THE EFFECT OF CONCOMITANT GASTROESOPHAGEAL REFLUX DISEASE ON CLINICAL COURSE AND LUNG FUNCTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

WPŁYW WSPÓŁLISTNIEJĄCEJ CHOROBY REFLUKSOWEJ PRZEŁYKU NA PRZEBIEG KLINICZNY I CZYNNOŚĆ PŁUC U PACJENTÓW Z PRZEWLEKŁĄ OBTRUSYJNĄ CHOROBĄ PŁUC

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THE EFFECT OF CONCOMITANT GASTROESOPHAGEAL REFLUX DISEASE ON CLINICAL COURSE AND LUNG FUNCTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Background. Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality in modern society and can lead to the development of comorbidities. Among the last, gastroesophageal reflux disease (GERD) is frequently present, but often gets a close attention from doctors in the treatment of pulmonary patients. The aim of the current study was to determine the characteristics of clinical and lung disorders in the pathogenesis of COPD with concomitant GERD.

Material and methods. We examined 113 COPD patients with isolated COPD or with COPD and concomitant GERD. All the patients underwent spirometry, endoscopy, radiological and pH-metric procedures.

Results. Many patients (95%) with concomitant pathology complained of heartburn, dysphagia, especially after meals, burning tongue, hoarseness and a lump in the throat. Among COPD patients without concomitant GERD, both clinical pulmonary manifestations met with almost the same frequency but were less pronounced (p<0.05). During the lung examination, we determined the level of FEV1, VC, FVC, FEF25-75 and FEV1/VFC, which differed significantly in COPD patients (p<0.05) compared to predicted normal values in human of the same sex, age, height and body weight. In the COPD with concomitant GERD cohort, a sharp decrease in spirometric indices was found compared to patients with isolated COPD (p<0.001).

Conclusions. COPD patients with concomitant GERD had significantly greater extraesophageal manifestations and lung disorders compared with COPD patients without comorbidity.

Keywords: gastroesophageal reflux disease, chronic obstructive pulmonary disease, comorbidity

Streszczenie

Wprowadzenie. Przewlekła obustronna choroba płuc (POChP) jest jednym z głównych przyczyn umieralności i zachorowań we współczesnym społeczeństwie, co w konsekwencji prowadzi do rozwoju chorób współistniejących. Choroba reflukowa przełyku (GERD) występuje często, ale zazwyczaj jest dokładnie badana u pacjentów z chorobami płuc. Celem badania jest określenie zaburzeń klinicznych i chorób płuc w patogenezie POChP z towarzyszącym GERD.

Materiał i metody. Przebadanych zostało 113 pacjentów z POChP z izolowaną POChP oraz z POChP ze współistniejącym GERD. Wszystkich poddano zabiegom, takim jak: spirometria, endoskopia, a także działaniom radiologicznym i pH-metrycznym.

 Wyniki. Większość pacjentów (95%) ze współistniejącą patologią skarżyła się na zgnięcie, dysfagię, zwłaszcza po spożyciu posiłków, pieczenie języka, chrypkę oraz występowanie guzka w gardle. W tym czasie wśród pacjentów z POChP bez współistniejącej GERD oba objawy kliniczne u 29% pacjentów były rzadsze (p<0.05). W czasie badania doznano poziom FWL 75%, FVC, FEF25-75%, FEV1/FVC, które znacznie różniły się u pacjentów z POChP (p<0.01) w porównaniu do normalnych wartości u osób tej samej płci, wieku, wzrostu i masy ciała. W grupie pacjentów z POChP z towarzyszącym GERD stwierdzono gwałtowny spadek wskaźników spirograficznych w porównaniu z pacjentami z izolowaną POChP (p<0.001).

Wnioski. Pacjenci z POChP ze współistniejącym GERD mieli znacznie większe objawy zapalnikiowe i choroby płuc w porównaniu z POChP, ale bez chorób współistniejących.

Słowa kluczowe: choroba reflukowa przełyku, przewlekła obstruacyjna choroba płuc, choroby współistniejące
Introduction

Chronic obstructive pulmonary disease (COPD) remains a major health problem as the global rates of COPD morbidity have rapidly increased. Mortality from COPD is more than 2 times higher than the death rate from lung cancer [1, 2]. Currently, COPD is not only a medical but also a social problem and can lead to the formation of significant complications and comorbidities [3, 4]. Gastroesophageal reflux disease (GERD), for example, has emerged as a COPD comorbidity and typically in clinical practice, it is one of the causes of worsening respiratory symptoms [5, 6]. Currently, prompt comprehensive diagnostics, prevention and treatment of COPD are among the most important challenges in the clinic [7, 8]. At the same time, the number of COPD patients with comorbid disorders, including GERD, is increasing [9, 10]. Many questions related to both the appearance of concomitant GERD in patients with COPD and its timely diagnosis do not have a clear answer. These issues often remain outside the field of view of medical doctors and require further research. Therefore, the aim of the study is to determine the effect of concomitant GERD in COPD patients on clinical manifestations and lung function.

Material and methods

This study was conducted at the pulmonological departments of Kharkiv Medical Academy of Postgraduate Education and City Clinical Hospital no. 13 in Kharkiv, Ukraine, from 2015-2018. The study was conducted in accordance with the basic provisions of the Council of Europe Convention on Human Rights and Biomedicine (dated 4th April 1997) and Helsinki Declaration of the World Medical Association on ethical principles of conducting scientific medical research with the participation of a person (1994-2008).

COPD diagnoses were made according to the recommendations of the GOLD (2018) [11] and the order of the Ministry of Health of Ukraine no. 499 from 28th October 2003. The GERD diagnosis was established according to ICD-10 based on a detailed survey, evaluation of complaints, history of the disease and the patient’s life. Diagnosis of both diseases was performed if the patient had cough and dyspnea and bothersome heartburn one or more times a week for the past 6 months (as recommended by the Mayo Clinic and the Montreal Consensus, 2006) [12, 13], and based on data from spirometry, endoscopy, radiological and pH-metric methods. Patients were excluded from the examination if they had a malignancy, Barrett's esophagus, active stomach ulcers or duodenal ulcers, autoimmune diseases, coronary heart disease, diabetes, asthma, pregnancy, or if the patient refused to participate in the study.

The study was approved by the Institutional Ethics Committee of Kharkiv Medical Academy of Postgraduate Education and City Clinical Hospital no. 13, Kharkiv. Written informed consent was obtained from all patients.

We observed 113 COPD patients of similar sex, age and duration of disease. Depending on the presence or absence of concomitant GERD, two groups were formed. The first group included 69 COPD patients with GERD, and the average age was 57.81 ± 7.82 years. The second group included 44 patients with COPD but without GERD, and the average age was 54.82 ± 9.43 years old. The frequency of clinical manifestations, complaints and physical conditions were recorded. Pulmonary function test variables (forced vital capacity (FVC [L]), vital capacity (VC [L]), forced expired volume in one second (FEV1 [L]), forced expiratory flow at 25%-75% vital capacity (FEF25-75 [L/sec]), and ratio of FEV1 to FVC (FEV1/FVC [%])) were conducted using the Spirosvit-3000 (Japan). For the tests, the patient inhaled deeply, holding their breath for a few seconds, and then exhaled as forcefully as possible into the breathing mask. The patient then received one dose of the bronchodilator salbutamol and after waiting 15 minutes, another set of measurements was performed. To estimate gastric secretion, the intragastric pH-metry method was used with application of calomelantimony electrodes (antral and framed) on the AI-2 (the Acidity Indicator machine, Ukraine) with the standard method. As the standard, we took mean values of 20 healthy people of the same age and sex who were the control group with an average age of 55.40 ± 4.18 years. Statistical data analysis was performed using the statistical package SPSS 16. We processed the research results by the variation statistics method with application of correlation analysis standard programs with the M, m average values calculation. Results were expressed as mean ± standard deviation (SD). A Student’s t-test was performed to assess the reliability indices. Analysis of variance (ANOVA) was used to analyze the differences among group means in a sample. Pearson’s correlation coefficients (r) was used to identify the associations between figures with 95% confidence interval (CI), and statistical significance was defined as a p<0.05.

Results and discussion

The clinical picture of the 69 patients with comorbidity was characterized by dyspnea (98%) and cough (94%), which was similar to patients with isolated COPD. At the same time, patients with comorbidity often
expressed extraesophageal manifestations of GERD and many complained of heartburn (97%), dysphagia, especially after meals (95%), as well as burning tongue (56%), hoarseness (58%), and a lump in the throat (61%). At that time, clinical pulmonary manifestations were met with almost the same frequency among COPD patients without concomitant GERD compared to patients with GERD but were less pronounced (p>0.05); 93% of patients experienced cough and 97% of patients experienced dyspnea. Moreover, these patients did not complain of heartburn and dysphagia, the main symptoms of GERD, with the exception of three patients who experienced recurrent heartburn, dysphagia and hoarseness, especially after a long dry cough (Table 1).

| Patients’ complaints | Patients with concomitant GERD (%) | COPD patients without comorbidity (%) |
|----------------------|------------------------------------|---------------------------------------|
| Dyspnea              | 98                                 | 97                                    |
| Cough                | 94                                 | 93                                    |
| Heartburn            | 97                                 | 7                                     |
| Dysphagia            | 95                                 | 7                                     |
| Burning tongue       | 56                                 | 0                                     |
| Hoarseness           | 58                                 | 7                                     |
| Lump in the throat   | 61                                 | 0                                     |

Thus, the COPD patients with concomitant GERD experienced a much higher level of extraesophageal manifestations compared with either the control group or with the group of COPD patients without GERD.

Analysis of spirometry data revealed that patients with comorbidity had a more pronounced decline in the main COPD indicators FEV$_1$, VC, FVC, FEF$_{25-75}$, and FEV$_1$/FVC compared to the predicted normal values in humans of the same sex, age, height and body weight (FEV$_1>$80%, FEV$_1$/FVC>70%). In patients with comorbidity, FEV$_1$, VC, FVC and FEV$_1$/FVC indices were significantly different (p<0.001) than patients with isolated COPD. The data are presented in Table 2.

| Patients’ spirometry indicators | COPD patients with concomitant GERD | COPD patients without comorbidity | Control group | $t_{1-2}$ | $t_{1-c}$ | $t_{2-c}$ |
|--------------------------------|-------------------------------------|----------------------------------|---------------|-----------|-----------|-----------|
| FEV$_1$ [L]                    | 57.28±9.95                         | 63.40±11.59                      | 96.68±6.30    | 2.89 ***  | 22.66 *** | 15.45 *** |
| VC [L]                         | 70.07±9.80                         | 76.72±8.46                       | 98.84±9.59    | 3.83 ***  | 12.77 *** | 9.60 ***  |
| FVC [L]                        | 68.72±6.29                         | 75.93±9.55                       | 96.80±7.02    | 4.43 ***  | 17.59 *** | 10.37 *** |
| FEF$_{25-75}$ [L/sec]          | 34.74±11.94                        | 39.45±13.86                      | 74.96±10.85   | 1.86 *    | 15.45 *** | 11.78 *** |
| FEV$_1$/FVC [%]                | 58.61±5.58                         | 66.07±12.84                      | 99.08±11.71   | 3.64 ***  | 16.61 *** | 10.86 *** |

Note: *p≤0.01; **p≤0.05; ***p≤0.01; ****p<0.001

Thus, we established a clear correlation between the frequency of clinical manifestations and the characteristics of lung function in COPD patients with concomitant GERD ($r_s$=-0.57—-0.66; p<0.01).

We found that the COPD patients with concomitant GERD had significantly greater extraesophageal manifestations compared with COPD patients without comorbidity. Such results were also obtained by other clinical researches that confirmed the presence of such comorbidity in COPD [14, 15, 16]. The obtained results have led us to consider that atypical clinical manifestations (heartburn, regurgitation, burning tongue, hoarseness) in COPD patients may be a factor that leads to the appearance of concomitant GERD. Previously, it was shown that COPD patients have pronounced lung disorders [17, 18]; in our research, we demonstrate that these were significantly more pronounced in COPD patients with concomitant GERD. Moreover, we found a clear correlation between the frequency of clinical manifestations and the characteristics of lung function in COPD patients with concomitant GERD. The obtained results have led us to consider that extraesophageal manifestations may be a factor that leads to a decline in respiratory function, feeding into COPD pathogenesis.

Conclusions

We found reliable differences in the spirometry indices of COPD patients with concomitant GERD compared with patients with isolated COPD. The obtained data permits development of additional pathogenic therapy with the aim of correcting gastrointestinal disorders of COPD patients with concomitant GERD.
Disclosures and acknowledgements

We thank all members of the research team. The author declares no conflict of interest regarding this article. The author declares that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975 as revised in 2008(5), as well as national laws. The study was approved by the ethics committee. Informed consent was obtained from all subjects included in the study. This work was not supported by any funding.

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