

Retrospective Cohort Study

Pre-lung transplant measures of reflux on impedance are superior to pH testing alone in predicting early allograft injury

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Abstract

AIM: To evaluate pre-lung transplant acid reflux on pH-testing *vs* corresponding bolus reflux on multi-channel intraluminal impedance (MII) to predict early allograft injury.

METHODS: This was a retrospective cohort study of lung transplant recipients who underwent pre-transplant combined MII-pH-testing at a tertiary care center from January 2007 to November 2012. Patients with pre-transplant fundoplication were excluded. Time-to-event analysis was performed using a Cox proportional hazards model to assess associations between measures of reflux on MII-pH testing and early allograft injury. Area under the receiver operating characteristic (ROC) curve (c-statistic) of the Cox model was calculated to assess the predictive value of each reflux parameter for early allograft injury. Six pH-testing parameters and their corresponding MII

measures were specified a priori. The pH parameters were upright, recumbent, and overall acid reflux exposure; elevated acid reflux exposure; total acid reflux episodes; and acid clearance time. The corresponding MII measures were upright, recumbent, and overall bolus reflux exposure; elevated bolus reflux exposure; total bolus reflux episodes; and bolus clearance time.

RESULTS: Thirty-two subjects (47% men, mean age: 55 years old) met the inclusion criteria of the study. Idiopathic pulmonary fibrosis (46.9%) represented the most common pulmonary diagnosis leading to transplantation. Baseline demographics, pre-transplant cardiopulmonary function, number of lungs transplanted (unilateral *vs* bilateral), and post-transplant proton pump inhibitor use were similar between reflux severity groups. The area under the ROC curve, or c-statistic, of each acid reflux parameter on pre-transplant pH-testing was lower than its bolus reflux counterpart on MII in the prediction of early allograft injury. In addition, the development of early allograft injury was significantly associated with three pre-transplant MII measures of bolus reflux: overall reflux exposure (HR = 1.18, 95%CI: 1.01-1.36, $P = 0.03$), recumbent reflux exposure (HR = 1.25, 95%CI: 1.04-1.50, $P = 0.01$) and bolus clearance (HR = 1.09, 95%CI: 1.01-1.17, $P = 0.02$), but not with any pH-testing parameter measuring acid reflux alone.

CONCLUSION: Pre-transplant MII measures of bolus reflux perform better than their pH-testing counterparts in predicting early allograft injury post-lung transplantation.

Key words: Gastroesophageal reflux; Lung transplant; Multichannel intraluminal impedance; pH-monitoring; Allograft injury

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Core tip: Gastroesophageal reflux has been associated with poor lung transplant outcomes, including allograft injury and rejection. While ambulatory pH-testing only measures acid reflux, multichannel intraluminal impedance (MII) assesses total bolus reflux, regardless of acidity. Comparison of pH-testing and MII measures of reflux in the prediction of lung transplant outcomes may improve and standardize pre-transplant reflux testing. Our study demonstrated that pre-transplant MII measures of bolus reflux perform better than their pH-testing counterparts to predict early allograft injury post-lung transplantation. MII should be performed alongside pH testing for reflux assessment during pre-lung transplant evaluation.

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INTRODUCTION

Lung transplantation remains a high risk solid-organ transplant modality^[1], with gastroesophageal reflux disease (GERD) being a prevalent risk factor for post-transplant morbidity^[2], resulting in development of bronchiolitis obliterans, chronic rejection and death^[3]. Evidence of inflammatory markers and pepsin in the bronchoalveolar fluid of subjects with acute rejection suggest that reflux and aspiration play a role in early allograft injury^[4-6], which are primary risk factors for chronic rejection^[7-9] and graft failure.

While pre-transplant pH testing has been used with increased frequency, given the association between severe acid reflux and poor transplant outcomes^[3], no formal recommendation exists regarding the optimal reflux testing modality among lung transplant candidates. At issue is the possibility that multichannel intraluminal impedance and pH (MII-pH), which permits the assessment of gastroesophageal reflux regardless of pH, may provide additional data to help predict lung transplant outcomes compared with pH data alone, which can only evaluate acid reflux at low pH levels. Our group demonstrated recently that early allograft injury, comprising both acute rejection and lymphocytic bronchiolitis, is associated with impedance measures of reflux severity on pre-transplant testing, including prolonged bolus clearance and increased distal reflux episodes^[10]. However, despite the identified association, additional benefits of using impedance over pH data alone could not be established, as a comparison of impedance and pH parameters in predicting transplant outcomes was beyond the scope of that study. Therefore, in this follow-up study, we aimed to compare the values of pre-transplant impedance and pH parameters in predicting early allograft injury in lung transplant recipients. We hypothesized that pre-transplant MII-pH measures of reflux severity are better than corresponding pH measures of acid reflux alone to predict early lung transplant outcomes.

MATERIALS AND METHODS

This was a retrospective cohort study of adult subjects (age > 18) who underwent pre-operative MII-pH testing and received lung transplantation in 2007-2013 at a tertiary care center. Only patients undergoing initial primary lung transplantation were included. None received pre-transplant surgical or endoscopic management for reflux, including Nissen fundoplication. Subjects who did not survive beyond the first 30 d after transplant were excluded a priori, as such early mortality most likely reflects post-operative

complications or hyperacute rejection unrelated to the present model of allograft injury under study.

Baseline characteristics (age at transplantation, gender and race), pulmonary diagnosis, and results of standard pre-transplant cardiopulmonary testing were recorded. ABO compatibility was assured for all donors and recipients before transplantation.

Pre-transplant MII-pH monitoring

All subjects included in the study underwent MII-pH monitoring (Sandhill Scientific Inc, Highland Ranch, CO, United States) before transplantation, after an overnight fast. The system included a portable electronic datalogger and a catheter with two pH electrodes (0, 15 cm) and eight impedance electrodes (-3, -1, 1, 3, 5, 9, 11, 13 cm). The catheter was passed into the esophagus transnasally and positioned with the distal pH electrode, 5 cm above the lower esophageal sphincter (LES). During the 24-h study, subjects were asked to remain upright during the day and recumbent at night, and maintain normal scheduled activities. Meal periods were documented by the patient *via* the datalogger and were excluded from analysis.

Impedance and pH results were analyzed with the assistance of a dedicated software package (Bioview Analysis, version 5.6.3.0, Sandhill Scientific Inc). Parameters of interest were specified a priori and included six pH measures of acid reflux and their corresponding impedance measures of reflux severity. These measures were acid exposure time vs total bolus exposure time in upright, recumbent, and overall positions, expressed as a percentage of total time in reflux; total acid reflux episodes vs total bolus reflux episodes; and acid clearance time vs bolus clearance time, expressed in seconds.

Following MII-pH testing, patients proceeded to transplantation at different intervals pending individual disease progression and organ availability.

Post-transplant care and diagnosis of early allograft injury

After transplantation, patients received standard immunosuppressive therapy with azathioprine or mycophenolate, tacrolimus and methylprednisolone^[11]. All patients underwent routine surveillance bronchoscopy with biopsy^[12,13] on a standard post-transplant schedule (at 1, 3, 6 and 12 mo), with additional diagnostic bronchoscopies following development of any clinical symptoms suggestive of infection or rejection, such as dyspnea, fever or increased secretions. Biopsies were graded in accordance with The International Society of Heart and Lung Transplantation (ISHLT) standards^[14]. The endpoint of early allograft injury was reached with the finding of rejection on transbronchial biopsy by ISHLT grading, with the sum of A and B grades greater than or equal to two. Minimal rejection grades of A1B0 or A0B1 were counted as meeting the endpoint if the patient presented with suggestive clinical symptoms

and received treatment with pulsed steroids.

Statistical analysis

Fisher's exact test for binary variables and student's *t*-test for continuous variables were performed to assess for differences between reflux severity groups. Survival analysis with the Cox proportional hazard model yielded hazard ratios with 95%CI for each specified pH variable and corresponding impedance measure of reflux severity, and its association with early allograft injury. Time-to-event was calculated from the date of transplant to date of biopsy diagnosing early allograft injury. Subjects not reaching the specified endpoint were censored at of death, post-transplant anti-reflux surgery or last evaluation by pulmonary transplant team, whichever was the earliest. The performance of each parameter in predicting early allograft injury was calculated by area under the receiver operating characteristic (ROC) curve or c-statistic for the Cox models. All statistical analyses were performed using SAS 9.3 statistical package (SAS Institute Inc., Cary, NC, United States), with an additional macro for calculation of c-statistics for survival analysis data^[15].

The study was approved by the Partners Healthcare Institutional Review Board prior to inception.

RESULTS

Thirty-two subjects (46.9% men, mean age 55 years) met the inclusion criteria for the study, with a median follow-up of 1.3 years. The most common pulmonary diagnosis leading to transplantation was idiopathic pulmonary fibrosis (IPF), accounting for 46.9% of cases. Seventeen patients (53.1%) underwent bilateral lung transplantation. There were eight deaths detected overall, with seven attributed to pulmonary complications including pneumonia (three subjects), pulmonary malignancy (two subjects), pulmonary hemorrhage (one subject), and acute rejection (one subject). Baseline cardiopulmonary characteristics were similar between reflux severity groups, as defined by impedance measurement (Table 1). Although the elevated reflux group had more IPF diagnoses and a higher pre-transplant FEV1/FVC ratio, these were not associated with early allograft injury on Cox univariate modeling, accounting for timing of outcomes. Post-transplant PPI use was also not associated with early allograft injury in this cohort. Over the time course of the study, 16 subjects (50.0%, out of 32 subjects overall) developed early allograft injury, with 14 (53.8%, out of 26 subjects with > 1 year follow-up) diagnosed within the first year after transplantation. Univariate analyses performed on the six pre-specified pH and corresponding impedance parameters of reflux demonstrated significant associations between three impedance measures of reflux (total reflux exposure, recumbent reflux exposure and bolus clearance) and early allograft

Table 1 Baseline characteristics demonstrating homogeneity of the pulmonary transplant study population

	Total (n = 32)	Normal distal reflux exposure (n = 13)	Increased distal reflux exposure (n = 19)
Follow-up (yr), median	1.3		
Male sex	15 (46.9)	7 (53.8)	8 (42.1)
BMI, mean \pm SD	26.7 \pm 4.97	26.7 \pm 4.47	26.7 \pm 5.40
Age at transplant (yr), mean	54.7 \pm 10.8	57.6 \pm 9.01	52.7 \pm 11.7
White race	30 (93.7)	13 (100)	17 (89.5)
Pulmonary diagnosis			
IPF	15 (46.9)	3 (23.1)	12 (63.2)
COPD	6 (18.7)	3 (23.1)	3 (15.8)
CF	6 (18.7)	2 (15.4)	4 (21.0)
COP	2 (6.25)	2 (15.4)	0
AAT	1 (3.13)	1 (7.69)	0
Sarcoid	1 (3.13)	1 (7.69)	0
Other	1 (3.13)	1 (7.69)	0
Cardiac function, Baseline			
LVH			
None	27 (84.4)	11 (84.6)	16 (84.2)
Any	5 (15.6)	2 (15.4)	3 (15.8)
LVEF, mean \pm SD	0.59 \pm 0.05	0.58 \pm 0.06	0.60 \pm 0.05
PCWP, mean \pm SD	9.97 \pm 4.62	11.5 \pm 4.99	8.89 \pm 4.15
PVR1, mean \pm SD	224.4 \pm 89.0	243.3 \pm 100.1	210.0 \pm 79.6
Pulmonary function, Baseline			
FVC	1.91 \pm 0.71	2.00 \pm 0.84	1.85 \pm 0.63
FVC, %-pred	0.48 \pm 0.14	0.50 \pm 0.16	0.47 \pm 0.12
FEV1	1.22 \pm 0.60	1.07 \pm 0.67	1.32 \pm 0.54
FEV1, %-pred	0.39 \pm 0.18	0.33 \pm 0.17	0.43 \pm 0.17
FEV1/FVC	0.65 \pm 0.24	0.54 \pm 0.24	0.73 \pm 0.21
Lungs transplanted			
Unilateral	15 (46.9)	7 (53.8)	8 (42.1)
Bilateral	17 (53.1)	6 (46.1)	11 (57.9)
Post-transplant PPI	24 (75.0)	10 (76.9)	14 (73.7)
Deaths, all cause	8 (25.0)	2 (15.4)	6 (31.6)
Deaths, pulmonary-related	7 (21.9)	2 (15.4)	5 (26.3)
Early allograft injury	16 (50.0)	5 (38.5)	11 (57.9)
BOS	2 (6.25)	1 (7.69)	1 (5.26)

¹PVR was not measured in two subjects. BMI: Body mass index; IPF: Idiopathic pulmonary fibrosis; COPD: Chronic obstructive pulmonary disease; CF: Cystic fibrosis; COP: Cryptogenic organizing pneumonia; AAT: Alpha-1-antitrypsin deficiency; LVH: Left ventricular hypertrophy; LVEF: Left ventricular ejection fraction; PCWP: Pulmonary capillary wedge pressure; PVR: Pulmonary vascular resistance; FVC: Forced vital capacity; %-pred: Percent of predicted value; FEV1: Forced expiratory volume in 1 second; PPI: Proton pump inhibitor; BOS: Bronchiolitis obliterans syndrome.

injury (Table 2). On comparing the areas under the ROC curve (c-statistic), every impedance parameter (measures of total reflux) was found to have greater predictive value for early allograft injury than the corresponding pH parameter alone (measures of acid reflux) (Table 3).

DISCUSSION

Our group has previously demonstrated that pre-transplant measures of reflux by impedance testing are associated with early allograft injury after lung

Table 2 Comparison of Cox univariate analyses of pH parameters of acid reflux and corresponding impedance measures of total reflux

	Univariate hazard ratio for time to acute rejection (95%CI)	P value
pH parameter of acid reflux		
Acid reflux exposure, upright	1.01 (0.93-1.09)	0.87
Acid reflux exposure, recumbent	1.06 (0.92-1.21)	0.42
Acid reflux exposure, overall	1.03 (0.93-1.15)	0.52
Elevated acid reflux exposure (> 4.2%)	1.06 (0.92-1.21)	0.93
Total acid reflux episodes	1.00 (0.97-1.03)	0.90
Acid clearance	1.00 (1.00-1.00)	0.13
Impedance parameter of total reflux		
Total reflux exposure, upright	1.11 (0.98-1.25)	0.11
Total reflux exposure, recumbent	1.25 (1.04-1.50)	0.01 ¹
Total reflux exposure, overall	1.18 (1.01-1.36)	0.03 ¹
Elevated total reflux exposure (> 1.4%)	1.88 (0.65-5.42)	0.24
Total reflux episodes	1.01 (1.00-1.02)	0.20
Bolus clearance	1.09 (1.01-1.17)	0.02 ¹

¹Statistically significant results in impedance measures of total bolus reflux.

transplantation^[10]. Based on that study, increased total reflux, not just acid reflux, may be associated with poorer early post-transplant outcomes. However, despite the identified association, an advantage of using impedance over pH-only testing in the prediction of post-transplant outcome was not established, as no study has directly compared the predictive values of the two modalities in transplant cohorts. In the present study, we specified six pH parameters of acid reflux severity and their corresponding impedance measures of total reflux that were obtained during MII-pH as part of pre-transplant evaluation. Notably, no pH-only measures of acid reflux were associated with the early allograft injury outcome, while three of the six corresponding impedance measures of total reflux were associated, suggesting that non-acid reflux may also play a role in allograft injury. Additionally, every impedance parameter was associated with a greater area under the ROC curve (c-statistic) than the corresponding pH-based parameter in predicting early allograft injury, suggesting that impedance data, specifically the added information regarding non-acid reflux, may offer advantages over pH-only parameters in predicting lung transplant outcomes. Taken together, the MII parameters of bolus reflux exposure in the recumbent position and bolus clearance time are the best predictors of early allograft injury, based on the significant univariate results and the higher c-statistic values.

The literature on non-acid reflux in lung transplantation is sparse. One study documented that approximately one-third of patients with increased reflux parameters following transplantation had exclusively increased non-acid reflux^[3], but there was no clear association with outcomes. A second study did identify an association between non-acid/total reflux and bronchiolitis obliterans^[16], and similar to our

Table 3 Area under the receiver operating characteristic curve or c-statistic comparing prediction value of pH-testing and corresponding impedance measures of reflux for early allograft injury

	Area under ROC/Harrell's c-stat
pH parameter of reflux	
Acid reflux exposure, upright	0.58
Acid reflux exposure, recumbent	0.69
Acid reflux exposure, overall	0.61
Elevated acid reflux exposure (> 4.2%)	0.39
Total acid reflux episodes	0.60
Acid clearance	0.64
Impedance parameter of reflux	
Total reflux exposure, upright	0.63
Total reflux exposure, recumbent	0.74
Total reflux exposure, overall	0.67
Elevated total reflux exposure (> 1.4%)	0.77
Total reflux episodes	0.64
Bolus clearance	0.74

Note that all values deriving from impedance measures are greater than those from pH measures, suggesting that impedance data are better predictors.

study, no association was detected between abnormal acid reflux and rejection outcomes. However, only measures of acid and bolus reflux exposure were assessed in that study, which alone may not be sufficient to justify the use of impedance testing in lung transplant evaluation. Finally, bile acid aspiration has been associated with biomarkers of injury following lung transplantation, suggesting a possible pathway for allograft injury attributable to non-acid reflux^[17].

The importance of documenting non-acid reflux and its possible contribution to lung transplant outcomes is twofold. First, treatments that target acid reflux, including various forms of anti-secretory medications, are less likely to have an effect on non-acid reflux^[18-20]. Thus, such treatments alone may be insufficient to completely mitigate the risk of allograft injury in lung transplant patients with reflux. Second, non-acid reflux may be a manifestation of other disease processes that require more specific evaluation and management, such as esophageal^[21] or gastrointestinal motility disorders^[22,23], which have yet to be studied widely in the lung transplant population. A review of medical records did not reveal a diagnosis of esophageal dysmotility or gastroparesis in any subjects in our cohort, though neither esophageal manometry nor gastric emptying studies were routinely performed before transplantation. These results may demonstrate a need for additional testing or treatment options in transplant recipients.

Another challenge in the lung transplantation population includes absence of clear clinical guidelines regarding esophageal function testing before transplantation. While pH testing has been used increasingly in pre-transplant assessment, impedance remains underutilized. Moreover, the value of impedance testing continues to be debated, even in

the management of typical GERD symptoms in non-transplant patients^[24-26]. The results of this study suggested that impedance may provide greater predictive value for post-transplant outcomes than conventional pH-based parameters for reflux. In particular, increased acid exposure time, defined by the proportion of time that the esophageal pH is < 4 and the most commonly used outcome from pH-monitoring, performed poorly in predicting early allograft injury post-transplant (c-statistic = 0.39). However, when its impedance-equivalent (elevated total reflux exposure) was used, the predictive value of the result significantly improved (c-statistic = 0.77). These results also support the need for assessment of additional reflux-related factors that may be targets for intervention to improve lung transplant outcomes, such as obesity^[27,28]. Better pre-transplant reflux data that are associated with post-transplant outcomes may help improve candidate risk assessment and planning of peri-transplant care. Therefore, our data would suggest a role for routine use of MII-pH as a standard part of pre-transplant evaluation for lung transplant candidates.

The strengths of this study include the homogeneity of the study population, with meticulous record keeping and follow-up. Specifically, all patients underwent post-transplant care as per the standardized protocol, including routine histological assessment of the allograft at regular intervals, thereby minimizing potential biases or any inter-provider variability in clinical management. Importantly, the overall rate of acute rejection within one year in our study corroborates published data, establishing the generalizability of our patient cohort^[29]. Finally, mechanistic plausibility has been discussed in our previous publication^[10], drawing from previous studies on biomarkers and lymphocytic infiltration to implicate reflux and aspiration in early allograft injury^[4,30].

Limitations of the study include the small sample size, which, however, was within the range of prior publications. The inclusion of transplant candidates receiving both MII and pH testing, as opposed to pH testing alone, may introduce an external selection bias impacting generalizability, although demographics and clinical history appear homogeneous within the cohort, as reported in Table 1. The study cohort also had a higher proportion of idiopathic pulmonary fibrosis patients than the overall lung transplant population^[1]; however, a variety of primary pulmonary conditions was represented without significant differences between comparison groups. Additionally, the relatively small study size and low number of acute rejection and lymphocytic bronchiolitis events individually resulted in poor association between each individual outcome and pre-transplant MII-pH parameters. However, both markers of early allograft injury have been identified as major risk factors for the development of subsequent Bronchiolitis obliterans syndrome

(BOS) and are treated similarly in clinical practice, with increased immunosuppression^[29]. Longer-term outcomes, such as bronchiolitis obliterans, could not be reliably assessed because MII-pH testing has only become more available and widely used in recent years. We hope that we will be able to assess such outcomes with continued recruitment, and in applying the findings from the present study. Finally, while our results support a relationship between reflux severity and early allograft injury, the actual pathways remain under investigation.

In summary, pre-transplant MII measures of bolus reflux are better predictors than their pH counterparts for the development of early allograft injury post-lung transplantation. These findings suggest that non-acid reflux may play a role in the development of early allograft injury, leading to chronic rejection and allograft failure. MII-pH appears to be more valuable than pH-monitoring alone in pre-lung transplant reflux assessment, outcome risk stratification, and planning of peri-transplant care: these findings would support the use of MII-pH rather than pH testing alone in this setting. Future research should focus on the optimal timing and application of MII-pH testing, and on treatments to manage non-acid and total reflux in lung transplant patients.

COMMENTS

Background

Gastroesophageal reflux (GER) has been associated with poorer outcomes following lung transplant. Patients may be predisposed to acute and chronic rejection, as GER may induce inflammatory cascades through aspiration. Current pre-transplant evaluations do not universally include standardized testing for reflux. While pH study monitors acid reflux, esophageal multichannel intraluminal impedance (MII) assesses total bolus reflux regardless of pH. Comparing the performance of pH vs MII testing in predicting post-transplant early allograft injury may help to clarify the role of reflux on lung transplant outcomes and establish a standard in pre-transplant testing for reflux.

Research frontiers

Previous studies have suggested that the addition of MII to pH testing may increase the yield of the test for GER. However, more recent studies evaluating MII and pH studies with regards to treatment outcome for GER have demonstrated more conflicting results, with some showing a higher value for pH study-based acid parameters than MII measurements in predicting the treatment outcomes for typical symptoms of GER. Comparative data between the two study modalities for extraesophageal manifestations of GER is even more scarce.

Innovations and breakthroughs

In this study, the authors compared the performance of pre-transplant acid reflux measures on pH testing vs corresponding bolus reflux parameters on MII in predicting early allograft injury after lung transplantation. This study is unique in directly comparing the predictive values of two testing modalities of reflux with regards to a clinical outcome for extraesophageal manifestation of GER. They found that pre-transplant MII measures of bolus reflux are better predictors than their pH counterparts for development of early allograft injury post-lung transplant. In particular, overall reflux exposure, recumbent reflux exposure and prolonged bolus clearance were associated with increased early allograft injury.

Applications

Reflux assessment with MII should be routinely performed during pre-transplant evaluation, given its improved predictive qualities over those of pH testing alone and its association with post-transplant outcome.

Terminology

MI refers to the test that measures refluxing of gastric content into the esophagus regardless of pH level. Different substances (air, liquid, solid) have different conductance, which is inversely proportional to impedance. A drop in impedance is seen when liquid refluxes into the esophagus, as air normally carries a higher impedance. This allows monitoring of any refluxate advancing into the esophagus. Bolus reflux refers to any refluxate going from the stomach into the esophagus, regardless of acidity.

Peer-review

An important study. The discussion is well organized and the conclusions are appropriate. Right now, pH-testing is the gold standard for the study of the function of the esophagus and the measure of acid reflux. If these results are confirmed in posterior randomized and prospective studies, it is possible that MII could substitute pH-testing for preoperative study of acid reflux in patients in which lung transplantation is going to be performed.

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