

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

WPLYW WSPÓLISTNIEJĄCEJ CHOROBY REFLUKSOWEJ PRZEŁYKU NA PRZEBIEG KLINICZNY I CZYNNOSĆ PŁUC U PACJENTÓW Z PRZEWLEKŁĄ OBTURACYJNĄ CHOROBA PŁUC

Anna Titkova^{1(A,B,C,D,E,F,G)}

¹Kharkiv Medical Academy of Postgraduate Education, Kharkiv, Ukraine

Authors' contribution
Wkład autorów:
A. Study design/planning
zaplanowanie badań
B. Data collection/entry
zebranie danych
C. Data analysis/statistics
dane – analiza i statystyki
D. Data interpretation
interpretacja danych
E. Preparation of manuscript
przygotowanie artykułu
F. Literature analysis/search
wyszukiwanie i analiza literatury
G. Funds collection
zebranie funduszy

Summary

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/FVC, 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 spirometry 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 obturacyjna choroba płuc (POChP) jest jedną z głównych przyczyn umieralności i zachorowań we współczesnym społeczeństwie, co w konsekwencji prowadzi do rozwoju chorób współistniejących. Choroba refluksowa 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 skarżyło się na zgagę, 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 w płucach spotkały się z prawie taką samą częstością, ale były mniej wyraźne ($p > 0,05$). Podczas badania płuc ustalono poziomy FEV₁, VC, FVC, FEF₂₅₋₇₅, FEV₁/FVC, które znacznie różniły się u pacjentów z POChP ($p < 0,05$) 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 spirometrycznych w porównaniu z pacjentami z izolowaną POChP ($p < 0,001$).

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

Słowa kluczowe: choroba refluksowa przełyku, przewlekła obturacyjna choroba płuc, choroby współistniejące

Tables: 2
Figures: 0
References: 18
Submitted: 2020 Jan 17
Accepted: 2020 March 2

Titkova A. The effect of concomitant gastroesophageal reflux disease on clinical course and lung function in patients with chronic obstructive pulmonary disease. Health Prob Civil. 2020; 14(1): 29-33. <https://doi.org/10.5114/hpc.2020.93560>

Address for correspondence / Adres korespondencyjny: Anna Titkova, Kharkiv Medical Academy of Postgraduate Education, Amosova Street 58, 61176 Kharkiv, Ukraine, e-mail: ann.titkov@gmail.com, phone: +380 577 118 024, ORCID: Anna Titkova <https://orcid.org/0000-0003-0672-4723>

Copyright: © Pope John Paul II State School of Higher Education in Biała Podlaska, Anna Titkova. This is an Open Access journal, all articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0) License (<http://creativecommons.org/licenses/by-nc-sa/4.0/>), allowing third parties to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material, provided the original work is properly cited and states its license.

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 (FEV_1 [L]), forced expiratory flow at 25%-75% vital capacity (FEF_{25-75} [L/sec]), and ratio of FEV_1 to FVC (FEV_1/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 \pm 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).

Table 1. Comparative evaluation of clinical symptoms between groups

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.

Table 2. Distribution of patients' spirometry indicators

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 ⁰	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: ⁰ $p\leq 0.1$; * $p\leq 0.05$; ** $p\leq 0.01$; *** $p\leq 0.001$

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.

References:

1. Garrow AP, Yorke J, Khan N, Vestbo J, Singh D, Tyson S. Systematic literature review of patient-reported outcome measures used in assessment and measurement of sleep disorders in chronic obstructive pulmonary disease. *International Journal of Chronic Obstructive Pulmonary Disease*. 2015; 10(1): 293-307. <https://doi.org/10.2147/COPD.S68093>
2. Soler-Cataluña JJ, Alcázar-Navarrete B, Miravittles M. The concept of control of COPD in clinical practice. *International Journal of Chronic Obstructive Pulmonary Disease*. 2014; 9: 1397-1405. <https://doi.org/10.2147/COPD.S71370>
3. Hill NS. High flow nasal cannula, is there a role in COPD?. *Tanaffos*. 2017; 16: S12.
4. Jolliffe DA, Greenberg L, Hooper RL, Mathysen C, Rafiq R, de Jongh R, et al. Vitamin D to prevent exacerbations of COPD: systematic review and meta-analysis of individual participant data from randomized controlled trials. *Thorax*. 2019; 74: 337.
5. Beghé B, Verduri A, Roca M, Fabbri LM. Exacerbation of respiratory symptoms in COPD patients may not be exacerbations of COPD. *Eur Respir J*. 2013; 41: 993-995. <https://doi.org/10.1183/09031936.00180812>
6. Lee AL, Goldstein RS. Gastroesophageal reflux disease in COPD: links and risks. *International Journal of Chronic Obstructive Pulmonary Disease*. 2015; 10: 1935-1949. <https://doi.org/10.2147/COPD.S77562>
7. Wedzicha JA, Miravittles M, Hurst JR, Calverley PMA, Albert RK, Anzueto A, et al. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*. 2017; 49: 1600791. <https://doi.org/10.1183/13993003.00791-2016>
8. Long B, April MD. Are shorter courses of corticosteroids as effective as longer courses in acute exacerbations of chronic obstructive pulmonary disease?. *Ann Emerg Med*. 2018; 72(6): 719-721. <https://doi.org/10.1016/j.annemergmed.2018.05.008>
9. Ajmera M, Raval AD, Shen C, Sambamoorthi U. Explaining the increased health care expenditures associated with gastroesophageal reflux disease among elderly Medicare beneficiaries with chronic obstructive pulmonary disease: a cost-decomposition analysis. *International Journal of Chronic Obstructive Pulmonary Disease*. 2014; 9(1): 339-348. <https://doi.org/10.2147/COPD.S59139>
10. Martinez CH, Okajima Y, Murray S, Washko GW, Martinez FJ, Silverman EK, et al. Impact of self-reported gastroesophageal reflux disease in subjects from COPD Gene cohort. *Respir Res*. 2014; 15: 62. <https://doi.org/10.1186/1465-9921-15-62>
11. Global Initiative for Chronic Obstructive Pulmonary Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease [Internet]. Fontana, WI: Global Initiative for Chronic Obstructive Pulmonary Disease; 2018 [cited 2018 Jan 18]. Available from: <http://www.goldcopd.org>
12. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol*. 2006; 101: 1900-1920.
13. Roman S, Gyawali CP, Savarino E, Yadlapati R, Zerbib F, Wu J, et al. Ambulatory reflux monitoring for diagnosis of gastroesophageal reflux disease: update of the Porto consensus and recommendations from an international consensus group. *Neurogastroenterol Motil*. 2017; 29(10): 1-15. <https://doi.org/10.1111/nmo.13067>
14. Aboumatar H, Naqibuddin M, Chung S, Chaudhry H, Kim SW, Saunders J, et al. Effect of a program combining transitional care and long-term self-management support on outcomes of hospitalized patients with chronic obstructive pulmonary disease: a randomized clinical trial. *JAMA*. 2018; 320(22): 2335-2343. <https://doi.org/10.1001/jama.2018.17933>
15. Shirai T, Mikamo M, Tsuchiya T, Shishido Y, Akita T, Morita S, et al. Real-world effect of gastroesophageal reflux disease on cough-related quality of life and disease status in asthma and COPD. *Allergol Int*. 2015; 64: 79-83. <https://doi.org/10.1016/j.alit.2014.08.001>

16. Hasegawa K, Sato S, Tanimura K, Fuseya Y, Uemasu K, Hamakawa Y, et al. Gastroesophageal reflux symptoms and nasal symptoms affect the severity of bronchitis symptoms in patients with chronic obstructive pulmonary disease. *Respir Investig*. 2018; 56(3): 230-237. <https://doi.org/10.1016/j.resinv.2018.01.001>
17. Usman U, Irfan M, Faisal M. Frequency of GERD in COPD patients. *APMC*. 2016; 10(3): 111-114.
18. Baumeler L, Papakonstantinou E, Milenkovic B, Lacombe A, Louis R, Aerts JG, et al. Therapy with proton-pump inhibitors for gastroesophageal reflux disease does not reduce the risk for severe exacerbations in COPD. *Respirology*. 2016; 21(5): 883. <https://doi.org/10.1111/resp.12758>