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## Lung diffusion capacity in children with respiratory symptoms and untreated GERD

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**Background:** Gastroesophageal reflux disease (GERD) is associated with many respiratory disorders, among which, chronic cough, laryngitis, and asthma are among the most common. We investigated lung function, including gas diffusion capacity, in children with poor asthma control or chronic laryngitis with untreated GERD.


**Material/Methods:** A total of 71 children, aged 6–17 years, with chronic respiratory and other symptoms suggestive for GERD, were enrolled and divided into 2 groups: chronic laryngitis and asthma. Participants underwent 24-hour pH monitoring and lung function assessment, measurement of single-breath diffusing capacity of the lung for carbon monoxide ( $DL_{CO}$ ), and fraction of exhaled nitric oxide ( $F_eNO$ ) measurement.

**Results:** 24-hour pH monitoring was positive for GERD in 92.1% of preselected children with asthma and 90.1% of children with chronic recurrent laryngitis. All flows ( $PEF$ ,  $MEF_{75}$ ,  $MEF_{50}$ , and  $MEF_{25}$ ) were significantly lower in the asthma group, while  $F_eNO$  and  $DL_{CO}$  were significantly lower in the laryngitis group. A significant inverse relationship was found between  $DL_{CO}$  and all reflux indexes in the laryngitis group. Each unit change of Johnson-DeMeester score and Boix-Ochoa score increased the odds for significantly lower  $DL_{CO}$  in laryngitis patients by 3.9% and 5.5%, respectively.

**Conclusions:** In children with uncontrolled asthma and chronic laryngitis, the regurgitation of gastric contents due to GERD contributes to poor asthma control and aggravation of chronic laryngitis. Despite having normal lung function, the gas diffusion capacity should be controlled in patients with GERD and chronic laryngitis, and it might be the very first abnormality in distal airways.

**MeSH Keywords:** **Pulmonary Diffusing Capacity • Laryngitis • Asthma • Gastroesophageal Reflux**

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## Background

Gastroesophageal reflux disease (GERD), the retrograde movement of gastric contents into the esophagus, is a common disorder associated with many forms of respiratory disorders, including asthma, COPD, pulmonary fibrosis, cystic fibrosis, scleroderma [1–4], and obstructive sleep apnea syndrome [5]. Untreated GERD impairs quality of life and can lead to respiratory and esophageal complications, including esophagitis, ulcerations, stricture, hemorrhage, and Barrett's esophagus (replacement of squamous epithelium with columnar epithelium, along with its tendency to become malignant) [6]. The spectrum of problems associated with GERD has expanded to extra-esophageal sites [7]. Chronic cough, laryngitis, and asthma are 3 major clinical problems that can be caused or triggered by GERD associated with dyspnea [8,9]. The exact relationship between GERD and asthma has been a source of constant debate. Asthma is a serious global health problem [10]. People of all ages and in countries throughout the world are affected by this chronic airway disorder that, when uncontrolled, can place severe limits on activities of daily life. The prevalence of asthma is increasing, especially among children. More recently, GERD has increasingly been appreciated as a common daily occurrence in children and adolescents. Asthma and GERD often present in tandem, with their coexistence being more frequent than would be expected for a chance occurrence [11]. GERD is more prevalent in asthmatics in comparison with a control population, and asthmatics frequently associate GERD symptoms (heartburn, regurgitation, swallowing difficulties) with their asthma symptoms [12]. Systematic reviews among adults with asthma show prevalence of GERD to be close to 60% [13]; whereas in children with asthma, prevalence of GERD is estimated to 19.3–80% [14]. Prevalence data vary across groups and may be dependent on whether acid reflux is defined by presence of symptoms or by abnormal results of 24-hour pH testing [15]. There are differences in clinical features of asthma regarding intensity of esophageal acid exposure in children. Symptoms of asthma in non-atopic individuals with early onset and difficult-to-control nighttime asthma attacks suggest the possibility of concomitant relevant GERD [16]. Dyspnea, as the most bothersome symptom in asthma and laryngitis (aside from airway obstruction) can be caused by low diffusing capacity of lungs due to interstitial involvement. Interstitial chemical pneumonitis in GERD is a result of micro- or macro-aspiration [17]. Recent studies suggest obtaining measurements of diffusing capacity in patients with GERD, while their dyspnea could be related to gas exchange impairment despite normal lung function [18]. The aim of our study was to assess the association of the level of the acid gastroesophageal reflux and the level of impairment of lung function, including gas diffusion, in children with uncontrolled asthma and/or chronic laryngitis.

## Material and Methods

### Patients

Seventy-one children and adolescents (6–17 years of age) of both sexes (30 boys and 41 girls) were preselected based on chronic respiratory (cough, sore throat, and hoarseness) and other symptoms (heartburn, regurgitation, nausea, and swallowing difficulties) suggestive for GERD and were prospectively evaluated. Informed consent was obtained from older children and adolescents and parents of all participants. The study was approved by the Ethics Committee of Children's Hospital Srebrnjak and conducted according to the guiding principles of the World Medical Association Declaration of Helsinki.

Patients had either uncontrolled asthma or chronic or recurrent laryngitis (suggestive for GERD) with no medical history of other relevant chronic respiratory disease. Thirty-eight (53.5%) patients had asthma and 33 (46.4%) were diagnosed with chronic or recurrent laryngitis. Asthma patients were previously diagnosed, regularly followed, and treated in our hospital, but in spite of the treatment (regular anti-inflammatory therapy) their asthma was uncontrolled or partially controlled according to GINA guidelines [19]. A full medical history was taken and a physical examination was performed. Information gathered from patients included: medical history, symptoms suggestive for GERD (heartburn, acid regurgitation, aggravated cough with intake of food that decreases lower esophageal sphincter pressure [e.g., chocolate, caffeine, peppermint, alcohol, and high-fat-containing foods]), hoarseness—especially in the morning, and weight gain before the onset of cough), previous diagnostic procedures, and medication usage [20]. None of the patients had previously undergone diagnostic procedures for GERD (either endoscopy or 24-h esophageal pH monitoring) or was treated with proton pump inhibitors or H<sub>2</sub> antihistamines. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. None of the patients had a BMI >95 percentile for age or BMI >30 kg/m<sup>2</sup> (for children older than 12 years). All patients were carefully examined by an ENT specialist for chronic laryngitis, which was defined as hoarseness, sore throat, weak or absent voice, constant need to clear the throat, and dry cough. Routine laboratory tests were performed, including CBC, hemoglobin level, C-reactive protein, blood glucose, and liver and kidney function tests.

### 24-hour pH monitoring and lung function

All patients underwent 24-hour pH monitoring as the criterion standard for the GERD diagnosis and the lung function assessment [21,22]. Twenty-four-hour pH monitoring was performed using a pH-probe (Medtronic). Spirometry was done using a computerized spirometer (Spirovit SP-200, Ganshorn,

**Table 1.** Patient demographics.

Characteristics	All (n=71)	Asthma (n=38)	Laryngitis (n=33)	Statistics	p
Sex, girls (%)	41 (57.8)	17 (44.7)	24 (72.7)	$\chi^2=5.671$	0.0173
Age, mean (SD), yrs	12.1 (3.1)	12.1 (3.4)	12.1 (2.7)	t=-0.052	0.9585
BMI, mean (SD), kg/m <sup>2</sup>	19.99 (3.60)	19.90 (3.76)	20.09 (3.46)	t=-0.203	0.8399

**Table 2.** Results of the 24h-pH monitoring.

Acid reflux indexes and number of reflux episodes	Asthma (n=38)	Laryngitis (n=33)	Statistics*	p
Positive fraction time with pH<4, mean (SD),%	5.62 (3.43)	7.05 (7.83)	t=-0.316	0.7526
Boix-Ochoa score, mean (SD)	37.75 (28.72)	44.84 (42.93)	t=-0.165	0.8692
Johnson-DeMeester score, mean (SD)	37.14 (31.48)	40.41 (37.50)	t=0.283	0.7779
No. of reflux episodes (total), mean (SD)	174 (102)	185 (223)	t=-0.830	0.4121
No. of reflux episodes (upright), mean (SD)	95 (72)	71 (68)	t=-1.163	0.2526
No. of reflux episodes (supine), mean (SD)	81 (63)	115 (175)	t=-0.530	0.5994
No. of long refluxes (total), mean (SD)	1.5 (1.9)	2.4 (2.6)	t=1.495	0.1438
No. of long refluxes (upright), mean (SD)	0.7 (1.6)	0.6 (0.8)	t=1.173	0.2486
No. of long refluxes (supine), mean (SD)	0.7 (1.1)	1.5 (2.1)	t=1.700	0.0979

\* Student's t-test was performed using normalized values for all reflux indexes and number of reflux episodes.

Germany) according to American Thoracic Society/European Respiratory Society (ATS/ERS) standards with the measurement of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV<sub>1</sub>), peak expiratory flow (PEF), maximal expiratory flow at 25 (MEF<sub>75</sub>), 50 (MEF<sub>50</sub>), and 75% (MEF<sub>25</sub>) of FVC, and are presented as a percent of predicted values [23,24]. Single-breath diffusing capacity of the lungs for carbon monoxide (DL<sub>CO</sub>) was measured using a rapid carbon monoxide and helium analyzer (PowerCube Diffusion, Ganshorn, Germany), which was calibrated prior to each measurement. Values for DL<sub>CO</sub> were obtained and reported as percent of predicted values according to ATS/ERS standards [25]. The single-breath, constant flow technique for fraction of exhaled nitric oxide (F<sub>E</sub>NO) measurement was used with the optimum flow rate of 50 mLs<sup>-1</sup> (Niox, Aerocrine AB, Sweden) according to ATS recommendations [23].

### Statistical analysis

Statistical analysis was performed using STATISTICA for Windows, version 7.1 (StatSoft, Inc. Tulsa, OK, USA). Minimal sample size per group (N=29) was calculated based on expected rho=0.5 with alpha=0.05 and statistical power of 80%. Basic descriptive summaries of data were obtained. Normality of quantitative variables was tested using the Kolmogorov-Smirnov test. Variables not having a normal distribution (reflux indexes and F<sub>E</sub>NO) were normalized using logarithmic transformation. Differences between investigated groups were

calculated using the chi-square test for categorical variables and Student's t-test for quantitative variables. Univariate and multivariate regression analyses were used to test for associations between variables. P<0.05 was considered as statistically significant for all analyses.

### Results

Patient demographics are presented in Table 1. There were more boys (55.3%) in the asthma group and more girls (72.7%) in the laryngitis group (p=0.0173). There were no significant differences for age and BMI between the groups with comparable data for both groups (p>0.05).

Three patients in both groups (7.9% in the asthma group and 9.1% in the laryngitis group) were negative for acid GER based on results of 24-h pH monitoring according to positive fraction time with pH<4, Boix-Ochoa or Johnson-DeMeester scores ( $\chi^2=0.012$ ; p=0.9112). Data presenting positive fraction time with pH<4, Boix-Ochoa and Johnson-DeMeester scores comparing groups are presented in Table 2. No significant differences for all of the acid reflux indexes between groups were found (p>0.05 for all, Table 2).

Lung function measurements are presented in Table 3. There were no significant differences between groups for FVC and FEV<sub>1</sub>

**Table 3.** Results of the lung function measurements.

Lung function parameters	Asthma (n=38)	Laryngitis (n=33)	Statistics*	p
FVC, mean (SD),% predicted	94.11 (13.24)	93.06 (9.83)	t=0.373	0.7105
FEV <sub>1</sub> , mean (SD),% predicted	91.53 (17.27)	98.94 (13.90)	t=-1.972	0.0526
PEF, mean (SD),% predicted	83.64 (15.22)	91.84 (16.39)	t=-2.140	0.0361
MEF <sub>75</sub> , mean (SD),% predicted	81.51 (17.05)	93.06 (19.28)	t=-2.641	0.0103
MEF <sub>50</sub> , mean (SD),% predicted	79.05 (21.39)	96.42 (26.94)	t=-3.027	0.0035
MEF <sub>25</sub> , mean (SD),% predicted	77.00 (27.18)	98.52 (36.21)	t=-2.853	0.0057
DL <sub>CO</sub> , mean (SD),% predicted	101.16 (20.63)	89.55 (23.96)	t=2.195	0.0316
F <sub>E</sub> NO, mean (SD), ppb	17.65 (15.22)	10.31 (5.61)	t=2.891*	0.0053

\* Student's t-test was performed using normalized values for F<sub>E</sub>NO.

(p=0.7105, p=0.0526; respectively), although FEV<sub>1</sub> was lower in the group with asthma (mean ±SD, asthma=91.53±17.27% predicted; laryngitis=98.94±13.90% predicted). All flows (PEF, MEF<sub>75</sub>, MEF<sub>50</sub>, and MEF<sub>25</sub>) were significantly lower in the asthma group (p=0.0361, p=0.0103, p=0.0035, p=0.0057; respectively). F<sub>E</sub>NO was significantly lower in the laryngitis group (mean±SD, asthma=17.65±15.22 ppb; laryngitis=10.31±5.61 ppb; t=2.891, p=0.0053). DL<sub>CO</sub> was also significantly lower in the laryngitis group (mean ±SD, asthma=101.16±20.63% predicted; laryngitis=89.55±23.96% predicted; t=2.195, p=0.0316), having a larger proportion of patients with values below the lower limit of normal (DL<sub>CO</sub> <70% of expected, asthma – 8.3%; laryngitis 21.2%).

A significant inverse correlation was found between DL<sub>CO</sub> and all reflux indexes: positive fraction time with pH <4, r=-0.461, p=0.007; Johnson-DeMeester score, r=-0.428, P=0.013; Boix-Ochoa score, r=-0.498, P=0.003 in patients with laryngitis. Also, in patients with laryngitis, a significant association was found for BMI with DL<sub>CO</sub>, inverse association of Boix-Ochoa score and F<sub>E</sub>NO, and marginal association with FVC (r=0.528, p=0.004; r=-0.401, p=0.038; r=0.374, p=0.050; respectively). On the contrary, no significant association was found in asthma patients between DL<sub>CO</sub> and reflux indexes (r=0.204, p=0.220; r=0.044, p=0.792; r=-0.099, p=0.556; respectively) or for other lung function parameters with reflux indexes, age, or BMI (p>0.05 for all). Univariate logistic regression showed that each unit change of Johnson-DeMeester score and Boix-Ochoa score increases the odds for significantly lower DL<sub>CO</sub> in laryngitis patients by 3.9% (OR 1.039, 95% CI 1.005–1.074, p=0.0197) and 5.5% (OR 1.055, 95% CI 1.014–1.098, p=0.0055), respectively. Multivariate stepwise regression analysis showed BMI and positive fraction time with pH<4 as significant independent predictors for DL<sub>CO</sub> in laryngitis patients (BMI β=0.460, SEβ=0.1489, t=3.091, p=0.0048; positive fraction time with pH<4 β=-0.430, SEβ=0.1489, t=-2.889, p=0.0079; R=0.677, F=10.598, p=0.0005 for the model).

## Discussion

The main finding of this study was the association of the level of severity of acid reflux in GERD with a reduction in gas diffusion capacity of lungs, demonstrated by a significant inverse correlation between DL<sub>CO</sub> and reflux indexes in patients with chronic/recurrent laryngitis and GERD. In multivariate analysis, reflux index and BMI were found to be significant predictors for DL<sub>CO</sub> in children with chronic laryngitis. Also, higher intensity of GERD (suggested by higher reflux index) was associated with lower level of eosinophil inflammation (suggested by lower levels of F<sub>E</sub>NO). There did not appear to be any other relevant part of the medical history to account for these gas exchange abnormalities. On the contrary, in patients with uncontrolled asthma and GERD, no significant association between DL<sub>CO</sub> and reflux indexes was found.

The possible explanation for these findings lies in the pathophysiological mechanisms of GERD. Gastroesophageal reflux – the movement of gastric contents in esophagus and throat – is connected with a number of respiratory conditions [18,26], including asthma exacerbations, pulmonary fibrosis, cystic fibrosis, obstructive sleep apnea syndrome, and the beginning and development of chronic laryngitis. As for the association of GERD with chronic laryngitis, laryngeal mucosa is believed to be more sensitive than esophageal mucosa because of the poorer expression of carbonic anhydrase, an enzyme which is one of the main components of mucosal protection [27,28]. This fact suggests that laryngeal tissue may be more susceptible to acid-induced injury.

Mechanisms explaining GERD's relation to asthma and asthma exacerbations include a vagally-mediated reflex triggered by acid in the esophagus [27,29,30], a local axonal reflex [31], heightened bronchial reactivity [32,33], and micro-aspiration of gastric acid [34,35]. The esophagus and bronchial tree share

the same embryonic foregut origin. Thus, acid in the esophagus, due to GERD, could stimulate acid-sensitive receptors, initiating a vagally-mediated reflex through shared esophageal and bronchial autonomic innervation.<sup>29</sup> Stimulation of esophageal acid-sensitive receptors interacts with cholinergic bronchial tone by vagally-mediated reflex, suggesting that GERD aggravates asthma by increasing bronchomotor responsiveness to other stimuli [36]. Another potential mechanism through which GERD affects lung function is aspiration of acid or bulk fluid into the airways, followed by aspiration into the lung parenchyma or alveolar tissue causing chronic inflammation; this micro-aspiration theory has been confirmed by many authors [34,35]. Chronic inflammation in the lung parenchyma may progress to pulmonary fibrosis with airway obstruction and gas exchange impairment.

Reduction in gas diffusion capacity of lungs in children diagnosed with chronic laryngitis in our study could be, therefore, explained by chemical inflammation (chemical pneumonitis) caused by acid aspiration. However, if the reason for inflammation lies in aspiration, the question that rises is, why was the same reduction in gas diffusion capacity not found in asthmatic patients with GERD, which also have regurgitation and aspiration, as well as laryngitis patients? This could be explained at least partly by the regular use of anti-inflammatory treatment (especially inhaled corticosteroids) that non-specifically suppresses inflammation in lung tissue and thus lessen tissue damage. Asthma as a chronic inflammatory disorder of the airways has been shown to have a higher gas exchange capacity, most probably because of the enhanced blood flow (in our study,  $DL_{CO}$  in asthmatics was 65–151% the expected flow) [37].

The inverse correlation between  $DL_{CO}$  and reflux indexes in patients with chronic laryngitis and GERD found in our study suggests that patients with severe GERD have greater reduction in gas diffusion capacity. Because  $DL_{CO}$  represents a comprehensive measure of alveolar-capillary gas exchange, lower values of  $DL_{CO}$  manifest more interstitial impairment, so we can speculate that more severe GERD can cause a chronic chemical pneumonitis to such an extent that it results in a clinically relevant impairment of lung diffusion capacity. Such a correlation was not shown for our asthmatic patients. Because patients with GERD and impaired  $DL_{CO}$  do not necessarily manifest low results on spirometry, we recommend evaluation of  $DL_{CO}$  in patients with GERD, even in cases with normal lung function tests (spirometry, body plethysmography).

Previously published results of GERD and gas diffusion reduction association are very limited; moreover, the published studies were conducted in adults. The association of gas exchange impairment in adult patients with severe GERD, who presented for obesity surgery, was reported by Schachter et al. [38] Patients enrolled in their study had no other lung

disease than asthma. Patients with severe GERD and asthma had reduced levels of diffusing capacity of the lungs for carbon monoxide compared with those patients without GERD, and there was no significant difference in other measures of lung function [38]. Anvari et al. showed an improvement in  $DL_{CO}$  at 6 and 12 months after Nissen fundoplication surgery for severe GERD [39]. Our study differs from the above-mentioned studies in study population (children vs. adults) and the fact that all included patients were previously diagnosed with asthma or chronic laryngitis with normal lung function and with a BMI <95 percentile for age or <30 kg/m<sup>2</sup> for children older than 12 years.

There are only a few studies on chemical pneumonitis in correlation with gastric content aspiration [40]. Pathogenesis of lung injury caused by acid aspiration is described by cascade of various substances such as cytokines, which are complements that activate neutrophils as primary mediators in acid aspiration pneumonitis. By conducting scintigraphy in patients with GERD, Ravelii et al. found 46% of patients with GERD also have aspiration; thus, they defined aspiration as the underlying reason for respiratory symptoms in their group of patients [41]. A study by Kudoh et al. identified GERD as an important risk factor for recurrent acute lung injury [42].

Mise et al. also studied the influence of gastroesophageal reflux in the lungs, focusing on the effect of GER on lung function and  $DL_{CO}$ . They also studied whether microaspiration of gastric contents directly influences non-specific inflammation in the lungs [18]. Comparing patients with recently diagnosed GERD and healthy controls, they found lower  $DL_{CO}$  in patients with GERD. As a conclusion, they recommended evaluation of  $DL_{CO}$  in patients with GERD [18]. Bonacin et al. showed statistically significant differences between GERD and non-GERD groups in FVC, FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, and PEF in their research on 86 patients. Among GERD group, values of  $DL_{CO}$  and  $DL_{CO}/VA$  were significantly lower and intrapulmonary shunt was significantly higher in comparison with the non-GERD group, confirming the correlation between GERD and damaged lung function. Their results suggest an additional pathological mechanism – development of intrapulmonary shunts due to the microatelectasis resulting from surfactant damage caused by microaspiration of stomach contents. The authors stated the need for early lung function testing in all GERD patients to detect subclinical loss of lung function, and they observed pathological values of lung function tests both in symptomatic and asymptomatic GERD patients [43].

The association between gastroesophageal reflux and asthma has not been clearly defined, and different studies show conflicting results in terms of whether GERD triggers asthma. There are a number of asthmatic patients with evaluated regurgitation, still not having GERD or their asthma not being

influenced by regurgitation. One fact should be emphasized: asthmatics are a heterogeneous group of patients in respect to their responses to different triggers; they demonstrate different sensitivity to a variety of stimuli (allergens, exercise, cold air, respiratory tract infections, air pollution, cigarette smoke, regurgitation, and stress). It is unlikely to clearly identify which factor or factors are leading to aggravation of asthma in a patient. It is not a surprise that some patients with GERD note an association between their GERD and respiratory symptoms, whereas others do not [44].

Asthmatic patients that were enrolled in our study had uncontrolled or partially controlled asthma in spite of adequate treatment regimen and compliance regarding medication usage. In such a subpopulation of asthmatics, a high prevalence of GERD can be found (in our study 92.1% asthmatics had positive acid GER). It is believed that in this subgroup of asthmatic patients GERD in some way contributes to the refractive nature of asthma [32,45–47]. Legget et al. conducted a study assessing GER in patients with difficult-to-control asthma and reported prevalence of reflux to be 55% or 35%, depending on the pH probe being in the distal or proximal part of the esophagus. Wong et al. reported that 56.7% of patients with difficult-to-control asthma were diagnosed with GERD [45,48].

The correlation of GERD with impaired lung function can be verified through improvement of lung function after being treated for GERD – either with proton pump inhibitors (PPI) or surgical (fundoplication) treatment. Studies regarding benefits of PPI treatment in patients with GERD and asthma reveal conflicting results. Early trials have reported improvement in pulmonary symptoms in patients with PPI treatment. In 1994 Meier et al. [49] conducted a double-blind, placebo-controlled study that evaluated lung function in asthmatic patients treated with 20 mg of omeprazole twice a day for 6 weeks, and found a 20% increase in FEV<sub>1</sub> in 27% of patients. Kiljander et al. [50] conducted a double-blind trial where patients with asthma and GERD were randomized to receive esomeprazole 40 mg or placebo twice daily for 16 weeks, and came to the conclusion that treatment with PPI improves PEF in tested patients. In 2009, Miceli Sopo et al. [51] published a review on pediatric studies regarding the PPI used to treat GERD and effect on asthma symptoms. After analyzing 4 studies, the most appropriately conducted study was the one by Størdal et al. [52], concluding that acid suppression in children with GERD and asthma does not improve asthma symptoms. Although another 3 studies [53–55] reported very good results of PPI treatment in children, their methodology was far weaker than that of Størdal et al. [51].

These conflicting results can be explained by differences in study design and outcome measures. As commented in a review by Wong et al. [45], the sample size of many studies has

been small, some of them have measured reported improvement in asthma symptoms, and the others have measured improvement in lung function tests. It is possible that subjective improvement in asthma symptoms takes place before the objective improvement in lung function tests. Also, studies differ in terms of PPI dosage and the duration of the treatment.

Our literature search of usefulness of proton pump inhibitors in patients with chronic laryngitis and GERD also revealed conflicting results [56]. A few studies have shown improvement after PPI treatment [57–60]. When compared to a control group treated with placebo, lansoprazole improved symptoms of laryngitis. More recent studies did not show a benefit from PPI treatment [56,61–63].

The second therapeutic option for GER is fundoplication. Salminen et al. conducted research among 40 patients with proven reflux laryngitis who underwent fundoplication, and revealed long-term benefit from surgical treatment [64]. The benefit from fundoplication in children with GERD was confirmed recently by Loots et al. [65].

Performing continuous follow-up on our study group of patients during and after finishing anti-reflux treatment would be useful to demonstrate whether reduced level of DL<sub>CO</sub> would normalize after PPI treatment. Its normalization would confirm our assumption that GERD has a great impact on the diffusing capacity of patients with chronic laryngitis.

## Conclusions

After performing 24-hour pH monitoring in a preselected group of patients with symptoms suggestive for GERD and having a poor asthma control or with chronic/recurrent laryngitis, we found acid GER in 92.1% of patients in the asthmatic group and 90.9% in the chronic laryngitis group. We found an inverse correlation of DL<sub>CO</sub> and reflux indexes in the chronic laryngitis group, with 21% of patients with clinically significant low DL<sub>CO</sub> values despite normal lung function measured by spirometry. Based on these data, we suggest that in patients with chronic laryngitis, even with a normal lung function, the gas diffusion capacity should be controlled because it might be very first abnormality in distal airways. In conclusion, we recommend performing 24-hour pH monitoring and lung diffusion capacity in patients with poor asthma control and chronic laryngitis when the major cause of their symptoms could be GERD.

## Conflicts of interest

Authors: Mirić Mirjana, Turkalj Mirjana, Nogalo Boro, Erceg Damir, Perica Marija and Plavec Davor hereby declare no conflicts of interest.

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