



Utilization of Quantitative Computed Tomography Assessment to Identify Bronchiolitis Obliterans Syndrome After Single Lung Transplantation

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Abstract

Objective To evaluate quantitative chest computed tomography (CT) methods for the detection of air trapping (AT) and to assess its diagnostic performance for the diagnosis of bronchiolitis obliterans syndrome (BOS) in single lung transplant (SLT) patients.

Methods Adult patients who had a SLT at a single transplant center and underwent CT scan after transplantation were retrospectively included. CT findings of air trapping were measured by three different methods: expiratory air-trapping index (ATI_{exp}), mean lung density on expiratory acquisition (MLD_{exp}) and expiratory to inspiratory ratio of mean lung density (*E/I*-ratio(MLD)). Sensitivity, specificity and diagnostic accuracy of the three methods for the detection of BOS status evaluated by serial routine measures of pulmonary function tests (gold standard) were assessed.

Results Forty-six SLT patients (52.2% females, mean age 58 ± 6 years) were included in the analysis, 12 (26%) patients with a diagnosis of BOS. Quantitative CT diagnosis of AT ranged from 26 to 35%. Sensitivity, specificity and accuracy of each method for the detection of BOS were 85.7%, 84.7% and 85.0% for ATI_{exp}, 78.5%, 93.4% and 90.0% for MLD and 64.2%, 89.1% and 83.3% *E/I*-ratio(MLD), respectively.

Conclusion Quantitative measures of AT obtained from standard CT are feasible and show high specificity and accuracy for the detection of BOS in SLT patients.

Keywords Computed tomography · Bronchiolitis obliterans syndrome · Single lung transplant · Air trapping

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Introduction

Long-term survival after lung transplantation (LT) is often hampered by chronic lung allograft dysfunction (CLAD), which is believed to reflect chronic rejection [1, 2]. CLAD, a term used to refer to all variants of pulmonary chronic dysfunction, affects up to 50% of lung transplant recipients within five years after surgery [3], and bronchiolitis obliterans syndrome (BOS) is the most common manifestation of CLAD [2]. Proposed by the Committee of the International Society for Heart and Lung Transplantation (ISHLT), the term BOS is a clinical description of bronchiolitis obliterans (BO), a histopathologic entity characterized by a fibroproliferative process of the small airways with multifocal obliteration of the terminal bronchiole [4]. Diagnostic criteria for BOS includes a persistent postoperative decline of the forced expiratory flow in one second (FEV1) by at least 20% in comparison to baseline for a minimum of 3 weeks. This decrease must not be explained by acute rejection, infection or other complications [3, 5, 6]. Transbronchial biopsy is frequently performed to detect infection or other entities that may be the cause of functional decline but it is rarely used to diagnose BO because of its low sensitivity [7]. In single lung transplant (SLT) patients, the interpretation of the decline of FEV1 for the diagnosis of BO is further confounded by the presence of a diseased native lung. [8].

Bilateral lung transplant has been favored in comparison to SLT because of perceived benefits in long-term survival and improvements in functional outcomes [9]. However, there has been a long-standing debate over the theme and considering all variables that occur in transplant practice, including disease indication, age of recipient, donor lung quality and organ scarcity, many centers around the world opt for SLT in a considerable number of patients [8, 10, 11]. Nonetheless, studies with this population have shown a tendency toward early onset of BOS when compared to patients with double lung transplant (DLT) [10–13]. Unlike DLT patients, SLT patients still have a diseased native lung, and its deterioration over time may render the correct interpretation of changes in recipient's FEV1 values challenging. Therefore, identification of other tools to assess for BOS in addition to PFTs would be highly desirable.

Computed tomography (CT) is commonly used in post-lung transplant patients in association with pulmonary function tests to detect and monitor complications. Findings frequently seen in patients with BOS include bronchiectasis, bronchial wall thickening, mucus plugging and AT [14]. Air trapping, an established parameter to assess small airways disease [15, 16] is defined as less than normal increase in the attenuation of the lung parenchyma

during expiration with lack of volume reduction [17]. In LT patients, the presence of AT on expiratory CT scans was postulated as an important sign of early chronic lung rejection [18–21]. Different CT measurements have been developed to assess post-lung transplant diagnosis of BOS [18–21], mainly in DLT, but no consensus yet has been reached on which method should be used.

The objectives of this study were to evaluate the presence of air trapping on chest CT using different quantitative methods, namely expiratory air-trapping index (ATI_{exp}), mean lung density (MLD) on expiratory acquisition and expiratory to inspiratory ratio of mean lung density (*E/I*-ratio(MLD)), and to assess the diagnostic performance of these quantitative methods for the diagnosis of BOS in SLT patients.

Materials and Methods

Patients

This institutional review board approved retrospective study was performed in SLT recipients from a single medical center with a mean of 40 lung transplants per year. All individuals older than 18 years of age who had undergone unilateral cadaveric lung transplantation between January 2012 and December 2018 and who underwent a CT scan at any time after transplantation were included. A CT scan is not routinely performed in asymptomatic patients at our lung transplant center, only when a surgical or clinical complication is suspected, or when an unexplained reduction in lung function occurs, including when BOS is suspected clinically or is under evaluation. Pulmonary function tests (PFT) are regularly performed during the routine postoperative visits. The presence of BOS and the BOS stages were classified according to the guidelines of the International Society for Heart and Lung Transplantation [5].

In order to avoid transitory postoperative CT findings and to allow a minimum of 4 spirometric tests performed, only outpatients CTs performed after the first 60 days post transplant were included. Patients with CT findings of lung infection, acute rejection, thoracic malignancy, previous lung surgery other than LT, bronchial narrowing or other reasons for a reduced FEV1, were excluded. In addition, patients with a restrictive pattern in lung function tests were also excluded (thus excluding restrictive CLAD). The maximum time interval allowed between PFT and CT was 30 days.

CT Protocol

All subjects underwent a paired unenhanced inspiratory and expiratory helical chest CT with 16 × 1.25 mm collimation (LightSpeed 16 Slice Pro, General Electric Healthcare Technologies, Waukesha, WI, USA). Scans were acquired

in a caudocranial direction using the following parameters: tube voltage, 120 kV; a fixed tube current for inspiratory image, 200 mAs; a fixed tube current for expiratory images, 50 mAs; pitch, 1.375. Images were reconstructed in axial, sagittal and coronal planes with a standard reconstruction kernel, data matrix of 512×512 , a field of view of 35–45 cm and a slice thickness and interval of 1.0 mm to achieve near-isotropic voxels.

Imaging Analysis

All examinations were analyzed in a commercially available workstation (Advantage Workstation 4.6, General Electric Healthcare Technologies, Waukesha, WI, USA). Inspiratory and expiratory CT images were evaluated using dedicated software designed for the assessment of segmented images from the chest wall, mediastinum, diaphragm, and airways. Automated segmentation of the transplanted lung from the chest wall and mediastinum was performed and the total lung volume and attenuation of all voxels included in the lung segmentation were quantified. The expiratory air-trapping index (ATI_{exp}) was calculated as the percentage of lung voxels with attenuation of -950 to -856 HU on expiratory CT images [15] (Fig. 1). Mean lung density (MLD) histograms were created for expiratory and inspiratory acquisitions for each subject, and the expiration and inspiration ratio of MLD (E/I -ratio(MLD)) was calculated [22, 23].

Measurements were performed by 2 thoracic radiologists in consensus, with a minimum of 10 years of experience, blinded to all clinical information. Analysis of all measurements required approximately five minutes per patient.

Pulmonary Function Tests

All PFTs were performed with a MasterScreen IOS device (Viasys Health Care Global, Loma Linda, CA, USA), at the same location and by a team of technicians trained in pulmonary function testing and in accordance with the Brazilian Thoracic Association criteria and the American Thoracic Society criteria [24, 25]. Reference values were derived for the Brazilian population [26].

Statistical Analysis

Data were presented as mean \pm standard deviation (SD), median or interquartile range or frequency and percentage. Using spirometric diagnosis of BOS as the gold standard, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for each of the quantitative CT findings: mean lung density expiration, expiration and inspiration ratio of MLD and expiratory air trapping index. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic capabilities of the quantitative CT findings in patients with

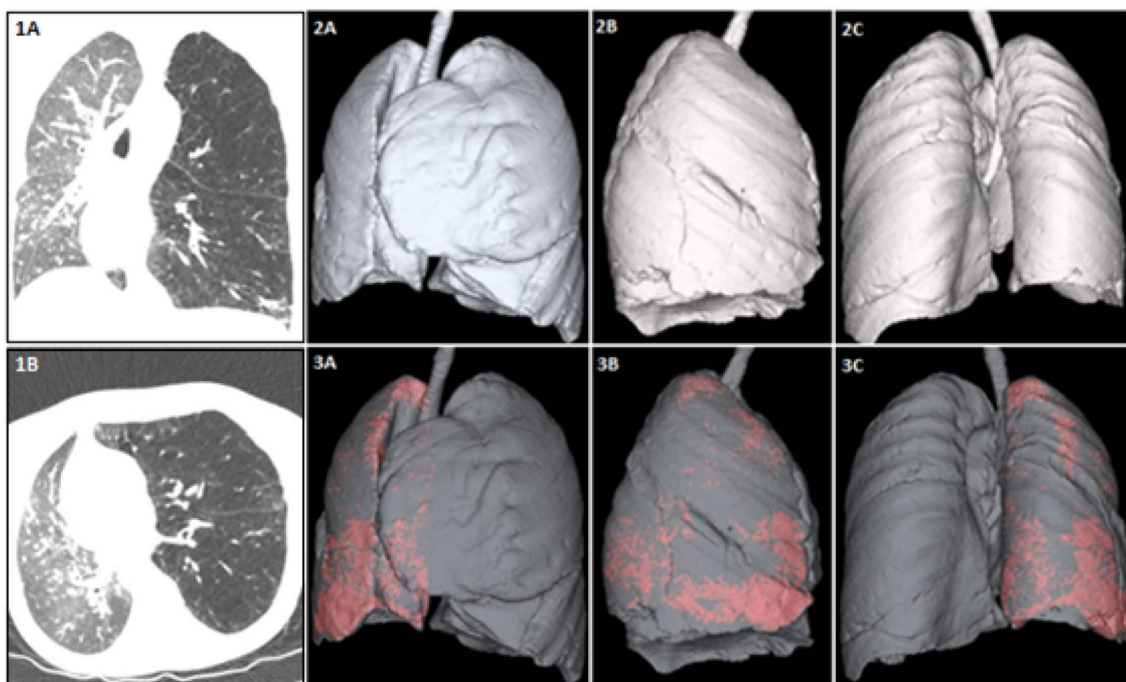


Fig. 1 Coronal (**1A**) and axial (**1B**) slices of expiratory high resolution CT scan of the chest from a single lung transplant patient with BOS. Images **2A**, **2B** e **2C** show the 3D-CT reconstruction of the lungs and images **3A**, **3B** e **3C** show the same 3D-CT reconstruction

highlighting areas of air trapping in the transplanted lung only (red color), represented by lung voxels with attenuation of -950 to -856 HU

BOS. In all cases, P values less than 0.05 were considered to be statistically significant. Statistical analyses were performed using the STATA v.15 (StataCorp, College Station, TX, USA).

Results

In total, 46 SLT patients were identified (mean age 58 ± 6 years; 24 females, 52.2%) and 12 patients fulfilled spirometric criteria for BOS. Sixty CTs were included in the study, 14 from patients with BOS. The average time between the diagnosis and CT scan was 7 months for those with BOS grade I, 14 months for those with BOS grade II and 38 months for patients with BOS grade III. Baseline

Table 1 Demographic and quantitative CT characteristics

Parameter	<i>n</i> = 46
Female	24 (52.2)
Age, years	58 ± 6
Diagnosis	
Pulmonary fibrosis	30 (65.2)
COPD	13 (28.3)
Lymphangiomyomatosis	2 (4.3)
Silicosis	1 (2.2)
Left side, LTx	23 (50.0)
Average elapsed time between the first available scan and the diagnosis of BOS, months	48 ± 32
BOS	12 (100)
I	4 (33.3)
II	5 (41.7)
III	3 (25.0)
Quantitative CT measurements	
Mean MLDEXP, HU	-666.1 ± 88.5
ATIexp	0.02 [0.01–0.11]
E/I-ratio	0.82 [0.75–0.92]

Data were presented as No (%), mean \pm SD or median [IQR]

COPD chronic obstructive pulmonary disease, BOS bronchiolitis obliterans syndrome, CT computed tomography, MLDEXP mean lung density expiration, MLD_{insp} mean lung density inspiration, ATI_{exp} air trapping index expiratory, ATI_{insp} air trapping index inspiratory, E/I-ratio expiratory per inspiratory ratio, LTx lung transplantation

Table 2 Diagnostic capability of the quantitative CT findings

Parameter	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
MLDEXP, HU	- 737	78.5	93.4	78.5	93.4	90.0
ATIexp	0.06	85.7	84.7	63.1	95.1	85.0
E/I-ratio(MLD)	0.93	64.2	89.1	64.2	89.1	83.3

PPV positive predictive value, NPV negative predictive value, CT computed tomography, MLDEXP mean lung density expiration, ATI_{exp} air trapping index expiratory, E/I-ratio(MLD) expiratory per inspiratory ratio of mean lung density

characteristics of the study subjects are shown in Table 1. The most common pre-transplant diseases requiring SLT were pulmonary fibrosis and COPD and left SLT was more common than right SLT. The mean time of BOS diagnosis after transplantation was $48 (\pm 32)$ months. From the 134 CTs available during the study period, 74 were excluded due to the following reasons: fungal or bacterial infection ($n = 38$), bronchial stenosis ($n = 9$), CT with lack of an expiratory scan ($n = 9$), acute rejection ($n = 8$), lung function test with restrictive pattern ($n = 4$), thoracic tumor ($n = 2$), pneumothorax ($n = 2$) and inability to perform the quantitative analysis due to severe motion artifacts ($n = 2$).

After applying the Operating Characteristic Curve (ROC curve), best threshold for each method were found and the prevalence of air trapping based on MLDEXP was 26% (95% CI 13–40), based on ATI_{exp} was 35% (95% CI 21–50) and based on E/I-ratio(MLD) was 28% (95% CI 15–42). All the measurements demonstrated a good diagnostic performance for diagnosing BOS, with an accuracy above of 83% (Table 2). Using the density of - 737 HU as a cut-off, the sensitivity and specificity of MLDEXP for predicting BOS was 78.5% and 93.4%, respectively. With a threshold index of 0.06, the ATI_{exp} showed a sensitivity of 85.7% and a specificity of 84.7%. The third measure, E/I-ratio(MLD) demonstrated a sensitivity of 64.2% and a specificity of 89.1% for a threshold ratio of 0.93. All three methods demonstrated a high area under the ROC curve for the diagnosis of BOS (Fig. 2). There were cases in which the CT parameters were positive and clinical and spirometric follow up was negative for BOS, including 7 for ATI_{exp}, 5 for E/I ratio (MLD) and for 3 MLDEXP.

Discussion

Bronchiolitis obliterans syndrome is a well-recognized complication that significantly limits long-term survival after lung transplantation [27]. The diagnosis of BOS by definition is only established in retrospect, challenging early identification of the disease. In addition, concern has been raised regarding the use of spirometry as the main diagnostic criteria due to the variability in both the spirometry test performance by the patient and spirometry interpretation

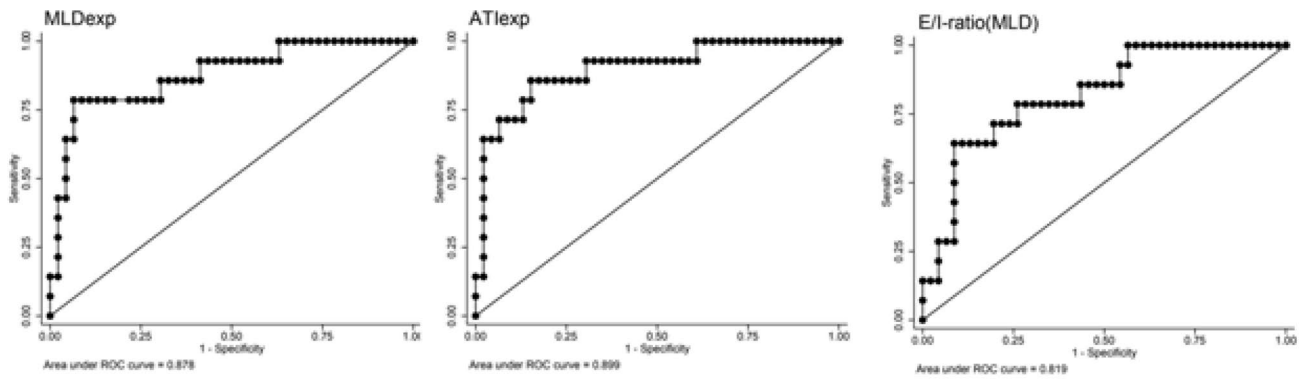


Fig. 2 Graphical representation of ROC curves for the three measurement methods

by the physician that may influence the diagnosis of BOS [28]. Additional tools to help improve the diagnosis of BOS would be, therefore, desirable. In the present study, we demonstrated that quantitative CT assessment of air trapping in single lung transplant patients is feasible and demonstrates high specificity and accuracy for the detection of BOS.

Air trapping is an accepted indirect sign of small airway remodeling and is present in different obstructive airway diseases, including chronic obstructive pulmonary disease [29] and asthma [15]. In post-lung transplant patients, BOS due to obliterative bronchiolitis is characterized by the presence of AT [30]. Previous studies have evaluated the detection of AT with CT in this population [19, 30–32], however, a standardized quantitative method has yet to be validated. We tested three automated and easy to perform quantitative CT parameters in a consecutive sample of SLT patients and demonstrated a high prevalence of AT in the transplanted lung, ranging from 26 to 35%.

All three CT parameters, MLDexp, ATlexp and *E/I*-ratio(MLD), were highly specific for the detection of BOS with excellent accuracy. Only a few studies have assessed quantitative AT parameters in patients post-LT, but none in SLT patients. Solyanik et al. [18] recently evaluated density mapping, a voxel-wise image measurement method based on registration of the inspiration and expiration CT datasets, *E/I*-ratio (MLD) and a threshold-based method in expiration, similar to our ATlexp, to assess the accuracy for detection and quantification of pathologic AT in DLT patients. All three methods showed a good correlation to the ratio of residual volume to total lung capacity obtained by body plethysmography, however density mapping and *E/I*-ratio (MLD) were more suitable to detect AT, with a higher accuracy. Dettmer et al. [3] used a longitudinal analysis to evaluate quantitative measurements of lung volume and lung density in bilateral lung transplant. The authors demonstrated that increase in lung volume and decrease in lung density when compared to prior CTs showed a marked correlation with BOS onset, suggesting a potential role for CT in

helping identifying patients with BOS at the first decrease in PFTs. Similarly to these investigations in DLT patients, our results add to the current knowledge that, in SLT patients, quantitative CT measurements of AT may also identify BOS with good accuracy.

Other methods for quantification of small airway disease have been evaluated more recently, including the ratio of expiratory and inspiratory MLD that can map the density of the whole lung and also allows regional assessment of the lung parenchyma [2, 18]. Parametric response mapping (PRM), a voxel-wise comparison of inspiratory and expiratory lung density seen on CT has also been tested for quantification of small airway disease in LT patients. The method showed value for monitoring the progression of BOS and for stratifying the risk of patient death in these patients [2, 33]. Verleden et al. used PRM to evaluate serial measurements from a stable to a diseased state (BOS) in the same patients and compared it to a control group. The authors found that functional small airways disease (corresponding to AT measures) increases at the time of BOS diagnoses and beyond [2]. We were unable to obtain serial measurements, nonetheless the quantitative methods we used indeed showed increased air trapping in patients with BOS. Although PRM may add important additional information, it is time-consuming and requires dedicated software analysis and a careful registration of the lungs. In addition, inadequate or variable inspiratory and expiratory efforts, the use of different CT scanners and settings may introduce important variability when using PRM for quantification of AT. All methods tested in the present study for the detection of AT and BOS are based on standard CT density measurements and are simple to perform.

In clinical practice, it is often not possible to differentiate between BOS and other etiologies at the time point of first decrease in lung function [3], a scenario even more challenging post-SLT, given the presence of one native diseased lung. The use of quantitative methods targeting the transplanted lung only, therefore, could allow more precise

identification of BOS and lead to early management. In addition, although all three parameters tested showed good diagnostic performance in isolation, perhaps a combination of them could offer a better strategy to identify different forms of CLAD, integrating both lung volume and density parameters. This hypothesis, however, needs to be tested in a larger sample of LT patients.

The present study has limitations, including the retrospective design and the small sample size from a single transplant center. The diagnostic performance of the quantitative CT parameters to detect BOS was tested against the results of PFTs. Pulmonary function tests have known shortcomings, particularly intraindividual and interrater variability, however, it is the basis of the current strategy used for diagnosing BOS. In addition, CT studies that were not suitable for quantitative analysis were excluded. Nonetheless, studies with minor breathing artifacts or suboptimal inspiratory or expiratory efforts, findings that are relatively common in clinical practice, were allowed.

Conclusion

We demonstrated the feasibility of three quantitative parameters to detect AT in SLT patients obtained from standard non-contrast-enhanced CT studies. In addition, when compared to the current diagnostic criteria based on pulmonary function tests, all three parameters showed a high specificity and overall accuracy for the detection of BOS in this specific population. The addition of these easy to perform parameters to the diagnostic strategy for the detection of chronic lung allograft dysfunction may improve early diagnosis of BOS in single lung transplant patients and deserves further investigation.

Compliance with Ethical Standards

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

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