Fundoplication to preserve allograft function after lung transplant: Systematic Review and Meta-Analysis

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Central Message (191/200)

In this meta-analysis of patients with Lung Transplant undergoing Anti-Reflux Surgery (ARS), the decline observed in Rate of Change of the FEV1 can be shown to plateau, which may be indicative of a reduction of the impact of BOS.

Perspective Statement (386/405)

There is limited evidence behind anti-reflux surgery (ARS) in the lung-transplant patient population, however gastroesophageal reflux is thought to be a main driver of Bronchiolitis Obliterans Syndrome. Within this meta-analysis, we demonstrate a declining FEV1 plateaus following ARS. The rate of change of FEV1 (ml/day) is a core outcome that may strengthen the evidence base for ARS.

Abstract

Objective: This review and pooled analysis sought to demonstrate objective evidence of improved graft function in lung transplant patients undergoing anti-reflux surgery (ARS).

Summary Background Data: ARS has been adopted in select patients with lung transplant for the past two decades across many centers. Outcomes have been reported sporadically as retrospective series and no pooled analysis has been performed.

Methods: In accordance with MOOSE guidelines, a search of PubMed Central, Medline, Google Scholar and Cochrane Library databases was performed. Papers documenting spirometry data pre- and post-ARS were reviewed and a random-effects model meta-analysis was performed on FEV1 values and the rate of change of FEV1.

Results: 6 papers were included in the meta-analysis. Regarding FEV1 before and after ARS, we observed a small increase in FEV1 values in studies reporting raw values in L/1sec (2.02+/-0.89 vs. 2.14+/-0.77, n=154) and % of predicted (77.1+/-22.1 vs. 81.2+/-26.95, n=45), with a 'small' pooled Cohen's d effect size of 0.159(p=0.114). When considering the rate of change of FEV1 (ml/day) we observed a significant difference in pre-ARS compared to post-ARS (-2.12 +/- 2.76 ml/day vs. +0.05+/-1.19, n=103). There was a pooled effect size of 1.702(p=0.013), a "large" effect of ARS on the rate of change of FEV1 values.

Conclusions: This meta-analysis of retrospective observational studies demonstrates that ARS might benefit patients with declining FEV1 examining the rate of change of FEV1 in the pre- and post-operative periods.

Introduction

In the transplanted lung, the development and progression of bronchiolitis obliterans syndrome (BOS) is widely regarded as the principle threat to long-term graft function. Alongside allograft rejection and infection, gastroesophageal reflux disease (GERD) is widely acknowledged to feature heavily in the fibrotic process that drives BOS[1]. Patients with GERD are recognized to be at a much higher risk of acute rejection following lung transplantation[2–4]. GERD has also been objectively and prospectively measured in the post-lung transplant population and demonstrated to have an incidence of over 50%[5].

The purported mechanisms behind the observed high incidence of GERD in patients post-lung transplantation are complex and likely multi-factorial; with injury to the vagus nerve[6], delayed gastric emptying, and medication related effects all implicated[7].Furthermore, the transplanted lung has increased risk of aspiration and aspiration-related lung injury; the reduced sensation in the airway means there is no afferent limb of the cough reflex, which is thought to continue for months to years after the transplantation[6]. Micro-aspiration and asymptomatic reflux affects a considerable proportion of lung-transplant recipients, which highlights the often-insidious nature of GERD related BOS[1,8]. Additionally, the presence of delayed-gastric emptying is an independent risk factor, alongside GERD, for chronic lung allograft dysfunction.

While there is recent evidence to suggest that medical management of acid reflux has benefits within the lung transplant population[9], there has also been a further benefit purported for anti-reflux surgery (ARS) in this context[10,11], and molecular analysis of bronchial epithelium demonstrates a marked inflammatory response in patients with reflux on medication alone[12]. Surgical management of reflux is now recognized to be safe and effective in the lung-transplant population; many studies have demonstrated good outcomes[13,14,23,15–22], including in patients with end stage lung disease prior to transplantation[24]. However, the level of evidence to support ARS is low, and work needs to be done to define the optimal timing for intervention[25], and there is an understandable reluctance to submit this group of complex patients to a randomization of therapy and timing thereof[26].

It is difficult to measure the extent and progression of disease using imaging or trans-bronchial biopsy techniques, therefore most clinicians use the surrogate of FEV1 (forced expiratory volume in 1 second) FEV1 can be affected by several factors within the early post-transplant period, including lifestyle changes, pulmonary rehabilitation, infection and acute rejection; however it is widely used as it is recognized to have a strong correlation both with onset and progression of BOS. In this systematic review and meta-analysis, we sought to demonstrate the effect of ARS on pre- and post-operative FEV1 values within the lung transplant population.

Methods:

An electronic search was carried out of PubMed Central, Medline, Google Scholar and Cochrane Library databases in addition to manual searching of references of selected articles. Only studies of adult patients, published in the English language between January 1970 and January 2017 were included. We included only studies where ARS was performed after lung transplant and where FEV1 was documented in the pre- and post-operative periods. We excluded case reports and series of fewer than 15 patients to reduce the confounding impact of a learning curve. We excluded published abstracts and unpublished studies. If data were part presented or insufficient, but the study were deemed to be otherwise includable within the analysis, we attempted to contact corresponding authors by email to gain the necessary data for inclusion. All studies were assessed for quality utilizing the National Heart, Lung and Blood Institute Study Quality Assessment[27]. Authors JD and DF performed the literature search, and quality assessment, JD and SE performed the data analysis.

We extracted, from each included paper, the number of patients, the indication for ARS, the mean FEV1 values before and after ARS surgery with associated standard deviations, noting the timing of these measurements relative to the surgery. Where data were presented with median and interquartile range, an assumption was used of $med \approx \bar{x}, IQR/1.35 \approx \sigma$ to allow comparative analysis and quantitative synthesis using approximated mean and standard deviation values [28]. Where possible we used the presented figure of the rate of change of FEV1 in the pre- and post-operative windows following the mixed linear model described by Fisher in 2005[29], an estimation of this was performed based on presented serial data if rate of change itself was not described and rate of change (ROC) was displayed in ml/day. Data are presented as a mean (standard deviation) throughout this manuscript unless otherwise denoted. Studies were assessed independently for reporting bias and quality by two observers and this was factored in to the outcome reporting of the pooled analysis.

Pooled analyses were performed in groups of similarly reported data of raw FEV1 values (L), FEV1 values as a percentage of predicted, and rate of change – values were converted to ml/day. In pooled analyses, a 2-way T-test was performed using pooled and weighted mean and variance values using GraphPad (https://www.graphpad.com/quickcalcs/contMenu/). For meta-analysis we used open source software OpenMetaAnalyst, an open source package using the back-end statistical engine of *R*[30,31]. In order to present data for FEV1 consistently, regardless of mode of presentation of the variable, we converted data to demonstrate an effect size, Cohen's *d*, calculated with Hedges and Olkin's bias corrected method and presented with 95% confidence intervals[32]. This measurement would demonstrate the size of an effect of an intervention on a study cohort, with a value of d=0.2 representing a small effect, d=0.5 a medium effect, and d>0.8 a large effect. The effect size allows for an estimation of clinical relevance as well as denoting statistical significance. The data for effect size was represented graphically using Forest plots accompanied with a calculated heterogeneity statistic (I^2.)

Results:

The MOOSE (Meta-analysis of Observational studies in epidemiology) guidelines for meta-analysis of observational studies were followed, the flowchart is shown in Fig.1. We identified 12 published articles documenting spirometry after ARS in the post-lung transplant population. In all studies, measuring spirometry in patients was a secondary outcome measure and reporting was variable in terms of documented frequency and timing of measurements, all studies were rated as "Good" or "Fair" by two independent assessors (JD and DF). 6 studies were excluded from the pooled analysis as data was insufficient, 4 due to a lack of pre- or post-op FEV1 presented in the published manuscript, 1 did not present data of sufficient quality (lacking standard deviation or range from which to perform statistical analysis), 1 performed ARS only in pre-transplant patients. All corresponding authors of these 6 excluded were contacted to gain adequate study data for inclusion within the analysis, none responded. These papers were unable to be used for comparison of pre- and post-ARS FEV1 values and therefore were used only in formulation of the discussion of this article along with the remaining 29 articles reviewed in full, some of which were not pertaining to lung transplant in adults.

The 6 articles included in the quantitative synthesis are summarized in Table 1&2 and the analysis of the data is displayed in Table 3. All series included were from different centres so were known not to included duplicate patient data. Study groups differed in their indications for ARS with all using symptomatic reflux, but some using asymptomatic or simply declining FEV1 with a suspicion of GERD. One study performed ARS routinely in cases of repeat transplant. We observed a small increase when pooling those studies reporting FEV1 values in L/1sec (n=154), 2.02(0.89) vs. 2.14(0.77), p=0.2 and, in those reporting as %predicted (n=45), 77.1(22.1) vs. 81.2(26.95), p=0.4 with a 'small' Cohen's *d* of 0.159(-0.038 – 0.356) (p=0.114). There was no evidence for heterogeneity of the effect of ARS on FEV1 between the studies $I^2 = 0\%$, p=0.4 (Figure 2).

Considering the rate of change of FEV1 (ml/day) which was calculated for 103 of the patients within the meta-analysis in 3 different studies, we observed a significant change, demonstrating a declining FEV1 in across the combined cohort of patients before ARS; -2.12(2.76) ml/day, compared to the same population post-ARS 0.05(1.19) ml/day ($p<0.0001$). Meta-analysis of effect size demonstrated a Cohen's *d* of 1.702(0.364-3.039) ($p=0.013$), a "large" effect of ARS on the rate of change of FEV1 [33]. Although all three studies individually had 'large' effect sizes, there was, however, evidence for significant heterogeneity; $I^2 = 92.7\%$, $p<0.001$ (Figure 3).

Discussion

This meta-analysis demonstrates an improvement in absolute and relative FEV1 values in post-transplant patients and a significant difference in pooled analysis of rate of change data; demonstrating a reversal of the deteriorating FEV1 values in patients who have received ARS post-lung transplant. Prior to this study there is no data outside of single-centre series to guide the decision-making process, in our graphical abstract we summarize this and demonstrate the key finding; that there is a statistically and clinically significant improvement in the rate of change of FEV1 following ARS.

Within the qualitative synthesis of 12 papers, containing series from high-volume lung transplant centers across the USA, United Kingdom and Australia, we identified studies reporting benefits of ARS over medical management of GERD on the FEV1 values in the post-transplant population, albeit acknowledgements are made that these two populations are not equivalent in terms of the severity of their reflux disease[4]. ARS appears to resolve subjective symptoms of GERD in all studies that explored this as an outcome measure (16–19,32). Only two study performed objective assessment of GERD in a half of their post-ARS population[14,15], reluctance among clinicians and third-party payer organizations to subject asymptomatic individuals to invasive tests was mentioned in several articles[4,13]. Where measured, Improvements in the inflammatory infiltrate within bronchial lavage samples were also noted[19,20,35].

Many centers, including the institutions of the authors, have adopted fundoplication surgery as a standard of care into the regional lung transplantation program[36]. However, a recent international guideline from the "Bronchiolitis Obliterans Syndrome Task Force" formed out of the International Society for Heart & Lung Transplant, the American Thoracic Society, and the European Respiratory Society, recognizes that the current level of evidence to support fundoplication is poor – consisting of single center retrospective cohort studies and case series[25]. This pooled analysis seems to demonstrate that an objective benefit of anti-reflux surgery can be quantified by measuring the rate of change of the FEV1. The use of the FEV1 measurement is an accepted surrogate for BOS; with deterioration in the spirometry accepted to correlate closely with a progression of the disease. The majority group of patients underwent ARS outside of the first year post-transplant, and as such wide intra-individual variability in FEV1 is less likely to have influenced the values obtained when using moving averages as has been done in the studies included.

As a review and pooled analysis of retrospective cohort studies, there are factors inherent to the included studies and the analysis methodology that limit the strength of evidence that can be provided here. Reporting bias, for example such that studies in which ARS is unsuccessful in preventing FEV1 decline are less likely to be published, is a potential problem. In a meta-analysis of randomized controlled trials, reporting bias is usually analyzed by means of a Funnel plot, however, this is not feasible here given the small number of studies and number of subjects described in each study.

All papers quote their pre-ARS spirometry values as the most recent result preceding surgery, however the timing of this was not clearly defined in all papers. Similarly, the most recent FEV1 value taken in follow up was used as a comparative value, however follow up periods within and between these retrospective studies were not consistent. Patients with incomplete follow up were excluded from the figures derived from each study, as such mortality is not factored into this analysis and since cause of death may be related to progressive failure of the lung allograft, there is a risk of over-emphasizing the benefits to the population when data is drawn only from survivors. All centers were similar in performing ARS in clinical GERD or persistently declining FEV1 in the absence of symptoms, with varying amounts of pre-operative work-up in the form of pH-testing and manometry as well as subjective, questionnaire based scoring. Furthermore, those studies where serial FEV1 measurements were taken were not always those with deteriorating lung function, and this is reflected in the high degree of heterogeneity demonstrated in Figure 3: In *Robertson et al.* the included patients are only those patients with pre-operative deteriorating FEV1 are included in the rate of change analysis and unfortunately, there was no rate of change data available for whole cohort. Comparatively, *Abbassi-Ghadi et al.* and *Pegna et al.* both display FEV1 rate of change data for the whole cohort. The large heterogeneity of the studies means that the pooled effect size should be interpreted with some caution; however the overall pooled effect is both statistically significant and a large effect, as such we feel the effects are likely to be generalizable. The small number of studies included within the final meta-analysis means that a sensitivity analysis was not deemed suitable to perform. We are also unable to analyze further whether prophylactic ARS has a different effect to those performed with concerns over graft function.

One confounder and potential alternative explanation for the results seen is that some centers may have only attempted to perform ARS in a patient considered “stable” enough to undergo further surgery and therefore their decline in ARS may not be represented accurately by a linear gradient. The paper by *Hoppo* and colleagues contains a graph depicting individualized gradients for FEV1 data (albeit without any scale or units) and does indeed display a small number of individuals with an improving FEV1 prior to ARS.

ARS has been shown to be safe and effective in patients with poor functional status but it is unclear to what extent this evidence has shaped practice across the centers reporting their results[13]. The adopted method of estimating values from mean and standard deviation assume a normal distribution of data and as such may prove to be error prone in the event of non-Gaussian data sets [28], this may be a contributing factor to the observed heterogeneity when exploring the effect of ARS on the rate of change of FEV1.

The strength of this study is that it is the first pooled analysis of studies describing outcome measures after ARS in the lung transplant population. The statistical methodology within the pooled analysis allows a definitive measure of rate of change of the FEV1 to demonstrate an effect of fundoplication. Antonoff's recent commentary paper in this journal heralds the difficulties in drawing conclusions from a retrospective review regarding timing of intervention[26], we feel that this pooled analysis of objectively measured outcomes is able to define the measure of success of ARS to be an improvement in the rate of change of FEV1, however there is insufficient evidence within this meta-analysis to recommend the timing of ARS. In fact, the included studies are all describing relatively late ARS (2-3 years after transplant,) compared to more modern series advocating earlier ARS (within 6 months of transplant). The most recent published cohort series, published by the team in Phoenix, AZ, although not included within this review since it was published after the analysis was performed, depicts an advantage to early fundoplication[23], and this aligns with large-volume series data from Duke and Harvard whereby early fundoplication in patients with GERD appears to improve BOS-free survival[37,38]. There is also evidence among the reviewed papers that ARS is safe also in patients with end-stage lung disease who are awaiting transplantation[17,21]. However, note must clearly be made that there are a proportion of patients who are not identified to have reflux disease prior to their transplant, but may develop GERD subsequent to surgery[4,39].

What this study is unable to determine, is whether improving spirometry values correlate to a prevention or halted progression of BOS. We are also unable to recommend ARS over no ARS, nor recommend the optimal timing of ARS which is increasingly being practiced.

Conclusion

This study represents, to the authors knowledge, the first systematic review and meta-analysis of the effects of fundoplication on measurable factors associated with BOS. Patients presenting with declining graft function will be managed with a variety of different medical strategies, among which ARS has taken a place. The ability of preventing reflux to actually improve lung function has been brought into question as pathophysiologically, the fibrotic process of obliterating bronchiolitis would not be reversed by reducing exposure to gastric content[18]. This review demonstrates a tangible, objectification of the evidence that, in the patients studied, a declining FEV1 does in fact seem to plateau, and clearly in some cases recover with ARS. We have used this statement, exemplified in Figure 4, as our Graphical Abstract. We would suggest that a rate of change of FEV1 is a core outcome that should be reported in all series of ARS after lung transplant; it is a relatively easily measured, and repeated, objective measure which gives a dynamic picture of lung function over an extended period; as denoted by the studies included within this review, a declining FEV1 is an indication for ARS in many centres, and we believe that formalizing this by mapping out the decline in mL/day would be a useful measure of outcome for any intervention in the patient with lung transplant, as well as for comparative efficacy in studies exploring early vs. late ARS along with those that have already been described.

References

1. Blondeau K, Mertens V, Vanaudenaerde BA, et al. Gastro-oesophageal reflux and gastric aspiration in lung transplant patients with or without chronic rejection. *Eur Respir J*. 2008;31(4):707-713. doi:10.1183/09031936.00064807

2. Shah N, Force SD, Mitchell PO, et al. Gastroesophageal reflux disease is associated with an increased rate of acute rejection in lung transplant allografts. *Transplant Proc*. 2010;42(7):2702-2706. doi:10.1016/j.transproceed.2010.05.155

3. Murthy SC, Nowicki ER, Mason DP, et al. Pretransplant gastroesophageal reflux compromises early outcomes after lung transplantation. *J Thorac Cardiovasc Surg*. 2011;142(1):47-52.e3. doi:10.1016/j.jtcvs.2011.04.028

4. Hartwig MG, Anderson DJ, Onaitis MW, et al. Fundoplication after lung transplantation prevents the allograft dysfunction associated with reflux. *Ann Thorac Surg*. 2011;92(2):462-468; discussion; 468-469. doi:10.1016/j.athoracsur.2011.04.035

5. Benden C, Aurora P, Curry J, Whitmore P, Priestley L, Elliott MJ. High prevalence of gastroesophageal reflux in children after lung transplantation. *Pediatr Pulmonol*. 2005;40(1):68-71. doi:10.1002/ppul.20234

6. Duarte AG, Myers AC. Cough reflex in lung transplant recipients. *Lung*. 2012;190:23-27. doi:10.1007/s00408-011-9352-x

7. Jamie Dy F, Freiberger D, Liu E, Boyer D, Visner G, Rosen R. Impact of gastroesophageal reflux and delayed gastric emptying on pediatric lung transplant outcomes. *J Heart Lung Transplant*. 2017;36(8):854-861. doi:10.1016/j.healun.2017.01.005

8. Hathorn KE, Chan WW, Lo W-K. Role of gastroesophageal reflux disease in lung transplantation. *World J Transplant*. 2017;7(2):103-116. doi:10.5500/wjt.v7.i2.103

9. Lo W-K, Goldberg HJ, Boukedes S, Burakoff R, Chan WW. Proton Pump Inhibitors Independently Protect Against Early Allograft Injury or Chronic Rejection After Lung Transplantation. *Dig Dis Sci*. 2018;63(2):403-410. doi:10.1007/s10620-017-4827-0

10. Davis CS, Shankaran V, Kovacs EJ, et al. Gastroesophageal reflux disease after lung transplantation: pathophysiology and implications for treatment. *Surgery*. 2010;148(4):737-744; discussion 744-5. doi:10.1016/j.surg.2010.07.011

11. Kiljander T, Rantanen T, Kellokumpu I, et al. Comparison of the effects of esomeprazole and fundoplication on airway responsiveness in patients with gastro-oesophageal reflux disease. *Clin Respir J*. 2013;7(3):281-287. doi:10.1111/crj.12005

12. Mertens V, Blondeau K, Vanaudenaerde B, et al. Gastric juice from patients “on” acid suppressive therapy can still provoke a significant inflammatory reaction by human bronchial epithelial cells. *J Clin Gastroenterol*. 2010;44(10):e230-5. doi:10.1097/MCG.0b013e3181d47dc4

13. Abbassi-Ghadi N, Kumar S, Cheung B, et al. Anti-reflux surgery for lung transplant recipients in the presence of impedance-detected duodenogastroesophageal reflux and bronchiolitis obliterans syndrome: a study of efficacy and safety. *J Heart Lung Transplant*. 2013;32(6):588-595. doi:10.1016/j.healun.2013.02.009

14. Pegna V, Mickevičius A, Tsang C. How useful is antireflux surgery in lung transplant patients with gastroesophageal reflux? *Medicina (Kaunas)*. 2014;50(6):318-322. doi:10.1016/j.medici.2014.11.006

15. Robertson AGN, Krishnan A, Ward C, et al. Anti-reflux surgery in lung transplant

recipients: outcomes and effects on quality of life. *Eur Respir J*. 2012;39(3):691-697. doi:10.1183/09031936.00061811

16. Burton PR, Button B, Brown W, et al. Medium-term outcome of fundoplication after lung transplantation. *Dis esophagus Off J Int Soc Dis Esophagus*. 2009;22(8):642-648. doi:10.1111/j.1442-2050.2009.00980.x

17. Hoppo T, Jarido V, Pennathur A, et al. Antireflux surgery preserves lung function in patients with gastroesophageal reflux disease and end-stage lung disease before and after lung transplantation. *Arch Surg*. 2011;146(9):1041-1047. doi:10.1001/archsurg.2011.216

18. Davis RD, Lau CL, Eubanks S, et al. Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation. *J Thorac Cardiovasc Surg*. 2003;125(3):533-542. doi:10.1067/mtc.2003.166

19. Fisichella PM, Davis CS, Gagermeier J, et al. Laparoscopic antireflux surgery for gastroesophageal reflux disease after lung transplantation. *J Surg Res*. 2011;170(2):e279-86. doi:10.1016/j.jss.2011.05.038

20. Hayes D, Kirkby S, S McCoy K, et al. Reduction of lipid-laden macrophage index after laparoscopic Nissen fundoplication in cystic fibrosis patients after lung transplantation. *Clin Transplant*. 2013;27(1):121-125. doi:10.1111/ctr.12020

21. Linden PA, Gilbert RJ, Yeap BY, et al. Laparoscopic fundoplication in patients with end-stage lung disease awaiting transplantation. *J Thorac Cardiovasc Surg*. 2006;131(2):438-446. doi:10.1016/j.jtcvs.2005.10.014

22. Lo W-K, Goldberg HJ, Burakoff R, Feldman N, Chan WW. Increased proximal acid

reflux is associated with early readmission following lung transplantation. *Neurogastroenterol Motil*. 2016;28(2):251-259. doi:10.1111/nmo.12720

23. Biswas Roy S, Elnahas S, Serrone R, et al. Early fundoplication is associated with slower decline in lung function after lung transplantation in patients with gastroesophageal reflux disease. *J Thorac Cardiovasc Surg*. 2018;155(6):2762-2771.e1. doi:10.1016/j.jtcvs.2018.02.009

24. Patti M. Antireflux surgery in lung transplant patients. *Gastroenterol Hepatol*. 2016;12(3):181-183. http://www.gastroenterologyandhepatology.net/files/2016/03/GERD-1.pdf%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=20160247566.

25. Meyer KC, Raghu G, Verleden GM, et al. An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. *Eur Respir J*. 2014;44(6):1479-1503. doi:10.1183/09031936.00107514

26. Antonoff MB. How much does early fundoplication for lung transplant recipients with gastroesophageal reflux disease truly help? Challenges in escaping the perils of retrospective review. *J Thorac Cardiovasc Surg*. 2018;155(6):2772-2773. doi:10.1016/j.jtcvs.2018.02.057

27. National Heart, Lung and Blood Institute Study Quality Assessment Tools. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

28. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135. doi:10.1186/1471-2288-14-135

29. Fisher AJ, Rutherford RM, Bozzino J, Parry G, Dark JH, Corris PA. The safety and efficacy of total lymphoid irradiation in progressive bronchiolitis obliterans syndrome after lung transplantation. *Am J Transplant*. 2005;5(3):537-543. doi:10.1111/j.1600-6143.2004.00709.x

30. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw*. 2010;36(3).

31. Wallace BC, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the gap between methodologists and end-users : R as a Computational Back-End. *J Stat Softw*. 2012;49(5):1-15.

32. Hedges L, Olkin I. *Statistical Methods for Meta-Analysis*. 1st ed. Elsevier; 1985. doi:10.1016/C2009-0-03396-0

33. Sawilowsky SS. New Effect Size Rules of Thumb. *J Mod Appl Stat Methods*. 2009;8(2):597-599. doi:10.22237/jmasm/1257035100

34. Lau CL, Palmer SM, Howell DN, et al. Laparoscopic antireflux surgery in the lung transplant population. *Surg Endosc*. 2002;16(12):1674-1678. doi:10.1007/s00464-001-8251-2

35. Fisichella PM, Davis CS, Lowery E, et al. Pulmonary immune changes early after laparoscopic antireflux surgery in lung transplant patients with gastroesophageal reflux disease. *J Surg Res*. 2012;177(2):e65-73. doi:10.1016/j.jss.2012.03.066

36. Zheng C, Kane TD, Kurland G, et al. Feasibility of laparoscopic Nissen fundoplication after pediatric lung or heart-lung transplantation: should this be the standard? *Surg Endosc*. 2011;25(1):249-254. doi:10.1007/s00464-010-1167-y

37. Cantu E, Appel JZ, Hartwig MG, et al. J. Maxwell Chamberlain Memorial Paper. Early fundoplication prevents chronic allograft dysfunction in patients with gastroesophageal reflux disease. *Ann Thorac Surg*. 2004;78(4):1142-1151; discussion 1142-51. doi:10.1016/j.athoracsur.2004.04.044

38. Lo W-K, Goldberg HJ, Wee J, Fisichella PM, Chan WW. Both Pre-Transplant and Early Post-Transplant Antireflux Surgery Prevent Development of Early Allograft Injury After Lung Transplantation. *J Gastrointest Surg*. 2016;20(1):111-118; discussion 118. doi:10.1007/s11605-015-2983-0

39. Hirji SA, Gulack BC, Englum BR, et al. Lung transplantation delays gastric motility in patients without prior gastrointestinal surgery-A single-center experience of 412 consecutive patients. *Clin Transplant*. 2017;31(10). doi:10.1111/ctr.13065

Figure Legends

Figure 1 – Flowchart of article screening and inclusion in accordance with MOOSE Guidlines (Meta-analysis Of Observational Studies in Epidemiology.) 193 studies were identified in the initial search, after exclusions, 41 were assessed for eligibility. 12 studies reported spirometry sufficiently to be included within the qualitative synthesis, 6 studies provided adequate data to be compared in the meta-analysis.

Figure 2. Forest Plot demonstrating pre- and post-operative FEV1 (Forced Expiratory Volume in 1 second) related to antireflux surgery, Cohen's D effect size is plotted to allow comparison of studies reporting in "L/1sec" and in "%-predicted." Effect size demonstrates a "small" effect, which did not reach statistical significance: *d* = 0.159 (95% CI -0.038 – 0.356) (p=0.114).

Figure 3. Forest plot demonstrating the effect of antireflux surgery on the rate of change of FEV1 (Forced Expiratory Volume in 1 second). The effect size demonstrates a "large" effect which was statistically significant: *d*= 1.702 (95% 0.364-3.039) (p=0.013).

Figure 4. Graphical Abstract: The key finding of the meta-analysis is demonstrated in this graphical abstract; after anti-reflux surgery (ARS) there is a significant effect noted within the data on the rate of change of the FEV1 (Forced Expiratory Volume in 1 second,) where a generally declining FEV1 appears to stabilize, this has been assessed using Cohen's D effect size which demonstrates a large effect of statistical significance (d=1.702[0.364 – 3.039], p=0.013).

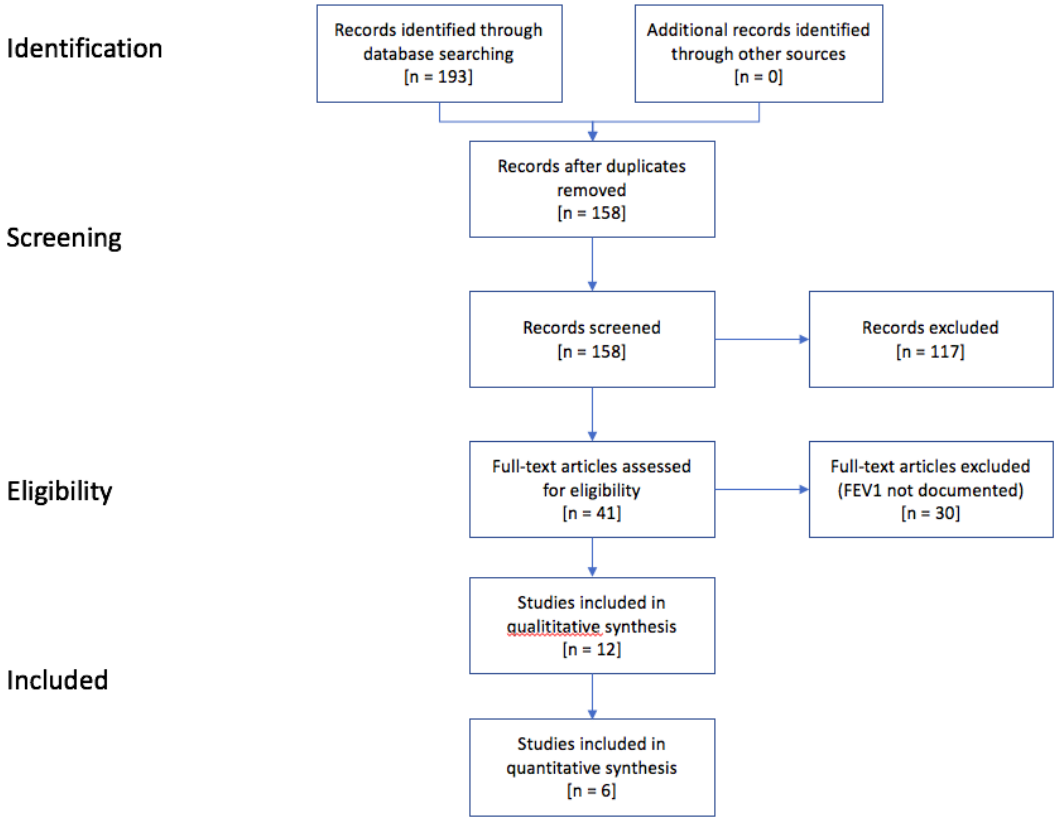
Table 1. Studies included in meta-analysis – Pre-operative evaluation of patients commonly included pH probe testing alongside pre-operative bronchoscopy. Indications for surgery always included symptomatic reflux and in some centers included deteriorating lung

function and suspected reflux, as well cases of redo transplant. Most centers employed a 360-degree posterior wrap (Nissen), however 270-degree posterior (Toupet) and 180 degree anterior (Dor) were also performed in selected cases.

Table 2 – Timing of surgery, reporting of spirometry and post-operative follow up in each study; the timing of anti-reflux surgery was variable, tending to take place 2-3 years after the lung transplant. The reported spirometry data prior to and following surgery was also varied in the measurements taken. The rate of change data are supplied by the authors in varying methods (reported mixed-linear models provided by Abbassi-Ghadi et al. and Robertson et al. compared to single patient lines for Hoppo et al. and population-representative histograms Pegna et al.)

Table 3. Data for FEV1 (Forced Expiratory Volume in 1 second) in patients pre- and post-anti-reflux surgery (ARS) displayed in the reported “L/1sec” or “%-predicted” and Rate of Change data (converted to ml/day and presented as mean (SD)). Student’s t-test of before/after ARS showed no difference in either studies reporting raw data or %-predicted, however the gradients of the rate of change data were significantly different with a decline observed pre-operatively and a plateau post-ARS (-2.12 ml/day vs. 0.05ml/day, $p<0.0001$) (* Rate of change data only available for 8 of the patients in the study)

Figure 1 – PRISMA Flowchart for screened articles



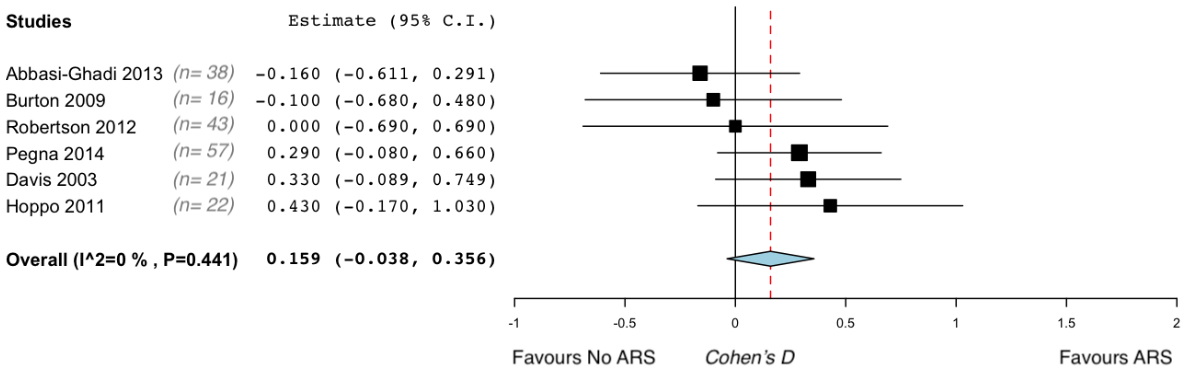


Figure 2

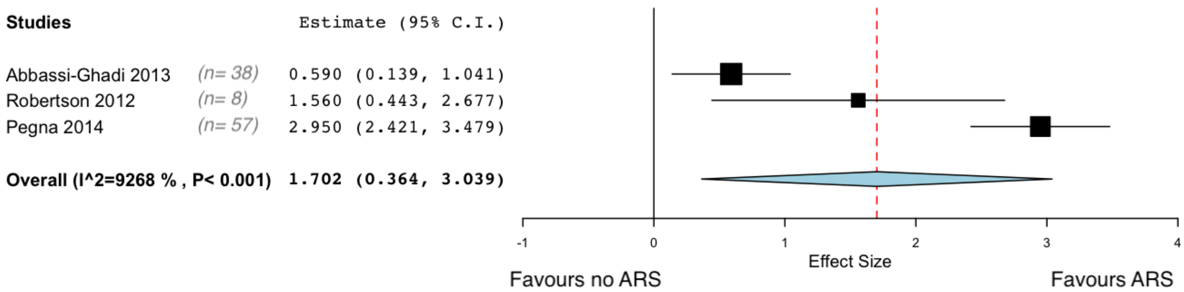


Figure 3

Study	Type of study	N	Indication for ARS in study (any of)	Technique	Pre-op work up of GERD
Abbassi-Ghadi et al. 2013	Retrospective cohort	38	Histologic evidence of gastroesophageal reflux aspiration Positive result on an impedance study with a consistent decline/fluctuating FEV Symptomatic reflux	Nissen (all)	Bronchoscopy +/- biopsy pH-impedance
Robertson et al. 2012	Prospective cohort	16	Symptomatic reflux refractory to medical management Reflux with deteriorating lung function Asymptomatic reflux with concerns regarding microaspiration	Nissen (all)	Bronchoscopy +/- biopsy Manometry pH-impedance, DeMeester, RSI, GIQLI
Davis et al. 2003	Retrospective cohort	43	Symptomatic reflux Aspiration Retransplant	39 Nissen / 4 Toupet (adhesions) G/GJ tubes (3) Pyloroplasty(6)	Bronchoscopy +/- biopsy pH probe Contrast swallow Manometry
Pegna et al. 2014	Retrospective cohort	57	Symptomatic reflux refractory to medical management Atypical reflux symptoms	Nissen (all)	Bronchoscopy +/- biopsy pH probe Endoscopy
Burton et al. 2009	Retrospective cohort	21	Deteriorating lung function, suspected reflux Symptomatic reflux	16 Toupet 5 Nissen + G tube (2)	Bronchoscopy +/- biopsy Endoscopy pH probe, DeMeester
Hoppo et al. 2011	Retrospective cohort	22	Symptomatic reflux Asymptomatic reflux	Nissen / Dor (numbers unclear)	Endoscopy, Barium Manometry, pH probe Impedance

Table 1

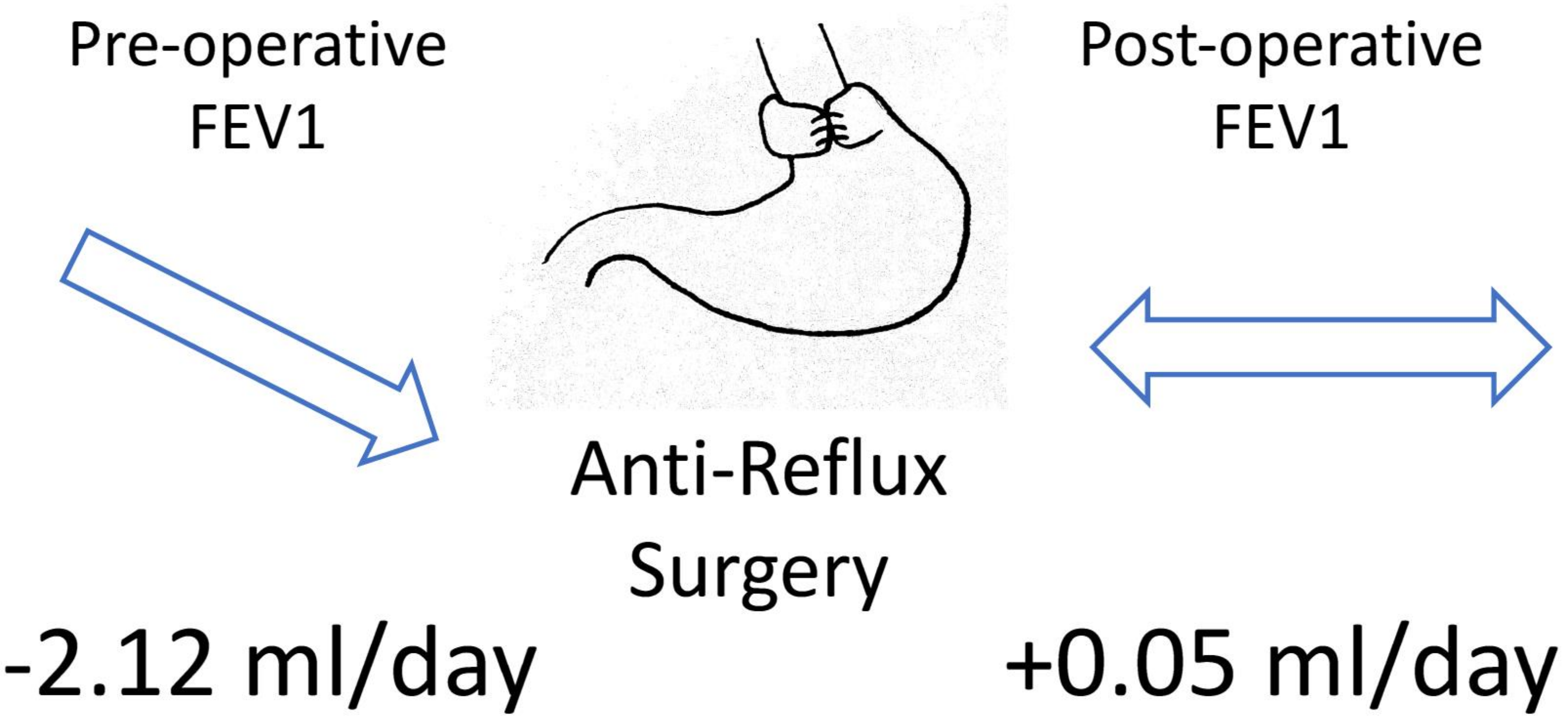
Study	Post-op evaluation of GERD	Timing of ARS relative to LTx	FEV1 pre-ARS	FEV1 post-ARS	Rate of change data
Abbassi-Ghadi et al. 2013	Routine follow-up (subjective)	Mean 1365 days (SD 1381) (Range 195-6406)	Mean value of the 3 readings preceding ARS (3 monthly)	Mean value of 3 most recent clinic visits (3 monthly)	Presented for all patients Calculated using trend line gradients over all pre-ARS readings (period = 815 +/- 1021 (29 – 4358), and all post-ARS readings (period = 477 +/- 474 (31-1758)
Robertson et al. 2012	DeMeester RSI, GIQLI	Mean 1053 days (SD 881)	Single pre-op reading – timing not stated	Single most recent value	Rate of change data presented in paper – all pre-ARS FEV1 and all post ARS FEV1 over Mean 1053 +/- 881 and 476 +/- 180 respectively
Davis et al. 2003	Routine follow-up (subjective)	Data not presented	Best single post LTx value	Single most recent value (at least 6 months post ARS)	No rate of change data
Pegna et al. 2014	pH probe (26/57)	Data not presented	Single value 3 months pre-op	Single value 3 months post-op Rate of change over mean 3.2 years (no SD / range)	Calculated from graph Pre-op at 6, 3 and immediate pre-op value Post of at 3,6,9,12 and 18 months post op
Burton et al. 2009	Reflux score (Carlsson)	Mean 768 days (range 145-1524)	6 months pre-op	6 months post-op	No rate of change data
Hoppo et al. 2011	Routine follow-up (subjective)	31 months (SD 24)	Immediate pre-op	Single most recent value	Rate of change as Line Graph – no units or scale drawn.

Table 2

		FEV1 (L)		FEV1 (%)		RoC FEV1 (ml/day)	
Study	n	Pre-ARS	Post-ARS	Pre-ARS	Post-ARS	Pre-ARS	Post-ARS
Abbassi-Ghadi et al. 2013	38	2.12 (0.89)	1.97(1.03)	-	-	-1.97 (1.03)	-0.41 (1.77)
Robertson et al. 2012	16	2.4 (0.97)	2.4 (0.71)	-	-	-3.18 (2.87)*	+0.31 (0.87)*
Davis et al. 2003	43	1.87 (0.98)	2.19(0.92)	-	-	-	-
Pegna et al. 2014	57	1.95 (0.80)	2.13(0.37)	-	-	-1.81 (0.83)	+0.33 (0.60)
Burton et al. 2009	23	-	-	72.9(20.9)	70.4 (26.8)	-	-
Hoppo et al. 2011	22	-	-	81.5(23.3)	92.5 (27.1)	-	-
Overall		2.02 (0.89)	2.14(0.77)	77.1(22.1)	81.2 (26.95)	-2.12 (2.76)	+0.05 (1.19)
		N = 154	p = NS	N = 45	p = NS	N = 103	**p<0.0001**

Table 3

Central Image



Graphical Abstract