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Anti-reflux surgery in lung transplant recipients: Outcomes and effects on quality of life

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Original Article

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Abbreviations
BOS= Bronchiolitis Obliterans Syndrome
GORD= Gastro-Oesophageal Reflux Disease

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ABSTRACT

Background: Fundoplication may improve survival post-lung transplant. Little is known on the effects of fundoplication on quality of life in these patients. The aim of this study was to assess safety of fundoplication in lung transplant recipients and its effects on quality of life.

Methods: Between 1st June 2008 and 31st December 2010, a prospective study of lung transplant recipients undergoing fundoplication was undertaken. Quality of life was assessed before and after surgery. Body mass index and pulmonary function were followed up.

Results: Sixteen patients, mean age 38years (+/-11.9years), underwent laparoscopic Nissen fundoplication. There was no peri-operative mortality or major complications. Mean hospital stay was 2.6 days (+/-0.9days). 15/16 patients were satisfied with the results of surgery post fundoplication. There was a significant improvement in Reflux Symptom Index and DeMeester questionnaires and GIQLI scores at six months. Median BMI decreased significantly post-fundoplication (p=0.01). Patients operated on for deteriorating lung function had a statistically significant decrease in the rate of lung function decline post-fundoplication (p=0.008).

Conclusion: Laparoscopic fundoplication is safe in selected lung transplant recipients. Patient benefit is suggested by improved symptoms and satisfaction. This procedure is acceptable, improves quality of life and may reduce deterioration of lung function.

Introduction:

Chronic microaspiration, secondary to extra-oesophageal reflux, may contribute to bronchiolitis obliterans syndrome (BOS) post-lung transplant. Up to 75% of lung transplant patients have demonstrable gastro-oesophageal reflux disease (GORD) [1-5]. Elevated biomarkers, pepsin and bile salts, have been documented in the broncho-alveolar lavage fluid post-transplant, suggesting microaspiration[6-8]. Early anti-reflux surgery may lead to protection of lung function and increased survival, through preventing microaspiration. Most of the impetus has been from Duke University where the majority of evidence originates[5]. There is a lack of basic information in this patient group including safety and assessments of quality of life. Such information is important because physiological post-operative complications are common post-fundoplication, and may lead to a reduction in quality of life, despite resolution of reflux symptoms. Specific complications include temporary dysphagia, nausea[10], discomfort from gas bloat and increased flatulence[2]. Only one study has looked at the effects of fundoplication on quality of life in this population, despite a high prevalence of foregut dysfunction[11]. This puts these patients at risk of physiological dysfunction and reduced quality of life after surgery. To date no transplant studies have been performed assessing the response of extra-oesophageal reflux symptoms to fundoplication.

The aim of this study was to assess the safety of fundoplication in lung transplant recipients and its effects on quality of life.

Methods:

A prospective study of all lung transplant recipients undergoing anti-reflux surgery between 1st June 2008 and 31st December 2010, at the Northern Oesophago-Gastric Unit was carried out. All lung transplant recipients, in this unit, are routinely prescribed prophylactic PPI therapy to prevent steroid induced ulceration. There was no distinction in patient management made between underlying pathologies (e.g. cystic fibrosis). Surgery was considered for patients with symptomatic reflux alone, refractory to proton pump inhibitor (PPI) therapy, or for reflux associated with deteriorating lung function. Patients with asymptomatic reflux were only considered for surgery if there were concerns about microaspiration. Maximal medical therapy was not considered for failed PPI therapy or suspected microaspiration, as it was felt that a mechanical barrier to reflux would better protect the allografts from microaspiration. Ethical approval for patient follow up was obtained from a local ethics committee (County Durham and Tees Valley 2 Research Ethics Committee).

Reflux status was assessed on proton pump inhibitor therapy**,** by oesophageal manometry, pH-impedance (Ohmega, MMS™, Utrecht, Netherlands) and endoscopy. Patients underwent a thorough pre-operative assessment to ensure fitness for surgery. Reflux status was defined by the presence of oesophageal or extra-oesophageal symptoms combined with objective evidence of GORD on pH-impedance and/or endoscopy. Patients did not undergo a post-fundoplication pH-impedance or endoscopic measurement of reflux status. Pulmonary function tests and bronchoscopy were routinely performed in the preoperative work-up. Patients were followed up clinically with emphasis on lung function, satisfaction with treatment and quality of life. The following questionnaires were used: the DeMeester Reflux Questionnaire, a validated standard reflux questionnaire; the Reflux Symptom Index (RSI) questionnaire, a validated laryngopharyngeal reflux questionnaire and the Gastro-Intestinal

quality of life index (GIQLI) a validated gastro-intestinal specific quality of life questionnaire [12-14]. These questionnaires covered oesophageal reflux symptoms (heartburn, dysphagia) extra-oesophageal reflux symptoms (cough, wheeze) and functional gastrointestinal symptoms that could be affected by fundoplication (bloating, flatus). These were assessed pre- and post-operatively. Pre and post fundoplication BMI were recorded. Patient satisfaction was assessed by directly questioning of patients.

Lung function was assessed in accordance with European Respiratory Society guidelines[15]. BOS scores were calculated using FEV_1 in accordance with International Society for Heart and Lung Transplantation guidelines[16, 17]. The rate of decline in FEV_1 was calculated in accordance with previous studies, namely, the measures of FEV_1 before fundoplication were plotted and the gradient between points from the baseline FEV_1 level to the time fundoplication was performed was calculated in millilitres per month. The same was done for the FEV_1 measurements after fundoplication, the last FEV_1 being the current one in patients still alive or the final FEV_1 in the patient who had died [18].

In our unit bronchoscopy is routinely performed at one week, one, three and six months and one year post-transplant. Further bronchoscopies are carried out when clinically indicated, by an unexplained drop in FEV_1. Pulmonary function tests are carried out routinely at every outpatient visit, on average every 3 months.

The RSI, DeMeester reflux questionnaire and GIQLI questionnaires were completed pre-operatively, 6 weeks and 6 months post-operatively. The GIQLI score was subdivided into symptomatic questions (n=17) and functional questions (n=19) to assess whether changes in quality of life were due to changes in symptoms or social functioning. Patients were asked about overall satisfaction with the result of surgery at 6 weeks and 6 months post-operatively. Questionnaires were filled out by patients with expert advice on hand to explain any concerns about questions and offer one to one advice.

Surgical technique

Laparoscopic Nissen fundoplication was performed. Access to the abdominal cavity was via 4 ports and an epigastric stab incision for the Nathanson retractor to retract the liver. Initially the oesophageal hiatus was dissected to mobilise the oesophagus. The posterior vagus was preserved and a window was created behind the oesophago-gastric junction. The posterior crura were repaired to tighten the hiatus, and a loose 360^{o} wrap was tailored with 3 Ethibond™ sutures (Ethicon, Somerville, NJ, USA). One further suture was used to anchor the wrap to the oesophagus and right crus. Percutaneous endoscopic gastrostomy (PEG) fistulae were repaired when present. These were divided with an Endostapler™ device (Ethicon, Somerville, NJ, USA). the PEG wound was excised and the deficit in the abdominal wall and skin were closed. Local anaesthesia was inserted into the peritoneal cavity and infiltrated in the wounds at the end of the procedure.

Statistical analysis was carried out with the help of a statistician. Initially a Kolmogorov-Smirnov test was performed to assess normality. Subsequently paired t-tests and two way ANOVAs were performed with a post-test Bonferroni correction. Figures were created using Graphpad Prism™ software (San Diego, CA, USA).

Results:

During this time period 109 lung transplants were performed. Seventeen patients were considered for fundoplication. One patient was managed conservatively due to lack of objective evidence of GORD on pH/impedance and endoscopy. Of seventeen patients offered fundoplication, sixteen (10 women, 6 men) with a mean age of 38.2 years (+/-11.9years), consented to and underwent fundoplication. Indications for lung transplant were cystic fibrosis 10, COPD/asthma 1, COPD 1, pulmonary fibrosis 3, pulmonary fibrosis/asthma 1. Thirteen underwent single sequential lung transplant, 2 had a right single lung transplant and 1 had a left single lung transplant. Indications for fundoplication were objective evidence of GORD on pH/impedance and/or endoscopy with either typical reflux symptoms (heartburn) (n=8) or typical (heartburn) and atypical extra-oesophageal symptoms (cough, wheeze) with deteriorating lung function (n=8). Symptoms occurred despite PPI therapy. Mean pre-operative BMI (+/-standard deviation) was 23.8 (+/- 4.4). Patient demographics are summarised in Table 2.

All patients had a diagnostic gastroscopy. 15/16 patients had a hiatus hernia (2-6cm). 8/16 has oesophagitis (grade A n=4), (grade B n=3), (grade C n=1). One patient had a small tongue of Barrett's oesophagus confirmed on histological assessment. Three patients had oesophageal candidiasis which was treated pre-operatively. A summary of pre-operative oesophageal physiology is shown in Table 1.

Operation

Pre-operative American Society of Anaesthesiology score was 2 (n=5) or 3 (n=11). FEV_1 (% predicted) was 80% +/-5% (mean +/-SD). Mean actual FEV_1 (+/-SD) was 2.4L +/- 0.97L. Fundoplication was performed at a mean of 1053 days post transplant (+/-SD) (+/-881days).

Mean intra-operative time was 93 minutes (+/-SD) (+/-20minutes). All patients had blood loss of less than 100ml. Four patients had a PEG fistula excised. No patients required an ITU stay. 5/16 patients were admitted electively to our High Dependency Unit for observation for 24 hours. Mean hospital stay was 2.6 days (+/-SD) (+/-0.9days). Longer stays were due to post-operative pain (in 2 patients with PEG fistulae repair), peri-operative dysphagia (n=1), a return to theatre or difficulty arranging transport home.

Morbidity and mortality

There were no deaths or serious post-operative complications. Two patients developed post-operative dysphagia. One of these patients returned to theatre the following day and underwent a laparoscopy and minor revision of fundoplication and subsequently made an uneventful recovery. In the other patient, barium swallow revealed no significant hold-up and symptoms subsequently resolved spontaneously.

Overall satisfaction with fundoplication

Overall 15/16 patients reported being satisfied at 6 weeks and 15/16 patients reported satisfaction at 6 months. At six weeks one patient was unsatisfied due to dysphagia. At six months one patient was unsatisfied due to pain at the site of their PEG fistula and abdominal bloating.

Quality of life

There was a statistically significant improvement in symptoms and quality of life scores over the first six months post-fundoplication. Kolmogorov-Smirnov analysis revealed the questionnaire data to be normally distributed. Questionnaires were completed by 15/16 patients. One patient, despite reporting high levels of satisfaction with their result, did not wish to spend time completing these questionnaires. Patient symptom and quality of life questionnaire scores are summarised in Table 3.

Reflux Symptom Index questionnaire

Pre-fundoplication RSI was positive on 8/15 patients and this decreased to 3/15 being positive for RSI by six weeks and 2/15 being positive at six months. The two way ANOVA revealed a statistically significant improvement in RSI score over the three time points ($p<0.001$). Post-test Bonferroni correction revealed a statistically significant improvement in mean (+/-SD) RSI score from 14 (+/- 7.1) pre-operatively to 6.7 (+/-7.9) at six weeks post-fundoplication ($p=0.021$) and 5.9 (+/-6.5) at six months ($p=0.003$) (Fig. 1a). The Bonferroni correction did not show a statistically significant difference between RSI scores at six weeks and six months.

DeMeester reflux questionnaire score

The two way ANOVA revealed a statistically significant improvement in DeMeester reflux questionnaire score over the three time points ($p<0.001$). Post-test Bonferroni correction revealed a statistically significant improvement in mean (+/-SD) DeMeester questionnaire score from 3.7 (+/-1.7) pre-operatively 1.5 (+/-1.6) at six weeks post-fundoplication ($p=0.012$) and 1.2 (+/-0.8) at six months ($p=0.003$) (Fig. 1b). The Bonferroni correction did not show a statistically significant difference between DeMeester questionnaire scores at six weeks and six months.

GIQLI

The two way ANOVA revealed a statistically significant improvement in RSI score over the three time points ($p=0.008$). Post-test Bonferroni correction revealed a statistically significant improvement in mean (+/-SD) GiQLI score from 96.5 (+/-34.4) pre-operatively to 112.4 (+/-22.4) at six months ($p=0.036$) (Fig. 1c). The Bonferroni correction did not show a statistically significant difference between GiQLI scores pre-operatively and at six weeks mean score (+/-SD) 105.1 (+/-27.6) nor six weeks and six months ($p=0.1$).

GIQLI sub-analysis

Symptoms

The two way ANOVA revealed a statistically significant improvement in symptom score from our GIQLI sub-analysis score over the three time points ($p<0.001$). Post-test Bonferroni correction revealed a statistically significant improvement in mean (+/-SD) symptom score from our GIQLI sub-analysis from 49.7 (+/-10.5) pre-operatively to 56.9 (+/-9.1) at six weeks post-fundoplication ($p=0.03$) and 58.7 (+/-7.6) at six months ($p=0.006$). The Bonferroni correction did not show a statistically significant difference between symptom score from our GIQLI sub-analysis at six weeks and six months.

Functional

The two way ANOVA revealed a statistically significant improvement in functional score from our GIQLI sub-analysis over the three time points ($p=0.036$). Post-test Bonferroni correction did not reveal which pairs reached statistical significance in their improvement in mean (+/-SD) functional score from our GIQLI sub-analysis score from 51.9 (+/-19.2) pre-operatively to 54 (+/-19.2) at six weeks post-fundoplication and 59.1 (+/-13.1) at six months ($p=0.09$), although there was a mean improvement of 7.2 points from pre-operative score to six months score. There was a trend to significance from pre-operative score to 6 months scores ($p=0.09$) and from six weeks to six months score ($p=0.11$).

Body mass index

Kolmogorov-Smirnov analysis revealed this data to be normally distributed. Mean (+/-) BMI significantly decreased from 23.8+/-4.4 pre-fundoplication to 22.6 +/-4.6 at six months post-fundoplication ($p=0.01$) (Fig. 2).

Lung function

Pre-fundoplication, nine patients had no evidence of BOS, whilst the remaining seven patients had BOSp (n=1), BOS1 (n=2), BOS 2 (n=1) and BOS 3 (n=3). Two patients had a

worsening BOS score from BOS 0 to 1 and BOS 2 to 3 respectively. Despite a slowing rate of decline the patient who deteriorated from BOS 2 to 3, died 482 days post-fundoplication from respiratory failure. The patient with BOSp had a reversal of this to BOS 0. All other patients remained stable.

Patients were followed up for a mean of 476 days post-fundoplication (+/-SD) (+/-180days). Mean (+/-SD) FEV_1 was similar pre-fundoplication 2.4L (+/-0.97L) and post-fundoplication 2.4L (+/-0.71L) (p=0.08).

Eight patients were operated on for deteriorating lung function. Of these eight, one patient had a reversal of BOS, two had a stabilisation of lung function and five had a decrease in the rate of deterioration. Kolmogorov-Smirnov analysis revealed this data to be normally distributed. In the eight patients operated on for deteriorating lung function there was a statistically significant decrease in the rate of decline of FEV_1 per day post fundoplication from a mean change (+/-SD) of -96.7ml/month (+/-87.3ml/month) pre-fundoplication to a mean change post fundoplication of +9.5ml/month (+/-26.5ml/month) post-fundoplication (p=0.008) (Fig. 3). Individual traces are shown in Fig 4.

Discussion

This study demonstrates that laparoscopic fundoplication in a transplant setting is safe. Patients reported a high level of satisfaction with the results of surgery at six weeks and at six months. This study also demonstrated that in this specialised patient population laparoscopic anti-reflux surgery is effective in reducing symptoms of GORD and improves quality of life. Our study also supports the possibility that fundoplication may impact positively on the loss of lung function seen in BOS.

The importance of these findings is that there is little knowledge regarding laparoscopic fundoplication in these patients, and potentially such surgery may have negative effects. Our data demonstrating improvements in symptoms and quality of life is therefore reassuring. More speculatively, the reduction of decline in lung function observed in this open study supports the theory that fundoplication may protect the lung allograft from microaspiration injury, and suggests the need for further trials.

There is no consensus regarding fundoplication in lung transplant recipients[19]. Small series of fundoplication have been reported in patients with end-stage lung disease[20, 21]. Not all these patients will undergo transplant and there are significant risks associated with performing this procedure in patients with very poor lung function. We have adopted a pragmatic approach, operating in the post-transplant period on patients with symptomatic reflux and those with evidence of reflux and deteriorating lung function. Based on the available transplant evidence laparoscopic Nissen fundoplication was favoured in our practice[22].

In the study of safety from Duke University, compared to the non-transplant population there were no significant differences in operative time and blood loss [23]. Our study has comparable intra-operative data and no patients in our series have needed conversion to an open operation. No intra-operative or peri-operative deaths have been reported by the Duke's group [5, 23, 24], although recently one death post-fundoplication has been reported[25]. We have experienced no mortality to date and no major complications were encountered. The Duke group have reported increased length of stay in the transplant population and a higher readmission rate, due to transplant co-morbidity[23]. Our results are comparable with this experience. The long post-operative stay may be partially explained by the fact that transplant patients have to travel greater distances than a local population. Overall our results suggest that laparoscopic fundoplication is safe in selected lung transplant recipients.

Over the last 20 years quality of life assessments have been established as end point outcomes. The GIQLI questionnaire has been recommended by the European Association for Endoscopic Surgery for the assessment of quality of life after fundoplication[26]. The DeMeester Reflux Questionnaire is validated to assess reflux symptoms and the RSI has been validated in non-transplant patients as a marker of extra-oesophageal reflux[13] and has been used to assess the effects of fundoplication on extra-oesophageal reflux[27, 28].

In non-transplant patients fundoplication has been shown to ameliorate reflux symptoms and improve quality of life[29]. This study showed that in lung transplant recipients there was an improvement in typical reflux symptoms. Although this may be expected it has also shown an improvement in quality of life post-fundoplication, despite the high prevalence of foregut dysfunction in this population[11]. Our sub-analysis of the data showed that improvement in quality of life occurs via both amelioration of symptoms and improved social functioning.

Questionnaires designed for the assessment of extra-oesophageal reflux have not previously been used in lung transplant recipients. Our finding of improvement in extra-oesophageal reflux symptoms in lung transplant recipients after fundoplication, is therefore novel. These symptoms include cough and hoarseness, which can be caused by extra-oesophageal reflux but may also represent primary respiratory symptoms. This finding further supports the theory that these patients experience laryngopharyngeal reflux[13, 27], which may precede micro-aspiration. It is unknown how the evolving changes in the lung transplant and BOS may affect extra-oesophageal reflux symptoms, but we believe improvements are possibly attributable to fundoplication.

The Melbourne group's study of fundoplication in lung transplantation described a decrease in mean BMI from 23kg/m^2 six months pre-operatively to 21kg/m^2 six months post-operatively. The current study's results are similar with a decrease in mean BMI from 23.8kg/m^2 to 22.6kg/m^2 six months post-operatively. The significance of this is unknown, but in selected patients post-fundoplication dietary advice and intervention may have an important role.

The Duke University Transplant Group have published several papers[5, 23, 24, 30, 31], each an update of a continuing program, with results suggesting that anti-reflux surgery may lead to increased survival and improved lung function post-transplantation[5]. Our study was not designed to assess the impact of fundoplication on lung function. In our series, mean FEV_1 did not deteriorate post fundoplication. Those patients operated on for deteriorating lung function underwent a statistically significant reduction in the loss of lung function, and one patient had a reversal of a subtle defect in lung function.

Our current study has several limitations. The numbers involved were small and patients had a variety of indications for surgery. Fundoplication was performed at different times after transplant and no patients were operated on within 90 days of transplant, the suggested optimum time for intervention[5], although, this study did not seek to define an optimum time for intervention. No control group was analysed and the study wasn't randomised. Further studies could include a focus on the effects of early fundoplication (within 90 days) on allograft function and long-term survival.

Almost all the evidence supporting fundoplication post-lung transplant originates from a single centre and only three other centres have published case series. Based on this evidence, we have tried to develop a series of pragmatic indications for those to be offered surgical interventions. The improvement in GORD symptoms and quality of life in these patients suggests that the developing indications for fundoplication post-lung transplant may include symptomatic GORD in fit patients. The reduction in deterioration of lung function post-fundoplication further supports a possible role of this therapy in the prevention of BOS, but further evidence is required including formal trials. Our study suggests that with careful design such studies are possible and can be safe in an extended series of patients.

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Fig 1a RSI Score over the first six months post fundoplication

Legend: Dotted line indicates a score of 13, the cut off for a normal/abnormal score. * denotes statistical significant difference from pre-operative values. Lines demonstrate mean values with standard deviation.

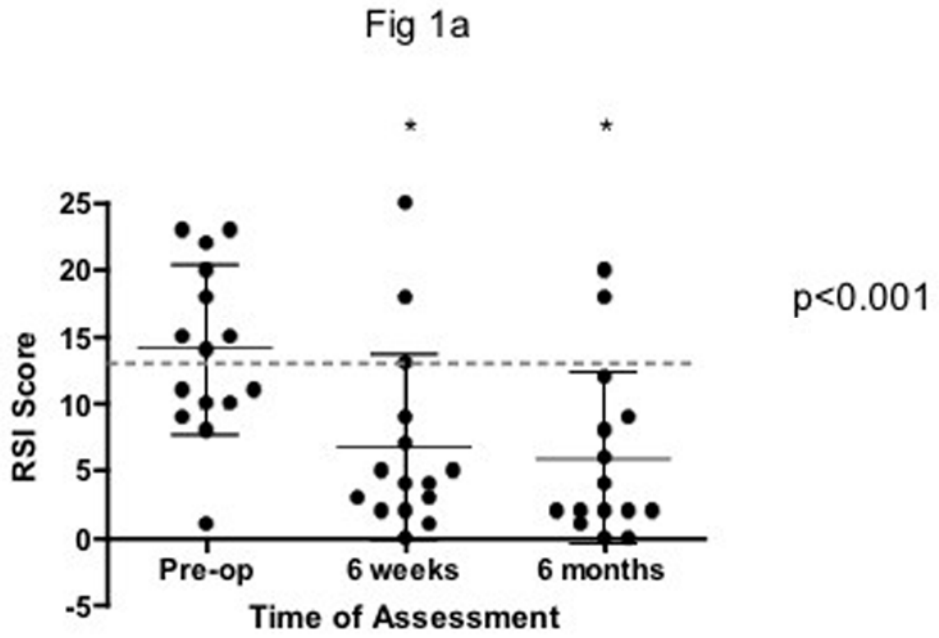

Fig 1b DeMeester Reflux Questionnaire Score over the first six months post fundoplication
Legend: * denotes statistical significant difference from pre-operative values. Lines demonstrate mean values with standard deviation.

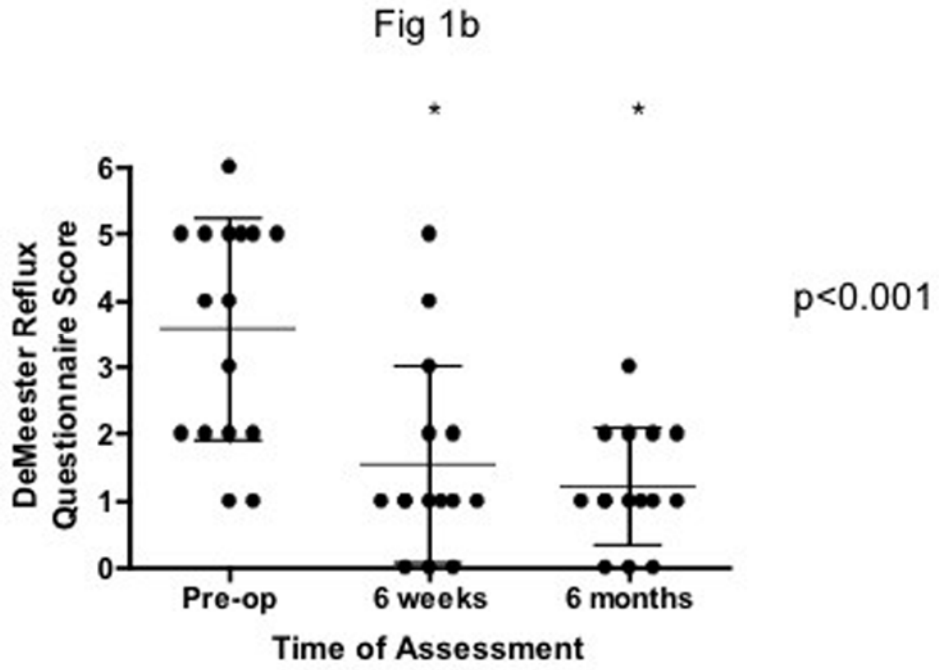

Fig 1c GIQLI Score over the first six months post fundoplication
Legend: * denotes statistical significant difference from pre-operative values. Lines demonstrate mean values with standard deviation.

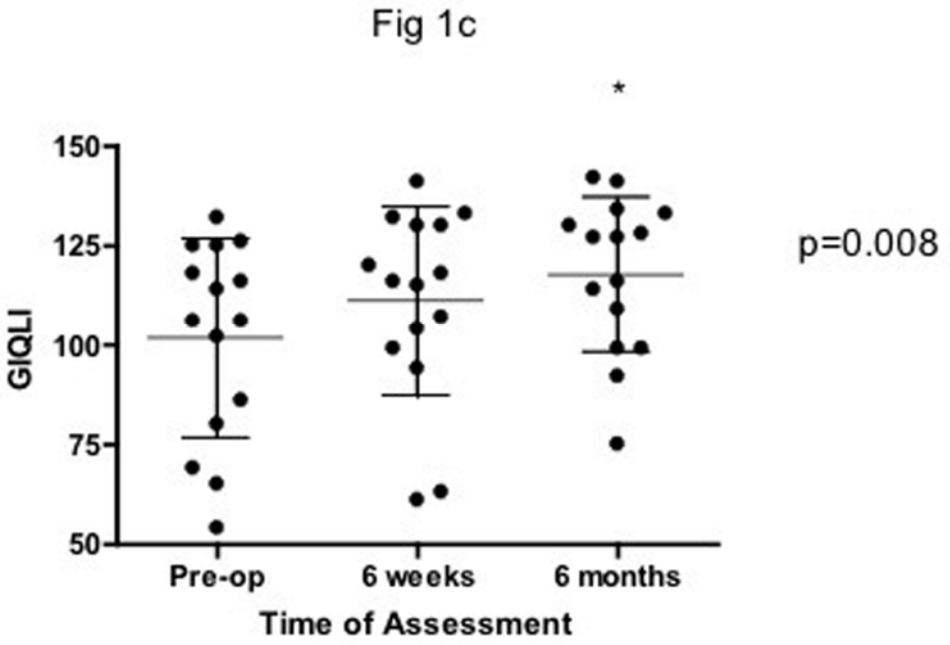

Fig 2 BMI Score pre-operatively and at six months post fundoplication
Legend: * denotes statistical significant difference from pre-operative values. Lines demonstrate mean values with standard deviation.

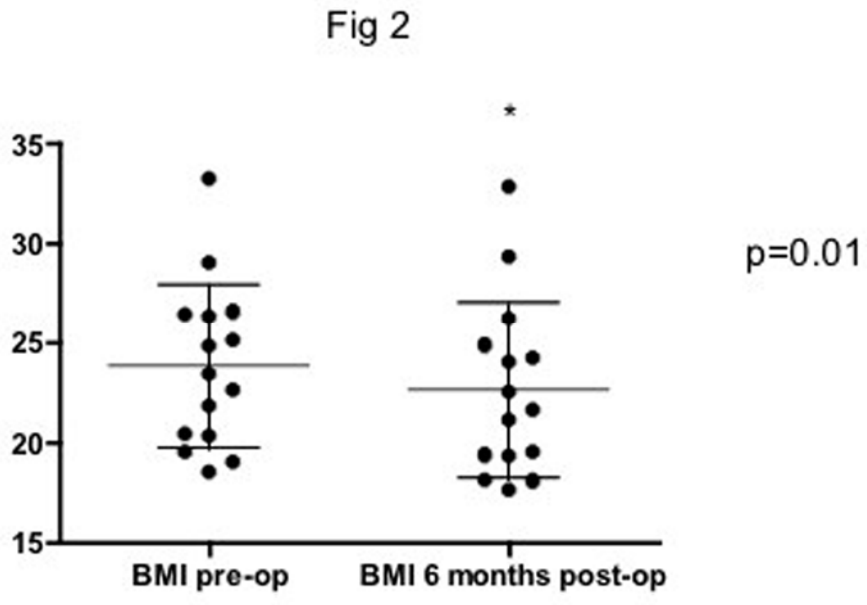

Fig 3 Rate of change of FEV_1 pre and post fundoplication in patients with deteriorating lung function
Legend: * denotes statistical significant difference from pre-operative values. Lines demonstrate mean values with standard deviation.

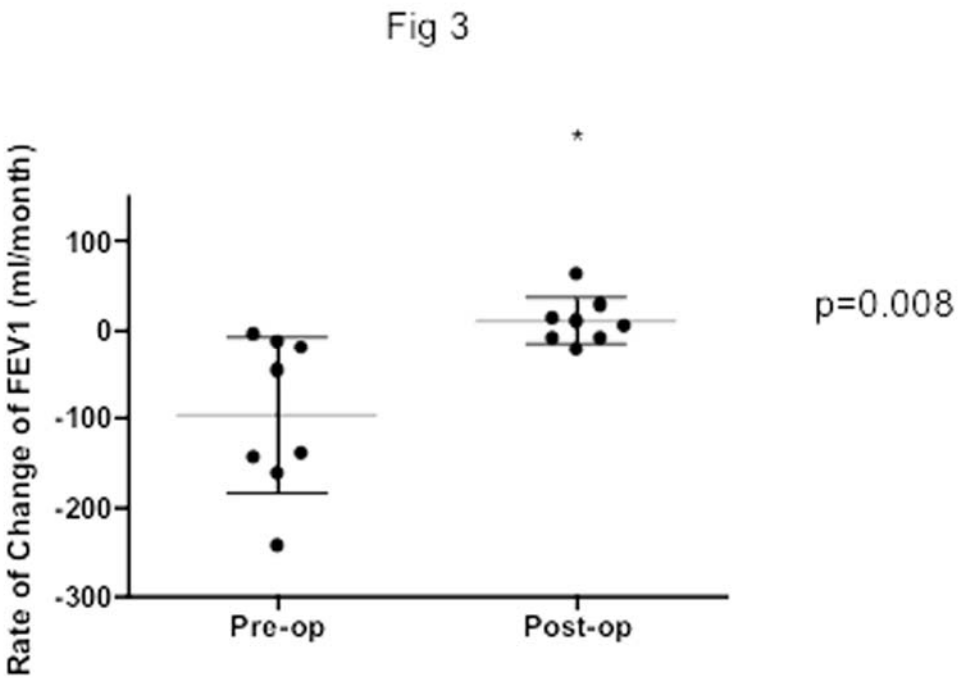

Fig 4 Changes in FEV_1 overtime pre and post fundoplication in patients with deteriorating lung function

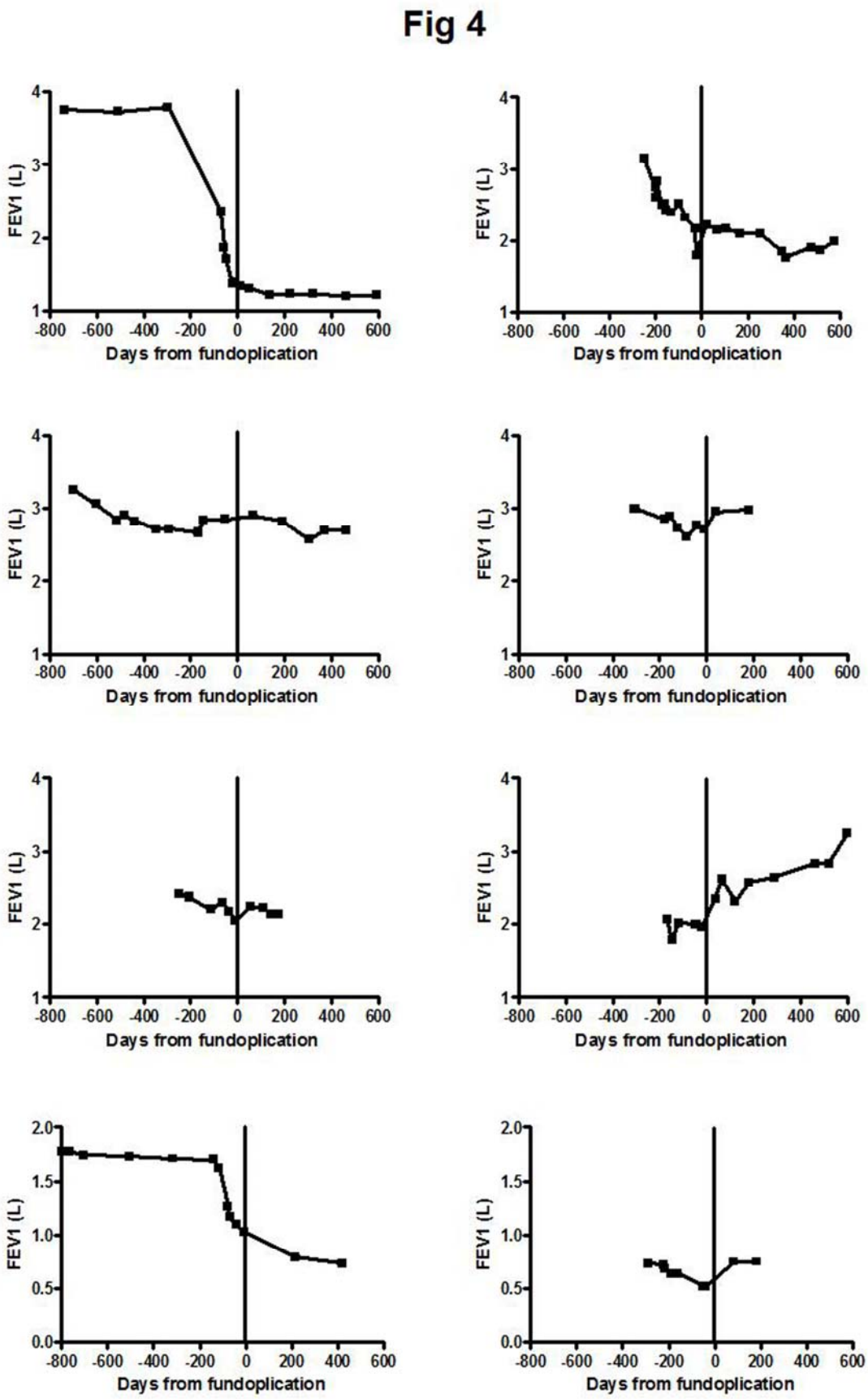

Table 1 Summary of Oesophageal Physiology

Legend: *NSD= Nonspecific Dysmotility, DOS= Diffuse Oesophageal Spasm

Table 2 Demographics of Study Patients

Table 3 Summary of Symptom & Quality of Life Questionnaire Scores

Table 1 Summary of Oesophageal Physiology

Oesophageal Physiology	Mean (+/- standard deviation)
Lower Oesophageal Sphincter	
Pressure	24.6mmHg +/-14.2
Length	2.8cm +/-0.7
Mean Distal Peristaltic Amplitude	64.3 mmHg +/-20.4
Peristalsis	
Normal	7
Abnormal	2 (NSD, DOS)*
Reflux Indices	
Acid Exposure	12.6% +/-7.3
DeMeester Score	49.5 +/-27.9
Oesophageal Volume Exposure	1.3% +/-0.4
Total Reflux Events	66 +/-27
Proximal Reflux Events	23 +/-15

Legend: *NSD= Nonspecific Dysmotility, DOS= Diffuse Oesophageal Spasm

Table 2 Demographics of Study Patients

Demographics	Mean (+/- standard deviation)
Age	38.2years +/-11.8
Sex	
-Male	6
-Female	10
Underlying Pathology	
-Cystic Fibrosis	10
-Pulmonary fibrosis	3
-Pulmonary Fibrosis/Asthma	1
-COPD	1
-COPD/Asthma	1
#Transplant	
-SSLT	13
-LSLT	1
-RSLT	2
BMI	23.8+/-4.4
FEV_1	2.4L +/-0.97
FEV_1 Predicted	80% +/-5
ASA	
-2	5
-3	11

Table 3 Summary of Symptom & Quality of Life Questionnaire Scores

	Pre-operative	Six weeks	Six months
DeMeester	3.7 (+/-1.7)	1.5 (+/-1.6)	1.2 (+/-0.8)
RSI	14 (+/-7.1)	6.7 (+/-7.9)	5.9 (+/-6.5)
GIQLI	96.5 (+/-34.4)	105.1 (+/-27.6)	112.4 (+/-22.4)
GIQLI subsets			
-symptoms	49.7 (+/-10.5)	56.9 (+/-9.1)	58.7 (+/-7.6)
-functional	51.9 (+/-19.2)	54 (+/-19.2)	59.1 (+/-13.1)

(values are mean +/-standard deviation)