



Differences of airway dimensions between patients with and without bronchiolitis obliterans syndrome after lung transplantation—Computer-assisted quantification of computed tomography



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ABSTRACT

Background: The aim of our retrospective study was to determine whether a dedicated software for assessment of airway morphology can detect differences in airway dimensions between patients with and without bronchiolitis obliterans syndrome (BOS), regarded as the clinical correlate of chronic lung allograft rejection.

Methods: 12 patients with and 14 patients without diagnosis of BOS were enrolled in the study. Evaluation of bronchial wall area percentage (WA%) and bronchial wall thickness (WT) in all follow-up CT scans was performed using a semiautomatic airway assessment tool. We assessed temporal changes (Δ WA%, Δ WT) and compared these morphological parameters with forced expiratory volume in one second (Δ FEV1).

Results: In patients with and without BOS, the temporal changes over the entire follow-up were 26.6%

versus 16.2% for Δ FEV1 ($p=0.034$), 14.2% versus 5.4% for Δ WA% ($p=0.003$) and 0.212 mm versus

0.064 mm for Δ WT ($p=0.011$).

Conclusions: We detected significant differences of the temporal changes of airway dimensions (Δ WA%, Δ WT) between lung transplant recipients with and without BOS. We conclude that computer-assisted bronchial wall measurements in CT scans might complement the information from pulmonary function tests and establish as a non-invasive method to confirm BOS in lung transplant recipients in the future.

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Abbreviations: BO, bronchiolitis obliterans; Dia, total bronchial diameter; DLTX, double-lung transplantation; FWHM, full-width-at-half-maximum-principle; ISHLT, International Society of Heart and Lung Transplantation; LTX, lung transplantation; SLTX, single-lung transplantation; WA%, bronchial wall area percentage; WT, bronchial wall thickness; YACTA, yet another CT analyzer; Δ Dia, temporal change of total bronchial diameter; Δ FEV1, temporal change of; Δ WA%, temporal change of bronchial wall area percentage; Δ WT, temporal change of bronchial wall thickness.

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1. Introduction

Regardless of improved immunosuppression, lung transplantation still has the highest rates of acute and chronic allograft rejection among all commonly transplanted solid organs [1]. Even though short-term survival rates have improved in recent years, chronic allograft rejection remains the most frequent reason for long-term hospitalization and death after lung transplantation [2]. Bronchiolitis Obliterans Syndrome (BOS) is regarded as the clinical correlate of chronic lung allograft rejection. About 60% of all patients develop BOS within five years after lung transplantation [3]. Clinical diagnosis of BOS is based on pulmonary function tests showing a drop of the forced expiratory volume in one second (FEV1) below an averaged baseline [4]. Histologically, chronic allograft rejection – sometimes referred to as lymphocytic bronchiolitis or bronchiolitis obliterans (BO) – can be confirmed by trans-bronchial biopsy. Histologic proof can be helpful but is not regarded as diagnostic gold standard [5], as biopsy can show falsely negative results due to patchy distribution of changes or can even be positive without apparent clinical symptoms [6,7]. As chest radiographs are frequently normal or only reveal unspecific changes, in this situation, CT is considered the imaging modality of choice as it can provide important additional information for the final diagnosis. The most important CT findings seen in lung transplant recipients with BOS are bronchial dilatation and bronchial wall thickening [8]. Nevertheless, bronchial wall thickening is an unspecific finding that can be detected in many different obstructive pulmonary diseases such as COPD, bronchial asthma, bronchitis, cystic fibrosis and bronchiolitis obliterans [9].

Most investigators reporting morphologic changes in CT images of patients with chronic rejection merely gave subjective descriptions of airway changes and concluded that CT changes alone do not allow for adequate differentiation between rejection and other pulmonary complications (e.g. infections) [10,11]. In summary, early diagnosis of chronic lung allograft rejection is important to initiate adequate treatment but is hampered by low specificity of changes detected by computed tomography (CT).

A more objective approach to airway assessment has emerged during the last few years but is still predominantly used for scientific purposes. Different techniques for quantitative bronchial wall measurements in CT scans have been described [12–14] and evaluated in different conditions including patients with chronic obstructive pulmonary disease (COPD) and tobacco smokers without clinical symptoms [15–17]. Historically, the first widely used method for quantitative bronchial wall measurements was the *full-width-at-half-maximum-principle* (FWHM) as described by Nakano et al. in Ref. [13]. Previous studies showed that FWHM is vulnerable to the so-called *blurring effect* of CT, which hampers size and density measurement of very small objects and leads to an overestimation of bronchial wall thickness (WT) for small airways [18–21]. A dedicated airway morphometry software (*YACTA module v.1.0.7.16*) allows for a more accurate airway wall assessment by applying an innovative algorithm minimizing the error introduced by the *blurring effect*. Like most FWHM-based tools, assessment of airway parameters with *YACTA module* is based on the ray-casting method, where a defined number of gray-level profiles across the bronchial wall are generated from a voxel in the middle of the bronchial lumen. In contrast to FWHM, these gray-level profiles are processed by an integral-based method which is based on integration of a density profile of Hounsfield units across the bronchus wall. Validation studies showed effective reduction of the blurring effect [19,20]. Previous studies showed that bronchial wall measurements correlate well with pulmonary function tests in patients with COPD [20,22], but to date, there are very few publications objectively quantifying airway changes in lung transplant recipients with BOS.

The aim of our retrospective study was to determine whether a dedicated software for the assessment of airway morphology can detect differences in airway dimensions between patients with and without bronchiolitis obliterans syndrome (BOS).

2. Material and methods

All 42 patients who underwent single or double lung transplantation in our institution within a period of six years were evaluated for inclusion in the retrospective study. All patients who ever showed an episode of acute rejection were excluded from further analysis as post-inflammatory changes due to an episode of acute rejection may mimic chronic rejection. Standard follow-up of the remaining 26 patients included history, physical examination and frequent pulmonary function tests (PFT). We recorded all PFTs (>1000, 27–80 per patient) and evaluated all CT scans (438, 4–17 per patient) of the study group over a time span of nearly eleven years. Chronic rejection, respectively BOS as its clinical correlate, was diagnosed according to the guidelines of the International Society of Heart and Lung Transplantation (ISHLT) [4]. According to these guidelines, diagnosis of BOS was based on a drop of FEV1 below a baseline of averaged post-transplant values. A drop of FEV1 regularly led to further diagnostic workup with CT. Other indications for CT were clinical symptoms such as cough, fever and dyspnea.

CT scans were performed either in a *high-resolution computed tomography* (HRCT) with a slice thickness of 1 mm and axial interscan gaps of 10 mm or, following the introduction of *multi-detector CT* (MDCT) scanners, continuous whole-lung MDCT scans with 1 mm slice thickness were acquired. All CT scans were performed in full inspiratory breath hold, using a standard reconstruction kernel and without application of intravenous contrast agent. As we evaluated data over a time span of 11 years of post-transplant follow-up, CT scans performed with differing scanner settings were processed. Nevertheless, *YACTA* module uses an automatic correction of the reconstruction kernel, reducing the influence of the scanning protocol [19]. No patient showed signs of infection on the day of the examination.

Morphometry with *YACTA module v.1.0.7.16* was performed in all follow-up CT scans in the patient population, starting with the first post-transplant examination. Bronchial wall measurements in CT scans were performed semiautomatically by manually choosing five orthogonally depicted airways (excluding the trachea and main stem bronchi) per lung, followed by assessment with *YACTA module* in a two-dimensional approach on a reconstructed axial CT slice. Of the five measuring points per unilateral lung, at least one point had to be located in every lobe. Special care was taken for the identification of bronchi that could be reproduced in all follow-up CT examinations and had none or only minimal contact to adjacent vessels (<15% of the circumference of the bronchial wall). Areas not appropriate for bronchial wall measurements as described in [9] (such as branching points of the bronchi and locations with dense structures adjacent to the bronchus) were excluded from evaluation. Whenever a bronchus was not detectable in one of the follow-up CT scans, another bronchus was chosen and re-evaluated in the prior studies or, if this was not possible, this bronchus was not used for further analysis. A total of 2190 airway cross sections were analyzed in 438 CT scans. Morphometry was performed by two different independent readers that were blinded to the diagnosis of BOS. Not every CT scan was analyzed by both readers, but 14 randomly chosen CT scans (112 measurement points in 7 HRCT scans and 7 MDCT scans) of 12 different patients (7 male, 5 female) were analyzed by both readers. Interobserver agreement was analyzed by using Spearman's rho. Duration of the semiautomated image processing was not recorded. The evaluation of an average case (five measuring points per unilateral lung) took approximately

Table 1

Temporal changes of FEV1 ($\Delta\text{FEV}1$) and of the morphological airway wall parameters (bronchial wall area percentage ($\Delta\text{WA}\%$), bronchial wall thickness (ΔWT)) showed significant differences between patients with and without BOS.

	without BOS (n = 20)			with BOS (n = 22)			p
	Range	Median	Interquartile Range	Range	Median	Interquartile Range	
$\Delta\text{FEV}1$ [%] (Fig. 1)	1.6–32.3	16.2	19.9	6.2–59.7	26.6	41.8	0.034
$\Delta\text{WA}\%$ [%] (Fig. 2)	0.79–28.78	5.4	10.1	0.57–34.06	14.2	12.0	0.003
ΔWT [mm] (Fig. 3)	0.21–0.71	0.064	0.09	0.06–0.95	0.212	0.21	0.011

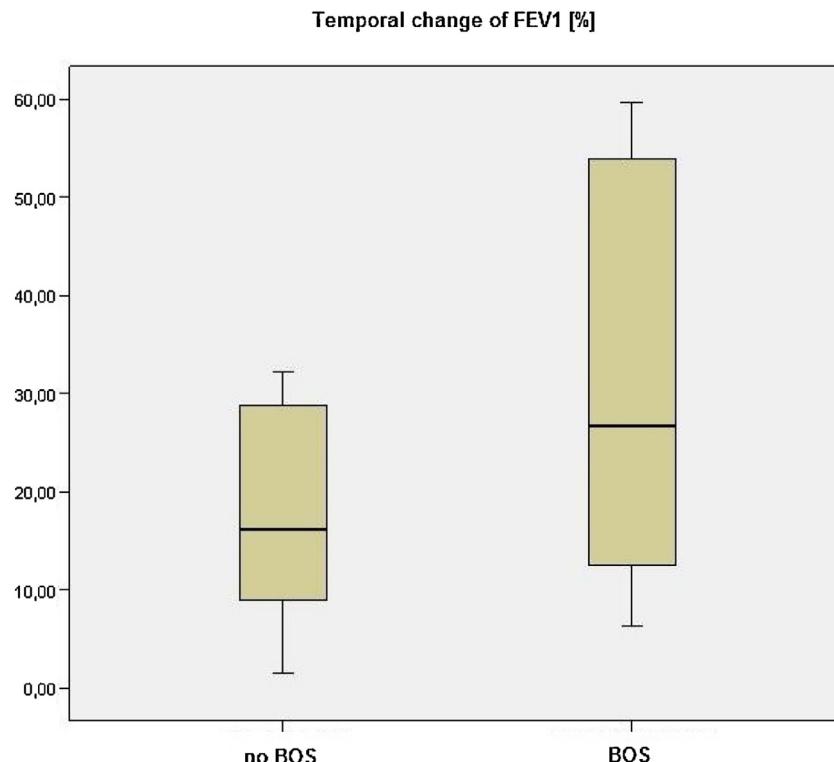


Fig. 1. Box-plot diagram demonstrating temporal changes of forced expiratory volume in one second ($\Delta\text{FEV}1$) in patients with and without BOS.

15–20 min, half of the time manual interaction and half of the time computing. The following morphological parameters were evaluated: (1) minimum/maximum wall area percentage (WA%). The wall area percentage represents the ratio of the airway wall area and the whole airway area (bronchial wall and bronchial lumen) on a single image slice. (2) minimum/maximum wall thickness (WT). The airway wall thickness was calculated as a median of all 256 gray-level profiles. Additionally, ten percent of the extreme values were excluded before calculation of the average wall thickness in millimeters to reduce the influence of outliers. Afterwards, the all-time lowest values of FEV1, WA% and WT was subtracted from the highest values of FEV1, WA% and WT to calculate the variability or temporal changes of these parameters ($\Delta\text{FEV}1$, $\Delta\text{WA}\%$, ΔWT) for each patient.

We expected $\Delta\text{WA}\%$ and ΔWT to be significantly different in patients with and without BOS. The level of significance for the testing of our thesis was fixed at $\alpha = 5\%$. Statistical analysis (Mann-Whitney U test) was performed using SPSS 17 software (SPSS Inc., Chicago, IL, USA). Subsequent statistical analysis of interobserver agreement (Spearman's rho, Bland-Altman plot) was performed using MedCalc 16.2.1 software (MedCalc Software bvba, Ostend, Belgium).

Due to the fact that this is an anonymized retrospective study, on behalf of the Institutional Review Board no ethics approval or written informed consent was needed.

3. Results

26 patients (13 female, 13 male) who received 42 unilateral lungs as lung transplants (12 single-lung transplantations (SLTX), 15 double-lung transplantations (DLTX) including 2 retransplantations) in our institution were enrolled in the study. The patients had a mean age of 43 years at the time of transplantation (without BOS 47.4, with BOS 39.0 years). Indications for lung transplantation were end stages of different diseases (10 lung emphysema of different causes, 6 cystic fibrosis, 4 idiopathic pulmonary fibrosis, 4 primary pulmonary hypertension, 1 sarcoidosis, 1 lymphangiomyomatosis).

Median of $\Delta\text{WA}\%$ was 5.4% (interquartile range 10.1%) without BOS and 14.2% (IQR 12.0%) with BOS. Median of ΔWT was 0.064 mm (IQR 0.09 mm) without BOS and 0.212 mm (IQR 0.21 mm) with BOS. Median of $\Delta\text{FEV}1$ was 16.2% (IQR 19.9%) without BOS and 26.6% (IQR 41.8%) with BOS. Differences between the tested groups are significant for $\Delta\text{FEV}1$, $\Delta\text{WA}\%$ and ΔWT . Difference was high with $p = 0.034$ for $\Delta\text{FEV}1$, $p = 0.003$ for $\Delta\text{WA}\%$ and $p = 0.011$ for ΔWT . Thus, the group of patients with BOS showed a 10.4% lower $\Delta\text{FEV}1$ than patients without BOS in their history. For patients with BOS, the $\Delta\text{WA}\%$ was 8.8% higher compared to patients without BOS and ΔWT was 0.148 mm higher. All results and p values are presented in Table 1 and Figs. 1–3.

Interobserver agreement in the assessment of the bronchial wall was excellent with Spearman's $\rho = 0.987$.

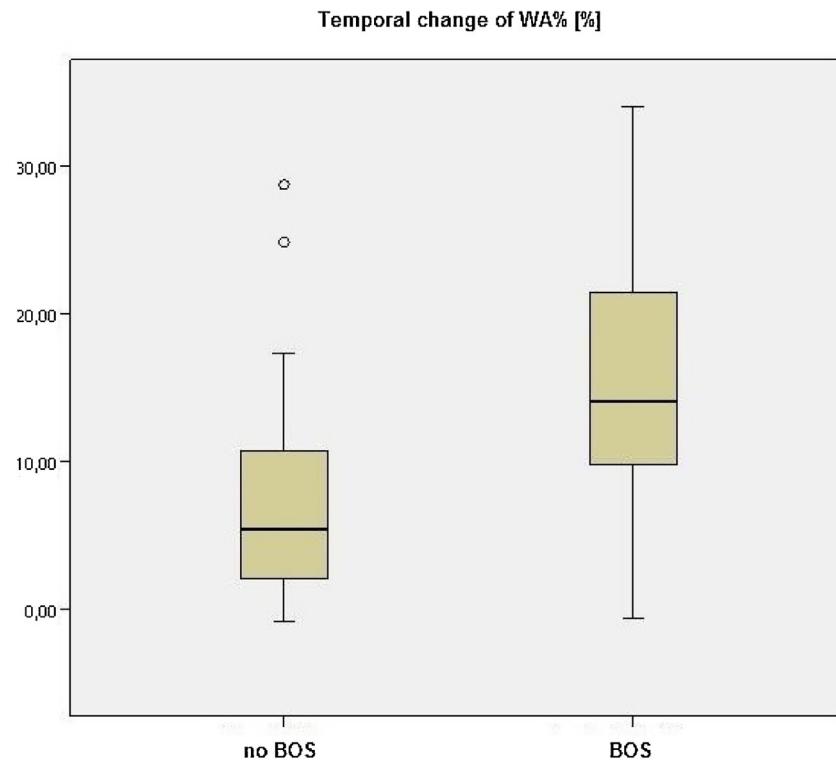


Fig. 2. Box-plot diagram demonstrating temporal changes of bronchial wall area percentage ($\Delta WA\%$) in patients with and without BOS (small circles represent outliers).

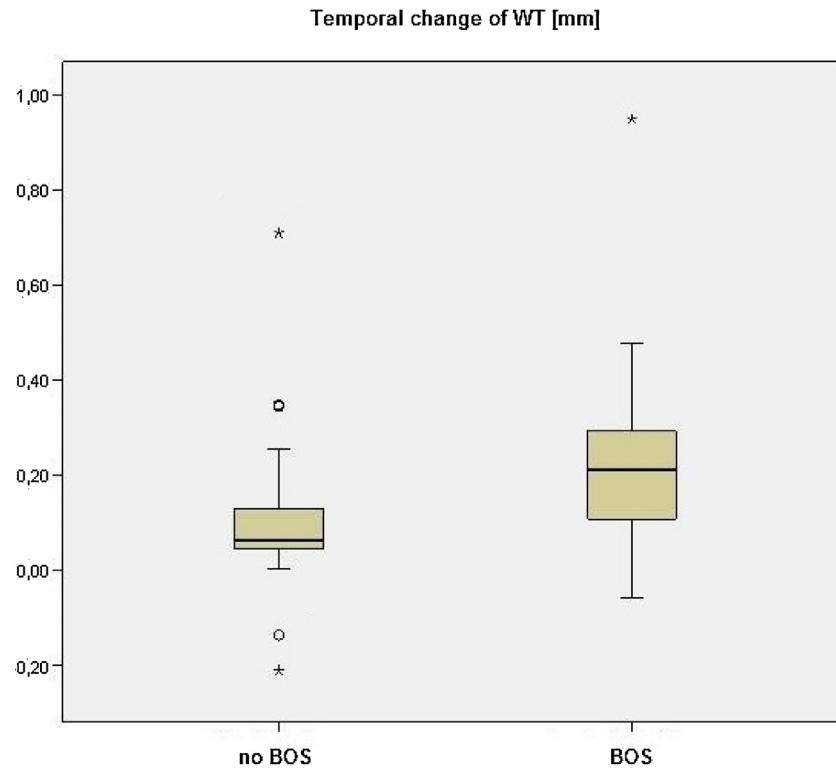


Fig. 3. Box-plot diagram demonstrating temporal changes of bronchial wall thickness (ΔWT) in patients with and without BOS (small circles and asterisks represent outliers).

(CI = 0.977–0.992, $p < 0.0001$) and a mean difference of 0.003 mm (CI = −0.0017–0.0077 mm) between both readers in Bland-Altman plot. These results are presented with a scatterplot (Fig. 4) and a Bland-Altman plot (Fig. 5).

4. Discussion

Bankier et al. investigated a significant correlation between the extent of air trapping and the severity of BOS already 15 years ago. The authors performed visual evaluation of air trapping in

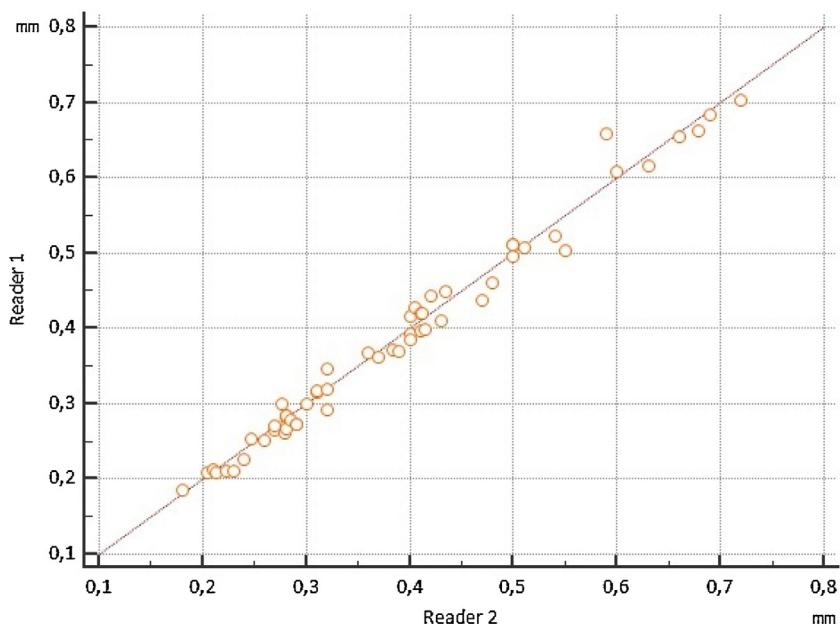


Fig. 4. Scatterplot of interobserver agreement analyzed with Spearman's rho. Spearman's coefficient of rank correlation rho is 0.987. The 95% confidence interval ranges from 0.977 to 0.992. The associated *p*-value is <0.0001 and the conclusion therefore is that there is excellent relationship between the two readers.

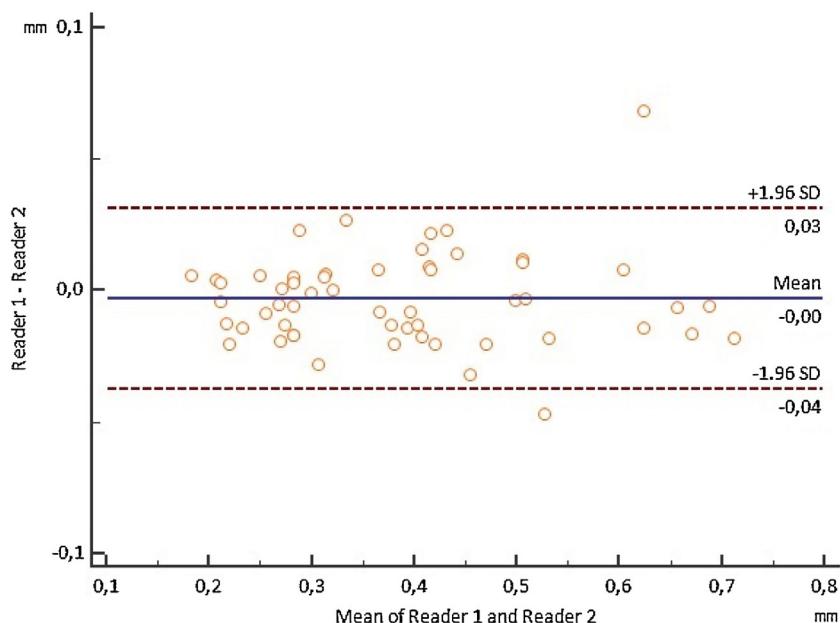


Fig. 5. Bland-Altman plot used to assess the repeatability of the measurements by two different readers. The differences between both readers are plotted against the averages of both readers. Mean difference between both readers is 0.003 mm of the measured value. The 95% confidence interval ranges from −0.0017 mm to 0.0077 mm.

expiratory CT scans and were able to show, that “at a threshold of 32%, air trapping is sensitive, specific and accurate for diagnosing BOS” [23]. Beside air trapping, airway changes are considered as the most sensitive marker for BOS [24]. Air trapping is caused by (inflammatory) small airway disease resulting in pulmonary obstruction, but to date, only few studies have used computer-assisted bronchial wall measurements in CT scans to investigate airway changes in lung transplant recipients. The aim of this study was to apply quantitative assessment of bronchial wall morphology, using a dedicated software tool, for the assessment of chronic lung transplant rejection.

Our data clearly show that bronchial wall thickening and luminal dilatation – the most common imaging findings in lung

transplant allograft rejection – can be detected and quantified using computer-assisted airway morphometry. In our study, we used bronchial wall thickness (WT) and wall area percentage (WA%) as objectively assessable measurements of airway wall thickening. So far, these parameters have been used more widely in studies measuring airway dimensions in other obstructive pulmonary diseases, such as Asthma and COPD [15–17,20]. In this study, the temporal changes of morphological parameters Δ WA% and Δ WT showed significant differences between lung transplant recipients with and without diagnosis of BOS, as well as the most important clinical parameter Δ FEV1 did.

The lung transplant recipient with deteriorated pulmonary function still poses a diagnostic challenge to the pulmonologist. A

drop of pulmonary function within function tests and corresponding clinical symptoms is not specific for BOS and may also be seen in other complications, such as pneumonia, pleural effusion, or stenosis of bronchial anastomoses. These conditions have to be ruled out as they require different therapeutic interventions which can be done by CT. The fact that the morphological parameters investigated in this study ($\Delta WA\%$, ΔWT) showed excellent differentiation between patients with and without BOS, clearly shows the potential role of morphological follow-up with objective airway assessment in lung transplant recipients.

The technique of computer-assisted CT-based bronchial wall measurements was feasible and robust but required manual interaction. Some of the CT datasets included in the analysis were acquired using a HRCT technique with typical interscan gaps of 10 mm. This method was the gold standard before MDCT was introduced. Current software tools allow an automated measurement of airway dimensions [9,25–27], but due to discontinuously acquired HRCT scans we had to perform semiautomated instead of automated analysis with manual selection of every bronchial cross-section, ensuring optimal correlation with previous examinations, which was time-consuming but did not hamper measurement quality. Application of the completely automated three-dimensional approach of our software, which requires no manual interaction, was not possible due to the CT data but will enable a time-saving application in future studies. A true limitation of our study is the small number of 26 patients (=42 unilateral lung transplants) investigated; however, this is in the range of sample sizes investigated in other studies concerning rejection after lung transplantation [6,11,24].

In a recently published study, Dettmer et al. correlated airway wall measurements of 25 patients with and 116 patients without BOS with pulmonary function parameters [28]. Their study and our study share a number of similarities of which the most important is that their dedicated software uses a modified version of the integral-based algorithm introduced by Weinheimer et al. [19]. Furthermore, they also processed CT scans with a standard reconstruction kernel and without i.v. contrast because a sharp kernel and i.v. contrast can significantly increase WT [9,29]. The authors report that only WA% in inspiration differed significantly between both groups [28]. Significant correlations of WA% in expiration and WT with pulmonary function parameters were not registered [28]. Therefore, the authors concluded, that WA% is a highly variable parameter which is not suitable to differentiate between patients with and without BOS.

In contrast to our study, Dettmer et al. used a software to calculate lung volumes from CT data and performed a lung volume correction of the airway wall measurements, followed by an univariate analysis with covariates [28]. This is a reasonable approach in order to reduce the influence of varying depths of inspiration during CT. In our study we were not able to perform lung volume measurements from CT scans due to the relevant amount of HRCT scans. From our point of view, this is the most important drawback of our study in comparison to their study. Furthermore, the sample size of our study is smaller.

Carefully respecting the disadvantages of our study, we also see advantages of our study design in comparison with the recent publication of Dettmer et al. We calculated temporal changes of all parameters ($\Delta FEV1$, $\Delta WA\%$, ΔWT) – and they showed significant differences between patients with and without BOS after lung transplantation. WT and WA% are not only influenced by lung volume but also by age, sex and size of a patient. We are convinced that evaluation of the temporal changes of these parameters is more suitable in order to differentiate between patients with and without BOS, than a measurement on a single date is. Furthermore, we think it is beneficial not only include patients with double lung transplantations and to perform at least one measurement in every lobe

of the transplanted lung. Dettmer et al. utilized only the posterior basal segmental bronchus of the right lung and the apicoposterior bronchus of the left lung for measurements [28]. Due to the variable and inhomogeneous distribution of BO, our method seems to have a higher probability to examine a truly affected airway.

In conclusion, the results of our study let us see a chance in establishing quantitative assessment of airways in clinical routine in the future. Our results should be confirmed in a prospectively controlled study considering the advantages of both study designs.

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