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TO EVALUATE THE PROFILE OF EDAC IN STABLE COPD PATIENTS AND PATIENTS WITH COPD EXACERBATION

Medicine

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ABSTRACT

OBJECTIVES: To evaluate the profile of EDAC in stable COPD patients and patients with COPD exacerbation and to determine whether there are clinical factors or functional variables that could influence the degree of expiratory collapse of central airways.

MATERIAL AND METHODS: It was a cross sectional case control study comprising of 90 subjects. They were allocated to 3 groups: COPD exacerbation, stable COPD and the control group with 30 subjects in each group. The degree of tracheobronchial collapse was evaluated by dynamic airway computed tomography (CT). The images were obtained at three different time points during the respiratory cycle and at three anatomic levels for each respiratory cycle.

RESULTS: Prevalence of EDAC was 3.33% in COPD patients when compared to the control population while the prevalence of EDAC was 6.67% in the exacerbation group as compared to the stable group in which none of the patients demonstrated EDAC.

CONCLUSION: Contradictory to the existing literature, our study demonstrated that the prevalence of EDAC is low in stable COPD patients. However, it's noteworthy that in acute exacerbation of COPD, EDAC was present in 6.67% of subjects reiterating the importance of maintaining a high index of suspicion for this entity which could be a plausible cause of persistent symptoms and may warrant therapy with non invasive ventilation.

KEYWORDS

Excessive Dynamic Airway Collapse, Tracheobronchomalacia, Chronic Obstructive Pulmonary Disease

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a vital public health problem and a major cause of chronic morbidity and mortality throughout the world. COPD was earlier estimated to be the fourth leading cause of death in the world in 2010 [1] and was projected to be the 3rd leading cause of death by 2020 [2]. COPD presents as dyspnea, cough and/or sputum production. The main risk factors for COPD are tobacco smoking, environmental exposures such as biomass fuel exposure, air pollution, host factors such as genetic abnormalities, abnormal lung development and accelerated aging [3]. Lifetime smoking exposure, the primary risk factor of COPD is quantified in "pack years", where one "pack year" is 20 cigarettes smoked/day for one year [4].

The number of deaths due to COPD in 2017 was 23% more than in 1990 [5]. The exact prevalence of COPD worldwide is largely unknown, but estimates have varied from 7-19%. COPD remained the most prevalent disease-specific chronic respiratory disease worldwide in 2017, accounting for 55·1% of chronic respiratory disease prevalence among men and 54·8% among women globally [6].

Expiratory Dynamic Airway Collapse (EDAC) is a clinical entity characterized by dynamic obstruction of the central airway, with excessive collapse (greater than 50%) of the membranous parts of the trachea and main bronchi during expiratory phase of respiration [7,8]. Although classically considered a type of Tracheobronchomalacia (TBM), today EDAC is considered to be a different entity and a lot of improvement can be achieved with minimal intervention. This similarity may delay the response to the ongoing treatment and worsen the typical presentation of the disease. The prevalence of EDAC is unknown, with a wide range of variability (13 to 53%) from a limited number of studies [8-13].

EDAC can occur frequently, impact pulmonary function and may be of considerable importance in diseases such as chronic obstructive pulmonary disease (COPD). EDAC may be of particular relevance in acute exacerbations of COPD (AECOPD) since exacerbations are accompanied by acute pathophysiological derangements and intrathoracic pressure changes that favor tracheal collapse [14]. To what extent EDAC is induced during AECOPD is currently not known and there have been no prospective investigations to estimate the prevalence or clinical associations of EDAC in AECOPD. Presentations as varied as cough, dyspnea, recurrent infections and difficulty weaning from respiratory support have been ascribed to the presence of EDAC [7] and accurate diagnosis may therefore have etiological, prognostic and management implications in COPD [15].

MATERIALS & METHODS

Cross sectional case control study of a group of patients with COPD and COPD exacerbation in which the degree of tracheobronchial collapse was evaluated by low-dose dynamic airway CT.

1. **Study design:** This was a cross sectional case control study of group of patients who were diagnosed with COPD and COPD exacerbation according to GOLD's [16] criteria and were treated consecutively at the outpatient and inpatient Respiratory Medicine Department at a tertiary care hospital from October 2018 – August 2020.

2. **Inclusion criteria:** patients diagnosed as COPD as per the GOLD guidelines who were of
   a. Age > 40 years
   b. Groups B, C and D as per GOLD's criteria (group A of COPD was excluded because of minimal symptoms in patients of this group).

3. **Exclusion criteria:-**
   a. Any neurological condition that could alter the pulmonary function.
   b. BMI > 35 kg/m^2
   c. Diagnosed case of Bronchial asthma or the asthma COPD overlap group
   d. Any mediastinal mass or chest wall lesion as evaluated by Chest radiographs.
   e. Patient with possible TBM excluded on the basis of history of prior intubation, enlargement of surrounding neck structures like goiter.

4. Participant information:-

We recorded clinical and socio-demographic data [age, sex, BMI, smoking history in pack-years], as well as the degree of dyspnea, measured by the modified Medical Research Council (mMRC) scale. All patients underwent Spirometry using Pony FX Spirometer (Cosmed, Rome, Italy) and a 6 Minute Walk Test (6MWT). Patients were classified into GOLD stages as per the measured forced expiratory volume inone second (FEV_1) assessed by Spirometry. The BODE index was then calculated with the above data for each participant.

The study included 3 groups with 30 participants each:

a. Group I- Patients with acute exacerbation of COPD diagnosed as per the GOLD's criteria.
b. Group II- Patients with stable COPD defined as per GOLD's criteria.
c. Group III- Control, subjects who did not have any obstructive airway disease or any other chronic respiratory illness.

5. Measurements:-

The degree of tracheobronchial collapse was evaluated by low-dose dynamic airway CT using a Multidetector CT, Philips Ingenuity. The images of region of interest were obtained in the craniocaudal direction at three different time points during the respiratory cycle (at the end of inspiration, the end of expiration, and during dynamic expiration), according to the protocol for the study of airway collapse[17-21].

The parameters that were used are as follows: Detector collimation 64 x 0.625 mm, thickness 1 mm, and a 0.891-mm pitch factor, rotation time 0.5 sec, movement 0.5mm. A previously validated low-dose technique was used with the following parameters: 100 mAs, 120 kVp, and CTDI vol 11.74. Each scan was analyzed by a radiologist.

Three axial images were visualized simultaneously at three anatomic levels for each respiratory cycle time-point examined (the aortic arch, main carina just after the division and at the level of main bronchus just below the carina). The cross-sectional area of the airway lumen was measured marking the inner wall of the airway with a specific tool. The percentage expiratory luminal collapse was calculated using the following formula [22]:

$$\text{Luminal collapse \%} = \frac{\text{Luminal AP diameter at (end-inspiration} - \text{dynamic expiration)}}{\text{Luminal AP diameter at end-inspiration}} \times 100$$

The point with the greatest degree of collapse (maximal point of collapse) was chosen for analysis. EDAC was considered when the expiratory collapse of airway lumen is >50% when due to invagination of posterior membrane [7, 8]. In each case, a printed plaque was produced that included nine images: One at end inspiration, one during dynamic expiration, and one at maximal forced expiration, at each of the three anatomical levels where diameters of the airway were measured.

6. STATISTICAL ANALYSIS:-

Quantitative variables were expressed as the mean and standard deviation (SD) and categorical variables as percentages and 95% confidence intervals. The correlation between the degree of collapse at the maximum point of collapse and the other quantitative variables was performed using Pearson's parametric test and the Spearman rank test. The comparison of quantitative variables was performed using Student's *t*-test. Data was considered statistically significant at $p < 0.05$. A logistic regression model was developed in order to evaluate the association between clinical and functional parameters and the presence of EDAC. The statistical analysis was performed using SPSS statistical software for Windows.

OBSERVATION AND RESULTS

In this cross-sectional study, 100 patients were scrutinized and 10 patients were excluded as they did not fulfill the study criteria and 90 adult patients were included in the study. They were allocated to Group I which included patients with COPD exacerbation, Group II which comprised of patients with stable COPD and Group III which was control with 30 patients in each group. All exclusion criteria were ruled out before including the patients in the present study.

The demographic profiles of patients when compared for Group I and Group II were similar with regard to age (years) (p value 0.7841), sex (p value 0.2504), weight (kgs) (p value 0.1556) height (cms) (p value 0.1556) , BMI (p value 0.6335) and smoking history (Table 1).

Table 1: Distribution of age, weight, height, BMI, sex and Pack years in the study population

VARIABLES	Group I	Group II	Group III	p value of Group I and II
Age (years)	66.07 ± 10.83	59.30 ± 10.84	36.40 ± 15.61	0.7841
Sex(M/F) N (%)	25/5 (83.33/16.67)	20/10 (66.67/33.33)	20/10 (66.67/33.33)	0.25042
Weight (kgs)	58.23 ± 14.28	64.1 ± 11.05	60.67 ± 9.24	0.1556
Height (cms)	157.77 ± 8.20	163.20 ± 7.86	162.07 ± 8.61	0.3031
BMI (kg/m^2)	23.67 ± 5.09	23.96 ± 3.37	22.95 ± 4.01	0.6335
Pack years	20.34 ± 19.45	11.54 ± 9.54	2.05 ± 5.17	0.0300

The age of the study population ranged between 42 years to 81 years amongst the COPD population with a mean age of 66.07 ± 10.83 years in Group I and 59.3 ± 10.84 in the Group II. The difference in age between the two groups was statistically insignificant (p value 0.7841). The degree of dyspnea was measured by the mMRC scale. In group I, 33.33% of the patients had grade 4 dyspnea while in group II, 60% of the patients had grade 2 dyspnea. In case of Group III, most of the patients had Grade 0 dyspnea, i.e. 83.33%.

The mean FEV_1 was 0.959 ± 0.31 L in the Group I as compared to 1.30 ± 0.38 L in Group II. The difference in FEV_1 between the two groups was statistically significant (p value 0.0003). The mean forced vital capacity (FVC) of Group I was 1.76 ± 0.55 liters as compared to 1.94 ± 0.52 liters in Group II. The difference in FVC amongst the two groups was statistically insignificant (p value 0.1979). The mean ratio of FEV1/FVC was 55.66 ± 13.03 % in group I as compared to 66.79 ± 7.92 % in the group II. The difference in FEV1/FVC was statistically significant (p value 0.0002) [Table 2].

Table 2: Distribution of FEV1, FVC, FEV1/FVC and 6-minute walk distance in the study population

VARIABLES	Group I	Group II	Group III	p value of Group I and II
FEV_1(in litres)	0.959 ± 0.31	1.30 ± 0.38	2.86 ± 0.87	0.0003
FVC (in litres)	1.76 ± 0.55	1.94 ± 0.52	3.17 ± 0.95	0.1979
FEV_1/FVC (in %)	55.66 ± 13.03	66.79 ± 7.92	89.76 ± 4.82	0.0002
6MWD (in metres)	249 ± 56.41	332 ± 55.17	583 ± 90.41	<0.0001

There was a statistically significant difference (p value <0.0001) in the mean 6-minute walk distance which was 249 ± 56.41 meters in group I as compared to 332 ± 55.17 meters in Group II. In case of group I, 53.33% of patients were in stage 4 while in case of Group II, 46.67% of them were in stage 2 COPD as categorized by FEV1 values assessed on Spirometry.

Patients of COPD can be categorized into four different groups based upon their symptoms and history of exacerbation. We have included only three groups in our study that are B, C and D and have excluded Group A because of minimal symptoms in patients in this group. In Group I, 53.33% of patients were in Group D whereas in Group II, 70% of the patients were in Group B.

BODE index comprises of Body mass index, degree of obstruction, dyspnea and exercise capacity. In Group I, 36.67% had a BODE index score of 7. In case of Group II, 30% of the patients had a BODE score of 3 while in Group III, 60% of the patients had a score of 0.

Numbers of exacerbations of COPD occurring in patients in the last year were also recorded. In group I, 50% of the patients had no exacerbations in the last year while only 3.33% patients had 3 exacerbations. Comparing it with group II, 66.66% of the patients had no exacerbation in the last year.

To define EDAC, percentage of expiratory luminal collapse should be more than 50%. The mean values of percentage of expiratory collapse at these three different levels in the three study groups are depicted in Table 3.

Table 3: Distribution of percentage of expiratory collapse in the study population

LEVELS OF MEASUREMENT	Group I	Group II	Group III	p value of Group I and II
% of collapse at Aortic Arch	15.3 ± 9.69	12.85 ± 8.28	8.63 ± 2.92	0.2968
% of collapse at left main carina	18.08 ± 11.42	14.74 ± 8.55	11.03 ± 4.26	0.2048
% of collapse at right main carina	20.33 ± 13.91	14.45 ± 8.18	11.14 ± 5.24	0.0507
% of collapse at left main bronchus	15.82 ± 10.04	13.12 ± 7.31	9.48 ± 4.53	0.2386
% of collapse at right main bronchus	16.40 ± 12.02	13.19 ± 7.72	9.02 ± 4.50	0.3418

The number of patients who showed EDAC were 2, 0 and 0 in Groups I, II and III respectively. On comparing Groups I and II, the difference in the mean values of percentage of expiratory collapse was insignificant at all the three levels. When all the three groups were compared, the difference between the mean values of expiratory collapse became significant depicting increased airway collapse in COPD patients compared to the patients with no airway disease.

DISCUSSION

The results of our study depicted that the prevalence of EDAC was 3.33% in COPD patients when compared to the control population where it was 0%. On further dividing the COPD population into stable and exacerbation groups, we found out that the prevalence of EDAC was much higher in the exacerbation group (6.67%) as compared to the stable group (0%). A probable hypothesis for this could be the influx of inflammatory cells and chemical mediators during exacerbation which could lead to weakening of tracheobronchial walls.

Even though COPD is a disease with diffuse involvement, in our patients with EDAC, the collapse was not diffuse but was affecting only one or two of the three points that were analyzed. This could compromise the existence of a possible relationship between the two entities. The degree of dynamic central airway collapse does not appear to be related to the patients epidemiological or clinical features. An analysis of the few published studies on this subject revealed certain similarities to and differences from the present study results. Many points of disagreement may be at least partly attributable to questions of definition of the entity, because until very recently (and even in some recent studies), EDAC was not considered to differ from other types of TBM [7,8,12,23]. This might also have influenced patient selection and the tools used to assess dynamic collapse.

The prevalence of EDAC in patients with COPD is not well-known because there are only a few studies that have examined this issue specifically ranging from 13-50% [10-13,21]. The most recent and relevant investigation conducted by Boiselle *et al* [10] found a much higher prevalence of EDAC of 20% in COPD patients using a higher threshold of collapse for diagnosis (>80%). A possible explanation of the difference could be the lack of spirometric monitoring in our study that could have underestimated EDAC because of low levels of maximal expiratory effort. However, prevalence was a little less in other studies [11, 12]. In a retrospective study of a large cohort of heavy smokers with emphysema, Ochs *et al.* [11] observed EDAC in 13.4% of patients. Sverzellati *et al*. [12] observed that 53% of patients with COPD had some type of TBM, although the typical morphology of EDAC ("expiratory frown sign" according to some authors) was quantified in only 18%. The results of other studies [8, 9, 13, 24] may not be comparable because EDAC cannot be differentiated from other types of malacia. Another reason could be the use of bronchoscopy as the diagnostic method which it is prone to subjective errors.

The degree of expiratory collapse did not appear to differ significantly between subjects with COPD and those without the disease. However, these data should be interpreted with caution because our study was not designed or intended to make such comparisons; thus, the results must be verified in a study with a larger sample population.

We observed no correlation between most of the variables. Ochs *et al*. [11] observed higher degree of collapse in women and increasing age which did not occur in our study. However, in our study and the one conducted by Sverzellati *et al*. [12], age was not a predictor of further collapse. In a study of patients with COPD, asthma, and TBM, Loring *et al*. [13] observed no correlation between the degree of obstruction (as measured by FEV_1) and the degree of central airway collapse, although both of our patients who showed EDAC had a low FEV1 of less than 1.21 L. In the study of Yarkin T et al. [25] EDAC was detected in 72% of patients in GOLD 3 and 4 stages; this was also consistent with our findings where both the patients with EDAC were in GOLD stage 3 or 4.

This study has limitations that should be discussed. First, there was no external assessment of the respiratory phase during image acquisition; therefore the absence of monitoring could decrease the measurements reliability. However, patient's thoracic movements were visualized from the outside through a glass wall that connects the room where CT was performed with the office where the ray technician was responsible for conducting the procedure. Therefore, there was a visual control of chest movements. And also, the noncompliant patients were not included as candidate to perform the measurements. The second was the small sample size; however, due to the paucity of studies, EDAC frequency is unknown both in healthy patients and patients with COPD so that adequate sample size estimation may not be accurate enough to design studies. Third was the absence of matching of the mean age of control group with the COPD group which could have affected the prevalence estimation. Finally, this study could have been followed up by repeat airway CT scans in patients with EDAC after the stabilization of the disease in order to confirm or refute our hypothesis indicating exacerbation as a risk factor for EDAC. Despite these limitations, we believe that our findings were interesting and could support further investigations to assess any plausible role of EDAC in acute exacerbation of COPD especially in patients with persistent symptoms of dyspnea and delineate those who might benefit from domiciliary noninvasive ventilation.

CONCLUSION

The occurrence of EDAC remains low in patients with stable COPD and the prevalence of abnormality appears to be increased in acute exacerbation of COPD. Further studies should focus on possible causes of EDAC and whether there is a predisposition to AECOPD in patients known to have EDAC. Clinicians caring for patients with COPD should consider EDAC as a possible contributing factor to breathlessness and other persistent airway symptoms.

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