocardial oxygen demand. Further, myocardial ischemia and left ventricular dysfunction which itself can promote wheezing, may complicate or be mistaken for an exacerbation of COPD.\(^3\)

Aim of our study was to assess the presence of various cardiovascular diseases (CVD) in patients hospitalized for AECOPD and its effect on the outcome.

**METHODS**

This prospective observational study was carried out at the internal medicine department at Civil Hospital Ahmedabad. The study duration was from January 2016 and December 2017. The study was approved by ethics committee of our hospital. All patients were informed about the study in detail and informed and written consent was obtained from all the patients. Patients who consented for the study were included in the study. The study included 436 patients of AECOPD admitted to emergency department.

Acute exacerbation in patients with COPD was diagnosed with following criteria.

**Symptoms of acute exacerbation of COPD**\(^8\)

The presence of any one of the following three major symptoms was considered as acute exacerbation:

- increased sputum volume,
- increased sputum purulence, or
- increased dyspnea.

In addition, patients may have had one or more symptoms of fever, sore throat or nasal discharge within past 5 days, increased wheezing, increased cough, increased respiratory rate >20% above baseline and increased heart rate >20% above baseline. Severity of an acute exacerbation of COPD was defined as type 1 when patients had all three symptoms, type 2 when patients had any two out of three symptoms, and type 3 when patients had any one out of three symptoms.

**Lung function tests**

FEV1 <1L indicate a severe exacerbation.\(^8\)

**Arterial blood gases**

\(\text{PaO}_2 <60 \text{ mmHg and/or} \text{ SaO}_2% <90\% \) with or without \(\text{PaCO}_2 >50\text{mmHg} \) on room air at rest indicate respiratory failure with \(pH >7.30\)–7.35 indicating severe exacerbation. In addition, \(\text{PaO}_2 <50 \text{ mmHg}, \text{PaCO}_2 >70\text{mmHg} \) and \(pH <7.30\) point towards a life-threatening episode that needs critical management.\(^8\)

Depending upon the presence and absence of associated CVD, patients were divided in two groups.

- Group 1: AECOPD with CVD: 137 patients (31.4%).
- Group 2: AECOPD without CVD: 299 patients (68.6%).

**Methods**

Following workup was done in all the patients included in the study:

1. Complete medical history including detailed history of smoking habit, occupational exposure, drug intake, duration of illness and history of any other diseases. Note was also made for severity of dyspnea. Severity of dyspnea was graded as per modified medical research council (mMRC) dyspnea scale.
2. Full clinical examination including chest examination.
3. Radiological evaluation with chest X-ray postero-anterior view (CXR). Non-contrast computed tomography (NCCT) including high resolution CT (HRCT) was done in patients who had lesion on CXR.
4. Pulmonary function tests (PFT) was done for the diagnosis of COPD. The diagnosis of COPD was confirmed based upon previous spirometry that was done before admission or was done prospectively when patients were clinically stable for at least 4 weeks. PFT were carried out using portable spirometer “Vitalograph COPD-6™” apparatus. The parameters obtained were Forced expiratory volume in the first second (FEV1) as absolute value and percentage of the predicted value (FEV1%), forced vital capacity (FVC) and FEV1%/FVC ratio. According to GOLD criteria, the subjects with airflow limitation and FEVI predicted >80% were identified as having mild airflow limitation (Class I), FEVI% predicted between 50 % and 80% were described as moderate (Class II), and FEVI% predicted between <50% and 30% were described as having severe airflow obstruction (Class III) while FEVI <30% were considered very severe (Class IV).
5. 12 lead electrocardiogram (ECG).
6. Transthoracic echocardiography (Echo): M-mode, 2-dimensional and Doppler Echo was performed as per standard protocol in all patients with the use of VIVID 7 machine (GE healthcare) equipped with...
multi-frequency transducer probe (range 2–4.3MHz). Parameters recorded were:

- Left ventricular ejection fraction (LVEF%) was calculated using formula: 
  \[ \text{LVEF\%} = \frac{\text{EDV} - \text{ESV}}{\text{EDV}} \times 100 \]

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- LVEF was also calculated by Modified Simpson’s Rule.

- Regional wall motion analysis was performed and graded according to 16 segment model of the American Society of Echocardiography (Normal=1, Hypokinetic=2, Akine\textit{tic}=3, Dyskine\textit{tic}=4, Aneurysm\textit{al}=5). Wall motion score index was obtained by dividing the sum of individual visualized segments score by the number of visualized segments.

- Measurements of right heart chambers were made according to established criteria. Right ventricular systolic pressure (RVSP) and pulmonary artery systolic pressure (sPAP) were determined by continuous wave Doppler echocardiography. Right atrial pressure was estimated according to caval dimensions. RVSP can be estimated from right atrial pressure using the equation 
  \[ \text{RVSP} = 4 \times (\text{VTR})^2 + \text{RAP} \]

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  RAP, where VTR is peak tricuspid velocity (TR) velocity (m/s) and RAP is mean right atrial pressure (mmHg). The mean RAP is estimated using inferior vena cava (IVC) size and reactivity as per American Society of Echocardiography (ASE) recommendations. The echocardiographic assessment was performed during diagnostic tests.9

7. Laboratory investigations: Complete blood count with peripheral smear, renal function test, liver function test, random blood sugar and room air arterial blood gas (ABG) analysis. ABG was analyzed using blood gas analyzer (ABL-330-Radiometer Copenhagen system).

Statistical analysis

All data were presented as mean±SD unless otherwise stated. Comparisons were performed by unpaired t tests for quantitative data. For qualitative data, was used. P value of <0.05 was used to indicate differences between the groups that were statistically significant. Data analysis was performed with a commercially available statistical analysis software package (SPSS 16.0 for Windows; SPSS; Chicago, IL, USA).

RESULTS

Out of 436 patients, there were 137 patients in group 1 (AECOPD with CVD) and 299 patients in group 2 (AECOPD without CVD). Mean age of the patients in group 1 was 58.44±5.1 years and in group 2 was 56.57±5.29 years. Age of patients in group 1 significantly higher than group 2 (p<0.0001) (Table 1). There were 124 (90.5%) smokers in group 1 and 272 (91%) smokers in group 2. Various type of smoking is shown in Table-1. Most common type of smoking in our patients was beedi smoking. However, in females chulha smoke was more common due to cooking habit in rural areas. In group 1, 9.5% patients were non-smoker while in group 2, 9% patients were non-smoker (Table 1).

| General characteristic | Group 1 (COPD with CVD) | Group 2 (COPD without CVD) | p value |
|------------------------|------------------------|---------------------------|---------|
| Age (years)            | 58.44±5.1 (45-75.5)    | 55.7±5.29 (48-72)         | <0.0001 |
| Age group              |                        |                           |         |
| <50 years              | 5 (3.6%)               | 33 (11%)                  | 0.018   |
| 50-59 years            | 82 (59.8%)             | 157 (52.5%)               | 0.184   |
| 60-69 years            | 44 (32.1%)             | 97 (32.5%)                | 0.965   |
| 70-80 years            | 6 (4.3%)               | 12 (4%)                   | 0.935   |
| Sex                    |                        |                           |         |
| Male                   | 101 (73.7%)            | 187 (62.5%)               | 0.029   |
| Female                 | 36 (26.2%)             | 112 (37.4%)               |         |
| Residence              |                        |                           |         |
| Rural                  | 76 (55.4%)             | 187 (62.5%)               | 0.245   |
| Urban                  | 61 (44.5%)             | 112 (37.4%)               |         |
| Smoking                |                        |                           |         |
| Non smoker             | 13 (9.4%)              | 27 (9%)                   | 0.980   |
| Smoker                 | 124 (90.5%)            | 272 (90.9%)               |         |
| Types of smoking       |                        |                           |         |
| Beedi                  | 65 (47.4%)             | 177 (59.1%)               | 0.028   |
| Cigarette              | 17 (12.4%)             | 43 (14.4%)                | 0.685   |
| Hookah                 | 5 (3.6%)               | 8 (2.6%)                  | 0.801   |
| Chulha (Hearth)        | 26 (18.9%)             | 25 (8.3%)                 | 0.002   |
| Combined               | 11 (8%)                | 19 (6.3%)                 | 0.661   |
| Pack/year              | 32.38±16.78            | 23.89±15.72               | <0.0001 |

Table 1: Demographic data of the patients in both groups.

| Characteristics       | Group 1 (COPD with CVD) | Group 2 (COPD without CVD) | p-value |
|-----------------------|------------------------|---------------------------|---------|
| Hospital stay (days)  | 9.12±1.06              | 6.89±1.32                 | <0.0001 |
| ABG                   |                        |                           |         |
| pH                    | 7.31±0.04              | 7.31±0.02                 | 1.000   |
| PO2                   | 58.73±6.71             | 59.87±5.08                | 0.051   |
| PCO2                  | 74.74±15.86            | 73.35±12.92               | 0.333   |
| HCO3                  | 32.89±4.11             | 34.73±3.76                | <0.0001 |
| SaO2                  | 91.44±5.23             | 87.67±3.86                | <0.0001 |
| No. of exacerbation/year |                        |                           |         |
| 1                     | 38 (27.7%)             | 172 (57.5%)               | <0.0001 |
| 2                     | 99 (72.2%)             | 127 (42.4%)               |         |
| Assisted ventilation  |                        |                           |         |
| Not required          | 70 (51.1%)             | 218 (72.9%)               | <0.0001 |
| BiPAP                 | 39 (28.4%)             | 58 (19.3%)                | 0.046   |
| Mechanical            | 28 (20.4%)             | 23 (7.7%)                 | 0.001   |
| CRP (mg/L)            | 7.74±7.36              | 3.32±2.47                 | <0.0001 |
| Mortality             | 16 (11.6%)             | 11 (3.6%)                 | 0.002   |

Table 2: Clinical data of the patients at the time of acute exacerbation of COPD.
Regarding base line clinical data of the patients, group 1 had significantly longer duration of hospital stay (p<0.0001), high CRP level (p<0.001), more frequent need for assisted ventilations either bi-level positive airway pressure (BiPAP) or mechanical ventilation (p<0.05), two or more exacerbations per year (p <0.0001) and the mortality (p<0.01) as shown in (Table 2).

Table 3: Severity of airflow limitations of both groups.

| Severity of airflow limitations | Group 1 (COPD with CVD) (n=137) | Group 2 COPD without CVD (n = 299) | p-value |
|--------------------------------|---------------------------------|----------------------------------|---------|
| GOLD mild                      | 0 (0%)                          | 46 (15.4%)                       | <0.0001 |
| GOLD moderate                  | 52 (38%)                        | 147 (49.2%)                      | 0.038   |
| GOLD severe                    | 75 (55.1%)                      | 91 (30.4%)                       | 0.020   |
| GOLD very severe               | 27 (19.7%)                      | 15 (5.0%)                        | <0.0001 |
| mMRC dyspnea                   |                                 |                                  |         |
| 0                              | 7 (5%)                          | 43 (14.4%)                       | 0.007   |
| 1                              | 21 (15.3%)                      | 75 (25.1%)                       | 0.031   |
| 2                              | 31 (22.6%)                      | 88 (29.4%)                       | 0.172   |
| 3                              | 39 (28.5%)                      | 69 (23.1%)                       | 0.275   |
| 4                              | 39 (28.5%)                      | 24 (8%)                          | <0.0001 |

As shown in Table 3, group 1 patients had significantly higher incidence of GOLD grade III (42.3%) and GOLD grade IV (19.7%) COPD. Also, group 1 patients had significantly higher incidence of mMRC dyspnea scale III (38.5%) and IV (28.5%) (Table 3).

In group 1 patients, most commonly symptom associated CVD was pulmonary hypertension (59.1%) followed by Systemic hypertension (HTN) 43% patients. Other associated CVD were arrhythmia (27%), ischemic heart disease (IHD) (24.1%) and congestive heart failure (CCF) (15.3%).

DISCUSSION

Relationship between respiratory and cardiovascular diseases has received a great attention in recent years. COPD is an independent risk factor for CVD even after adjusting for the remaining factors and increases the risk of prevalence of CVD from RR 1.7 (95% CI, 1.5-1.9) in GOLD grade I to RR 2.4 (95% CI 1.9-3.0) in GOLD grade III/IV.10,11

There might be a common pathophysiology process for both. Researches have stated that systemic inflammation produced by COPD could be the link between COPD and development of CVD as both COPD and arteriosclerosis are considered inflammatory diseases.12 In a study by Maclay et al, they found that compared with healthy controls, patients with COPD had increased circulating platelet–monocyte aggregates, which were further increased during AECOPD.13 These aggregates are a potential pathogenic mechanism of atherosclerosis. Two other studies also tend to throw a light on this issue. Both these studies found increased plasma levels of the cardiac biomarkers NT-proBNP and troponin T in a significant number of patients hospitalized for AECOPD. Both the markers predicted the increased mortality even after adjusting for other predictors such as PaCO2 or CURB65 score.14,15 Together these studies suggest that cardiovascular involvement in AECOPD may be an important determinant of poor prognosis and death.

There is a broad spectrum association of cardiovascular complications and AECOPD. PAH and RV dysfunction are commonly associated with Stable COPD and this association becomes further significant with increasing severity of COPD. Our results showed that the presence of associated CVD not only significantly increased frequency of exacerbation of COPD but also significantly increased the duration of hospital stay and mortality in patients with AECOPD. Our results are in congruence with study by Donaldson et al.16 In their review of the data of 25857 patients with COPD over a period of 2-years, they found 2.3-fold increased risk of myocardial infarction 1–5 days after an AECOPD. Similarly, in a retrospective post-mortem study of patients who died within 24 h of hospitalization for AECOPD, cardiac failure and thromboembolism were found to be the principal causes of death.17

Both COPD and CVD may be part of the aging process as both have higher prevalence with advancing age. The prevalence of COPD is about 6-fold higher in patients >70 years compared with those 40 years old. Similarly, the prevalence of CVD is 17 higher in patients >65 years compared to those between 18 years–44 years.18 In present study, we also found that in COPD patients, patients with associated CVD were significantly older (58.4±5.1 years) compared to patients without CVD (55.5±5.29 years). Present results are also in agreement with Cui et al.19 They also found significantly increased prevalence of various types of CVD in COPD patients with increasing age.

In current study, majority patients with AECOPD with CVDs were male (74%). Similar to present results, Almagro et al, De Torres et al and El-Shabrawy and Eldamanhory also found higher preponderance of CVD in males COPD patients compared to females COPD patients.1,2,21 This may be explained by the difference in prevalence of smoking in males and females and the protective effect of estrogen in females.

Regarding smoking, similar to Lucas-Ramos, we also found smoking to be significantly more in COPD patients with CVD than in patients without CVD.10

Authors also found significantly higher CRP in COPD patients with CVD than patients without CVD. Similar results were obtained by Sin and Man in their National Health and Nutrition Examination Survey study.22 Two other studies have also significant negative co-relation
between FEV1 and CRP. In one study, low FEV1 was associated with higher levels of CRP and a higher frequency of coronary artery calcification.23 In another study, Kim et al. also found an inverse relationship between FEV1 and CRP level.24

In our study, we also found that patients with COPD and CVD suffered two or more exacerbation per year. They had significantly higher need for mechanical ventilation (20.4% versus 7.7%) and longer duration of hospital stay (9.12 ±0.6 days versus 6.89±1.32 days) compared to COPD patients without CVD reported by Garcia et al, El-Shabrawy and Eldamanhory and Wang Y et al.1,25,26 In agreement with Cataluña et al authors also found significantly higher mortality in COPD with CVD group (11.7% versus 3.7%) compared to COPD without CVD group.27 This higher incidence of mortality is because of higher incidence of arrhythmia, AMI, and CHF in CVD patients.

In present study, 31.5% patients had arrhythmia. As in other studies, most common arrhythmia was atrial fibrillation (AF), atrial flutter and non-sustained ventricular tachycardia (NSVT).28,29 Significant proportions of these arrhythmia may be attributed to associated IHD.30

In our study, IHD was present in 27.8% patients and CCF in 21.3% patients. Studies have reported 16.7% -23.9% incidence of CCF.1,19 It is proposed that coexistence of COPD in patients with IHD increases the risk of myocardial infarction. Myocardial infarction may result in left heart failure that in long-term leads to RV dysfunction resulting in CCF.31 In present study, authors found inverse relation between FEV1 and CVDs. Studies have found FEV1 as an independent predictor of cardiovascular mortality in COPD and for every 10% decrease in FEV1 there is increase of about 28% in fatal coronary events and 20% in non-fatal coronary events among subjects with mild to moderate COPD.32,33

CONCLUSION

The prevalence of CVD in patients hospitalized for AECOPD is high. Age, sex and CVD trends, as well as life style changes, should be considered when prevention and control strategies are formulated.

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