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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 (ΔWA%, ΔWT) and compared these morphological parameters with forced expiratory volume in one second (ΔFEV1).
Results: In patients with and without BOS, the temporal changes over the entire follow-up were 26.6% versus 16.2% for ΔFEV1 ($p = 0.034$), 14.2% versus 5.4% for ΔWA% ($p = 0.003$) and 0.212 mm versus 0.064 mm for ΔWT ($p = 0.011$).
Conclusions: We detected significant differences of the temporal changes of airway dimensions (ΔWA%, ΔWT) 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.

Abbrevations: 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; ΔDia, temporal change of total bronchial diameter; ΔFEV1, temporal change of; ΔWA%, temporal change of bronchial wall area percentage; ΔWT, 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 transbronchial 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* technique (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