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Prevalence of hiatal hernia by blinded MDCT in patients with IPF

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Running head: Reflux medication protective in IPF with hiatus hernia

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Abstract

Introduction: Hiatal hernia (HH) is associated with gastroesophageal reflux (GER) and/or GER disease (GERD) and may contribute to idiopathic pulmonary fibrosis (IPF). We hypothesized that HH evaluated by computed tomography (CT) is more common in IPF than asthma or COPD, and correlates with abnormal GER by pH probe testing.

Methods: Rates of HH were compared in three cohorts: IPF (N=100), COPD (N=60) and asthma (N=24) and evaluated for inter-observer agreement. In IPF, symptoms and anti-reflux medications were correlated with diffusing capacity (DLCO) and composite physiologic index (CPI). HH was correlated with pH probe testing in IPF patients (N=14).

Results: HH was higher in IPF (39%) than either COPD (13.3%, $p<0.0001$) or asthma (16.67%, $p<0.02$). The HH inter-observer k agreement was substantial in IPF (k 0.78) and asthma (k 0.70), and moderate in COPD (k 0.42). In IPF, HH did not correlate with lung function excepting those on anti-reflux therapy; who had a better DLCO ($p<0.04$) and CPI ($p<0.04$). HH correlated with GER by DeMeester scores ($p<0.04$).

Conclusion: HH is more common in IPF than COPD or asthma. In an IPF cohort, HH correlated with higher Demeester scores, confirming GERD. Presence alone of HH was not associated with decreased lung function.

Word count: 200

Key words: Interstitial lung disease, gastroesophageal reflux disease, hiatus hernia

Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common of the interstitial pneumonias (1) and has no effective therapy (2). The pathophysiology of IPF involves recurrent epithelial injury and subsequent aberrant fibroblast proliferation (3). Abnormal gastroesophageal reflux (GER) and GER disease (GERD) has been recognized as a risk factor for IPF (4) and may have a role in repeated epithelial injury and disease progression (5). Although acid aspiration has been linked to the pathogenesis of IPF by some authors (5,6), the mechanism and relationship of abnormal GER/GERD to causality, progression, or treatment of IPF has not been adequately addressed. One report cites an incidence of abnormal GER of 87% when assessed by ambulatory pH monitoring (7), while use of anti-GER therapy was associated with a stable course in another report (8). However, questions regarding testing and treatment for GER/D in larger populations of patients with IPF remain unanswered.

A majority of patients with IPF have pathologic reflux (9,10), however what constitutes sufficient/abnormal reflux to cause damage to the lungs is unclear. Additionally the presence of symptoms does not distinguish between those with and without reflux. In general, reflux is associated with the presence of hiatus hernia (HH) (11) which is known to alter the integrity of the lower esophageal sphincter (LES). As a result, HH has been weakly associated with episodes of micro-aspiration (acidic and non-acidic), diminished LES pressures and with increased risk of erosive esophagitis (12). In one case series, use of fundoplication in IPF patients with abnormal GER/GERD and HH who failed medical therapy resulted in stabilization of oxygen requirements (13).

The presence of HH is classically determined by a barium esophagram to identify the location of the LES in relationship to the crus of the diaphragm. Modern computed tomography

(CT) using continuous high resolution helical acquisition provides an alternative and recognized method (14) for evaluation of the anatomy of the esophagus in relationship to the diaphragm and thus determination of the presence of HH. Although hiatal hernias are routinely diagnosed on thoracic CT scans, the degree of accuracy and the level of agreement between radiologists has not been formally evaluated for this task.

Given the relationship between HH and GER/D, we hypothesized that HH is more common in IPF patients than in two other lung diseases known to be associated with HH and abnormal GER/GERD, asthma and COPD (15,16). Asthma is associated with high rates of abnormal GER/GERD and rates of HH upwards of 50% (17), both of which are much higher than the population in general. The prevalence of HH increases with both age and obstructive physiology and is seen in up to 56% in the 7^{th} and 8^{th} decades of life and up to 84% of those with emphysema in one study (18). We thought that assessing HH in patients with lung disease would be more valuable as a control group than the general population because these populations have higher rates of abnormal GER/GERD and are better matched for age and comorbidities.

We also hypothesized that high resolution Multidetector CT (MDCT) can reasonably diagnose HH, as judged by inter-observer agreement. We further hypothesized that the use of anti reflux medications, such as proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H2RA), in patients with IPF and HH may reduce lung injury as measured by pulmonary function and Composite Physiologic Index (CPI), indicating a role for abnormal GER/GERD as cause of lung injury in IPF.

Since it has previously been demonstrated in other diseases that HH is associated with increased acid exposure (11,12), we sought to explain our findings by determining if the

presence of HH on MDCT is linked to an altered acidic exposure as demonstrated on pH probe testing in patients with IPF.

Some of the results of this study have been previously reported in abstract form at the ATS International Conference in May 2009 (19).

Methods

Study Population

A retrospective analysis was conducted at the University of Chicago. This study was approved by the Institutional Review Board at The University of Chicago.

The *IPF Cohort* consisted of 180 patients seen in the Interstitial Lung Disease Clinic between September 2005 and July 2008 who were consented and prospectively enrolled into a longitudinal database and selected by a single investigator (I.N.). Only patients with an available CT scan (N = 123) and a verified diagnosis (by I.N. and M.S.) of IPF according to the ATS/ERS diagnostic criteria (4) were included, leaving a final total of 100 subjects. 37 subjects had a confirmed usual interstitial pneumonitis (UIP) histopathology pattern on a surgical biopsy. The remaining subjects all had a typical UIP honeycomb pattern on CT diagnostic of IPF and no alternative diagnoses after a thorough evaluation (20).

The Asthma Cohort consisted of 24 patients who met ATS criteria for a diagnosis of severe asthma (21) who were consented and prospectively enrolled into a separate longitudinal database and had undergone MDCT as part of their clinical evaluation.

The *COPD Cohort* consisted of 240 patients with an ICD9 code for COPD from a general pulmonary clinic who had undergone a recent MDCT scan. 61 cases were randomly selected as a cohort for study.

IPF Esophageal Function Testing (EFT) Cohort consisted of 14 patients referred to the Swallowing Center at the University of Chicago at a pulmonologist' discretion between October 1, 2008 and October 1, 2010. All 14 patients had a verified diagnosis (by I.N., S.T. and S.P.) of IPF according to the ATS/ERS diagnostic criteria (4). 7 of the 14 subjects had a confirmed UIP histopathology on a surgical biopsy and/or lung explants. The remaining 7 subjects had a honeycomb pattern on CT felt definitive of IPF and no alternative diagnoses.

Determination of hiatus hernia

All scans were performed on Philips CT scanners with 64 slice machines used for the majority, and other cases were performed on 256 slice and 16 slice units. All patients were scanned using helical acquisition during a single breath hold at 120 kV (or 140 kV for exceptionally large patients) and mAs was varied according to patient size and weight. Expiration and prone scans were acquired at 1.00mm collimation with 10 mm intervals. Images were reconstructed axially at 3mm slice thickness with both B (standard) and D (detail) filters, and at 1mm slice thickness with a D filter. Axial MIPs (maximum intensity projection) were reconstructed at 10mm thickness with 5mm overlap. Coronal slabs and MINIPs (minimum intensity projection) images, were also reviewed. Prone and expiration scans were reconstructed at 1mm thick with a D filter. Source images (0.9mm) were archived in all cases.

MDCT scans were randomly ordered and reviewed independently without prior knowledge of diagnosis by two chest radiologists (S.Z., H.M.), using axial and coronal images with mediastinal window settings. The presence of HH was determined by evaluation of the esophagus in relation to the diaphragm by recognized anatomical definitions. (Figure 1) Each HH was classified as Type I – IV as previously described (22). Recognizing that that these types were established by esophageal barium studies or endoscopy, we further divided type I HH into

grades of A: “Possible”, B: “Probable” and C: “Definite” to establish a Likert scale for the level of confidence of interpretation. In all cohorts, a “Present” HH was then defined as type I with grade “Probable” or “Definite”, and type II-IV in which both radiologists agreed. “Absent” HH was defined as absent or type I with grade “possible”. Cases with discordant readings between radiologists were labeled “indeterminate”, and were removed from further analysis. From this grading system the prevalence of HH and a k statistic for agreement were calculated.

Relationship between HH, lung severity, symptoms and anti reflux therapy in the IPF cohort

Study subjects underwent pulmonary function testing per ATS guidelines (23). Lung severity was assessed by forced vital capacity as percent predicted (FVC%), diffusing capacity as percent predicted (DLCO%), and CPI, which has previously been shown to be associated with mortality (24).

Symptoms of reflux and the use of PPI and H2RA were determined from a questionnaire completed at the time of initial patient visit. In subjects with data from both pulmonary function testing and from questionnaires, the use of anti reflux medication and association with level of severity in patients with or without HH was evaluated.

Relationship between HH on MDCT and EFTs

Esophageal manometry

Medications that interfere with esophageal motility were discontinued 48 hours prior to the procedure. After an overnight fast, esophageal manometry was performed using a solid state catheter with 5 circumferential pressure sensors (Sandhill Scientific, Highlands Ranch, CO). Lower esophageal sphincter (LES) pressure and length were determined using the station pull-through technique, with 0.5cm increments between stations. Esophageal peristalsis was measured with ten swallows of 5ml of water given at 30-s intervals. Peristaltic wave amplitude,

duration and velocity were recorded at 3, 8, 13, 18cm above the manometrically determined LES. Peristaltic wave amplitude was independently calculated for the distal esophagus (3 and 8 cm above the LES, DEA) and for the proximal esophagus (13 and 18cm above the LES, PEA). Final manometric reporting was done using the Spechler and Castell criteria (25).

Ambulatory pH monitoring

Prior to testing, acid reducing medications were discontinued for 3 days for histamine H_2-receptors antagonists and 10 days for proton pump inhibitors. A dual sensor pH probe in which the lower sensor was placed 5cm above the superior border of the manometrically determined LES and the proximal sensor was placed 15cm above the distal sensor was used. Patients were instructed to eat an unrestricted diet and avoid acid suppressing medications during the study. Patients were given a diary to describe symptoms and events. Based on the collected data, a composite reflux score (DeMeester score) was calculated for the distal esophagus. The data were analyzed using a commercial software program. (BioView, Sandhill Scientific, Highlands Ranch, CO). A DeMeester score above 14.7 was considered abnormal (26). Patients were considered to have abnormal proximal reflux if the acid exposure was above 1% (27).

Statistical Analysis

Data are reported as mean ± standard deviation, median (range), and proportions. Comparisons between clinical and radiologic findings were made using the Chi-Square test and Fischer's exact tests as appropriate. Esophageal Function tests, Symptoms, treatment, FVC%, DLCO%, and CPI were analyzed using two tailed t-tests. Levels of agreement were analyzed using k statistics (28).

Results

Demographics of IPF, COPD and asthma groups:

One hundred and eighty four HRCTs were reviewed in patients at the University of Chicago in 100 subjects with IPF, 60 subjects with COPD from the general pulmonary clinic and 24 subjects with asthma from the Refractory Obstructive Lung Disease Clinic. Demographic and clinical characteristics of study subjects are shown in table 1. The percentage of male subjects was 70% in IPF, 53% in COPD, and 25% in asthma. The mean ages of each cohort at the time of MDCT collection were 68.5±9.0 years for IPF, 67.5±8.6 years for COPD and 52.3 ±17.4 years for asthma.

The IPF EFT cohort consisted of 14 patients, 9 of which were male. The average age was 60.4+10.8 years (Table 3).

Prevalence of hiatus hernia in the IPF, COPD and asthma groups:

The rate of HH as defined by agreement between both radiologists was statistically significantly higher in IPF at 39% (CI 30.9-47%) than either the COPD cohort (13.3%, CI 6.11-20.55%, $p<0.00009$) or asthma cohort (16.67%, CI 4.15-29.19, $p<0.0139$) (Table 1). The inter-observer k statistic of determination of HH by HRCT demonstrated substantial agreement ($k=0.78$) in IPF, moderate agreement ($k=0.42$) in COPD and substantial agreement ($k=0.70$) in asthma.

Evaluation of level of disease severity and HH in IPF cohort:

To analyze the relationship between HH and IPF we examined cases in which there were both: 1) agreement between radiologist review and 2) pulmonary function data available for analysis. Of the 100 cases with IPF, 11 were excluded as they were indeterminate for presence or absence of HH disease, and 15 cases had incomplete pulmonary function data. The remaining 74

cases constituted the IPF cohort. Data on symptoms and the use of anti therapy was available in these 74 cases.

There were no differences noted in age, race, gender, symptoms or use of anti reflux medications between IPF patients with or without HH (Table 2). Mean FVC%, DLCO% and CPI did not differ significantly between groups (Table 2). When IPF patients with HH were further examined by use or non-use of anti-reflux medications, significant differences were noted in the DLCO% which was 40.9±15.0 in patients without therapy versus 55.7±19.9 with on patients with therapy ($p<0.02$). Similarly, the CPI demonstrated a difference with therapy: 56.0±13.5 without therapy versus 44.8±15.0 with therapy ($p<0.03$) (Figure 2).

This subgroup of IPF patients with HH and PFT results was 33. Of the 14 not on anti reflux medication and with HH, 11 were Caucasian, 2 were Hispanic, and 1 was African American. Only 1 of 14 patients noted reflux symptoms on our intake evaluation questionnaire. 4 of 14 were on prednisone therapy at the time of evaluation. Of the 19 patients with HH on anti reflux therapy, 16 were Caucasian, 1 was Asian, and 2 were African American. 8 of the 19 had active complaints of reflux on our intake evaluation questionnaire. 4 of 19 were on prednisone therapy at the time of evaluation. 18 of 19 were on PPIs and 1 of 19 was on a H2 Blocker.

HH and the IPF Esophageal Function Testing Cohort:

The demographic for this group are in Table 3. Analysis of manometry demonstrated a shortened total LES length in those with HH on MDCT at 2.4 cm compared with those IPF patients without HH noted on MDCT at 3.4 cm ($p<0.02$). The distal pH probe demonstrated a significantly higher DeMeester score in the HH group of 22.8 compared to 10.2 for the non HH group (p value <0.04). Trends were noted in the percent of events that were in the upright

position and in events noted to be greater than 5 minutes with both in the direction of greater acidic exposure for the HH group.

Discussion

Idiopathic pulmonary fibrosis is a complex disease with an unknown etiology. Central to the current hypothesis of causation is an alveolar epithelial injury repair model involving serial lung injury and aberrant repair. Factors implicated in the injury process include a genetic predisposition and environmental factors such as tobacco smoke (4, 29). Micro-aspiration may also have a causative or disease modifying role in some patients. We sought to study if HH as typically evaluated by radiologists could be reliably determined on MDCT, whether there was an increased prevalence of HH in patients with IPF compared to other common pulmonary diseases with known increased rates of abnormal GER/GERD and HH such as asthma and COPD, and whether treatment of abnormal GER/GERD in patients with both IPF and HH was associated with disease severity as measured by pulmonary function. We then sought to determine if there was a relationship between an HH on MDCT and acid exposure.

Our approach demonstrates a methodology for determining the presence of a HH using recognition of anatomical structures on HRCT. Traditionally, HH was demonstrated by barium contrast esophagram. This has given way to measurement of esophageal acid reflux by 24 hr pH probe monitoring and of acidic and non acidic reflux by esophageal impedence. Even with barium contrast esophagram there is no consensus regarding the differentiation of key anatomic structures such as the phrenic ampulla, which is physiological, from a HH, which is pathological. There is agreement that the lower esophageal ring must be at least 1-2 cm above the level of the diaphragmatic hiatus to diagnose a HH (30). The level of confidence in interpretation is therefore important. To maintain rigor in our interpretation, the radiologists read the CTs in mediastinal

window settings to minimize interpretation of the lung parenchyma and had no prior knowledge of the clinical diagnosis. Furthermore, we accepted only cases with complete agreement between radiologists for HH across all three cohorts. Our results demonstrated a prevalence of HH in subjects with IPF that was double that seen in asthma, a disease with rates of both abnormal GER/GERD and HH known to be higher than the population at large (16-18). We also compared the prevalence of HH in IPF to patients with COPD. Since HH increases with advancing age (31) and with COPD (18), this cohort provided a useful comparator, superior to the general populace. The prevalence of HH in the IPF cohort was substantially higher than either group. Asthma and COPD, as obstructive lung diseases, may have increased intra-thoracic pressures that may predispose the diaphragm to pathophysiologic changes favoring HH. It is certainly reasonable that restrictive diseases may provide alternative alterations to predispose to HH or that the HH is the inciting reason for the development of the restriction. In either event the rate of HH is highest in IPF in this study. Therefore, much like prior published data in abnormal GER/GERD (7, 9), HH has a much higher prevalence in IPF compared to that seen in other common pulmonary diseases.

It has been suggested that abnormal GER/GERD plays a role the pathogenesis of IPF (32). Raghu et al. (7) also demonstrated a high prevalence of abnormal GER/GERD in an IPF cohort compared to an asthma cohort. In that prospective study, there was no correlation with disease severity. Indeed a limitation in that study is that it is unclear what type and how much reflux might be injurious. In another study examining 18 subjects with severe, end-stage IPF, the prevalence of abnormal GER/GERD by pH monitoring was 66%; this was not associated with symptoms but was associated with hypotensive LES tone and abnormal esophageal peristalsis (33). To date, no study demonstrating the presence of abnormal GER/GERD either by symptoms

or 24-hour pH monitoring in subjects with IPF has demonstrated any association with disease severity. Because of this, there has been a debate as to whether or not acid reflux disease or non-acidic particulate reflux is responsible for the damage caused by micro-aspiration.

In our study, of the 16 patients with active recorded symptoms, 15 were on anti reflux therapy. 25 subjects on therapy were asymptomatic at the time of evaluation. There were no differences in severity of lung disease when assessed only by use of anti reflux medications. Nine of 33 subjects with HH had symptoms while 7 of 44 subjects without HH had symptoms. These do not differ statistically. Eight of 19 subjects in the group with HH on anti reflux therapy had symptoms compared with only 1 of 14 for the group with HH not on anti reflux therapy. Therefore symptoms would seem to drive therapy, while symptoms and therapy alone correlate poorly with either disease severity, or with presence or absence of HH.

We sought to test whether the presence of HH was associated with differences in severity of disease in IPF. The pathophysiology of GER and micro-aspiration is multi-factorial with variable presentation within any patient group. Both an incompetent LES and HH are associated with reflux disease (11). Classically, acid reflux is determined by duration, frequency and extent of distal esophageal acid exposure by the DeMeester score (20), while detecting non-acid reflux is an inherent limitation of pH studies. Multichannel intraluminal impedance testing examines reflux events independently of pH (35).

To date no study has demonstrated a correlation between disease severity in IPF and abnormal GER/GERD. Indeed, in our cohort, HH alone was not associated with any differences in severity. We then postulated that the frequent use of anti reflux therapy in the community might temper or mitigate the damage caused by the refluxate and prevent a decline in lung function. When we analyzed differences in patients with HH with and without treatment, both

the DLCO % and the CPI (as a measure of overall severity) were significantly better in treated patients. We explored the CPI as it includes an adjustment for obstructive lung disease by incorporating the FEV1 as well as the FVC and DLCO. There were no differences between treatment groups in the IPF patients without the presence of HH (data not shown). It is also possible that patients with abnormal GER/GERD symptoms are diagnosed sooner and therefore have less severe disease. Our data demonstrate that there was no difference in level of disease by any measure when patients were analyzed by presence or absence of symptoms. Additionally severity in the groups with and without the use of anti reflux medications in those without symptoms or without HH did not differ either. These data suggest that treatment may mitigate a decline in lung function in subjects with IPF and HH only.

Our study does not answer several questions. Is the use of anti-reflux therapy sufficient? Indeed, IPF subjects with HH who received anti-reflux therapy had similar pulmonary function test results as those subjects without a HH. However pulmonary function was lower in subjects with HH who did not receive anti-reflux therapy. We acknowledge that while acid reflux may be worse than non acid reflux, non acid reflux may still be important from the standpoint of disease pathogenesis and progression. This is supported by the high prevalence of non-acid reflux demonstrated in studies to date (10). We also acknowledge that micro-aspiration is likely not the only mechanism of alveolar injury. The prevalence of smoking, a factor clearly associated with IPF, is very high in IPF subjects (29). Other environmental exposures are also possible contributors (29), and we did not examine these.

We recognize that an exact correlation should not be expected. However, what constitutes significant reflux is unclear in both the pulmonary (29) and the gastroenterology literature (36). Several studies in non IPF cases clearly support both a higher prevalence of

refluxate, both acidic and non acidic, symptomatic and asymptomatic, in patients with a compromised LES as a result of a HH (15, 37, 38).

Our IPF Esophageal Function Tests cohort confirms the previous knowledge of the association between HH and increased acid exposure. An acknowledged mechanism is alteration of the LES. Our findings indicate that IPF patients can be identified by CT as having an HH, and that the presence of this finding is associated with a clinically higher DeMeester score and shorter LES length.

Another question is whether HH is a contributor to IPF or whether HH is a result of lung restriction leading to displacement of the diaphragm that in turn causes HH. If the later were true, it would be expected that severity of disease would be higher in all HH cases. However, in our study only subjects with untreated HH had more severe pulmonary disease. It is possible that the higher rate of symptoms in the HH group on anti reflux therapy lead to discovery of earlier disease. But this did hold true when the entire cohort was evaluated for reflux symptoms.

Limitations

Our study was an observational study with data gathered retrospectively. It was not a blinded randomized trial of anti reflux therapy in IPF and did not evaluate patients over time. Specifically, we do not know when and if patients instituted anti reflux therapy or if patients not on anti reflux therapy at entry initiated therapy at a later time point. There were no controls for treatment, nor do we have any outcome data. Therefore, we have not explored or demonstrated long term outcomes such as longitudinal changes in pulmonary function tests, survival or acute exacerbations. While we observed that HH on MDCT correlated with greater acid exposure as measured by a DeMeester score on pH probe in a small cohort, the intensity, frequency and extent of abnormal acid reflux were not evaluated in the cohort at large. Thus, we cannot

determine the longitudinal effect of anti reflux medicines as therapy for IPF and caution against such an interpretation.

We can only speculate that anti-reflux treatment directed against abnormal acid GER/GERD may be helpful in the subset of patients as the patients receiving pharmacological interventions to suppress abnormal acid GER were associated with improved measurements of lung function (DLCO, CPI). It must however be noted that this speculation is based on the assumption that HH patients have abnormal acid reflux and that pharmaceutical intervention corrects this reflux if present.

Conclusions

Our study demonstrates that HH can be determined with very good agreement on MDCT in patients with IPF, and that the prevalence of HH is higher in IPF than in other common pulmonary diseases. Our study further suggests that in patients with IPF and HH on MDCT, anti-reflux treatment directed against abnormal GER/GERD warrants further studies to determine the effectiveness of anti-reflux therapy for patients with IPF.

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Table 1. Demographic, inter-observer agreement and rates of hiatus hernia (HH)

Cohorts	Entire Cohort	IPF	COPD	Asthma
Demographics				
N	184	100	60	24
Age in Years	65.6	67.5	68.5	52.8
% Males	58.7%	70.0%	53.3%	25.0%
Level of Agreement				
k	0.70	0.78	0.42	0.86
95% Cl	(0.59-0.81)	(0.66-0.90)	(0.17-0.67)	(.60-1.00)
Rates of HH				
Rate	27.7%	39%	13.3%	16.7%
95% Cl	(22.29-33.25)	(30.98-47.02)	(6.11-20.55)	(4.15-29.19)
P values for HH rates compared to IPF			0.00009	0.0139

Table 2 A. Severity of disease in IPF by symptoms and use of anti reflux medications.

IPF Cohort**	N	Age	FVC%	+/- SD	DLCO%	+/-SD	CPI	+/- SD
+ anti reflux medications	35	68	69.0	18.5	44.4	17.3	53.7	14.4
- anti reflux medications	39	65	69.2	16.9	50.6	19.5	48.2	13.9
Reflux symptoms present*	16	64	74.2	20.8	50.5	23.4	46.9	16.9
Reflux symptoms absent	58	67	67.7	16.5	46.9	17.2	51.9	13.5
+ anti reflux medications	25	67	66.0	13.0	49.9	17.4	53.4	12.4
- anti reflux medications	33	69	69.0	18.8	44.7	17.1	53.7	14.2

*15/16 subjects were on anti reflux medications
**None statistically significant

Table 2 B. Severity of disease in IPF by hiatus hernia (HH) & use of anti reflux medications in those with HH.

IPF Cohort	N	Age	FVC%	± SD	DLCO%	± SD	CPI	± SD
HH absent	44	66.5	70.1	17.9	47.8	19.2	50.7	14.5
HH present	33	67.0	70.1	18.4	49.5	19.3	49.6	15.2
+ anti reflux medications	19	66.8	73.7	17.2	55.7*	19.9	44.8	15.0
- anti reflux medications	14	67.2	65.1	19.5	40.9*	15.0	56.0*	13.5
*p values			NS		<0.03		<0.04	

Table 3. IPF EFT Cohort

	Absent HH	+/-SD	Present HH	+/-SD	p values
Demographics and PFTs					
N	5		9		
Age	62		60		
Male	3		6		
FVC% of predicted	59.8		64.4		NS
DLCO% of predicted	34.8		45		NS
Manometry					
LES Pressure	24.78	12.10	23.28	12.41	0.83
Hypotensive LES (<14mm Hg)	20%	NA	20%	NA	NA
Total LES length	3.42	0.51	2.39	0.80	0.01
Abd LES length	2.40	1.47	1.34	0.92	0.20
UES pressure	32.28	12.18	40.39	23.67	0.43
Esophageal pH findings					
Proximal Probe					
No of reflux events	60.25	35.51	65.44	65.92	0.86
Events >5 minutes	1.50	1.73	2.28	2.44	0.53
Percent time pH <4	3.20	2.10	4.28	3.23	0.49
Percent time upright	4.23	3.49	6.34	5.58	0.43
Percent time supine	1.38	1.70	2.36	3.11	0.48
Distal PROBE:					
No of reflux events	25.25	19.00	58.86	64.98	0.24
Events >5 minutes	0.00	0.00	1.29	1.60	0.08
Percent time pH <4	0.55	0.44	2.82	3.06	0.22
Percent time upright	0.88	0.82	4.04	3.79	0.07
Percent time supine	0.08	0.15	1.84	3.41	0.22
DeMeester Score	10.20	7.74	22.79	11.26	0.03

Figure 1

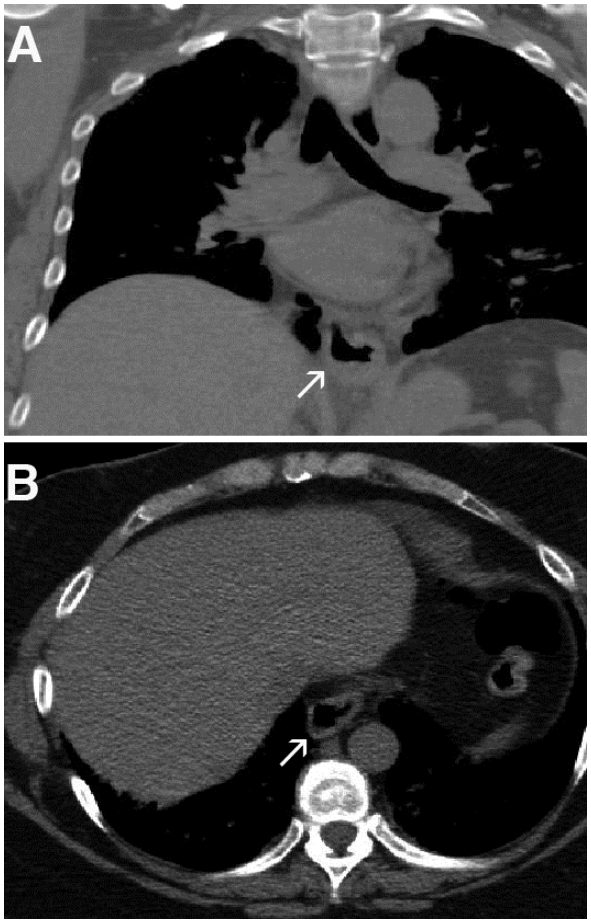
A
B

Figure 2

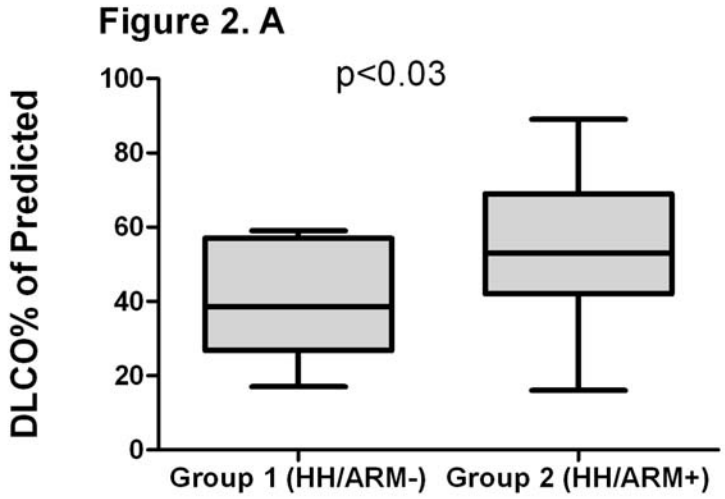
Figure 2. A
p<0.03
DLCO% of Predicted
100
80
60
40
20
0
Group 1 (HH/ARM-)
Group 2 (HH/ARM+)

Figure 2. B