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Quantitative Computed Tomography Assessment of Bronchiolitis Obliterans Syndrome after Lung Transplantation

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Computed tomography; lung transplantation; bronchiolitis obliterans syndrome; airway disease; quantitative

Introduction

Bronchiolitis obliterans syndrome (BOS) is a form of irreversible airflow obstruction and is a clinical manifestation of chronic allograft rejection following lung transplantation.^{1,2} Despite advances in the field, the 5-year mortality remains approximately 50% with the majority of post transplant complications occurring after the first year being attributable to BOS/chronic allograft rejection.^{1,2}

BOS is associated with numerous risk factors including medication noncompliance, cytomegalovirus infection, gastro-esophageal reflux disease, acute cellular rejection, air pollution and interstitial pneumonitis, and its development and progression are associated with a 3-fold increase in the risk of death at 3 years.^{3–11} Currently, the presence and progression of BOS are primarily defined by spirometry, which can be variable from test to test and is partially effort dependent.

Our prior work in BOS following allogeneic hematopoietic stem cell transplantation (HSCT) demonstrated that airway remodeling in BOS is characterized by central airway dilation, and the degree of this dilation is associated with impairments in lung function and the progression of BOS.¹² We hypothesized that a similar phenomenon is present in patients following lung transplantation. Therefore, we performed an exploratory analysis of clinically acquired computed tomography (CT) scans and autopsies from a cohort of over 200 patients who underwent lung transplantation at our institution to assess the association between the presence and progression of BOS and quantitative CT measures of proximal airway and vessel morphology as well as their pathologic correlates.

METHODS

Subjects

All patients who received a cadaveric lung transplant at the Brigham and Women's Hospital (n=204) between December 1, 2002 and December 31, 2010 were included in this study. The medical records for each of these subjects were reviewed for availability of lung autopsy tissue, longitudinal measures of lung function, and clinically acquired CT scans of the chest available for analysis. CT scans and measures of lung function were included if they were acquired within 90 days of each other. In addition, patients with extensive interstitial disease on CT that did not allow for identification of 16 airways and vessels (8 for unilateral transplants) were excluded. The Institutional Review Board at Brigham and Women's Hospital, Boston, MA, approved this study.

Pulmonary Function Testing—Per the post-lung transplantation protocol at our institution, spirometric measures of lung function (Morgan Scientific, Inc) are obtained at every lung transplant clinic visit without the administration of a short acting inhaled

bronchodilator using standards published by the American Thoracic Society.¹³ Lung function data collected for this study included forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), and forced expiratory flow between 25–75% (FEF_{25–75}).

Baseline FEV₁ value was defined as the average of the two highest post transplant measurements obtained at least 3 weeks apart without bronchodilators. The presence of BOS was defined using baseline spirometry and using consensus criteria as previously described: BOS Stage 1: FEV₁ 66%–80% of baseline, BOS Stage 2: FEV₁ 51–65% of baseline and Stage 3: FEV₁ 50% of baseline.^{14–16} For this study BOS was considered present at Stage BOS 1. Subjects without BOS were defined as controls.

CT scans

As discussed above, the clinical data of all subjects who had undergone lung transplantation during the specified time period were reviewed for CT scans of the chest that could be used for quantitative assessment. As anticipated with clinically acquired data, it was apparent that subjects had one of two types of CT scan available: volumetric CT scans acquired with intravenous contrast for the detection of pulmonary embolism (CT pulmonary angiogram protocol - CTPA) and non-contrast non-volumetric CT scans consisting of 1mm axial slices spaced either every 1 or 2 cm, which are frequently described as high resolution CT (HRCT) scans. In addition, it was noted that no subject had more than one follow up CTPA available, the presence of which would allow for the investigation of BOS progression over time. Thus, as this was an exploratory study, both groups were included, but due to the heterogeneity of the imaging data, specifically with regard to the technique for the longitudinal measurement of airway and vessel characteristics, they were analyzed separately as discussed below.

Volumetric CT Scan Analysis

Subjects were included if they had a minimum of two clinically CTPA scans available for longitudinal airway/vessel analysis. If a subject had more than 2 of such CT scans, the two scans spanning the largest time interval were selected. Images were reconstructed using a high spatial frequency algorithm with 1mm – 1.25mm slice thickness at 1mm intervals. Analysts who were blinded to the clinical diagnosis made the following measurements using the phase congruency method implemented via Airway Inspector (www.airwayinspector.org) of the 3rd and 4th generation B1 and B10 airways and adjoining vessels in the transplanted lung(s) airway internal lumen perimeter (PI), wall thickness, wall area percent (WA%: 100* wall area/total bronchial area) and airway lumen area (AI).^{17–19} The vessel cross sectional area (CSA) of the vessels adjoining these airways was measured by upper thresholding the slice corresponding to the adjacent vessels with a cut-off level of –500 HU and isolating the vessel cross section using a connected components technique. The CSA was then computed by integrating the area of the pixels labeled as vessel. Note that in those with bilateral lung transplants, all measurements were made in both lungs and averaged. Additional measures performed included CT measured total lung volume, which was calculated as described previously.²⁰ Due to the small size of this cohort, subjects in it were categorized only as either controls or BOS cases based on the aforementioned spirometric criteria.

Non-volumetric CT Scan - BOS Progression Analysis

Patients were included in this analysis if they had a non-contrast HRCT available at the time of, or prior to the diagnosis of BOS and 2 additional longitudinal non-contrast HRCT scans conducted after their baseline CT scan. If more than 3 non-contrast HRCT scans were available, then the CT scan closest to the baseline FEV₁ was utilized for scan 1, the latest available for scan 3, and the CT scan closest to the median days between these scans was used for CT 2. This cohort was initially divided into two groups as described above. In addition, in order to leverage the greater number of subjects and CT scans that were available for this cohort, and to help further define the imaging findings associated with BOS progression, the BOS group was subdivided further into BOS non-progressors (NP) (defined as those with spirometric improvement or <10% decline in FEV₁ between scan 2 and scan 3) (n=22) and BOS progressors (defined as those with a >10% decline in FEV₁ between scan 2 to scan 3) (n=24). In this cohort, because of the non-volumetric (non-adjacent) spacing of the CT images, measurements of the same segmental airway and vessel could not be made reliably on all three of a subject's CT scans as was done for the volumetric data. Therefore, based upon a technique used in prior studies, the airway and vessel measurements described in the analysis of volumetric CT scans above were instead performed on a total of 16 airways (8 for unilateral transplants) with 4 in each quadrant (i.e., the right and left upper lobes and the right and left lower lobes) and then averaged for each CT scan. These averages were then compared longitudinally.²¹⁻²⁴

Pathology

For the subgroup of subjects for whom autopsy samples were available, sequential sections of lung tissue were stained with hematoxylin and eosin, Masson's trichrome, and Verhoeff elastic stains. Two pathologists blinded to the clinical diagnosis evaluated the specimens utilizing the International Society of Heart Lung Transplant working formulation for the grading of pulmonary allograft rejection and arteriopathy.^{16,25} Allograft rejection and arteriopathy were graded as present or absent. In addition, proximal cartilaginous and small non-cartilaginous peripheral airways were reviewed for presence or absence of subepithelial fibrosis and/or intraluminal granulation tissue.^{26,27} Of note, the pathology subgroup represented subjects from both of the CT cohorts described above and subjects not included in the CT analysis.

Statistical Analysis

Data are presented as medians and inter quartile range where appropriate. Within each separate CT cohort, the relationship between direct CT measures of airway remodeling and spirometry was evaluated using Spearman correlation. Wilcoxon rank sum tests were used for between group comparisons of the change in measures of airway morphology, change in A/V ratios, and change in spirometric values over the period of observation. A/V ratios were log transformed for normality and logistic regression analysis was performed to further investigate the association between the A/V ratio and the presence or absence of BOS when adjusted for age, sex and CT derived lung volume. For the pathological analysis Fisher's Exact Test was used for between group comparisons. P values less than 0.05 were considered statistically significant. Analyses were performed with SAS v. 9.3. (Cary, NC).

RESULTS

Cohort

Nintey-four of the 204 (46.1%) subjects met our criteria for inclusion in the study. There were 4 subjects in the volumetric CTPA group that overlapped with the non-volumetric non-contrast HRCT group. There were 5 Subjects in the pathology group overlapped with the non-contrast HRCT group and 2 subjects overlapped with the CTPA group. Fifteen subjects (7.4%) in total were excluded for interstitial changes on CT that did not allow for airway and vessel measurements. (Figure 1) In total 242 CT scans from 84 subjects were included in this study.

Volumetric QCT analysis—Twenty-two of the 204 subjects (10.8%) had 2 or more volumetric CTPA scans available for airway and vascular analysis (Table 1A). None of the subjects in this group had significant enough interstitial disease to prevent airway and vessel measurements.

The median interval between the volumetric CTPA and PFTs was 0 days [−7.8; 15.3]. The median days post transplant for scan 1 for patients identified as controls and BOS was 8 days [5.5; 51.5] and 352 days [73.0; 574.5] respectively. The median days between scan 1 and scan 2 for controls and BOS cases was 251 days [138.5; 607] and 164 days [74.5; 1839] respectively.

Thirteen of these subjects met diagnostic criteria for BOS and 9 were classified as controls. The median change in FEV₁ was 2.5% [−14.2; 5.2] for the controls and −17.9% [−26.6; −10.8] for those with BOS (p<0.01). There was no association between the percent change in lung function (FEV₁) and the percent change in PI in the controls (n=9, r=0.55, p=NS). There was an inverse relationship between the percent change in FEV₁ and the percent change in PI (n=13, r = −0.73, p<0.005), in patients with BOS (Table 2). This change in airway morphology was also evident when assessing AI, as there was a statistically significant increase in the AI in the cases as compared to controls, (30.6 [25.6; 40.1] vs. 4.2 [−8.0; 11.0], p=0.02) (Figure 2). Finally, when examining the vasculature, there was a statistically significant decrease in the vascular CSA in the cases as compared to the controls (−19.9 [−40.4; −6.4] vs. 6.3 [−6.8; 27.6], p=0.02).

Non-volumetric CT Scan – BOS Progression Analysis—Sixty-six subjects (32%) had three HRCT scans available for analysis (Table 1B). Twenty patients were categorized as controls, 22 as BOS NP and 24 as BOS progressors based on the criteria described above. Fifteen subjects (7.4%) of this cohort were excluded for interstitial changes on CT that did not allow for airway and vessel measurements.

The median days between the non-volumetric CT and PFTs was 0 days [−0.75; 0.75]. The median days post transplant for the first CT scan 1 for the controls, NP and BOS progressors was 71 days [40; 328], 39 days [19; 159] and 91 days [39; 165] respectively. The median days post transplant for the second CT scan for controls, NP and BOS progressors was 368 days [122; 885], 656 days [215; 1229] and 500 days [281; 1004] respectively. And the

median days post transplant for the third CT scan for the controls, NP and BOS progressors was 685 days [382; 1610], 1257 days [566; 2649] and 1079 days [792; 1391] respectively.

At the time of the baseline scan (scan 1) there was no difference in the FEV₁ and A/V ratio between the 3 groups (p=NS and p=NS respectively) (Table 3 and Figure 3). With regard to progression over time, as expected based on their case definition, control subjects' FEV₁ remained unchanged between the three scans (p=NS) (Table 3 and Figure 3). Similarly their A/V ratio did not change over time. (p=NS) (Table 3 and Figure 4).

Non-progressor subjects' FEV₁ declined significantly between scans 1 and 2 (p<0.001) and increased significantly between scan 2 and 3 (p<0.001). (Table 3 and Figure 3). There was no significant change in the A/V ratio between scans despite the observed changes in lung function (p=NS) (Table 3 and Figure 4).

BOS progressor subjects demonstrated a significant decline in FEV₁ between scans 1 and 2 (p=0.001) and between 2 and 3 (p<0.001) (Table 3 and Figure 3). In addition, they had a significant increase in the A/V ratio between scan 1 and scan 2 (p<0.001) and between scan 2 and 3 (p<0.001). (Table 3 and Figure 4).

There was no statistically significant difference in quantitative lung volume measurements between group's p=NS, data not shown. After adjustment for age, gender and lung volumes, the differences in A/V ratio across groups remained statistically significant. We performed a subset analysis after removing the 9 subjects who overlapped between the volumetric and pathology cohort and the non-volumetric cohort and there was no change in the statistical significance between groups, data not shown. Figure 5 represents a HRCT imaging of a subject before and after the diagnosis of BOS (BOS progressor) and demonstrates the observed airway dilation and a reduction in vascular cross sectional area.

Pathologic Analysis—Seventeen of the 204 subjects (8.3%) of our cohort had archival autopsy tissue available for histopathologic analysis. Baseline characteristics of these subjects and the clinical cause of death as reported on the autopsy report are depicted in Table 1C and Table 4 respectively.

The median days post transplant for autopsy patients identified as controls and those with BOS was 182 days [160; 296] and 782 days [314; 1760] respectively. The median days between PFTs and autopsy for controls and those with BOS was 46 days [20; 75] and 63 days [39; 84] respectively.

Proximal cartilaginous airways and small non cartilaginous airways were inadequately sampled in one control and 2 BOS subjects. A greater percentage of BOS subjects demonstrated proximal airway fibrosis as compared to controls, (p=0.003). Although more BOS subjects had proximal and distal arteriopathy as compared to the controls, this difference did not reach statistical significance (Table 5). Figure 6 is a representative image of proximal airway and vessel (generation<5) fibrosis in a patient with BOS as compared to a control.

DISCUSSION

In this retrospective exploratory examination of clinically acquired data from lung transplant recipients at our institution we found CT evidence of bronchiectatic dilation of the large airways in subjects with BOS that is proportional to the degree of expiratory airflow obstruction. More specifically, using a method which is analogous to the visual assessment of such airway disease, we employed an objective measure of airway lumen area and its ratio to the cross sectional area of the adjacent blood vessel, and found it to be increased in those subjects with progressive BOS by spirometry. The clinical acquisition of the CT scans in this study meant that two cohorts, with different types of CT scans, were analyzed. The volumetric data of the first cohort allowed for the direct anatomically matched longitudinal analysis of airway and vessel morphology, and demonstrated that in patients with BOS, a decline in lung function was associated with a statistically significant increase in airway lumen area and a decrease in vessel cross sectional area. Similar findings using averaged values of airway and vessel diameter in the subjects with progressive BOS in the non-volumetric CT scans suggest that either type of CT scan can be used effectively for this type of analysis. This potentially dramatically increases the number of clinical CT scans that can be used for this type of analysis.

These results are consistent with our previous investigation of BOS following HSCT where we found that airway remodeling is characterized by lumen dilation in proportion to decrements in the FEV₁.¹² Other, visual analysis based radiologic studies have demonstrated that the development of BOS following lung transplantation is associated with evidence of decreased peripheral vascular markings, bronchiectatic dilation of the central airways, and gas trapping on expiratory imaging.^{28–37} However, to this point, quantitative methods for image analysis in this population have largely focused on expiratory gas trapping which has been reported to be sensitive for the detection of BOS and its subsequent progression, with limited investigation into any change that may occur in the proximal airways.^{38,39}

In this study, we also found significant histopathologic evidence of central airway fibrosis, and possible, but not significant, evidence of proximal and distal arteriopathy in patients with clinically defined BOS. To date there are limited published data on the pathological changes that occur in the proximal airways in patients with BOS following lung transplantation. Glanville et al demonstrated that lymphocytic bronchiolitis is associated with an increased risk of BOS after lung transplantation, and Greenland et al found an association of large-airway lymphocytic bronchitis with BOS.^{40,41} But, much of the published data available on proximal airway remodeling is from patients who have undergone HSCT where necropsy has demonstrated airway dilation, lymphocytic bronchitis/bronchiolitis, intraluminal granulation tissue, and cicatricial bronchiolitis obliterans (BO).^{42–45}

The literature on pulmonary vascular disease and remodeling in patients with BOS following lung transplantation is also limited. In a retrospective study Sagar et al, demonstrated that that pulmonary arteriopathy was more prevalent in patients with pathologic BO than without BO (84% vs. 4%, $p < 0.0001$).²⁷ This group hypothesized that perivascular inflammation

involving the allograft pulmonary arteries, veins, capillaries and the airway microcirculation led to pulmonary vascular remodeling, parenchymal fibrosis, and allograft airway injury.²⁷

While many of our findings are significant, our data consists of a retrospective assessment of clinically acquired data and as such there may be confounding related to the timing at which patients received a CT scan or autopsy. Additional potential confounders include the presence or absence of restrictive allograft syndrome in our cohort. This syndrome has been recently identified as a form of chronic allograft dysfunction that is associated with interstitial lung disease and a lower survival.^{46–48} Patients with significant interstitial lung disease were excluded from our analysis if it prevented the airways and vessels from being identified and measured. As restrictive allograft syndrome and BOS can overlap this exclusion may mean that our study cohort is not representative of all patients with BOS. As a result of low numbers in our CTPA and pathology cohorts, there was also overlap between all three cohorts. To account for this we re-analyzed our data removing the 9 subjects from the Non-contrast HRCT cohort who overlapped with the CTPA and Pathology cohort. There was no change in the significance of our reported results, data not shown.

In summary, our results suggest that bronchiectatic remodeling of the airways as assessed by objective measures of airway dilation and reductions in vascular cross sectional area occurs in proportion to the severity of airflow limitation in BOS. Given the somewhat variable nature of FEV₁, these radiologic findings provide additional evidence that objective analysis of CT scans may have clinical utility in such a patient population. Additional prospective work is needed to replicate these findings, further analyze the histopathologic analogues of airway remodeling on CT, and determine the relative contribution that these imaging measures make to the standard clinical screening process for BOS.

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Abbreviation List

BOS	bronchiolitis obliterans syndrome
HSCT	hematopoietic stem cell transplantation
FEV₁	forced expiratory volume in 1 second
FVC	forced vital capacity
FEF_{25–75}	forced expiratory flow between 25–75%
ISHLT	International Society of Heart Lung Transplant
CTPA	CT pulmonary angiogram
HRCT	high resolution computed tomographic

PI	airway internal lumen perimeter
WA %	wall area percent
SQRTWA	square root of wall area
AI	airway lumen area
CSA	cross sectional area
NP	non-progressors
A/V ratio	airway vessel ratio
PFTs	pulmonary function tests

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* Subjects excluded for: < 3 non-contrast HRCT and CT and PFTs did not meet inclusion criteria.

+ 4 Subjects in the CTPA group overlapped with the non-contrast HRCT group

° 5 Subjects in the pathology group overlapped with the non-contrast HRCT group and 2 subjects overlapped with the CTPA group.

Figure 1.
Flow sheet inclusion criteria

Figure 2.
Change in AI and PI between the two CT time points in the volumetric cohort for controls and those with BOS median [IQR].

Figure 3.

FEV₁ as percentage of baseline for each time point in controls, BOS non-progressors (NP) and BOS progressors (BOS), median [IQR].

Figure 4.

A/V ratio as percentage of baseline for each time point in controls, BOS non-progressors (NP) and BOS progressors (BOS), median [IQR].

Pre BOS**Post BOS**

Figure 5. Representative images of subject with progressive BOS demonstrating airway dilation and vascular pruning.

Figure 6.

Trichrome stained: a) Cross-section of lobar bronchus (generation < 5) from patient with clinical BOS with fibrotic, expanded submucosa and dilated lymphatic channels (arrowheads). b) Cross-section of lobar bronchus from control patient demonstrating normal submucosal thickness and organization. c) Cross-sections of small vasculature from patient with clinical BOS showing eccentric deposition of extracellular material (*) between elastic lamina (at arrow, elastin stain in inset) and endothelial cell layer. d) Cross-sections of small

vasculature from control patient demonstrating little to no tissue or extracellular material between the blood-filled lumen and elastic lamina (elastin stain in inset).

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Table 1

A) Baseline Characteristics of 22 patients with CTPA scans		
A	CONTROL N=9	BOS N=13
Age inYears	55.8 [46.5; 59.3]	58.1 [51.2; 62.5]
Baseline FEV ₁	1.87 [1.30; 2.96]	1.90 [1.57; 2.23]
Gender (female)	3 (10.3%)	3 (23.1%)
Single lung tx	5 (55.6%)	9 (69.2%)
Reason for transplant		
COPD/Emphysema	3 (33.3%)	4 (30.8%)
A1AT Deficiency	0 (0%)	1 (7.7%)
Pulmonary Fibrosis	6 (66.7%)	6 (46.2%)
Cystic Fibrosis	0 (0%)	0 (0%)
Other	0 (0%)	2 (15.4%)

B) Baseline Characteristics of 66 patients with non-volumetric HRCT scans available			
B	CONTROL N=20	NP N=22	BOS N=24
Age inYears	52.3 [30.6; 62.3]	57.5 [50.4; 60.6]	53.7 [40.2; 60.6]
Baseline FEV ₁	2.03 [1.58; 2.64]	1.92 [1.39; 2.31]	1.87 [1.58; 2.39]
Gender (female)	8 (40%)	8 (36%)	11 (46%)
Single lung tx	13 (65%)	8 (36%)	16 (67%)
Reason for transplant			
COPD/Emphysema	5 (25%)	11 (50%)	6 (25%)
A1AT Deficiency	0 (0%)	2 (9.1%)	2 (8.3%)
Pulmonary Fibrosis	8 (40%)	5 (22.7%)	8 (33.3%)
Cystic Fibrosis	7 (35%)	1 (4.5%)	5 (20.8%)
Other	0 (0%)	3 (13.6%)	3 (12.5%)

C) Baseline Characteristics of 17 patients with Autopsy Tissue available		
C	CONTROL N=7	BOS N=10
Age inYears	31.3 [24.5; 49.0]	52 [37.7; 60.73]
FEV ₁ % baseline	92.0 [89.2; 102.3]	43.7 [37.2; 70.0]
Gender (female)	4 (57%)	5 (50%)
Single lung tx	2 (29%)	3 (30%)
Reason for transplant		
COPD/Emphysema	2 (29%)	2 (20%)
A1AT Deficiency	0 (0%)	0 (0%)
Pulmonary Fibrosis	1 (14%)	4 (40%)
Cystic Fibrosis	4 (57%)	2 (20%)
Other	0 (0%)	2 (20%)

Table 2

Spearman correlation coefficients (r Values) for the % change in Pi with pulmonary function tests. BOS n = 13 control n=9.

BOS		
PFT	r VALUE	p VALUE
FEV ₁	−0.73	<0.005
FVC	−0.47	NS
FEF _{25–75}	0.13	NS
Control		
FEV ₁	0.55	NS
FVC	0.50	NS
FEF _{25–75}	−0.15	NS

Table 3

FEV1 and A/V ratio for subjects with non-volumetric HRCTs

	FEV1 % predicted			A/V Ratio		
	Controls	Non-progressors	Progressors	Controls	Non-progressors	Progressors
Scan 1	90.5 [74.6, 98.5]	90.8 [86.9; 99.5]	90.6 [82.4; 101.1]	0.51 [0.39, 0.59]	0.44 [0.36; 0.54]	0.40 [0.30; 0.46]
Scan 2	88.8 [85.8, 93.1]	73.7 [65.5; 79.3]	82.3 [71.2; 89.5]	0.42 [0.38, 0.49]	0.40 [0.32; 0.51]	0.64 [0.49; 0.84]
Scan 3	94.4 [86.1, 97.9]	82.4 [79.3; 88.7]	47.1 [37.3; 61.6]	0.41 [0.36, 0.50]	0.41 [0.34; 0.56]	0.95 [0.73; 1.22]

Table 4

Cause of death autopsy cohort

		Cause of Death	Autopsy Findings
1	BOS	Respiratory Failure	Polymicrobial pneumonia
2	BOS	Respiratory Failure	ARDS/NSCLC
3	BOS	Respiratory Failure	Aspiration with acute and chronic pneumonitis
4	BOS	Respiratory Failure	Acute and chronic rejection - C-Diff
5	BOS	Respiratory Failure	Organizing pneumonia/DAD
6	BOS	Respiratory Failure	Pneumonia, acute and chronic rejection
7	BOS	Respiratory Failure	Pneumonia, PTLN
8	BOS	Respiratory Failure	Chronic graft rejection
9	BOS	Respiratory Failure	Pneumonia with acute rejection
10	BOS	Respiratory Failure	OB/chronic rejection
11	Control	Respiratory Failure	Viral Pneumonia, chronic rejection
12	Control	Respiratory Failure	Pneumonia
13	Control	Respiratory Failure	Severe necrotizing pneumonia
14	Control	Respiratory Failure	Severe necrotizing pneumonia, PTLN
15	Control	Respiratory Failure	Viral pneumonia, recurrent SCCA
16	Control	Respiratory Failure	Fungal pneumonia/sepsis
17	Control	Respiratory Failure	Necrotizing bacterial pneumonia

Table 5

Pathologic evaluation of proximal and distal airways and proximal and distal pulmonary arteries

	Proximal Airway Fibrosis	Distal Airway OB	Proximal arteriopathy	Distal arteriopathy
Control (n=7)	1 (16.67%)	2 (33.3%)	2 (33.3%)	1 (16.7%)
BOS (n=10)	8 (100%)*	7 (87.5%)	5 (71.4%)	5 (71.4%)

*
P<0.05