

# Original Article

## Prevalence of gastroesophageal reflux in lung transplant candidates with advanced lung disease\*

Prevalência de refluxo gastroesofágico em pacientes com doença pulmonar avançada candidatos a transplante pulmonar

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### Abstract

**Objective:** To assess the esophageal function profile and the prevalence of gastroesophageal reflux (GER) in lung transplant candidates. **Methods:** From July of 2005 to November of 2006, a prospective study was conducted involving 55 candidates for lung transplantation at the Santa Casa de Misericórdia Hospital in Porto Alegre, Brazil. Prior to transplantation, patients underwent outpatient stationary esophageal manometry and 24-h esophageal pH-metry using one and two electrodes. **Results:** Abnormal esophageal manometry was documented in 80% of the patients, and 24% of the patients presented pathological acid reflux. Digestive symptoms presented sensitivity and specificity for GER of 50% and 61%, respectively. Of the patients with chronic obstructive pulmonary disease, 94% presented abnormal esophageal manometry, and 80% presented lower esophageal sphincter hypotonia, making it the most common finding. Patients with bronchiectasis presented the highest prevalence of GER (50%). **Conclusions:** In patients with advanced lung disease, GER is highly prevalent. In the population studied, digestive symptoms of GER were not predictive of pathological acid reflux. The role that GER plays in chronic rejection should be examined and clarified in future studies.

**Keywords:** Gastroesophageal reflux; Lung transplantation; Manometry; Esophageal pH monitoring.

### Resumo

**Objetivo:** Avaliar o perfil funcional do esôfago e a prevalência de refluxo gastroesofágico (RGE) em pacientes candidatos a transplante pulmonar. **Métodos:** Foram analisados prospectivamente, entre junho de 2005 e novembro de 2006, 55 pacientes candidatos a transplante pulmonar da Santa Casa de Misericórdia de Porto Alegre. Os pacientes foram submetidos a esofagomanometria estacionária e pHmetria esofágica ambulatorial de 24 h de um e dois eletrodos antes de serem submetidos ao transplante pulmonar. **Resultados:** A esofagomanometria foi anormal em 80% dos pacientes e a pHmetria revelou RGE ácido patológico em 24%. Os sintomas digestivos apresentaram sensibilidade de 50% e especificidade de 61% para RGE. Dos pacientes com doença pulmonar obstrutiva crônica, 94% apresentaram alteração à manometria, e 80% apresentaram hipotonia do esfíncter inferior, que foi o achado mais freqüente. Pacientes com bronquiectasias apresentaram a maior prevalência de RGE (50%). **Conclusões:** O achado freqüente em pacientes com doença pulmonar avançada é RGE. Na população examinada, a presença de sintomas digestivos de RGE não foi preditiva de refluxo ácido patológico. A contribuição do RGE na rejeição crônica deve ser considerada e requer estudos posteriores para seu esclarecimento.

**Descritores:** Refluxo gastroesofágico; Transplante de pulmão; Manometria; Monitoramento do pH esofágico.

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## Introduction

Advances in surgical techniques, methods of lung preservation, and postoperative intensive care, as well as specific protocols for the care of donors, allow a survival rate of 95% in the immediate postoperative period following lung transplantation, this rate ranging from 70% to 75% in the first year after transplantation. However, the five-year survival rate remains 50%, a figure lower than that obtained in cadaveric donor renal (68%) and cardiac (63%) transplantation.<sup>(1)</sup> Late mortality in lung transplant recipients has been attributed to a progressive deterioration of pulmonary function caused by bronchiolitis obliterans. Introduced in 1993,<sup>(2)</sup> the term bronchiolitis obliterans syndrome (BOS) has been used to describe a deterioration in post-transplant pulmonary function that cannot be explained by stenosis of the bronchial anastomosis, infection, or acute rejection. Despite there being various causes proposed for BOS, some of them currently have well-established associations, such as pneumonitis caused by cytomegalovirus, number and timing of acute rejection episodes, and antigenicity against human leukocyte antigen.<sup>(3)</sup> Among other causes, the establishment of a causal relationship with gastroesophageal reflux (GER) has received considerable attention. Recent studies have demonstrated improvement in pulmonary function in patients with BOS who were submitted to fundoplication, thereby rousing interest in evaluating GER as a possible causal agent of BOS.<sup>(2,4-6)</sup>

Given the need to obtain data on the presence of GER in lung transplant candidates in Brazil, this study assessed the prevalence and characteristics of GER in lung transplant candidates, correlating the findings of 24-h esophageal pH-metry with those of the evaluation of esophageal function by esophageal manometry. Based on these data, further studies will be designed in order to evaluate the incidence of post-transplant reflux, as well as its potential association with late graft dysfunction.

## Methods

The clinical study protocol was evaluated and approved by the Ethics in Research Committee of the institution (protocol 065/05). From July of 2005 to November of 2006, 55 lung transplant candidates were evaluated in the Santa Casa de Misericórdia Hospital in Porto Alegre. The patients

were prospectively evaluated by stationary esophageal manometry and 24-h esophageal pH-metry. The exclusion criteria were having a history of gastrointestinal surgery, being a candidate for a second transplantation, and presenting an acute infectious process. In the interview preceding the test, the patients gave written informed consent, and were asked about the presence of gastrointestinal symptoms, such as heartburn, dysphagia, epigastric pain, and reflux, as well as about underlying diseases. The patients were asked to discontinue the use of proton pump inhibitors for at least 72 h and the use of antihistamines for 48 h before the test. Stationary esophageal manometry was performed using a 6-pressure-channel catheter (Synectics, Stockholm, Sweden) with 3 distal radial and 3 proximal channels 5 cm apart, perforated by a capillary pneumohydraulic pump (Mui Scientific®, Mississauga, Canada). Pressures were obtained using a digital polygraph (Polygraph®; Synectics, Stockholm, Sweden) connected to a personal computer with software for real-time pressure readings (Polygram®; Synectics, Stockholm, Sweden). The catheter was introduced through the nose using the station pull through technique, with localization and measurement of sphincter pressure, as well as analysis of esophageal body motor profile, using previously determined parameters of normality.<sup>(7)</sup> Immediately after the end of esophageal manometry, a semi-disposable pH-metry catheter with one or two antimony electrodes (Synectics, Stockholm, Sweden or Alácer Biomédica, São Paulo, Brazil) was introduced through the nose, and the distal electrode was positioned at 5 cm above the upper limit of the lower esophageal sphincter, which had been previously located by esophageal manometry. In the two-electrode catheters, the distance between the proximal and the distal electrode was 15 cm. The electrode was connected to a portable detector (Mk III; Synectics, Stockholm, Sweden) and remained connected for 24 h, during which the patient recorded meal and positioning times on a diary. At the end of pH-metry, data were transferred to a personal computer with analysis software (Esophogram®; Synectics, Stockholm, Sweden). The parameters analyzed and the score used were those described by Johnson & DeMeester.<sup>(8)</sup>

The statistical analysis was carried out using the Statistical Package for the Social Sciences, version 12.0 (SPSS Inc., Chicago, IL, USA). The Student's

**Table 1** – Underlying lung diseases in 55 lung transplant candidates.

Pathology	n	%
Chronic obstructive pulmonary disease	17	31
Fibrosis	17	31
Bronchiectasis	7	13
Pneumoconiosis	8	15
Cystic fibrosis	3	5
Lymphangioliomyomatosis	3	5
Total	55	100

t-test was used when there was normal distribution in the variable, and the Kruskal-Wallis test followed by the Mann-Whitney U test was used to compare continuous variables. The analyses were performed considering the total number of patients and the subgroups, divided by pathology, obtaining a score greater than 5. The level of statistical significance was set at  $p < 0.05$ .

## Results

The data related to the distribution of digestive symptoms and pulmonary function are described in Tables 1 and 2. Of the 55 patients, 23 (42%) presented digestive symptoms, most of whom had chronic obstructive pulmonary disease (COPD) or pulmonary fibrosis. All 55 patients completed the manometry test satisfactorily, whereas 53 (96%) completed the pH-metry test, since 2 patients could not tolerate the presence of the catheter. Of those 53 tests, 40 were performed using a one-channel pH-metry catheter, and 13 were performed using a two-channel catheter. Mean esophageal length (including the sphincters) measured by manometry was  $28.1 \pm 2.4$  cm. Manometry was considered abnormal in 44 patients (80%), 25 (57%) of whom were asymptomatic and 19 (43%) of whom presented typical symptoms of GER. Lower esopha-

geal sphincter hypotonia was the most common finding—30 patients (54%)—and mean lower esophageal sphincter tone in all patients studied was  $12 \pm 4.7$  mmHg, there being no significant difference between symptomatic and asymptomatic patients ( $14 \pm 5.1$  mmHg and  $12 \pm 4.6$  mmHg, respectively,  $p > 0.05$ ). Upper esophageal sphincter hypotonia, without detectable changes in pharyngeal-cricopharyngeal coordination, was detected in 8 patients (14%). The analysis of the manometry findings grouped by underlying disease identified a greater number of abnormal tests in the patients with COPD than in the patients with any of the remaining diseases (Table 3). The presence of GER-related symptoms was observed in 23 patients (42%). Of those, 9 (39%) presented retrosternal pain, and 23 (96%) presented heartburn. In 18 patients (34%), pH-metry was abnormal, 12 of whom (23%) presented pathological acid GER and 6 of whom (12.5%) presented a quantitative reduction in the number of reflux episodes, suggesting the possibility of hypochlorhydria, concomitant alkaline GER, or concomitant residual pharmacological acid ablation. Regarding the presence of digestive symptoms, pH-metry sensitivity and specificity for GER was 50% and 61%, respectively, in this group, with a positive predictive value of 27% and a negative predictive value of 81%. Digestive symptom sensitivity and specificity related to the esophageal manometry results were, respectively, 43% and 64%, with a positive predictive value of 83% and a negative predictive value of 22%. The pH-metry results, according to the presence or absence of digestive symptoms, are summarized in Table 4. Only 5 patients (9%) presented abnormal pH-metry without detectable manometric abnormalities, whereas 6 other patients (11%) presented no manometric or pH-metric changes. In the individuals submitted to pH-metry using a two-electrode cath-

**Table 2** – Demographic and functional data of 55 lung transplant candidates.

Pathology	Age <sup>a</sup>	F/M	TLC% <sup>a</sup>	RV% <sup>a</sup>	FVC% <sup>a</sup>	FEV <sub>1</sub> % <sup>a</sup>	DLCO% <sup>a</sup>
COPD	54	9/8	90	173	50	24	37
Fibrosis	62	9/8	49	46	49	53	26
Pneumoconiosis	40	0/8	44	75	25	2	34
Bronchiectasis	41	3/4	44	103	39	20	40
Others	30	4/2	57	135	48	27	28

<sup>a</sup>Median values. F/M: ratio between females and males; TLC: total lung capacity; RV: residual volume; FVC: forced vital capacity; FEV<sub>1</sub>: forced expiratory volume in one second; DLCO: diffusing capacity of the lung for carbon monoxide; and COPD: chronic obstructive pulmonary disease.

**Table 3** - Esophageal manometry findings and the respective percentages of abnormal tests distributed by underlying lung disease.

Variable	COPD	Fibrosis	Pneumoconiosis	Bronchiectasis	Others
LES tone (mmHg) <sup>a</sup>	11	14.8	11.5	10	15.9
UES tone (mmHg) <sup>a</sup>	63	82	57	89	82
Abnormal test, n (%)	16 (94)	13 (76)	7 (88)	5 (71)	3 (50)
LES hypotonia, n (%)	12 (71)	6 (35)	6 (75)	4 (57)	2 (33)
UES hypotonia, n (%)	3 (18)	3 (18)	0 (0)	1 (14)	1 (17)

<sup>a</sup>Values expressed as mean. COPD: chronic obstructive pulmonary disease; LES: lower esophageal sphincter (normal tone values: 14-40 mmHg)<sup>(6)</sup>; and UES: upper esophageal sphincter (normal tone values: 40-180 mmHg).<sup>(7)</sup>

eter, the number of acid reflux episodes that reached the proximal electrode was greater (in percentage terms) in the patients with digestive symptoms than in the asymptomatic patients. The pH-metry results distributed by underlying lung disease revealed that none of the diseases presented a median DeMeester score above the normal range (a score of 14.95), despite the fact that the patients with bronchiectasis presented a greater number of abnormal pH-metry tests (Table 5).

## Discussion

Lung transplantation is the treatment of choice for advanced lung diseases. Despite the advances in immunosuppression and postoperative care, one of the limiting factors for five-year survival continues to be bronchiolitis obliterans, an irreversible, chronic process of distal airway fibrosis with progressive airflow obstruction. The clinical expression of the entity is represented by BOS, characterized by a decrease in forced expiratory volume in one second equal to or greater than 10% in relation to the best post-transplant spirometry or forced expiratory flow between 25% and 75% of forced vital capacity lower than 75% of the mean of the two best values in a 3-week interval,<sup>(9)</sup> which cannot be attributed to infection, acute rejection, or stenosis of the anastomosis.<sup>(10)</sup> Currently, BOS accounts for 30% of related deaths 3 years after lung transplantation, affecting between 50% and 60% of all lung transplant recipients 5 years after transplantation.<sup>(11)</sup> The 3-year incidence of BOS after lung transplantation at our institution is similar to that of post-transplant literature (31%; unpublished data). Chief among the factors that contribute to the onset and progression of BOS are immunologically mediated lesions. Despite the advances obtained in immunosuppression over the years, late survival

after lung transplantation remains unaltered, favoring the hypothesis that non-immunological factors can be involved. The presence of microaspiration secondary to GER has been postulated as a contributing factor to the genesis of BOS.<sup>(10)</sup> Some authors,<sup>(2)</sup> in a retrospective analysis of lung transplant recipients, demonstrated that, over the course of the disease, pulmonary function was better in the recipients who did not present GER, or in those in whom reflux was treated early, than in the recipients who still presented GER after transplantation. The same authors reported that recipients who did not have pathological reflux or who underwent early GER treatment presented a five-year mortality rate similar to that of cardiac or renal transplant recipients. Experimental studies have also described the association between GER and the development of distal airway fibrosis after lung transplantation.<sup>(11)</sup> The impact of GER in other respiratory diseases is of note. Recently, in a randomized, prospective study, we demonstrated that treatment of GER with a proton pump inhibitor significantly improved the quality of life and the symptom scores of asthma patients with GER.<sup>(12)</sup>

Histologically, two forms of bronchiolitis obliterans have been identified in lung transplant recipients. A relatively acellular form, consisting of a fibrosing process that is limited to the terminal bronchioles, and another form that is associated with microaspiration, represented by a focal, cellular inflammatory process that extends into the distal alveolar spaces.<sup>(13,14)</sup>

Defense mechanisms, such as cough reflex and mucociliary activity, are frequently altered in lung transplant recipients. Mucociliary clearance is reduced in up to 15% of normal values in this population, a fact that can explain why even short exposure of the graft to gastric content can result

**Table 4** – Findings of outpatient 24-h esophageal pH-metry grouped by presence of digestive symptoms.

Variable	Normal	All (n = 53)		Symptomatic (n = 22)		Asymptomatic (n = 31)	
		R	n (%)	R	n (%)	R	n (%)
% total time	<4.2	1.1	11 (21)	1.2	5 (23)	0.9	6 (19)
% time standing	<6.3	1.6	8 (15)	1.8	23 (23)	1.4	3 (10)
% time supine	<1.5	0.1	11 (21)	0.1	6 (27)	0.1	5 (16)
Number of episodes	<50	30	13 (25)	30.5	5 (23)	30	8 (26)
Number of episodes > 5 min	<3	0	7 (13)	0	3 (14)	0	4 (13)
Longest episode (min)	<9.2	3	11 (21)	3	6 (27)	3	6 (19)
DeMeester score	<15	5.5	12 (23)	5.7	6 (27)	5.5	6 (19)
Number of episodes (proximal)	-	7	-	7	-	7.5	-
% episodes (proximal)	-	27	-	37	-	22.5	-

R: results, values expressed as mean.

in an intense inflammatory reaction and fibrosis. In addition to causing damage by direct effect, gastric content can also be involved in the immune response to the graft, increasing the local inflammatory response.<sup>(11)</sup> Furthermore, other factors have been experimentally described as contributing to the decrease in mucociliary transport velocity, such as bronchial transection and the use of cyclosporin A, both of which are common denominators in lung transplantation.<sup>(15,16)</sup>

In the present study, we investigated the prevalence of GER and manometric abnormalities in a population of lung transplant candidates with advanced lung disease in an attempt to later make it possible to evaluate the impact of GER on the late performance of the post-lung transplant graft. In the population studied, the prevalence of pathological acid GER was 23%, somewhat lower than those reported in the literature—32%<sup>(14)</sup> and 35%<sup>(5)</sup>, which might be due to the small sample evaluated in our study. Recently, some authors<sup>(14)</sup> have described lower esophageal sphincter (LES) hypotonia as the most common manometry finding in such patients

(72% of the cases). When stratified by lung disease, the same authors found LES hypotonia in 71% of the patients with COPD and in 54% of the patients with idiopathic pulmonary fibrosis, findings somewhat similar to those of our study (71% and 35%, respectively). The presence of GER stratified by lung disease revealed a prevalence of 19% among the patients with COPD and of 32% among the patients with idiopathic pulmonary fibrosis.<sup>(14)</sup> In the general population of patients with COPD, the prevalence also ranges from 30% to 40%.<sup>(17)</sup> The correlation between symptoms and reflux in lung transplant candidates has been described in 42% of the symptomatic patients and in 14% of the asymptomatic patients.<sup>(10,14)</sup> As in another study,<sup>(5)</sup> our sample revealed no association between reflux and abnormal esophageal manometry in patients with advanced lung disease.

Other respiratory manifestations can also be accompanied by esophageal dysmotility. In a recent study carried out in our Laboratory of Digestive Motility, esophageal manometry revealed esophageal body dysmotility in 186 (30%) of the

**Table 5** – Findings of outpatient 24-h esophageal pH-metry distributed by pulmonary pathology.

Variable	Normal	COPD		Fibrosis		Pneumoconiosis		Bronchiectasis		Others	
		R	n (%)	R	n (%)	R	n (%)	R	n (%)	R	n (%)
% total time	<4.2	0.8	3 (19)	0.7	2 (12)	1.35	2 (25)	2.65	2 (33)	1.5	2 (33)
% time standing	<6.3	1.25	3 (19)	1.6	3 (18)	1.4	1 (13)	2.15	1 (17)	1.7	0 (0)
% time supine	<1.5	0.1	3 (19)	0	1 (6)	0.05	2 (25)	3.2	3 (50)	0.5	2 (33)
Number of episodes	<5	22.5	5 (31)	27	4 (24)	29.5	2 (25)	44	2 (33)	30.5	0 (0)
Episodes > 5 min	<3	0	2 (13)	0	2 (12)	0.5	0 (0)	0	1 (17)	0	2 (33)
Longest episode (min)	<9.2	2	3 (19)	3	2 (12)	5.5	2 (25)	4	2 (33)	2.5	2 (33)
DeMeester score	<15	4.1	3 (19)	4.3	2 (12)	7.6	2 (25)	13.8	3 (50)	7.3	2 (33)

COPD: chronic obstructive pulmonary disease; and R: results, values expressed as mean.

622 patients presenting respiratory manifestations with and without digestive symptoms of GER. The prevalence of esophageal body abnormalities was higher in the tests of the asthma patients with and without digestive symptoms (32.7%) than in the tests of the remaining patients, whereas 42% of the esophageal manometry tests of patients with digestive symptoms of GER presented esophageal body dysmotility.<sup>(18,19)</sup> The prevalence of GER in the population of lung transplant candidates is important, since it defines the physiological profile of the esophagus in this population, making it possible to compare these results with post-lung transplant late evolution and mortality. The analysis of the data from pH-metry using two electrodes revealed that the symptomatic patients were the ones who had the most exposure to acid reflux in the proximal electrode, as described by some authors.<sup>(14)</sup> The evaluation of this population of patients by pH-metry using two electrodes is useful because it can detect reflux episodes that reach the proximal esophagus, suggesting the possibility of microaspiration. This finding has been analyzed by other authors,<sup>(20)</sup> who demonstrated the presence of microaspiration in asthma patients with GER using prolonged intratracheal pH-metry. However, such findings should be analyzed with caution since, unlike the data obtained in the distal electrode, there is no established standard of normality for pH-metry in the proximal electrode. In addition, the possibility of cranial displacement of the proximal electrode due to swallowing frequently causes capture artifacts that make it even more difficult to interpret the data. Pharmacological acid ablation of these patients has not significantly changed their evolution, suggesting that other factors, such as alkaline reflux, can be involved in the etiopathogenesis of graft changes. Our study demonstrates that 30% of the abnormal pH-metry tests presented a significant decrease in or absence of acid GER, suggesting the hypothesis of coexistence of alkaline or mixed GER. Other more accurate diagnostic techniques, such as bioimpedance, which detects GER by the esophageal flow rather than by the pH change, can present additional information in the future.

A difficulty inherent in the prospective evaluation of GER in lung transplant candidates is the need for studies involving large patient samples in order to achieve statistical power, since the DeMeester score in the normal population has a large standard

deviation. A way to overcome this problem is to carry out multicenter studies. In fact, the prevalence of GER in the population of lung transplant candidates seems to be higher than that in the general population, which is approximately 5%,<sup>(17)</sup> and the correlation between GER and the development of post-transplant chronic lung rejection should be further investigated.

We conclude that, in this study, the prevalence of acid GER in lung transplant candidates was higher than that in the general population. In addition, the presence of symptoms was not predictive of GER or of abnormal esophageal manometry in the population studied. The highest prevalence of GER occurred in patients with bronchiectasis, whereas abnormal esophageal manometry prevailed in patients with COPD, in whom LES hypotonia was the most common finding.

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