Effect of gastroesophageal reflux disease on spirometry, lung diffusion, and impulse oscillometry

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Background Gastroesophageal reflux disease (GERD) is known to be associated with many forms of respiratory diseases, including asthma, pulmonary fibrosis, cystic fibrosis, and obstructive sleep apnea syndrome. It is frequently coexistent, and may be causative or may exacerbate pre-existing lung disease. The main purpose of this study was to assess the effects of GERD on spirometry, lung diffusion, and impulse oscillometry.

Patients and methods This study included 48 consecutive newly endoscopically diagnosed GERD patients with no pulmonary symptoms or previous smoking history who attended the Gastrointestinal Clinic at Ain Shams Hospital and Misr University for Science and Technology with complaints of reflux symptoms. Spirometry, lung diffusion, and oscillometry were performed in all included patients.

Results There were statistically significant differences between cases with different grades of reflux as regards age. Most of the patients were included within grade B GERD with the highest mean age being 46.33±11.51. However, there was no significant difference as regards sex. There were statistically significant differences between cases with different grades of reflux as regards forced expiratory volume at the first second/forced vital capacity, maximum expiratory flow 25–75, and diffusing capacity of the lung for carbon monoxide (DLCO), but there was a highly statistically significant difference regarding residual volume/total lung capacity and residual volume. The grade of reflux was the only independent factor affecting DLCO, and grade B patients showed lower DLCO compared with grade A patients. There was a statistically significant positive correlation between grades of reflux and forced expiratory volume at the first second/forced vital capacity, maximum expiratory flow 25–75, and maximum mid-expiratory flow/peak expiratory flow, and a statistically significant negative correlation between grades of reflux and R20. There was a negative correlation between grades of reflux and DLCO, but it was not significant.

Conclusion GERD severity is associated with impairment of gas exchange (DLCO) and central airway affection (R20) on impulse oscillometry. This may be due to microaspiration of gastric acid or fluid into the airways.

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Keywords: gastroesophageal reflux, lung diffusion, oscillometry, spirometry

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Introduction

Gastroesophageal reflux disease (GERD) occurs when the amount of gastric juice that refluxes into the esophagus exceeds the normal limit, causing symptoms with or without associated esophageal mucosal injury [1]. It is known to be associated with many forms of respiratory diseases, including asthma, pulmonary fibrosis, cystic fibrosis, and obstructive sleep apnea syndrome [2]. It is frequently coexistent and may be causative or may exacerbate pre-existing lung disease. The esophagus and lung share common embryonic foregut origins and vagal innervations, and hence it is not surprising that GERD is a potential asthma trigger, a cause of chronic cough, and may impact other lung diseases [3]. There are two major mechanisms by which GERD may influence the lung: a vagally mediated reflex, and microaspiration. Both mechanisms are active in both animal models and humans [4]. Abnormal esophageal peristalsis may be an important contributor to extraesophageal symptoms of reflux by prolonging esophageal acid clearance time (i.e. refluxate remains in the proximal esophagus for a longer time) [5]. It is increasingly recognized that gaseous or particulate acid or nonacid reflux is associated with a variety of respiratory conditions, including chronic cough [6], asthma, chronic obstructive pulmonary disease (COPD), and bronchiectasis [7]. Detection of pepsin and bile salts in bronchoalveolar lavage fluid provides unequivocal evidence of aspiration of refluxate into the lower respiratory tract, which is referred to as microaspiration in the absence of a classical major clinical aspiration event [8]. The potential mechanisms by which GERD affects lung function are aspiration of acid or bulk fluid into the airways and then aspiration into the lung parenchyma or alveolar tissue, causing chronic inflammation [9]. Chronic inflammation in the lung parenchyma may

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progress to pulmonary fibrosis with airway obstruction and gas exchange impairment. Lung inflammation, primarily mediated through neuroinflammatory mediators (substance P and tachykinins), also develops in response to esophageal acid. Gastroesophageal reflux is a frequent cause of chronic persistent cough [10]. Approximately 10% of chronic persistent coughpatients have prominent GERD symptoms; however, GERD can be clinically 'silent' in up to 75% of patients with GERD-related cough. Clinicians should suspect clinically silent GERD in the nonsmoker who is not exposed to irritants and who is not taking ACE inhibitors [11]. Empiric GERD therapy in selected patients results in cough resolution in 79% [12]. Asthmatics have a high GERD prevalence and have predisposing factors for GERD development. Therapy for GERD has the potential to improve asthma symptoms [13]. Similar to chronic cough, GERD may be clinically 'silent' in up to 65% of asthmatics who do not have GERD symptoms [14]. Patients with COPD have a higher incidence of heartburn and dysphagia and are more likely to use GERD medications than matched controls [15]. In all, 25% of the IPF patients with GERD did not have the 'typical' symptoms associated with GERD [16,17]. Histopathological analysis may support a diagnosis of reflux and aspiration in selected cases of pulmonary parenchymal injury [18]. A distinct histological pattern of 'centrilobular fibrosis' or 'peribronchiolar fibrosis' has been described that is possibly associated with GERD and aspiration [19]. It can be speculated that gastroesophageal reflux may play a role in the development of this distinct interstitial lung disease as aspirated material from gastroesohpageal and extraesophageal reflux would have a propensity to cause interstitial pneumonia. This type of reflux may elicit symptoms of hoarseness, throat clearing, cough, wheeze, and breathlessness, and the threshold for manifesting these symptoms depends on neural sensitivity of the larynx and airways [20]. The precise injurious agents in refluxate have not been characterized in detail but may include enzymes, acids, and bile salts. Nonetheless, the airways and alveoli would seem to be poorly designed to resist the noxious refluxate once it has traversed past the larynx. Some patients would respond to airway microaspiration with cough or wheeze, whereas in others the refluxate is transported to the distal airspaces, where it may induce alveolar epithelial injury or apoptosis. To evaluate these abnormalities more sensitive tools that are not dependent on patient effort are needed. Recently, the impulse oscillation system (IOS) has been introduced as a new system for the forced oscillation test. It is a noninvasive test, not dependent on the patient's effort, and measures airway resistance and compliance using electrical impulses [21].

Patients and methods

Samples and selection criteria (patients selection)

Between November 2013 and February 2015 we selected 48 consecutive newly diagnosed GERD patients among those who attended the Gastrointestinal Clinic at Ain Shams Hospital and Misr University for Science and Technology and had complaints of reflux symptoms. All patients gave signed, informed consent. A full medical history was taken and a physical examination was performed. The diagnosis of GERD was established by history, clinical manifestations, and endoscopy. Information on GERD included history, previous investigations, and medication usage. None of the patients had significant lung disease, and they were all nonsmokers, without COPD, asthma, or other respiratory disease. Patients who smoked and those with known respiratory diseases, ischemic heart disease, heart failure, liver disorders, or malignancies were excluded from the study. Also excluded were pregnant or lactating mothers and those who refused to undergo an upper gastrointestinal endoscopy. All enrolled patients underwent an upper gastrointestinal endoscopy conducted by an expert gastroenterologist using Olympus 160 equipment (Olympus GIF 160; Olympus company, Japan, Tokyo). Reflux esophagitis was defined as the presence of a mucosal break at the distal part of the esophagus and classified according to the Los Angeles (LA) Classification System. LA Classification of reflux esophagitis includes the following: LA grade A, $\geq$1 isolated mucosal breaks $\leq$5 mm long; LA grade B, $\geq$1 isolated mucosal breaks $>$5 mm long; LA grade C, $\geq$1 mucosal breaks bridging the tops of folds but involving $<$75% of the circumference; and LA grade D, $\geq$1 mucosal breaks bridging the tops of folds and involving $>$75% of the circumference [22] (Fig. 1).

Gastroesophageal reflux disease evaluation

The severity and frequency of heartburn, pain, or regurgitation were scored using the validated Vigneri scale (range: 0–27) [23]. No patients received proton pump inhibitors, H_2-blockers, or prokinetics agents before the study. The pH sensor was positioned using manometry. The reflux index was defined as the pH less than 4 or number of episodes with a pH less than 4 during 24 hours is diagnostic [24].

Pulmonary functional evaluation

Impulse oscillometry

All patients with reflux esophagitis underwent IOS testing by a force oscillation instrument (Enrich Jaeger, Hoechberg, Germany). Total impedance of the respiratory system determines the magnitude and phases of flow oscillation that result from pressure fluctuation. According to the relationship between

flow and pressure, 'respiratory impedance' can be subdivided into 'resistance and reactance' where 'resistance' represents the total effect of the lung and chest wall and 'reactance' shows the net effect of two opposite forces (elastic and inertial). We measured respiratory impedance for 30 s during tidal breathing. Respiratory resistance was measured at low frequency (5 Hz=R5) for total respiratory resistance and at high frequency (20 Hz or R20) for proximal respiratory resistance. Respiratory reactance was measured at a frequency of 5 Hz (Xr5). After comparing R5 and R20 with normal values, they were reported as the percentage of predicted value.

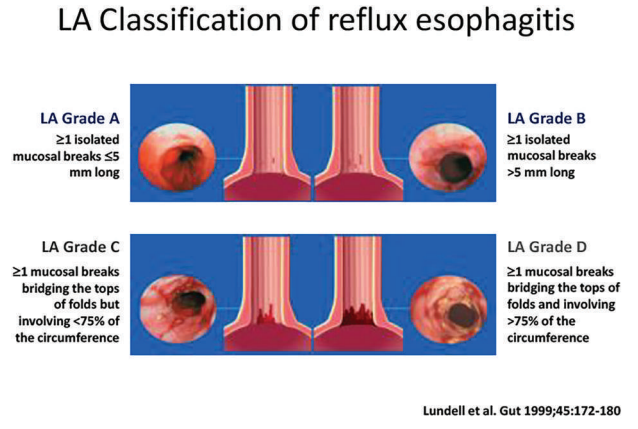
Spirometry

Spirometry was performed at the beginning of the study for each patient to measure forced vital capacity (FVC), forced expiratory volume at the first second (FEV_1), forced expiratory flow 25–75%, and peak expiratory flow rate. FEV_1 more than 80% of predicted value, FVC more than 80% of predicted value, FEV_1/FVC more than 70%, an forced expiratory flow 25–75% value that was more than 80%, and a peak expiratory flow rate more than 80% were all considered normal.

Diffusion lung capacity

Single-breath diffusing capacity of the lung for carbon monoxide (DLCO) was measured using a rapid carbon monoxide and methane analyzer, which was calibrated before each measurement. Values for DLCO and DLCO corrected for alveolar volume (V_a) [DLCO/V_a] were obtained and are reported as percentage predicted values. All instrumentation met American Thoracic Society standards, and tests were performed following them. Lung volumes were obtained and are reported as percentage predicted values [25].

Figure 1



LA classification of reflux esophagitis. LA, Los Angeles.

Statistical analysis

Continuous variables are expressed as mean and SD. Categorical variables are expressed as frequencies and percentages. Analysis of variance was used to assess the statistical significance of the difference between more than two study group means. The χ^2 and Fisher's exact test were used to examine the relationship between categorical variables. Spearman's correlation was used to assess the correlation between grade and PFT. Linear regression was used for studying independent factors affecting DLCO. A significance level of P less than 0.05 was used in all tests. All statistical procedures were carried out using SPSS, version 15 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

A total of 24 women and 24 men with GERD (mean age: 42.38±11.72 years) were evaluated in this study; most of them (27 patients, 56.2%) were classified as grade B GERD (Table 1). The mean FEV_1 was 97.34 ±15.18, the mean FVC±SD was 100.41±12.59,the mean FEV_1/FVC was 81.64±10.78,and the mean DLCO was 82.69±8.78 (Table 2).

There was a statistically significant difference between cases with different grades of reflux as regards age (P=0.022); most of the patients were included within grade B GERD with the highest mean age being 46.33 ±11.51. However, there was no significant difference as regards sex (Table 3). There was a statistically significant difference between cases with different grades of reflux as regards FEV_1/FVC% (P=0.02), maximum expiratory flow 25–75 (P=0.046), and DLCO (P=0.036), whereas there was a highly statistically significant difference regarding residual volume/total lung capacity and residual volume (P=0.001 for each) (Table 4 and Fig. 2).

The grade of reflux was the only independent factor affecting DLCO, and grade B patients showed lower DLCO compared with grade A patients (with

Table 1 Description of personal data (age and sex) and grades of reflux among the studied cases

	Mean±SD	Minimum	Maximum
Age	42.38±11.72	26.00	60.00
Sex (%)			
Male	24±50.0		
Female	24±50.0		
Grade of reflux (%)			
A	12±25.0		
B	27±56.2		
C	9±18.8		
D	0±0		

regression coefficient −7.50, P=0.024), as shown in Table 5. There was a statistically significant positive correlation between grades of reflux and FEV_1/FVC, maximum expiratory flow 25–75, and maximum mid-expiratory flow/peak expiratory flow, and a statistically significant negative correlation between grades of reflux and R20. There was a negative correlation between grades of reflux and DLCO, but it was not significant (Table 6 and Figs. 3 and 4).

Discussion

The principal finding of this study was that severe GERD, defined on the basis of pH monitoring and/or gastroscopy, is associated with a reduction in gas diffusion (DLCO) (there was a negative correlation between grades of reflux and DLCO, but it was not significant, which may be attributed to the small number of patients included within this study).

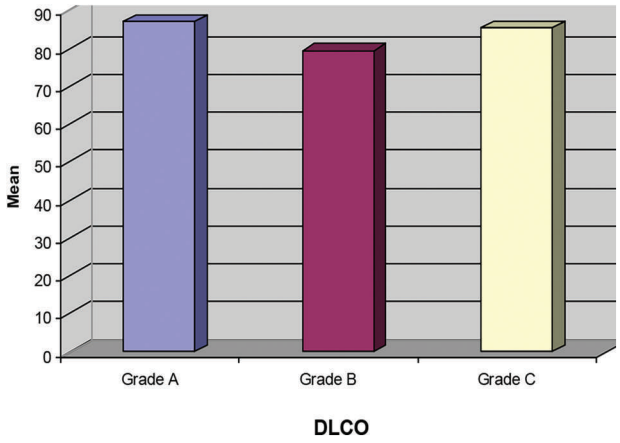
Table 2 Description of pulmonary function parameters among the studied cases

	Mean±SD	Minimum	Maximum
FEV_1%	97.34±15.18	68.00	119.00
FVC%	100.41±12.59	78.00	120.00
FEV_1/FVC	81.64±10.78	48.00	99.70
FEF 25–75	81.69±20.76	40.00	120.00
MMEF/PEF	79.38±23.31	40.00	123.00
DLCO	82.69±8.78	71.00	102.00
R5	148.40±32.59	92.00	206.00
R20	137.13±36.99	63.00	203.00
TLC	83.62±6.58	74.00	95.00
RV/TLC	77.84±14.90	58.00	100.00
RV	65.25±11.87	45.00	83.00
X5	0.15±0.06	0.05	0.31
X5 (%)			
Abnormal	24±53.3		
Normal	21±46.7		

DLCO, diffusing capacity of the lung for carbon monoxide; FEF 25–75%, forced expiratory flow 25–75%; FEV_1, forced expiratory volume at the first second; FVC, forced vital capacity; MMEF/PEF, maximum mid-expiratory flow/peak expiratory flow; R20, respiratory resistance at high frequency; R5, respiratory resistance at low frequency; RV, residual volume; TLC, total lung capacity; X5, reactant at 5 Hz.

There did not appear to be any other relevant medical history to account for these gas exchange abnormalities. These study results were in accordance with those of Anvari *et al*. [26] who showed an improvement in DLCO at 6 and 12 months after Nissen fundoplication surgery for severe GERD. Our results were also in agree with those of Linda *et al*. [27], who found that severe GERD was associated with a reduction in gas diffusion as well. The potential mechanisms responsible for the impairment in gas diffusion include microaspiration into the tracheobronchial tree, causing airway inflammation with subsequent ventilation/perfusion ratio maldistribution, suggesting an element of alveolar capillary membrane dysfunction. Acidification or irritation of the airways could cause an increase in airway inflammation and may exacerbate pre-existing lung disease [28]. In this study, gas diffusion impairment in subjects with increased severity of GERD in the absence of significant spirometric abnormalities with respect to FEV_1%, FVC%, or FEV_1/FVC, but with significant negative affection of central airways as detected by IOS with increased severity of GERD, suggests that we may be looking at the earliest

Figure 2



Distribution of DLCO among cases with different grades of reflux. DLCO, diffusing capacity of the lung for carbon monoxide.

Table 3 Comparison between cases with different grades of reflux as regards personal data

	Grade of reflux (mean±SD)				
	A	B	C	P	Significance
Age	38.50±13.18	46.33±11.51	35.67±3.50	0.022	S
Sex (%)					
Male	6±50.0	12±44.4	6±66.7	0.623**	NS
Female	6±50.0	15±55.6	3±33.3		

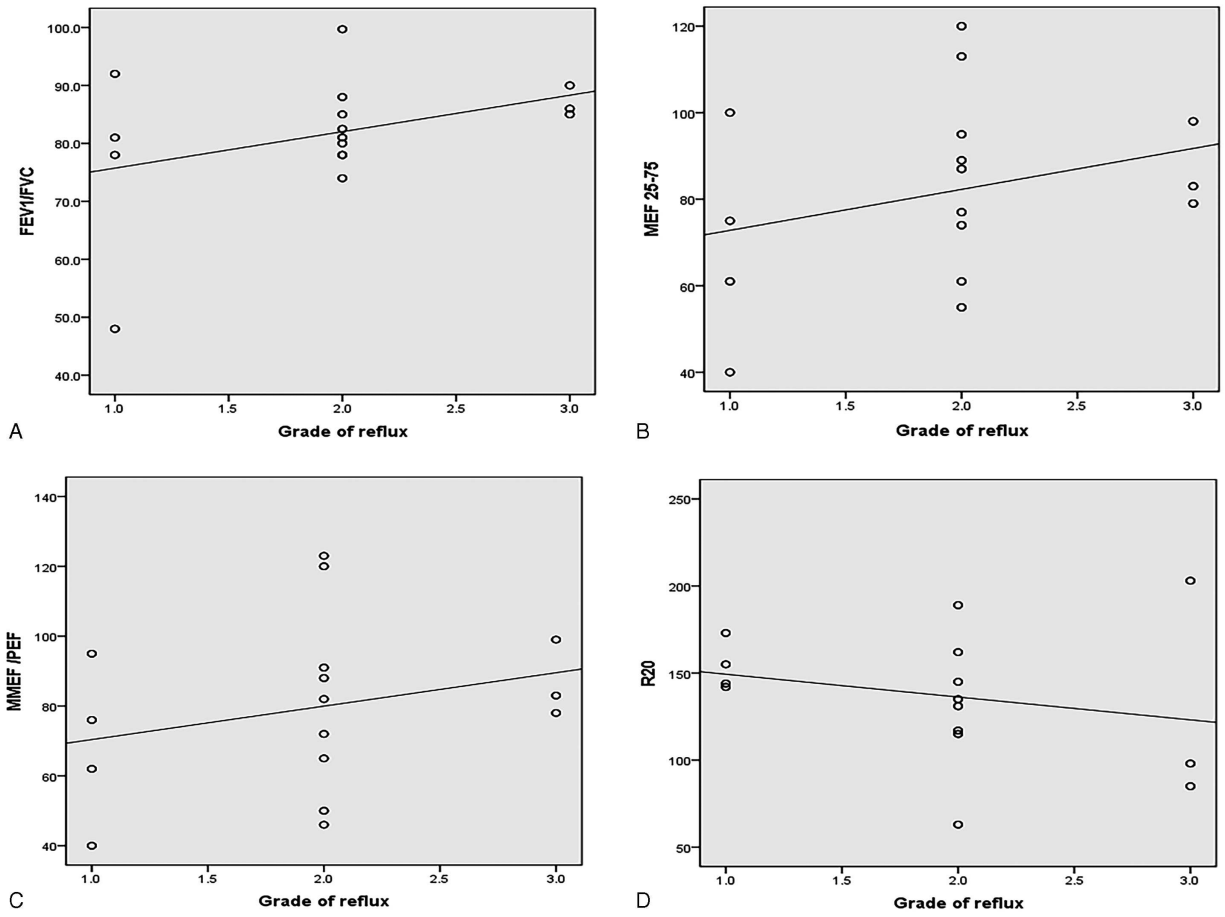
Grade A vs. grade B (S), grade A vs. grade C (NS), grade B vs. grade C (S).
NS, nonsignificant; S, significant.

Table 4 Comparison between cases with different grades of reflux as regards PFT parameters

	Grade of reflux (mean±SD)				
	A	B	C	*P*	Significance
FEV_1%	90.75±15.59	99.17±16.28	100.67±8.41	0.217	NS
FVC%	103.00±9.83	99.67±15.05	99.17±7.04	0.717	NS
FEV_1/FVC%	74.75±17.02	82.91±7.22	87.00±2.29	0.02	S^A
FEF 25–75%	69.00±22.78	85.67±20.90	86.67±8.67	0.046	S^B
MMEF/PEF%	68.25±20.97	81.89±26.20	86.67±9.50	0.140	NS
DLCO	87.00±11.18	79.43±6.02	85.50±8.22	0.036	S^C
R5	160.00±6.40	147.00±30.55	136.67±52.35	0.260	NS
R20	153.50±12.85	132.13±35.39	128.67±56.03	0.199	NS
TLC	84.50±11.50	83.00±4.77	85.00±0.00	0.842	NS
RV/TLC	90.75±10.13	68.50±8.37	98.70±0.00	0.001	HS^D
RV	76.00±2.19	57.40±6.82	83.00±0.00	0.001	HS^D
X5 predicted	0.14±0.07	0.17±0.07	0.14±0.02	0.478	NS

DLCO, diffusing capacity of the lung for carbon monoxide; FEF 25–75%, forced expiratory flow 25–75%; FEV_1, forced expiratory volume at the first second; FVC, forced vital capacity; HS, highly significant; MMEF/PEF, maximum mid-expiratory flow/peak expiratory flow; NS, nonsignificant; PFT, pulmonary function test; R20, respiratory resistance at high frequency; R5, respiratory resistance at low frequency; RV, residual volume; S, significant; TLC, total lung capacity; X5, reactant at 5 Hz.

Figure 3



Diagrams that explain the correlation between grades of reflux and PFT parameters. FEV_1, forced expiratory volume at the first second; FVC, forced vital capacity; MEF, maximum expiratory flow; MMEF/PEF, maximum mid-expiratory flow/peak expiratory flow; PFT, pulmonary function test; R20, respiratory resistance at high frequency.

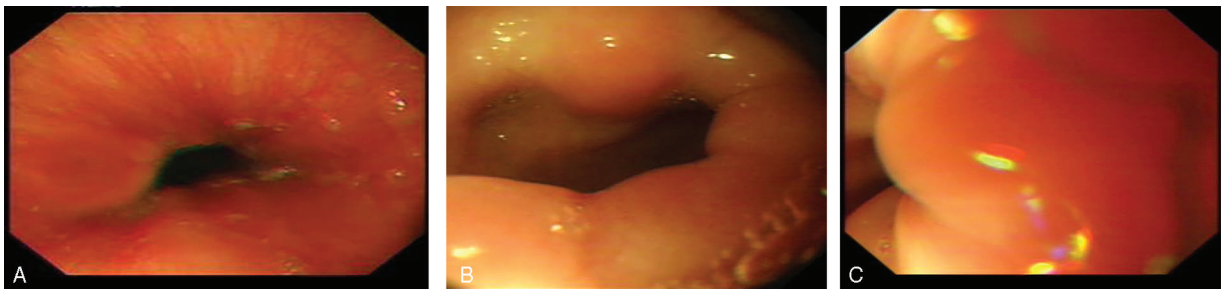
measurable dysfunction in a progressive pathway in the evolution of progressive pulmonary fibrosis detected by DLCO. A case can then be put forward for determining the severity in patients with severe GER using lung function tests, including DLCO, and if these findings reveal a deteriorating condition, in the absence of another cause, more aggressive treatment for GERD may be started to prevent lung

Table 5 Regression the effects of independent factors on DLCO

				95% CI for regression coefficients	
	Regression coefficients	*P*	Significance	Lower bound	Upper bound
Age	0.004	0.978	NS	−0.254	0.261
Sex	−1.291	0.649	NS	−7.008	4.427
Grade A*					
Grade B	**−7.502**	**0.024**	S	**−13.97**	**−1.035**
Grade C	−1.496	0.725	NS	−10.073	7.080

CI, confidence interval; NS, nonsignificant; S, significant.

Figure 4



Endoscopic grades of GERD. GERD, gastroesophageal reflux disease.

damage. Another fact is that IOS is a more sensitive tool for earlier detection of central or large airway affection in these patients rather than spirometry, which failed to detect airway obstruction in the studied group of patients in whom it was detected by IOS (Table 6). These results were in accordance with those of Linda *et al.* [27], who found gas diffusion impairment in patients with severe GER in the absence of spirometric abnormality in their study, but they did not subject their patient population to IOS. In patients with chronic lung disease, the treatment of GERD may be an important aspect of overall management. Because the oscillometry test does not take long to perform and is not dependent on patient effort, it may be of more benefit than spirometry, particularly for children and the elderly. In the present study both oscillometry and spirometry were used to evaluate GERD patients who had no respiratory symptoms. It was observed that all patients had significant respiratory values among different grades of reflux (Table 4), but failed to evoke significant valuable correlation among the different grades of reflux (Table 6). However, at the same time the oscillometry findings revealed that airway resistance was high at a frequency of 20 Hz (R20) among the studied patients. According to the results of the present study, patients with GERD, even in the absence of respiratory symptoms, might have increased airway resistance that could not be elicited by spirometry. Thus, IOS must be performed as a more sensitive tool for early detection of airway resistance or obstruction among GERD patients. These results were in agreement with several studies that reported the superiority of IOS for detecting abnormal airway resistance. Evans compared spirometry and IOS parameters in normal volunteers at rest and after hyperventilation with cold air and an exercise challenge. He observed that oscillometry test results were more sensitive than spirometry in the detection of postchallenge increased airway resistance [29–31]. In an interesting study by Bidad *et al.* [32], IOS was more sensitive than spirometry in diagnosing asthma among pregnant women. A study by Kanda and colleagues compared IOS and spirometry results of a group of patients with COPD or asthma with those of normal individuals who were nonsmokers. In that study IOS was more sensitive than spirometry for detecting abnormal airway resistance [29]. It has been reported that IOS has increased sensitivity in detecting certain occupation-induced airway hypersensitivities [33]. Thus, it is reasonable to presume that patients with GERD have subtle airway hyper-responsiveness, of whom a minority progress to asthma. These were in accordance with the results of Eidani and colleagues, who evaluated the effect of treatment with high-dose omeprazole on the objective parameters and found that oscillometry was more sensitive in detecting increased airway resistance, whereas spirometric indices were already within normal limits at the beginning of the study and improved by the end of treatment. Thus, it is an important tool for

Table 6 Correlation between grade of reflux and PFT parameters

Pulmonary function results	Grade of reflux
FEV_1%	
ρ^a	0.271
P	0.062
Significance	NS
FVC%	
ρ^a	–0.102
P	0.491
Significance	NS
FEV_1/FVC%	
ρ^a	**0.357**
P	**0.013**
Significance	S
FEF 25–75%	
ρ^a	**0.292**
P	**0.044**
Significance	S
MMEF/PEF%	
ρ^a	**0.320**
P	**0.027**
Significance	S
DLCO	
ρ^a	–0.105
P	0.524
Significance	NS
R5	
ρ^a	–0.205
P	0.177
Significance	NS
R20	
ρ^a	**–0.299**
P	**0.046**
Significance	S
X5 predicted	
ρ^a	–0.040
P	0.792
Significance	NS
TLC	
ρ^a	0.083
P	0.700
Significance	NS
RV/TLC	
ρ^a	–0.179
P	0.403
Significance	NS
RV	
ρ^a	–0.096
P	0.655
Significance	NS

DLCO, diffusing capacity of the lung for carbon monoxide; FEF 25–75%, forced expiratory flow 25–75%; FEV_1, forced expiratory volume at the first second; FVC, forced vital capacity; HS, highly significant; MMEF/PEF, maximum mid-expiratory flow/peak expiratory flow; NS, nonsignificant; R20, respiratory resistance at high frequency; PFT, pulmonary function test; R5, respiratory resistance at low frequency; RV, residual volume; S, significant; TLC, total lung capacity; X5, reactant at 5 Hz.
aSpearman's coefficient (correlation between grades of reflux and PFT parameters).

follow-up as well [34]. The lack of a control group may lead to some difficulties in interpreting the results. Additionally, the final sample size was small.

Conclusion

There appears to be mildly increased airway resistance in some patients with GERD even in the absence of respiratory symptoms. Oscillometry may be more sensitive than spirometry in the identification of these subtle abnormalities. GERD severity is associated with impairment of gas exchange (DLCO).

It is recommended to test for early lung diffusion and airway obstruction among GERD patients even in the absence of respiratory symptoms in order to avoid further complications.

Acknowledgements

Conflicts of interest

None declared.

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