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Feasibility of laparoscopic Nissen fundoplication after pediatric lung or heart–lung transplantation: should this be the standard?

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Abstract
Background Five-year graft survival in the pediatric lung transplant (LTxp) population is less than 50%, with obliterative bronchiolitis (OB) the leading cause of death at 1, 3, and 5 years post-transplant. Bronchiolitis obliterans syndrome (BOS), defined using spirometry values, is the clinical surrogate for the histological diagnosis of obliterative bronchiolitis. Surgical correction of documented gastroesophageal reflux disease (GERD) has been proposed as a means to potentially delay the onset of BOS and prolong allograft survival in adults before or after lung transplantation but only one such study exists in children. We have examined the safety and possible benefits of laparoscopic antireflux surgery in pediatric patients following lung (LTxp) and heart–lung transplantation (HLTxp).
Methods An Institutional Review Board (IRB)-approved retrospective chart review was performed to evaluate the outcomes and complications of laparoscopic antireflux surgery in pediatric lung and heart–lung transplant patients. Spirometry data were collected for BOS staging using BOS criteria for children.
Results Twenty-five lung and heart–lung transplants were performed between January 2003 and July 2009. Eleven transplant recipients, including six double-lung and five heart–lung (HLTxp), with a median age of 11.7 years (range 5.1–18.4 years), underwent a total of 12 laparoscopic Nissen fundoplications at a median of 427 days after transplant (range 51–2310 days). GERD was determined based upon clinical impression, pH probe study, gastric emptying study, and/or esophagram in all patients. Three patients already had a gastrostomy tube in place and two had one placed at the time of fundoplication. There were no conversions to open surgery, 30-day readmissions, or 30-day mortalities. Complications included one exploratory laparoscopy for free air 6 days after laparoscopic Nissen fundoplication for a gastric perforation that had spontaneously sealed. Another patient required a revision laparoscopic Nissen 822 days following the initial fundoplication for a paraesophageal hernia and recurrent GERD. The average length of hospital stay was 4.4 ± 1.7 days. Nine of the 12 fundoplications were performed in patients with baseline spirometry values prior to fundoplication and who could also complete spirometry reliably. One of these nine operations was associated with improvement in BOS stage 6 months after fundoplication; seven were associated with no change in BOS stage; and one was associated with a decline in BOS stage.
Conclusion It is feasible to perform laparoscopic Nissen fundoplication in pediatric lung and heart–lung transplant recipients without mortality or significant morbidity for the treatment of GERD. The real effect on pulmonary function cannot be assessed due to our small sample size and lack of reproducible spirometry in our younger patients. Additional

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studies are needed to elucidate the relationship between antireflux surgery and the potential for improving pulmonary allograft function and survival in children which has been previously observed in adult patients.

Keywords GORD/GERD (gastro-oesophageal reflux disease) · Paediatrics · Pulmonary (lungs) · Transplantation

With advancements in transplant care, lung transplantation (LTxp) has become an effective treatment for end-stage lung disease (ESLD). However, chronic allograft rejection seriously limits the long-term survival of LTxp patients. Five-year graft survival in the pediatric LTxp population is less than 50%, significantly lower when compared to other solid-organ transplants in the pediatric population such as liver (74%) and kidney (94%) [1]. Chronic rejection is characterized on histological examination by obliterative bronchiolitis (OB) or the inflammation and fibrosis of small airways leading to their progressive occlusion. OB is the leading cause of death at 1, 3, and 5 years after transplant in the pediatric LTxp population [2].

Due to the poor yield of transbronchial biopsy, bronchiolitis obliterans syndrome (BOS) is used as a clinical surrogate for the histological diagnosis of OB. BOS is defined by declines in forced expiratory volume in 1 s (FEV_1) and mid-expiratory flow rate ($FEF_{25–75}$), not accounted for by confounding conditions such infection, acute rejection, anastomotic problems, and disease recurrence [3]. Hence, chronic rejection or BOS is a diagnosis of exclusion. Although initially posed as a hypothetical risk and not classified as a confounding factor, gastroesophageal reflux disease (GERD) in recent years has been increasingly linked to the onset and progression of BOS [3–5].

We have evaluated our lung and heart–lung transplant patients who have undergone laparoscopic antireflux surgery to assess the risks and potential benefit of preventing GERD in those patients who were felt to be having declining pulmonary function tests at the time of referral for fundoplication. While laparoscopic fundoplication has been shown to be safe in the adult LTxp population either before or after the LTxp, there has been only one published study on the effect of fundoplication after LTxp in the pediatric population [6–9].

Methods

Since 1985, the lung and heart–lung transplant program at Children's Hospital of Pittsburgh (CHP) of UPMC has performed 111 transplants (3 single lung, 65 double-lung, and 53 heart–lung). Since 2004, after initial data on surgical correction of reflux in the adult lung transplant population were published, we have been selectively performing laparoscopic Nissen fundoplications in pediatric LTxp patients for the treatment of GERD. An IRB-approved retrospective chart review (#7100012) was performed on the records of all 25 pediatric patients who underwent lung or heart–lung transplant operations at CHP between January 2003 and July 2009. Of these patients (19 double-lung, 6 heart–lung), 11 patients (6 double-lung, 5 heart–lung) underwent 12 post-transplant laparoscopic Nissen fundoplications for the treatment of GERD (one patient required a revision of her original Nissen fundoplication). GERD was diagnosed on a clinical basis, by pH probe, upper gastrointestinal series, or gastric emptying study in all patients and followed up with additional studies when necessary. No protocol for routine pH monitoring, radiographic or nuclear medicine studies for reflux was used.

Per institutional protocol, all patients received induction immunosuppression with rabbit thymoglobulin after LTxp. Immunosuppression was maintained with tacrolimus, mycophenolate mofetil, prednisone, or methylprednisolone, and occasionally sirolimus. All patients also received appropriate infection prophylaxis as well as an acid suppression regimen that included either an H_2 blocker or a proton pump inhibitor (PPI). Erythromycin and metoclopromide were also used to improve gastric motility in select patients. Patients were followed with routine pulmonary function tests (PFTs) every 4–6 weeks for the first year post-transplant, every 2 months for the second year, and every 3–6 months for the third year and beyond. Scheduled surveillance flexible bronchoscopy was performed along with transbronchial biopsies and bronchoalveolar lavage. PFTs and bronchoscopy were performed at increasing frequency at any time when the patient showed clinical deterioration.

Chronic rejection was suspected based on clinical symptoms, declining forced expiratory volume in 1 s (FEV_1) or mid-expiratory flow rate ($FEF_{25–75}$), or pathologic evidence based on bronchoscopy and biopsy. Where stable baseline FEV_1 and $FEF_{25–75}$ could be established, BOS severity was scored according to the updated classification criteria as described previously [3].

Data for fundoplication, including complications, conversions to open surgery, 30-day readmission, and 30-day mortalities, were recorded. Length of hospital stay (LOS) and estimated blood loss (EBL) are reported as mean ± standard deviation. In those children who had stable baseline spirometry values prior to fundoplication and who could complete PFTs reliably, BOS score and average FEV_1 values 3 months before Nissen fundoplication were compared to BOS score and average FEV_1 values during the 1–6-month interval after surgery using Student's *t* test.

Results

Twenty-five lung (LTxp) or heart–lung transplants (HLTxp) were performed between January 2004 and July 2009. Eleven recipients, including six double-lung and five heart–lung, underwent a total of 12 laparoscopic Nissen fundoplications at a median of 427 days (range 51–2310 days) after lung transplantation. The etiology of pulmonary failure for this group is given in Table 1. GERD was determined based upon clinical impression and/or esophagram, pH probe study, or gastric emptying study (milk scan) in all patients. Nine of the 11 patients who underwent fundoplication showed delayed gastric emptying. A total of five patients already had a gastrostomy tube in place (patient 4, 7, and 11 Table 2) or had one placed at the time of fundoplication (patients 1 and 3 Table 2). Table 2 gives the age and the pulmonary function data for all patients. One patient (patient 6 in Table 2) required laparoscopic Nissen revision 822 days after the initial fundoplication after developing a paraesophageal hernia and recurrent GERD. The average age at transplantation was 9.6 years (range 4.6–15.9 years). These patients underwent fundoplication at an average of 11.7 years (range 5.1–18.4 years). There were no 30-day readmissions for surgical complications nor 30-day mortality following fundoplication. The operative time for the 12 fundoplications was 126.3 ± 30.7 min. The EBL during surgery was 9.2 ± 4.2 cc. There were no intraoperative complications or conversion to open surgery. Postoperative complications included one exploratory laparoscopy for free air 6 days post-Nissen from an anterior gastric perforation that was sealed spontaneously by omentum (patient 2 in Table 2). Another patient developed a paraesophageal hernia requiring laparoscopic revision 822 days after the initial fundoplication for recurrent GERD symptoms [patient 6(2) in Table 2], although esophagogastroduodenoscopy (EGD) and milk scan in this patient did not show evidence of reflux. The average length of hospital stay was 4.4 ± 1.7 days.

Table 1 Demographics and etiology of end-stage lung disease (ESLD)

	Fundoplication after lung transplant ($n = 11$)
Sex (M/F)	7/4 (5/6)
Type of transplant (lung/heart–lung)	6/5
Age at transplant [mean (range)] (years)	9.6 (4.6–18.4)
Etiology	
Radiation-induced pulmonary fibrosis	2
Emphysema	1
Pulmonary hypertension from CHD	4
Pulmonary hypertension from BPD	1
Primary pulmonary hypertension	2
Cystic fibrosis	1

CHD congenital heart disease, *BPD* bronchopulmonary dysplasia

In patients with sufficient surgical follow-up, 7 of 10 operations were associated with subjective improvement in GERD symptoms. Two patients (3 and 5 in Table 2), whose predominant reflux symptom was cough, had persistent cough after fundoplication despite negative studies for recurrent reflux. Of the five patients who had completed post-fundoplication milk scan or barium swallow, all were negative for reflux [patients 3, 4, 5, 6(1), and 9 in Table 2]. Nine of 12 fundoplications were performed in patients with baseline spirometry values prior to fundoplication. In Table 2, *n* is the number of FEV_1 values averaged during

Table 2 Pulmonary function before and after laparoscopic Nissen fundoplication

Patient	Age at LTxp	Age at Fundo (years)	Baseline FEV_1 %	FEV_1% pre-Fundo	BOS pre	FEV_1% post-Fundo	BOS post	*p* FEV_1%
1	6.1	6.2	N/A	39.5 ± 6.4 ($n = 2$)	*N*/A	55.0 ± 19.6 ($n = 5$)	N/A	–
2	15.4	16.9	121	44.0 ± 6.2 ($n = 3$)	3	21.6 ± 6.6 ($n = 5$)	3	0.003
3	15.2	15.4	53.5	43.3 ± 6.6 ($n = 4$)	0p	52.3 ± 10.4 ($n = 8$)	0	–
4	4.8	6.5	79.5	75.5 ± 2.1 ($n = 2$)	0	78.8 ± 12.1 ($n = 4$)	0	0.74
5	5.3	7.7	121	97.1 ± 8.8 ($n = 7$)	0p	97.3 ± 4.3 ($n = 4$)	0p	0.97
6(1)	15.4	16.1	72.5	54.1 ± 5.8 ($n = 8$)	1	52.8 ± 10.1 ($n = 9$)	1	0.75
6(2)		18.3	92.5	68.2 ± 8.8 ($n = 4$)	1	64.7 ± 9.7 ($n = 6$)	1	0.58
7	5.8	6.4	N/A	*N*/A	N/A	*N*/A	N/A	–
8	4.9	5.1	86.5	67.2 ± 19.1 ($n = 6$)	1	81.6 ± 14.4 ($n = 9$)	0p	0.24
9	4.6	6.1	59.5	44.0 ± 12.0 ($n = 3$)	1	43.7 ± 7.5 ($n = 6$)	1	0.96
10	12.1	18.4	100.0	69.2 ± 5.8 ($n = 6$)	1	56.3 ± 4.7 ($n = 3$)	2	0.013
11	15.9	16.8	66.5	64.5 ± 7.8 ($n = 2$)	0p	67 ($n = 1$)	0p	

Baseline FEV_1% FEV_1 % predicted values at baseline, *FEV_1% pre-fundo* average of FEV_1 data collected 3 months before, *FEV_1% post-fundo* average FEV_1 1–6 months after fundoplication, *n* number of FEV_1 values averaged during those periods

those periods. The *p* values reveal no significant difference between the FEV_1 values before and after fundoplication. Patient 7 has a tracheostomy and could not perform routine PFT. Patients 1 and 3 underwent fundoplications within 60 days after LTxp and did not establish stable baseline FEV_1 values prior to fundoplication.

Although most of our patients could complete spirometry, there was large intraperformer variability due to their young age. The average FEV_1 percent predicted (FEV_1%) values 3 months before fundoplication and 6 months after fundoplication are given in Table 2. In eight patients with stable spirometry established prior to fundoplication and a post-fundoplication follow-up of at least 6 months, three showed improvement in their average FEV_1% predicted value and three showed a slight decline in their average FEV_1% predicted value, although these changes did not reach statistical significance. Patient 2 in Table 2 showed a significant drop in FEV_1% predicted value post-fundoplication, but his pulmonary function had been steadily declining for 7 months prior to fundoplication due to antirejection medication noncompliance. Fundoplication was done, in part, as a last resort to stabilize this patient's pulmonary function. This is also the patient who had the gastric perforation discovered and managed laparoscopically on postoperative day 6 from initial laparoscopic Nissen fundoplication. The rate of this patient's declining FEV_1% predicted value actually slowed after fundoplication but he died 29 months after lung transplant and 11 months after fundoplication. Patient 10 in Table 2, who had her fundoplication 2310 days after her transplant, also experienced a significant decline in her FEV_1% predicted value. In this patient, a suspicion for GERD was prompted by a decline in her PFTs. Six months after her Nissen, she is currently followed by an adult transplant pulmonologist at a different institution where she is being evaluated for a second transplant. She is also the only patient who experienced a decline in her BOS stage. One patient (8 in Table 2) had an improvement in BOS stage from 1 to 0p.

Only one patient had biopsy-proven OB from a sample collected 5 months after Nissen fundoplication [patient 6(1) in Table 2]. All but one patient (11 in Table 3) had at least one episode of acute cellular rejection (ACR) either before or after fundoplication, with only four patients experiencing recurrent ACR episodes (2–5 times) prior to fundoplication. Two of these four patients did not have another episode of ACR after fundoplication, whereas patients 2 and 10 were not biopsied further due to their progressive ESLD (Table 3).

Table 3 Incidence of acute cellular rejection before or after fundoplication

Patient	ACR before fundoplication	ACR after fundoplication
1	0	1 (A2)
2	5 (A1, A1, A2, A2, A2.5)	N/A
3	1 (A1)	0
4	1 (A1)	0
5	3 (A1.5, A2, A1)	0
6(1)	4 (A2, A1, A1, A2)	0
6(2)	0	0
7	0	1 (A min)
8	1 (A1)	?
9	0	1 (A min)
10	2 (A2, A2)	N/A
11	0	0

ACR acute cellular rejection

Discussion

Over 1600 pediatric lung and heart–lung transplants were performed worldwide for the treatment of end-stage lung disease (ESLD) from 1984 to 2007. This accounts for approximately 5% of all lung transplants and 15% of all heart–lung transplants during this time period [2]. Obliterative bronchiolitis continues to be a major limitation to the long-term survival of pediatric lung transplant recipients as it is in adults and it may be attributed to the proliferation of granulation tissue, airway fibrosis, and occlusion [10].

GERD has previously been linked to a number of other respiratory diseases, including asthma, idiopathic pulmonary fibrosis, and cystic fibrosis [11–14]. Pulmonary symptoms present as one of the atypical presentations of GERD and is observed with a prevalence as high as 35–68% in patients with ESLD [5–7, 15–17]. The exact mechanism behind the interaction between respiratory diseases and GERD is unknown. The problem of GERD may be exacerbated by the LTxp process where the reported incidence of GERD may be as high as 65–80% [18, 19].

Surgical correction of reflux has been shown to stabilize or improve the pulmonary symptoms in patients with asthma and ESLD [16, 20, 21]. A similar theory has been applied to the LTxp population with regard to BOS. Multiple studies in adults have shown that antireflux surgery, when performed early after LTxp [8, 9, 22, 23] or prior to LTxp [16, 24], is safe and can potentially delay the onset of BOS and prolong allograft survival in this complex patient population. While laparoscopic fundoplication have been shown to be safe in adult LTxp recipients, there has only been one study to date on the effect of antireflux surgery after LTxp in the pediatric population [6]. This group determined antireflux surgery to be safe, although, as in our series, there was no direct comparison of medical versus surgical therapy for GERD in LTxp patients. The time frame following lung transplantation in which fundoplication was performed ranged from 104 to 202 days for their

five patients [6] compared to 51–2310 days in our study. Our study also included six patients younger than age 10, which has not been documented before in the literature.

There are a number of limitations in our study, such as the small number of patients and its retrospective nature, which limit the conclusions we can draw from this review. We also did not compare our group of patients to those who did not undergo fundoplication nor to patients who underwent fundoplication prior to lung transplantation since many of these antireflux operations were performed via an open method and in a different era. There were also more patients who had pulmonary hypertension associated with congenital heart disease which resulted in the need for heart and lung transplantation. These demographic differences limit our ability to apply our results across the broad range of all pediatric LTxp patients. Another potential confounder is the routine use of proton pump inhibitors or H_2 receptor antagonists at our institution which may have contributed to the insensitivity in detecting GERD by some methods.

One limitation that requires special mention is the use of PFTs in our patients. Normally, PFTs cannot be performed reliably until the age of 5 years and some of our younger patients struggled with this task. There is also a learning curve associated with the performance of PFTs which may confound the measurements. Furthermore, although using % FEV_1 is recommended for the diagnosis of BOS in pediatric patients due the unique issue of growth, it is still uncertain how the rate and the quality of the growth of the transplanted lung compare to those of the native lung and hence predict FEV_1 values [25, 26].

We showed that laparoscopic Nissen fundoplication can be performed for the treatment of GERD in pediatric LTxp recipients as young as 5 years old without mortality or significant morbidity. Furthermore, the majority of our patients tolerated Nissen fundoplication without significant decline in FEV_1% predicted values or BOS score. The two patients who did not seem to benefit from Nissen fundoplication were (1) the only patient with an initial BOS of 3 and who did not comply with immunosuppressive therapy and subsequently developed gastric perforation, and (2) the patient who underwent fundoplication over 6 years after lung transplantation. It is unknown if the surgical correction of GERD improves pulmonary function or extends long-term survival in the pediatric LTxp population. Our results and those of Benden [6] did not demonstrate any consistent effect of fundoplication on pulmonary function. However, if such a benefit exists, as suggested in the adult literature, it raises two questions. First, should Nissen fundoplication be performed in LTxp patients solely for the improvement of pulmonary function and anticipated delay of the onset of BO? Cantu et al. [23] demonstrated that in a group of lung transplant patients with follow-up longer than 3 years with reflux, those who underwent fundoplication early had an improved actuarial and BOS-free survival even when compared to patients without reflux. The second question pertains to the timing of fundoplication relative to lung transplantation. All of our patients underwent fundoplication following lung transplantation as did those patients in the only other pediatric series [6]. The ideal timing for screening for GERD and surgically intervening in the pediatric population is unknown. It could be that improved outcomes would be recognized if antireflux surgery was performed much sooner after transplantation or even prior to LTxp. Adult studies have shown that laparoscopic antireflux surgery can be performed in ESLD patients before transplantation for the treatment of GERD [16, 24, 27]. Linden et al. [16] showed that there was a stabilization of oxygen requirement in ESLD patients who underwent fundoplication prior to lung transplantation. Although 15 of 19 patients in their series eventually underwent transplantation, only 2 of 15 patients in another series underwent lung transplantation following fundoplication [27].

A call for the standardization of antireflux surgery in adult lung transplant patients has been proposed since there may be potential benefit in these high-risk patients [28]. In addition, since aspiration and GERD are prevalent among patients with advanced lung disease, the clinical significance of these events and the best tests to determine how adverse outcomes in these patients can be prevented are important goals [29].

In conclusion, it is feasible to offer laparoscopic Nissen fundoplication in pediatric lung transplant patients with the potential benefit of preventing GERD and without causing significant harm to these patients. Because no decline in BOS stage or % FEV_1 was observed in most of our patients 6 months after antireflux surgery, we cannot confirm the possible benefit of fundoplication on pulmonary function due to our small sample size and the large intraperformer variability during spirometry. Additional studies aimed at elucidating the relationship between antireflux surgery and the potential for improving pulmonary allograft function and survival in children should be performed in a prospective randomized controlled manner involving multiple centers or by utilizing a registry to study enough patients to produce meaningful results.

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