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Increased gastro-oesophageal reflux disease in patients with severe COPD

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ABSTRACT: The prevalence and clinical consequences of gastro-oesophageal reflux disease (GERD) in chronic obstructive pulmonary disease (COPD) are not well characterised.

The present study prospectively studied 42 males with COPD (forced expiratory volume in one second % predicted: 35%, range 20–49) and 16 healthy volunteers of similar age without respiratory or gastro-oesophageal symptoms. The diagnosis of GERD was confirmed using oesophageal 24 h pH monitoring. In the current study group, reflux symptoms were measured using the Vigneri score, cough and dyspnoea with the modified Medical Research Council questionnaire, and pulmonary function with bronchodilator response and health status using St George's Respiratory Questionnaire.

Pathological reflux was documented in 26 out of 42 patients (62%) and in three volunteers (19%). In patients with GERD, 15 patients (58%) did not report any reflux symptoms. There were no differences in symptoms, health status, bronchodilator treatment and pulmonary function test between patients with and without GERD. Oxygen desaturation coincided with episodes of increased oesophageal acidity in 40% of patients with GERD.

Patients with severe chronic obstructive pulmonary disease have a high prevalence of asymptomatic gastro-oesophageal reflux. The association between this reflux and oxygen desaturation deserves further attention.

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Over recent years, chronic obstructive pulmonary disease (COPD) has suffered important conceptual changes. COPD is now believed to result from chronic airway inflammation as a response to inhaled particles, primarily cigarette smoking [1]. In addition, COPD is also believed to cause important systemic effects that may influence the clinical manifestations of the disease and importantly, impact on its outcomes [1].

Gastro-oesophageal reflux disease (GERD) is a common condition, affecting ~20% of the adult population [2]. Pathological acid reflux can cause important oesophageal diseases like Barrett's metaplasia, ulcerative oesophagitis and oesophageal adenocarcinoma [3]. In patients with asthma, GERD can worsen respiratory symptoms, which respond to the specific treatment for GERD [4]. In addition to asthma [5], previous studies have reported a high prevalence of GERD in other respiratory disorders, including chronic cough [6], upper respiratory complaints [7], obstructive sleep apnoea [8], and idiopathic pulmonary fibrosis [9]. However, many patients who suffer from GERD often do not have typical symptoms such as heartburn or regurgitation [5]. Therefore, 24 h oesophageal pH monitoring has become the most important tool to confirm the diagnosis of GERD, with a sensitivity and specificity of ~90% [10, 11].

To the knowledge of the present authors, only four prospective studies have investigated the relationship between GERD and COPD [12–15]. Three of these studies showed an increased prevalence. However, in two of these studies [12, 13], GERD was diagnosed by scinti-scanning and short-term (3 h) pH monitoring after a test meal. In the other [15], GERD was evaluated only by survey. Moreover, only one study used 24 h pH monitoring in 12 COPD patients without a control population [14]. The authors of the latter study found no increased prevalence of GERD [14].

The association between GERD and COPD seems logical as there are anatomical changes that could favour the development of reflux. These changes include: increased central drive; flattening of the diaphragm and increased intra-abdominal and negative intrathoracic pressure. These, in combination with the use of medication, *e.g.* theophylline and β_2-agonists which may decrease the lower oesophageal sphincter pressure, could facilitate reflux of gastric content [16, 17].

Given the uncertainty and the potential importance of GERD in patients with COPD, the current prospective study utilised 24 h pH monitoring as the diagnostic tool. Healthy volunteers served as controls.

Methods

Patient Selection

A total of 51 consecutive patients were recruited and all patients gave signed, informed consent. The study was approved

by the Human Review Board. Inclusion criteria included: a history of smoking $\geqslant$20 pack·yrs^{-1}; forced expiratory volume in one second % predicted (FEV1 % pred) <50%; FEV1/forced vital capacity <0.7; total lung capacity (TLC) $\geqslant$80% pred; and stability for 6 weeks. Exclusion criteria were: FEV1 increase of >15% or 200 mL after bronchodilator; history of asthma; sleep apnoea; peptic ulcer disease; and alcohol abuse.

Sixteen healthy volunteers were enrolled as a control group. These subjects were nonactive smokers without COPD or other respiratory disease, no GERD symptoms and a Vigneri score of <2.

Gastro-oesophageal reflux disease evaluation

The severity and frequency of heartburn, pain or regurgitation were scored using the validated Vigneri scale (range: 0–27) [18]. No patients received proton pump inhibitors, H_2-blockers, or prokinetics agents for the week prior to the study. Antacids were withheld on the day of the study. The pH sensor was positioned using manometry. Seven patients rejected the test and two were excluded due to problems in placement of the catheter (increase in cough and dyspnoea). These nine patients were similar in all aspects to the patients included in the study.

The reflux index was defined as the percentage of time with a pH <4. A value >4.5% is diagnostic [19, 20]. The index validity was confirmed with a healthy, historical control group of 12 subjects taken from the hospital where the present study was undertaken, all of whom had <4.5% in the 24 h pH monitoring.

In a diary, the patients recorded the time of heartburn, regurgitation, chest pain, cough, meals, medication, ethanol intake, tobacco and an increase in dyspnoea. In 20 patients a visual analogue scale (VAS) dyspnoea was measured every 2 h during awake periods. In 32 patients 24 h simultaneous pulse oximetry readings were recorded.

Pulmonary Function

Spirometry and lung volume tests were performed. The carbon monoxide diffusing capacity of the lung (DL,CO) was determined with the single breath technique. Maximal inspiratory and expiratory pressures (PImax and PEmax, respectively) were measured at residual volume and TLC, respectively. Arterial blood gases were obtained while breathing air. Inspiratory capacity was subtracted from TLC to obtain the end expiratory lung volume. Manometry was used to measure gastric (PGA), oesophageal (PPL) and transdiaphragmatic pressure (PDI=PGA-PPL).

Clinical Outcomes

Body Mass Index (BMI) was measured, and dyspnoea was scored with the modified Medical Research Council scale [21]. Chronic cough was defined as daily cough for >3 months. Health status was evaluated with the St George's Respiratory Questionnaire [22].

Statistics

Considering 20% as the prevalence of GERD in normals and assuming that a doubling of this percentage is clinically significant, the present study estimated 14 subjects and 42 patients (r=1:3) as the number needed to have an α error of 5% and β error of 20% with a power of 80%. Data are presented as median (range) for quantitative variables with abnormal distribution. Fisher's exact or Mann-Whitney U-test was used to compare both groups. Variables were correlated using Spearman's correlation coefficient. To determine the association between GERD and the independent variables, binary multiple logistical regression analysis was used. A p-value <0.05 was considered statistically significant.

Results

A total of 42 male patients with severe COPD and oesophageal 24 h pH monitoring were enrolled (table 1). The clinical characteristics and comparisons between patients and controls are shown in table 2. A total of 26 (62%) patients from the COPD group (males) and three subjects (19%) from the control group (14 males, two females) had abnormal distal acid reflux (p=0.003) (fig. 1). The median age was similar for both groups and the BMI was lower in patients with COPD.

Using the Vigneri score [18], only 15 (36%) of the COPD patients presented with $\geqslant$one GERD symptoms. There was no correlation between this score and the data obtained from the 24 h pH monitoring (fig. 2). From the 26 patients with GERD, 73% had a combined reflux pattern (supine and upright) and only 27% had an upright reflux pattern.

Eleven patients with COPD reported still smoking (10–20 cigarettes·day^{-1}) and seven of these cases (64%) had GERD.

Table 1. – Baseline pulmonary function tests, dyspnoea, health-related quality of life and use of pulmonary medication in chronic obstructive pulmonary disease (COPD) patients

COPD subjects n	42
FVC % pred	67 (40–97)
TLC % pred	114 (84–163)
EELV L	5.1 (2.9–8)
DL,CO % pred	74 (28–122)
PImax % pred	52 (20–96)
PDI cmH_2O	17 (10–25)
P_{a,O_2} kPa	8.4 (6.1–11.2)
P_{a,CO_2} kPa	6.4 (5.0–8.8)
Dyspnoea MMRC	1 (0–4)
SGRQ	42 (8–83)
Inhaled anticholinergic	98
Inhaled β-agonist	98
Inhaled corticosteroids	88
Theophylline	45

Data are presented as % or median (5th–95th percentiles). FVC: forced vital capacity; TLC: total lung capacity; EELV: end expiratory lung volume; DL,CO: carbon monoxide diffusion capacity; PImax: maximal inspiratory pressure; PDI: transdiaphragmatic pressure; P_{a,O_2}: arterial oxygen pressure; P_{a,CO_2}: arterial carbon dioxide pressure; MMRC: modified Medical Research Council; SGRQ: St George's respiratory questionnaire.

Table 2. – Anthropometric data of the study population

	Controls	COPD	p-value
Subjects n	16	42	
Sex M:F	14:2	42:0	
Age yrs	67 (47–78)	68 (47–78)	NS
BMI	31 (25–40)	28 (19–33)	0.041
FEV1 % pred	106 (81–130)	35 (20–49)	

Data are presented as median (5th–95th percentiles). COPD: chronic obstructive pulmonary disease; M: males; F: females; BMI: body mass index; FEV1 % pred: forced expiratory volume in one second % predicted. NS: nonsignificant.

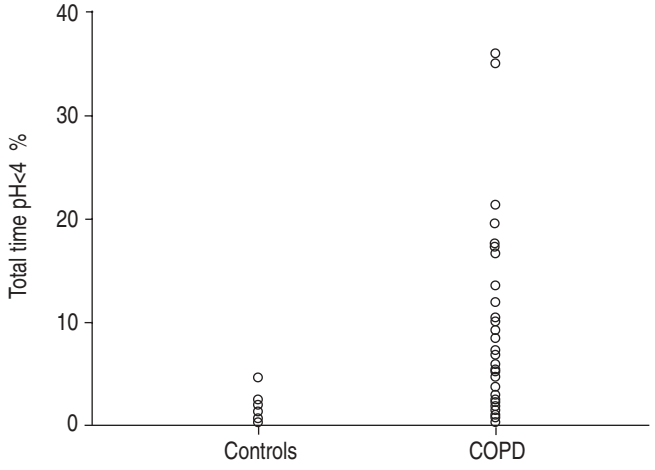

Fig. 1. – The percentage of time that patients and controls had oesophageal pH value <4. The patients with chronic obstructive pulmonary disease (COPD) had a higher prevalence of gastro-oesophageal reflux compared with the healthy controls.

Forty-one patients (98%) were using inhaled anticholinergics and β-agonists. Thirty-seven patients (88%) were on inhaled steroids. Nineteen patients (45%) were taking theophylline, and the proportion was similar between the group with GERD and the group without it (68% *versus* 56%, p=nonsignificant). The theophylline level in both groups ranged between 5–17 mg·dL^{-1}. There was only one patient without bronchodilator treatment (table 1).

Using logistical regression analysis, no respiratory parameters were associated with the presence of GERD. In addition, the diagnosis of GERD was not related to the presence of chronic cough (64% GERD in the chronic cough group *versus* 61% GERD in the group without cough).

During the pH monitoring time, six patients (23%) referred to heartburn and/or regurgitation (usually of minimal intensity) from the COPD group with GERD and only two patients (13%) in the COPD group without GERD. However, this difference was not statistically significant.

In 20 COPD patients (10 with GERD) dyspnoea was measured using the VAS. This increased in one patient with COPD and GERD and in four patients with COPD without GERD. None of these cases had episodes of reflux during the worsening of dyspnoea.

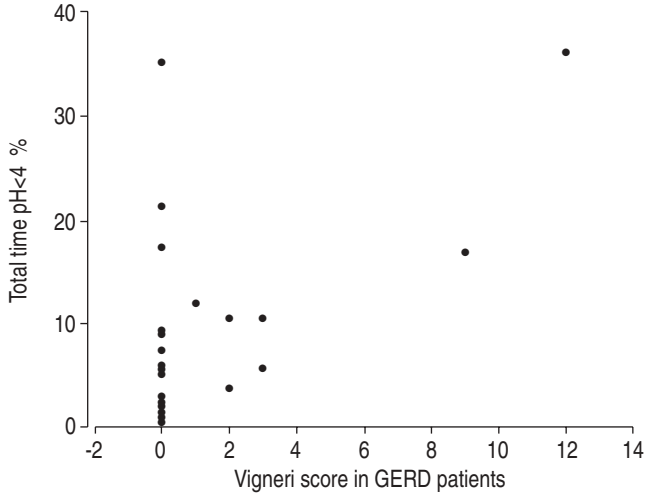

Fig. 2. – The percentage of time that patients had oesophageal pH values <4 and its relationship to the clinical symptoms of gastro-oesophageal reflux disease (GERD), as defined by the Vigneri score.

Simultaneous oximetry and 24 h pH monitoring was performed in 32 patients, including 18 of the COPD patients with GERD. In this group, technical problems were encountered when registering the oximetry in two patients, and in another one, the use of supplemental oxygen during the test precluded its use in the analysis. Therefore, the oxymetric changes associated with GERD were evaluated in only 15 out of the 18 patients with GERD. In six cases (40%), there was very good synchrony between the development of GERD and oxygen desaturation (fig. 3). All patients had an Epworth score <9 and only one of them had an apnoea-hypopnoea·h^{-1} index of 14 by polisomnography.

Discussion

The current prospective cohort study has shown that COPD is associated with an abnormally high prevalence of oesophageal acid reflux when compared to volunteers of similar age. However, most COPD patients do not have typical symptoms of GERD, *e.g.* as heartburn or regurgitation. In addition, the presence of GERD is not associated with alterations in clinical outcomes and lung function. Some patients manifest oxygen desaturation that coincides with periods of acid reflux.

The relationship between respiratory disorders and GERD is evolving. In patients with asthma, the evidence supports several mechanisms by which GERD may exacerbate asthma symptoms, they include: oesophago-bronchial reflex; heightened bronchial reactivity; and microaspiration [23–25]. These mechanisms could be extrapolated to patients with COPD, who suffer from abnormal thoraco-abdominal functional anatomy resulting in increased gastric and negative intrathoracic pressure. Although it is believed that COPD is associated with peptic ulcer disease, this association has not been systematically evaluated. Furthermore, the true prevalence of GERD in COPD patients has to date been evaluated in only four studies [12–15].

DAVID *et al.* [12] diagnosed GERD in 29 out of 47 COPD patients (61%) with a mean FEV1 of 67% pred. DAVID *et al.* [12] chose, as a pathological threshold for GERD, a gastric pH <5 maintained >5% of the recorded time. Compared with the patients in the present study, the DAVID *et al.* [12] study population had a lower degree of obstruction and was studied only using pH monitoring for 3 h after a meal. In addition, there were no controls and there was no investigation of the clinical correlates of GERD. DUCULONÉ *et al.* [13] reported the presence of GERD in 17 of 30 patients with severe COPD (57%). Again, these authors diagnosed GERD using scintiscanning and short-term pH monitoring for 3 h after a test meal. GERD was defined by the number of events with pH <5 and the peaks with pH <2. In contrast to the current results, only 29% of patients with GERD had no reflux symptoms and there was little clinical information attempting to correlate the presence of GERD with any outcome. In agreement with the presented data, pulmonary function tests in the study by DUCULONÉ *et al.* [13] did not show any differences between patients with and without reflux. In the only report where patients were studied with 24 h pH monitoring, ORR *et al.* [14] did not find GERD in 12 patients with COPD, even though the majority of the patients had a positive history of reflux-related symptoms. However, the population in the study by ORR *et al.* [14] was not comparable with the present study because nine of the 12 COPD patients had a positive bronchodilator response in the spirometry test and may have had asthma.

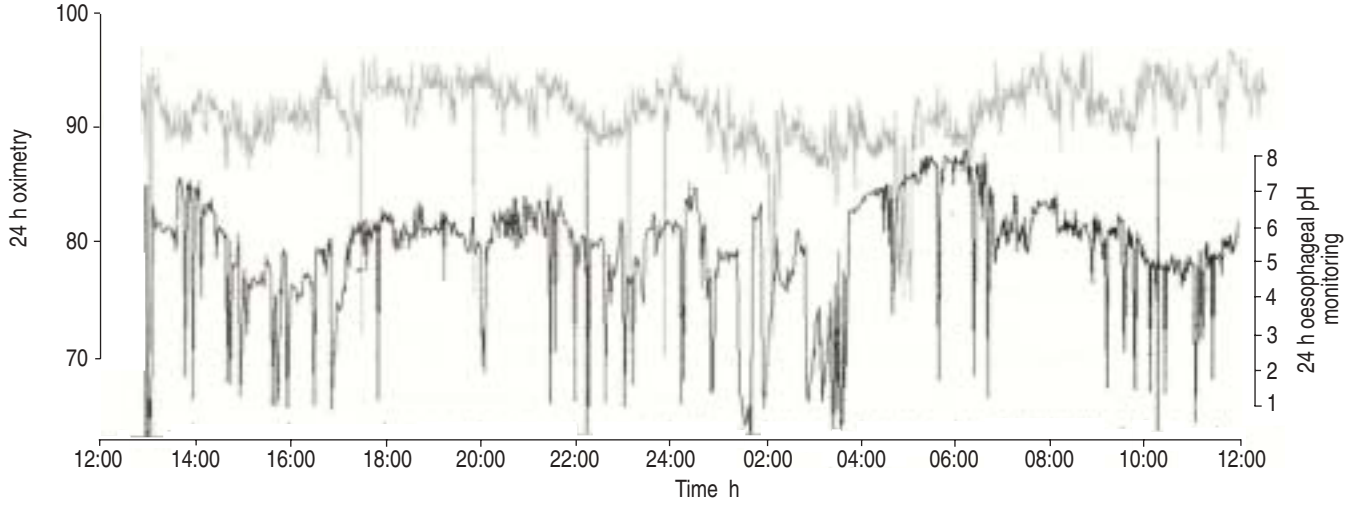

Fig. 3. – Superimposed graphs of simultaneous oesophageal pH monitoring and oxygen saturation in one of the six patients with chronic obstructive pulmonary disease and gastro-oesophageal reflux disease who had synchronous changes in both variables.

Recently, MOKHLESSI *et al.* [15], using a modified version of a validated GERD questionnaire given to >100 patients, observed a high prevalence of mild GERD symptoms in patients with COPD. MOKHLESSI *et al.* [15] also showed a trend to higher prevalence in severe COPD patients, similar to the current study (~30%). Unfortunately, there were no objective measurements of acid reflux and the validity of the observation or its relationship to any clinical outcome is weak at best. The current study confirms a high prevalence of GERD, but surprisingly, its presence was not associated with significant outcome changes.

In the current work, several of the possible factors that could decrease lower oesophageal sphincter pressure and predispose to GERD were analysed. The first was age, even though elderly patients have a higher prevalence of GERD [26], although age was not important in the current study's regression analysis. Similarly, obesity was not found to be an important factor. Most patients did not take alcohol and only 26% were still smoking in the present study. However, patients who smoked did not have an increased incidence of GERD. The influence of inhaled β-agonists and anticholinergics in GERD seem to be minimal because >94% of the patients with and without GERD were using these medications. Although theophylline may cause important gastro-oesophageal motility dysfunction, this was not translated into significant GERD in the current study population.

Functional and anatomical diaphragmatic changes have been implicated as important factors in the genesis of GERD [25]. The present authors did not find that pulmonary hyperinflation and transdiaphragmatic pressures influenced the presence of GERD as there were no differences in lung volumes, inspiratory capacity, $P\mathrm{Imax}$ or transdiaphragmatic pressure between patients with GERD and those without it.

Most of the current patients with GERD were asymptomatic. This has been described recently in patients with other respiratory disorders. HARDING *et al.* [5] observed a prevalence of 16 out of 26 (62%) abnormal 24 h oesophageal pH tests in asthma patients without reflux symptoms. TOBIN *et al.* [9] reported only four of 16 subjects (25%) with typical reflux symptoms in patients with pulmonary idiopathic fibrosis with GERD. In addition, GERD was not found to cause more respiratory symptoms (chronic cough and dyspnoea) or worsen the quality of life scores. This finding is in agreement with that of TOMONAGA *et al.* [27] who showed that GERD was not correlated with recurrent daily cough. The lack of relationship between GERD and respiratory symptoms was also observed in another study [14], where the patients with worsening dyspnoea did not have GERD during the periods of pH monitoring.

A new and interesting contribution by the present study is the simultaneous 24 h monitoring of oximetry and oesophageal pH in a significant number of the patients studied. The authors of the current work found that at night, 40% of patients studied had coincident episodes of oxygen desaturation and decreased pH, mostly in the supine position. Unfortunately, a cause-effect relationship could not be established because some patients (60%) had GERD which did not coincide with desaturation or with lack of desaturation. Nevertheless, the more frequent espisodes of desaturation in COPD patients with GERD supports the concept of "hypotense sphincter" of the lower oesophageal sphincter during the night [28, 29]. The current authors' findings also suggest that the relationship between oesophageal reflux and night-time oxygen desaturation and its clinical implication deserves further attention.

The present study had some limitations. It could be argued that the sample size may not allow the detection of differences in lung function between COPD patients with and without GERD, therefore, incorporating a type II error. However, the present authors' principal goal was to study the prevalence of GERD in COPD patients, being the only controlled study to use 24 h pH monitoring to prove it. In addition, the presented report is the largest study to date, with a significant difference of 80% confidence in the power analysis. Another limitation of the current study was the biased selection in the control group, selecting patients with practically no symptoms of GERD, with a Vigneri score <2. However, in order to have a "gold standard" for "normals" it had to be made certain that patients with clinically significant regurgitation were not included in the present study. The very strict definition of GERD using 24 h pH monitoring tends to minimise the relationship between COPD and GERD. Indeed, some authors have defined GERD using a more relaxed definition: an abnormal distal oesophageal acid reflux index of >5% [14] or >5.78% [30]. Using these parameters, the current study population would have a higher GERD prevalence of 60% and 53%, respectively. On the other hand, whether nonacid reflux is important in COPD is an open question that was not examined in the present study. Finally, it is important to note that females were not included. This was not by design, as the

current authors offered the possibility, independent of sex, to join the study. This probably reflects the problem of underdiagnosis of COPD in females and particularly Spain due to the relatively late beginning of smoking among females.

In conclusion, the present study reports a high prevalence of abnormal oesophageal acid reflux in patients with severe chronic obstructive pulmonary disease. Most of the patients lacked typical gastro-oesophageal reflux disease symptoms. Finally, the association between night-time oesophageal reflux and oxygen desaturation deserves further attention.

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