Detection of Chronic Allograft Dysfunction using Ventilation-Weighted Fourier Decomposition Lung MRI

Andreas Voskrebenzev[1,2], Lena Becker[1,2], Marcel Gutberlet[1,2], Christian Schönfeld[1,2], Julius Renne[1,2], Jan Hinrichs[1,2], Till Kaireit[1,2], Tobias Welte[2,3], Frank Wacker[1,2], Jens Gottlieb[2,3], and Jens Vogel-Claussen[1,2]

[1]*Institute of Diagnostic and Interventional Radiology, Medical School Hanover, Hanover, Germany,* [2]*German Centre for Lung Research, Hanover, Germany,* [3]*Department of Pneumology, Medical School Hanover, Hanover, Germany*

Target Audience: MR scientists and physicians interested in lung MRI and the assessment of regional pulmonary ventilation.

Purpose: Despite its benefits, mortality rates for lung transplantation are higher than those of any other solid-organ transplantation, reaching 50% at 5 years. Long-term survival is limited by a form of chronic allograft dysfunction known as bronchiolitis obliterans syndrome (BOS). BOS affects 40% of lung transplant recipients at 5 years and is the leading cause of death beyond the first year of transplantation [1]. Fourier Decomposition (FD) is a method to calculate ventilation-weighted images of the lung without the need of any contrast agent [2] and has been validated with single photon emission tomography [3]. The purpose of this cross-sectional study was to evaluate if ventilation-weighted FD-MRI can differentiate between BOS stages after lung transplantation.

Method: 66 subjects after double-lung transplantation were enrolled in the study (37 BOS 0, 9 BOS 0p, 20 BOS 1-3) after exclusion of patients with single lung transplants (n=9), with post-operative diaphragm paresis (n=3) and with lung infection (n=1). As a control group twelve healthy non-smoking volunteers were included. The MRI protocol consisted of three coronal (anterior, mid, posterior) slices of the lung. For FD, 200 images were acquired using a spoiled gradient echo sequence on a 1.5T scanner with FOV 500 x 500 mm², matrix size 128 x 96, slice thickness 15 mm, T_E / T_R: 0.67 ms / 3 ms, flip angle 8° over a period of one minute at a temporal resolution of 288 ms.

After a non-rigid image registration (ANTS [4]) of the dynamic series of images to a reference image in mid position between end-inspiration and end-expiration a low-pass filter was applied to generate a series of ventilation-weighted images. Fractional ventilation (FV) was calculated by averaging the signals of the end-inspiratory and end-expiratory images and using the following formula: $FV = (S_{Exp} - S_{Insp})/S_{Exp}$ [5]. Lungs were segmented manually, excluding the great central vessels.

The pathophysiology of BOS (bronchial wall fibrosis and inflammation leading to bronchial air trapping and obstruction) suggests that the statistical dispersion of ventilation will correlate with disease severity (Figure 1). Since the mean value of FV is a function of respiratory volume it is convenient to use a statistical measure, which is invariant at different respiratory volumes like the quartile coefficient of dispersion (QCD). The QCD was calculated for all slices and a slice volume weighted average value for each subject was obtained. Also the relative amount of voxels below different FV cutoff values was tested to assess disease severity. According to the Jarque-Bera test all samples were not normally distributed ($p<0.001$). Median is provided for each group with the 25% and 75% quartile. Kruskal-Wallis one-way analysis of variance was performed as omnibus test. Then a Mann-Whitney U-test was evaluated for the following group-pairs: Volunteers/ BOS 0; BOS 0/ BOS 0p; BOS 0/ BOS 1-3; BOS 0p/ BOS 1-3. According to Bonferroni the significance level of 0.05 was corrected to 0.0125. Voxel values of all subjects in one group were combined into one sample and used for kernel density estimation (KDE) [6] to evaluate the distribution of FV as a function of BOS stage. Mean and skewness of the estimated distributions are provided.

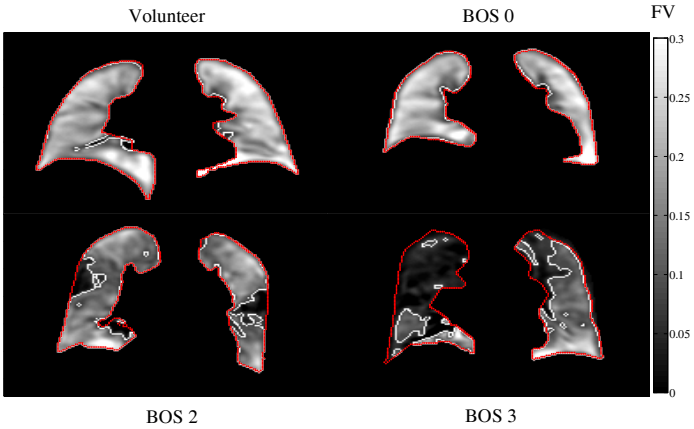
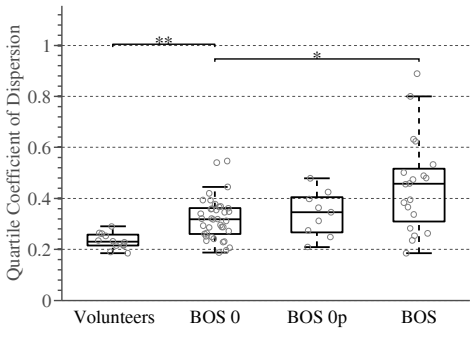


Figure 1 Fractional ventilation (FV) maps of a healthy volunteer and three patients after lung transplantation. Red line indicates the segmentation and white line shows the borders to areas below 0.075 FV. The relative amount of voxels below 0.075 is 3% for a volunteer, 4% for a BOS 0 patient, 17% for a BOS 2 patient and 57% for a BOS 3 patient.

Results: The QCD of FV increased according to the stage of disease: volunteers 0.23 (0.21-0.26), BOS 0 0.32 (0.26-0.36), BOS 0P 0.34 (0.27-0.40), BOS 1-3 0.45 (0.31-0.51), Kruskal-Wallis $p<0.001$. The Mann-Whitney U-test (Figure 2) showed significant differences of QCD between volunteers and BOS 0 ($p<0.0003$), BOS 0 and BOS 1-3 ($p<0.004$). While asymmetric distributions are found for the BOS 0, BOS 0P and BOS 1-3 samples (skewness of 0.70, 0.73 and 0.98) in the case of the volunteers a nearly symmetric distribution (skewness of 0.14) is observed. Lower mean values according to disease severity from 0.17 (volunteers) to 0.13 (BOS 0) and 0.10 (BOS 1-3) were present (Figure 3). The relative amount of voxels below 0.05 and 0.075 FV was increasing with disease severity (Kruskal-Wallis $p<0.001$, Figure 1).



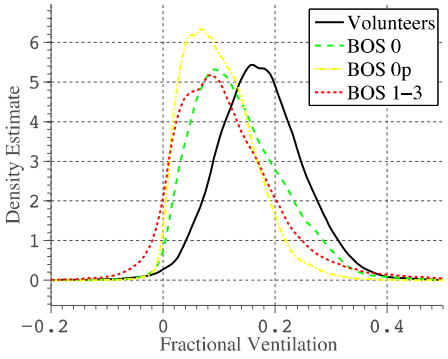


Figure 2 (left) Boxplot presentation of the quartile coefficient of dispersion for the four tested groups. There is an evident increase of median and dispersion towards BOS.
*= $p<0.004$, **=$p<0.0003$

Figure 3 (right) Density distributions of FV for different BOS stages. Notice the increased amount of voxels with FV below zero for BOS 1-3. Negative values can be caused by noise in not ventilated regions.

Discussion and Conclusion: The results confirm the initial hypothesis that a measure of dispersion is suited to differentiate between different BOS stages. Similar (not shown) results were obtained using threshold parameters. A limitation of this study is the partial coverage of the lung parenchyma and limited spacial resolution.

Conclusion: Ventilation-weighted FD images can be used to visualize areas of hypo-ventilation, assess regional ventilation heterogeneity and differentiate between BOS stages in patients after double lung transplantation.

References: [1] Christie, J. D. *et al.* (2008), *J Heart Lung Transplant* 27, 957-969; [2] Bauman, G. *et al.* (2009), *MRM* 62, 656-664; [3] Bauman, G. *et al.* (2011), *Radiology* 260, 551-559; [4] Avants, B. B. *et al.* (2011) *NeuroImage* 54, 2033-2044; [5] Zapke, M. *et al.* (2006), *Resp Research* 7, 106-114; [6] Paarzen E. (1962) Ann. Math. Stat. 33, 1065-1076

This work was supported by a grant from the German Federal Ministry of Education and Research (IFB-Tx, reference number: 01EO1302) and the German Centre for Lung Research (DZL).