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## Original Research Article

# How useful is antireflux surgery in lung transplant patients with gastroesophageal reflux?

Victoria Pegna<sup>a</sup>, Antanas Mickevičius<sup>b,\*</sup>, Clement Tsang<sup>c</sup>

<sup>a</sup>Bristol Royal Infirmary, Bristol, UK

<sup>b</sup>Department of Surgery, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania

<sup>c</sup>St Vincent's Hospital, Sydney, Australia

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## ABSTRACT

**Background and objective:** Respiratory function deteriorates over time after lung transplant. Reflux disease with pulmonary complications is a possible cause of this decline. This case series we aim to assess whether respiratory function improves after Nissen fundoplication in lung transplant patients and if surgery reduces gastroesophageal reflux disease (GERD) symptoms and use of proton pump inhibitors (PPIs).

**Materials and methods:** A retrospective case series of lung transplant patients with reflux disease and Nissen fundoplication. Clinical symptoms, pH-metry data, use of PPIs were recorded before the procedure and up to 18 months postoperatively. The FEV<sub>1</sub> values before and after Nissen fundoplication were recorded at 3 monthly intervals. Patients' satisfaction scores were recorded before operation and postoperatively.

**Results:** A total of 64 lung transplant patients were selected. After Nissen fundoplication, the pH studies were done on 26 patients. The mean overall acid exposure fraction was 1.03% ( $P < 0.05$ ). FEV<sub>1</sub> declined for 6 months postoperatively and then gradually improved. The comparison of FEV<sub>1</sub> at 3 months preoperatively to 3 months postoperatively showed no significant difference ( $P = 0.067$ ) as well as at 6 months. A significant improvement in clinical GERD symptoms was achieved after antireflux surgery; however, the patients remained receiving PPIs.

**Conclusions:** NF has been established as a safe operation for lung transplant patients. Late Nissen fundoplication did not improve lung function significantly amongst lung transplanted patients; however, patients with symptomatic GERD may have benefited from Nissen fundoplication in terms of symptom relief. A multicenter randomized control trial is needed to assess the effect of early unselected reflux control on respiratory function and graft survival.

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\* Corresponding author at: Department of Surgery, Medical Academy, Lithuanian University of Health Sciences, Eivenių 2, 50161 Kaunas, Lithuania.

E-mail address: [a\\_mickevicius@yahoo.com](mailto:a_mickevicius@yahoo.com) (A. Mickevičius).

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## 1. Introduction

Over the past 25 years lung transplantation has been an important option for patients with end stage lung disease. The survival rate has improved; however, despite the development of immunosuppressive agents, the mean survival for single lung transplant is still 5 years and for double lung transplant about 5.9 years [1].

The causes of death include graft failure, diffuse alveolar damage, chronic allograft rejection or chronic graft dysfunction, which manifests as bronchiolitis obliterans syndrome (BOS). BOS is the leading cause of mortality within the first year accounting for over 40% of deaths [2]. The incidences of BOS approaches 50% within five years of transplantation.

Many factors have been reported as risk factors for BOS. Microaspiration secondary to gastro-esophageal reflux disease has been suggested to be a potential contributor to lung allograft dysfunction and development of bronchiolitis obliterans [1]. The microaspiration can be controlled by antireflux surgery.

Gastroesophageal reflux disease (GERD) is common in post-transplant patients firstly because the vagus nerve transection during transplant surgery. Injuries to the vagal nerves are common due to direct trauma and electrocoagulation. This leads to delayed gastric emptying and distal esophageal dysmotility, promoting reflux posttransplant [3,4]. A study had shown as many as 90% of the post lung transplant patients have experienced delayed gastric emptying [4,5].

Although proton pump inhibitors (PPIs) can reduce the acid production, other gastric content such as bile salts from microaspiration can also result in aspiration pneumonia. The study by D'Ovidio et al. found that patients with a presence of bile in bronchoalveolar lavage fluid developed BOS more quickly [4]. Davis et al. also found that the survival of lung transplanted patient was significantly better in patients who had either normal pH studies or who had fundoplication particularly if performed before the late stages of bronchiolitis obliterans syndrome [5].

Therefore, the aim of this study was to assess whether respiratory function improved after Nissen fundoplication in lung transplant patients and if surgery reduced GERD symptoms and use of (PPIs).

## 2. Materials and methods

A retrospective case series including lung transplanted patients with reflux disease who had undergone antireflux surgery between 2004 and 2010 at St Vincent's Public and Private Hospital, Sydney, Australia was analyzed. The indications for Nissen fundoplication were either symptoms of reflux disease or a positive pH study. Demographic data, clinical symptoms of reflux disease, pH study results, complications, whether the surgery performed reduced the use of PPIs, patients' satisfaction scores and safety of this procedure were analyzed. Satisfaction scores were analyzed by discussing pre and postoperative symptoms in clinic with the patients, and then recording whether they were satisfied or not with the outcome.

All the operations were performed by the same surgeon or under his supervision. Laparoscopic Nissen fundoplication was performed in all cases. Patients were all taking immunosuppressive medications. Postoperatively they were managed in ICU or HDU and under supervision of the transplant team. A single person was responsible of collecting and tabulating the raw data by reviewing the hospital medical records and the correspondents from the specialist consultation rooms.

Forced expiratory volume in 1 s (FEV<sub>1</sub>) values were collected to evaluate lung function at 3 monthly intervals. The first measurement was recorded 6 months preoperatively, and the last one was taken 18 months postoperatively.

### 2.1. Statistical analysis

The Student t test was used to compare mean values. In cases with an abnormal distribution, nonparametric statistics assessment was used. If the frequency of the variable was low, and fewer than 30 investigations were performed, the Fisher exact test was used. Significance was defined as a P value less than 0.05.

Ethics approval had been obtained for this low-risk study.

## 3. Results

Of the 218 patients who underwent lung transplant surgery between February 2002 and December 2009, 64 (29%) underwent antireflux surgery.

The mean age of the patients was 41 years (SD 13.6; range 16–61), and there were 30 women. Fifty patients had bilateral sequential single lung transplantation, six patients had a single lung transplant, and eight patients underwent a heart–lung transplant before antireflux surgery.

The mean age at which Nissen fundoplication was performed was 45 years (range 17–68). There were no conversions to open surgery. Of these 64 patients, 57 completed follow-up.

The time line since the patients had lung transplant surgery and antireflux surgery was calculated from when the patient was last seen. The mean survival time posttransplant was 6.6 years. The mean survival time from when Nissen fundoplication was performed was 3.2 years. The mean time from initial transplant to the time that the patients required Nissen fundoplication was 3.3 years.

51 of the 61 patients (clinical symptoms of three patients were not recorded sufficiently for evaluation) had typical GERD symptoms before antireflux surgery despite receiving regular PPIs. Regurgitation, reflux and nocturnal coughing were common among this group of patients. All the patients were unsatisfied with their condition preoperatively (Table).

All the patients underwent 24 h pH-metry before the antireflux procedure. The overall acid exposure fraction was 14.4% (SD 12.7%) (normal range up to 4%). The range was from 1.1% to 72%. The nocturnal values range from 0% to 50% and the mean value was 15.4% (SD 12.9%) (normal range up to 2%).

There were no postoperative deaths. Four complications occurred early postoperatively. One patient had febrile neutropenia, two patients had early dysphagia, and one had sputum retention. All complications were resolved.

**Table – Surgery results.**

	Heartburn		Dysphagia		Self-satisfaction score	
	Positive	Negative	Positive	Negative	Satisfied	Unsatisfied
Before surgery	54 (88.5)	7 (11.5)	51 (83.6)	10 (16.4)	0 (0)	64 (100)
After surgery	7 (11.5)	54 (88.5)	5 (8.2)	56 (91.8)	56 (87.5)	8 (12.5)
P value	<0.05		<0.05		<0.05	
Values are number (percentage).						

A total of 47 patients had no further symptoms of GERD during the follow-up period. Five patients had slight reflux; two patients had moderate reflux with dysphagia. On endoscopy these two patients were found to have recurrence of their hiatus hernia at 2 and 3 years postoperatively, respectively. They did not require re-operation. Five other patients had a controllable postoperative dysphagia, which did not require any additional interventions.

All the patients were encouraged to repeat pH studies after surgery. However, due to these studies being uncomfortable for the patients, only 26 agreed with follow-up investigation. The overall acid exposure fraction decreased significantly up to 1.16% (SD 2.4%) ( $P < 0.05$ ). The range was from 0% to 9.5%. Nocturnal acid exposure also decreased significantly up to 3.6% (SD 5.8%) ( $P < 0.05$ ) with the range from 0% to 10.4%. However, with the postoperative data of only 26 patients, conclusions cannot be drawn from these results.

The median FEV<sub>1</sub> remained constant postoperatively and then showed a trend toward an improvement. The two-tailed t test comparing results at 3 months preoperative to 3 months postoperative showed no significant difference ( $P = 0.067$ ). The comparison at 6 months pre- and postoperatively also did not show a significant difference (Figure).

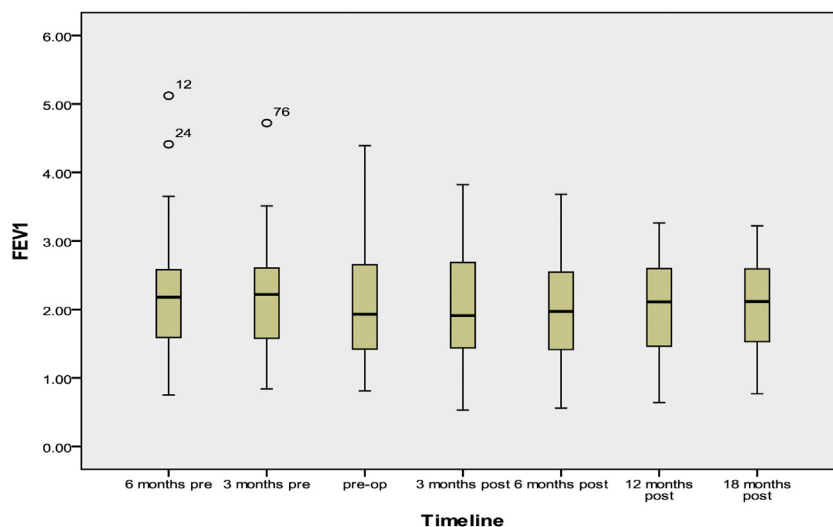
Despite normal acid exposure level in the lower esophagus, all the 64 patients were given PPIs on their latest follow-up visit. However, 56 (87.5%) of them were satisfied with the results of antireflux surgery (Table).

#### 4. Discussion

This trial was intended to serve as additional evidence looking for the possibility of slowing the progression of bronchiolitis obliterans syndrome and improving the survival of lung transplanted patients with reflux disease. This is one of the biggest case series looking at Nissen fundoplication lung posttransplant and it clearly demonstrates that it is a safe procedure, and is helpful in controlling reflux. There is currently no consensus amongst transplant physicians regarding antireflux surgery versus conservative management as well as the optimal time posttransplant when antireflux surgery safely and most effectively could be performed.

This is a descriptive study and it is difficult to draw any significant conclusions from our findings. The limitations of this study include its retrospective nature and small number of patients. The patient selection may be biased with more healthy and fit patients being offered the surgical option. However, this is one of specific case series reported, we expect the presented data are useful to serve as a starting point for further studies.

Prior to this study, we speculated that this group of patients would have asymptomatic reflux disease with a diagnosis made by pH studies (due to vagal nerve damage). However, 84% of patients had symptomatic reflux disease even receiving regular PPIs. Furthermore, all of them were dissatisfied with

**Figure – Changes in the median value of FEV<sub>1</sub> over time.**

their condition. A further study looking at the health related quality of life changes over time, of lung transplanted patients, would be interesting.

This study found Nissen fundoplication to be safe in lung transplant patients. Out of the 64 patients undergoing this procedure there were no deaths or life threatening complications. Our data are comparable with the finding of other studies looking at antireflux surgery in lung transplant patients [6–8].

It is difficult to prove that Nissen fundoplication had an influence on lung function, because of the many confounding variables that affect lung function tests. This includes age, pre-morbid condition, immunosuppressive medications, and reasons for transplantation. It is impossible to exclude these and other factors' continuous effect on respiratory function.

There is evidence that the refluxate can cause acute lung deterioration and start an acute/chronic inflammatory response [9–11]. The aim of antireflux surgery is to prevent reflux and aspiration of gastric content, in an attempt to prevent deterioration of respiratory function in lung transplant patients. Even with optimal dosing of PPIs, there is strong evidence to support the superiority of antireflux surgery to prevent pepsin and bile reflux into the lungs and subsequent alveolar damage [5,12–14]. However, in our series, 6 months after Nissen fundoplication, the mean FEV<sub>1</sub> only had a trend toward improvement, and this was not significant. The median value remained constant, again, with a trend toward improvement but not significant. In general, we cannot expect a positive effect on lung function immediately after fundoplication because of chronic long lasting bronchiolitis. It is also possible that our sample size of 64 was too small to show a difference or that it is due to beta error. Having a larger sample size may improve the accuracy and outcome of the study. Time from transplant to antireflux surgery is the other factor that can play a significant role in preserving posttransplant lung function. Some authors in small series have shown superiority with early fundoplication [13,15] in preventing deterioration of lung function. In this study we present results of relatively late posttransplant fundoplication. We started from a reserved approach, however, after acknowledging fundoplication is a safe procedure for lung transplant patients; over the last years our policy has changed to earlier antireflux procedures when pathological reflux is detected.

In this study the preoperative pH measurements were done, but only 26 patients had follow-up pH studies performed. This may be because it is uncomfortable for the patients to have a 24 h probe in their nose again. However, of the 26 that had the study done, most of them had an acid contact fraction less than the preoperative overall contact fraction.

The other aspect in follow-up of this cohort of lung transplant patients lays in their quality of life. GERD symptoms have a great influence on patients' quality of life [16–18]. Most of the patients were symptomatic and dissatisfied with their condition before antireflux surgery, even with long-term PPIs. Resolution of reflux symptoms as well as significant improvement in satisfaction with their condition was observed after antireflux procedures. These data support other authors findings [19,20]: Burton in 2009 found that after laparoscopic Toupet fundoplication in lung transplant patients 88% of the

patients rated the surgery as excellent, Robertson et al. noticed significant improvement in reflux symptoms index and gastrointestinal quality of life scores. However most of the studies evaluate short-term fundoplication effect. On background of our data we have long lasting (>18 months) positive effect of antireflux surgery.

All the patients of our study were given PPIs preoperatively, and all 64 patients received PPIs on their latest follow-up postoperatively. Our expectation was that the antireflux surgery would reduce the need to take regular PPIs. The reason for continued PPI use in all patients is unknown. It is possible that because some proportion of the patients still had reflux symptoms they may have preferred to be given PPIs, and they are continued as a form of “dependency”. Otherwise an influence from GP doctors is possible or patients may have been continued these medications prophylactically. However unnecessary use of PPI among immunosuppressive patients may have unfavorable effects caused by elevating intragastric pH leading to possibility for increase of bacterial flora and subsequent aspiration of bacteria into the lungs [21]. Further studies could be useful to determine optimal guidelines for PPI use in lung transplant patients, most notably after antireflux procedures are done.

From this observational study we found that our cohort of patients survived for a mean of 6.6 years. The literature review showed that the 5-year survival of these patients was around 5.9 years [1,22]. It is not possible in our study to see if there is a survival benefit in patients who had Nissen fundoplication, but for future studies this question can be answered.

## 5. Conclusions

Laparoscopic antireflux surgery has been established as a safe operation for lung transplant patients. Late antireflux surgery did not improve lung function significantly amongst lung transplant patients. Patients with symptomatic GERD could benefit from Nissen fundoplication in terms of symptom relief and a subjective satisfaction with the reduction in their symptoms. However an immediate positive effect on lung function after fundoplication is unlikely because of chronic long lasting broncheolitis. A multicenter randomized control trial is needed to assess the effect of early unselected reflux control on respiratory function and graft survival.

## Conflict of interest

The authors state no conflict of interest.

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