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Gastroesophageal reflux disease and pulmonary function: A potential role of the dead space extension

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
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Summary

Background: To evaluate the differences in the existence and size of dead space in patients with and without Gastroesophageal Reflux Disease (GERD and non-GERD) expressed through the size of intrapulmonary shunt (Q**S**/Q**T**).

Material/Methods: The study enrolled 86 subjects – 43 patients referred for endoscopy because of symptoms of GERD (heartburn, acid regurgitation, dysfagia) and 43 healthy subjects with similar anthropometric characteristics without GERD symptoms. Based on endoscopy findings, patients were classified into the erosive reflux disease (ERD) group and non-erosive reflux disease (NERD) group. Spirometry values, single-breath diffusing capacity of the lung for carbon monoxide (DLCO) and intrapulmonary shunt (venous shunt – QS/QT) determined by the oxygen method were measured in all participants.

Results: Statistically significant differences between GERD and non-GERD groups in FVC (p=0.034), FEV1 (p=0.002), FEV1/FVC (p=0.001), and PEF (p=0.001) were observed. There were no statistically significant differences in FEF 25% (p=0.859), FEF 50% (p=0.850), and FEF 75% (p=0.058). Values of DLCO (p=0.006) and DLCO/VA (p=0.001) were significantly lower and QS/QT was significantly higher (p=0.001) in the GERD group than in the non-GERD group. However, in both groups the average values of DLCO and DLCO/VA expressed as a percentage of predictive values were within normal range, while the value of QS/QT in the GERD group showed pathological (6.0%) mean value (normal value ⩽5.0%). There were no significant differences in respiratory function test results between patients with ERD and NERD.

Conclusions: Our results suggest that microaspiration of stomach contents may cause surfactant damage, development of microatelectasis, and dead space expansion with consequent increase of intrapulmonary (venous) shunt.

key words: **GERD • intrapulmonary shunt • lung extraesophageal manifestations**

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Background

Gastroesophageal reflux disease (GERD), a disorder caused by the reflux of gastric contents into the esophagus, is associated with some respiratory diseases (eg, asthma, pulmonary fibrosis, and sleep apnea in adults) [1–7]. It is possible that microaspiration of gastric acid into the airways and lung parenchyma causes onset or exacerbation of chronic inflammation, while vagal mediated esophageal-bronchial reflex participate in the onset or worsening bronchoconstriction [8–10]. Both of these mechanisms may result in worsening of respiratory function observed in patients with respiratory diseases. Furthermore, when extraesophageal symptoms due to reflux are suspected, some current guidelines suggest an empiric trial of PPI therapy (provided there are no red flag signs or symptoms such as dysphagia and weight loss) [3]. The response to antireflux therapy has ranged from 60% to 98% in patients with suspected extra-esophageal reflux-related symptoms, and studies often have shown mixed results, leading to confusion regarding the importance of the association between reflux and extraesophageal symptoms [3,11–14].

However, it is possible that airway inflammation and/or bronchoconstriction due to microaspiration or esophageal reflexes are not the only mechanisms contributing to the worsening of respiratory function. We hypothesized that microaspiration of gastric contents into the lungs may cause damage to the surfactant, with the consequent collapse of alveoli and development of microatelectasis. This is manifested by impaired diffusion of gases and with expansion of dead space, which is reflecting as an increasing intrapulmonary shunt. Therefore, in the present study we aimed to evaluate the differences in the existence and size of dead space in patients with and without GERD expressed through the size of intrapulmonary shunt.

Material and Methods

This case-control study was conducted from January 2009 to March 2010 in the Department of Internal Medicine, Split Clinical Hospital Center, Split, Croatia. The study enrolled 86 subjects – 43 patients referred for endoscopy because of symptoms of GERD (heartburn, acid regurgitation, dysfagia) and 43 healthy subjects without GERD symptoms. The studied groups consisted of 14 (32.6%) males and 29 (67.4%) females with similar anthropometric characteristics. We excluded patients with acute or chronic pulmonary diseases, pregnancy, laryngeal stenosis, obesity (BMI $\geq$30 kg/m^2), cardiac, renal, and liver diseases, alcohol and tobacco use, and use of any medication with potential effects on test parameters (eg, theophylline, corticosteroids, acid-suppressive drugs such as proton-pump inhibitors and histamine-2-receptor antagonists, and non-steroidal anti-inflammatory drugs). The study was conducted according to the principles of the Declaration of Helsinki and was approved by the hospital ethics committee. All participants enrolled in the study gave informed consent.

Endoscopic assessment

Esophagogastroduodenoscopy (EGDS) was performed (Olympus Evis Exera II – 2951 Olympus Medical System Corp., Tokyo, Japan) in GERD patients. EGDS was performed under local anesthesia (Xylocain spray; Astra, Wedel, Germany) and the patients received verbal reassurance and no medication. The endoscopic examinations were performed by 2 experienced endoscopists blinded to other patients' clinical and laboratory characteristics, and examinations were successfully completed and well tolerated by all patients.

The diagnosis of esophagitis was made based on the Los Angeles classification [15,16]. Based on endoscopy findings, patients were classified into the erosive reflux disease (ERD) group (patients with definite endoscopic evidence of reflux esophagitis) and the non-erosive reflux disease (NERD) group (patients with typical reflux symptoms but with normal endoscopy findings).

Pulmonary function tests

Lung function studies were performed for all participants in this study by a qualified technician blinded to the presence or severity of GERD. We used a Cosmed-PFT4ergo (Rome, Italy) device equipped with bidirectional digital turbine flowmeter, oxygen sensor (O_2), carbon dioxide sensor (CO_2), carbon monoxide sensor (CO) and methane sensor (CH_4). Software used was PFT suite version 8.0b. All measurements were performed in accordance to the Pulmonary Function Test Guidelines established in 2005 by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) [17]. Values are reported as percent predicted values proposed by the European Coal and Steel Community in 1983 [18]. All of the following respiratory functions were considered and recorded; forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), FEV1/FVC, peak expiratory flow (PEF) and forced expiratory flow at 25%, 50%, and 75% of the vital capacity (FEF 25–75%). All of these respiratory functions are reported as percent predicted values. Values less than 80% of predicted value were considered abnormal.

Single-breath diffusing capacity of the lung for carbon monoxide (DLCO) was measured using a rapid carbon monoxide and methane analyzer, which was calibrated prior to each measurement. Values for DLCO and DLCO/VA corrected for alveolar volume (VA) [DLCO/VA] were obtained and expressed as percent of predicted value [19]. Values less than 80% of predicted value were considered abnormal. Standardization of the single-breath determination of carbon monoxide uptake in the lung was in accordance with the Pulmonary Function Test Guidelines established in 2005 by the ATS/ERS [20].

Intrapulmonary shunt (venous shunt – QS/QT) was determined by the oxygen method, by measuring the Acid-Base Status (ABS) and blood gases before and after breathing 100% oxygen for 15 min (ABL5; Radiometer; Kopenhagen; Denmark). Value of the shunt was read out from the nomogram by Chiang [21]. Values less than 5% were considered normal.

Statistical analysis

Statistical analysis was performed using the StatSoft statistical software package (Statistica 8). Continuous data are presented as the mean and standard deviation (M ±SD).

Table 1. Anthropometric characteristics of the study population.

Variables	GERD n=43	non-GERD n=43	p	ERD n=23	NERD n=20	p
Age (years)	52.1±13.6	51.3±13.5	0.793	46.9±12.6	58.0±12.4	0.006
Height (cm)	169.6±8.8	167.2±8.6	0.203	171.4±8.6	167.6±8.7	0.149
Weight (kg)	75.7±16.5	73.6±16.7	0.543	73.4±17.3	78.5±15.5	0.321
BMI (kg/m^2)	26.2±4.5	26.1±4.6	0.971	24.7±4.1	27.9±4.5	0.020

Values are expressed as mean ±SD.

Table 2. Lung function test results.

Variables	GERD n=43	non-GERD n=43	p	ERD n=23	NERD n=20	p
FVC,% pr.	107.2±12.5	102.6±6.8	0.034	111.9±11.4	101.9±11.7	0.007
FEV1,% pr.	104.9±15.1	97.2±5.1	0.002	108.4±11.5	100.9±18.0	0.103
FEV1/FVC,%pr.	105.7±13.3	95.1±7.5	0.001	103.3±8.4	108.5±17.1	0.199
PEF,% pr.	88.2±21.2	105.4±5.5	0.001	92.6±21.9	83.2±19.7	0.148
FEF75,% pr.	88.7±25.0	97.5±6.2	0.058	93.3±25.1	83.4±24.4	0.200
FEF50,% pr.	93.6±31.0	94.5±5.5	0.850	95.1±26.5	91.8±36.2	0.731
FEF25,% pr.	93.2±35.5	92.3±5.6	0.859	96.7±39.1	89.3±31.4	0.503

% pr. – % of predicted value. Values are expressed as mean ±SD. Differences between groups were assessed using the Student's *t* test.

Table 3. DLCO, DLCO/VA and QS/QT test results.

Variables	GERD n=43	non-GERD n=43	p	ERD n=23	NERD n=20	p
DLCO, % pr.	88.1±19.1	96.7±5.9	0.006	83.6±16.9	93.3±20.5	0.094
DLCO/VA, % pr.	83.2±21.3	99.1±5.8	0.001	82.8±19.7	83.6±23.5	0.907
QS/QT, %	6.0±3.0	3.5±0.5	0.001	6.2±2.7	5.7±3.4	0.566

% pr. – % of predicted value. Values are expressed as mean ±SD. Differences between groups were assessed using ANOVA with the Tukey method of *post hoc* analysis.

The normality of distribution was assessed by Kolmogorov-Smirnov test. The differences between groups were assessed using Student's *t* test. One-way analysis of variance (ANOVA) with the Tukey method of post-hoc analysis was used to analyze the means of grouped data. All statistical tests were 2-sided. The level of statistical significance was defined as $p<0.05$.

Results

A total of 86 participants were recruited for the study. They were categorized into the GERD group (n=43), which was further subdivided into an ERD group (n=23) and a NERD group (n=20), and the control group (n=43). The basic anthropometric characteristics are presented in Table 1. Differences between ERD and NERD group in age (p=0.006) and BMI (0.020) were observed. Differences between studied groups in other anthropometric characteristics were not observed.

Results of pulmonary function tests are presented in Table 2. Mean values of lung function tests of all groups expressed as a percentage of predicted value were mostly within the normal range. Statistically significant differences between GERD and non-GERD groups in FVC (p=0.034), FEV1 (p=0.002), FEV1/FVC (p=0.001), and PEF (p=0.001) were observed. Significant differences between FEF 25%-75% were not revealed. The only statistical significant difference between ERD and NERD groups was FVC value (p=0.007).

Values of DLCO (p=0.006) and DLCO/VA (p=0.001) were significantly lower and QS/QT was significantly higher (p=0.001) in the GERD than in the non-GERD group (Table 3). However, in both groups the average values of DLCO and DLCO/VA expressed as a percentage of predictive values were within normal range. In contrast, the value of QS/QT in the GERD group showed a pathological mean value (6.0%).

Discussion

The results of our study demonstrated significant differences in respiratory function tests in GERD patients as compared

with non-GERD patients. However, according to previous studies that have shown an impairment of gas exchange and/or impairment in spirometric functions [22,23], our study for the first time revealed significant differences in QS/QT values between both groups. In that context, our results suggest extension of pulmonary dead space as the potential new additional mechanism responsible for lung function damage in GERD patients. At the same time, our results did not confirm a possible difference in respiratory function between groups with (ERD) or without (NERD) endoscopicaly presented esophageal injury. The possible explanation could be that for the symptoms of extraesophageal reflux, lower esophageal sphincter weakness is more important than the inflammation of the esophagus. A limitation of our study is its small sample size. Further studies with larger numbers of patients are required to clarify possible difference in respiratory function between these 2 groups patients.

Although gastroesophageal reflux is known to be associated with some forms of respiratory disease [1–4], the impact of gastroesophageal reflux on respiratory parameters has been most frequently studied in patients with asthma [6,7]. There is growing epidemiological evidence of an association between GERD and asthma, as well as of a strong correlation between reflux episodes and respiratory symptoms [6]. It has been reported that patients with esophagitis are more likely to have asthma than patients without esophagitis. Also, an improvement in asthma symptoms and lung function associated with medical or surgical treatment for severe gastroesophageal reflux has been observed in several studies [11–14,24]. Moreover, current guidelines suggest that patients with both asthma and symptomatic GERD should be treated with acid-suppressive medications. Consideration of antireflux medication for patients who have poorly controlled asthma without GERD symptoms has also been proposed [3,7,11–14].

The most frequently cited mechanisms by which a gastroesophageal reflux affects lung function are aspiration of gastric fluid into the airways and lung parenchyma with consecutive chronic inflammation and its progression to pulmonary fibrosis, which results in airway obstruction and gas exchange impairment, and bronchoconstriction caused by vagal-mediated esophageal-bronchial reflex [5,6,8–10]. Our results suggest that potential mechanisms responsible for the impairment of lung function may include microaspiration into the tracheobronchial tree and alveoli causing surfactant damage and development of microatelectasis, which result in impairment of gas diffusion and ventilation/perfusion ratio maldistribution. Specifically, development of microatelectasis resulted in dead space expansion, which is manifested as increased value of intrapulmonary shunt (Q_S/Q_T). However, statistically significant differences in spirometric functions and diffusion parameters in GERD as compared to non-GERD groups also confirm both previously cited pathophysiological mechanisms associated with respiratory dysfunction in patients with gastro esophageal reflux. Importantly, in GERD and non-GERD groups the average values of spirometric and diffusing capacity parameters expressed as a percentage of predictive values were within normal range. In contrast, only the value of Q_S/Q_T, which reflects intrapulmonary shunt due to dead space extension, in the GERD group showed a pathological value.

Previously studies have revealed statistically significant differences in respiratory symptoms and functional tests in GERD patients, with a positive correlation with degree of gastroesophageal reflux severity [22,23]. Maher and Darwish reported serious loss of respiratory function in ERD compared with NERD patients [24]. Contrary to their results, in our study there were no significant differences in respiratory function test results between patients with ERD and patients with NERD.

The results of our study are reinforced by the fact that our study groups lacked other conditions with potential impact on lung function (eg, tobacco use, renal or hepatic disease, cardiac, pulmonary or connective tissue disease). Therefore, it is unlikely that another cause may significantly affect the demonstrated changes.

Recently, it has been reported that gastroesophageal reflux may contribute to the pathogenesis of idiopathic pulmonary fibrosis [25,26]. Our results suggest the possibility that early recognition and treatment of gastroesophageal reflux may be able to prevent loss of lung function and possibly influence the course of lung disease causally associated with GERD.

Conclusions

Our results confirmed the correlation between GERD and damaged lung function. Moreover, besides the earlier mentioned mechanisms (decreased gas exchange capacity due to direct damage of the alveolocapillary membrane and impaired functional test results because of neural mediated bronchoconstriction), our results suggest an additional pathological mechanism – development of intrapulmonary shunts due to the microatelectasis resulted from surfactant damage caused by microaspiration of stomach contents. Finally, pathological values of lung function test results in GERD patients with mild respiratory symptoms or without them impose the need for early lung function testing in all GERD patients in order to detect subclinical loss of lung function.

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