Multi-Center Study for Clinical Stage Classification of Smoking-Related COPD: Oxygen-Enhanced MRI vs. Quantitatively Assessed MDCT

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Introduction: Chronic obstructive pulmonary disease (COPD) is currently the fourth-leading cause of mortality and the twelfth-leading cause of disability, and by the year 2020 it is expected to be the third-leading cause of death and the fifth-leading cause of disability worldwide (1, 2). The diagnosis of COPD largely relies on a history of exposure to noxious stimuli (mainly cigarette smoke) and abnormal lung function test results. In addition, it has been suggested that chest radiography, CT and nuclear medicine ventilation and/or perfusion studies are useful for the evaluation of morphological changes or regional pulmonary functional changes. Recently, oxygen-enhanced MR imaging (O_2-enhanced MRI) as well as hyperpolarized noble gas MR imaging have been proposed as useful procedures for assessment of regional morphological and functional changes in COPD and other pulmonary diseases (3-9). It has been reported that O_2-enhanced MRI could be used for the detection of regional ventilation and alveolocapillary gas transfer of molecular oxygen (3-9). However, the literature shows no publications dealing with prospective and direct comparison of the capability of quantitatively assessed thin-section CT using the density-masked CT technique (quantitative CT) and of O_2-enhanced MRI for smoking-related functional loss assessment and clinical stage classification of smoking-related COPD in a large prospective cohort, such as multi-center trials in various countries. We hypothesized that a multi-center trial could demonstrate that, in addition to quantitative CT, O_2-enhanced MRI may also be used for pulmonary functional loss assessment and clinical stage classification of smoking-related COPD. The purpose of the multi-center trial conducted for this purpose was to prospectively and directly compare the efficacy of O_2-enhanced MRI and quantitative CT for smoking-related pulmonary functional loss assessment and clinical stage classification of smoking-related COPD.

Materials and Methods: A total of 250 smokers (180 men and 70 women; age range: 40-85 years, mean age: 63 years) prospectively underwent pulmonary function test (FEV_1/FVC%, $\%FEV_1$ and $\%DL_{CO}/V_A$), 16-detector row CT and O_2-enhanced MR examinations. Lifetime smoking exposures of all subjects were also quantitatively assessed by using "pack years" (range: 8-250 pack years, mean: 61 pack years). The results of the pulmonary function test were used to select 160 smokers (120 men and 40 women; age range: 40-80 years, mean age: 62 years), who were then classified into the following four age- and gender-matched groups by using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline: 'Smokers without COPD (n=40)', 'Mild COPD (n=40)', 'Moderate COPD (n=40)', and 'Severe or Very Severe COPD (n=40)'. O_2-enhanced MR images were obtained with inhaled oxygen as the T1 contrast agent. The T1-weighted images were continually collected by means of a respiratory synchronized half-Fourier acquisition centrically-reordered inversion recovery single-shot turbo spin-echo (HASTE) pulse sequence and three 1.5 T scanners (Gyroscan Intera and Achieva; Philips Medical Systems, Best, The Netherlands). For a quantitative estimate of the CT-based functional lung volume (CT-based FLV), all MDCT data were transferred to a personal computer and analyzed by using proprietary software with the density-masked CT technique. To visualize the relative enhancement map of O_2-enhanced MR imaging, O_2-enhanced MR images were expressed as the percentage change between the oxygen-enhanced and baseline images by using commercially available software. The mean relative enhancement ratio (MRER) for every subject was determined as the average of the relative enhancement ratio measured from regions of interest (ROIs) drawn over both lungs on the coronal section. To compare the efficacy of O2-enhanced MRI and quantitative CT for pulmonary functional loss assessment, MRER and CT-based FLV were correlated with lifetime smoking exposure, FEV_1/FVC%, $\%FEV_1$ and $\%DL_{CO}/V_A$. To determine the efficacy of the two methods for clinical stage classification, MRER and CT-based FLV of non-smoking subjects were compared with those of subjects at all stages of COPD by using the analysis of variance (ANOVA) followed by Fisher's Protected Least Significant Difference test.

Results: Correlations among lifetime smoking exposure, pulmonary functional parameters such as FEV_1/FVC%, FEV_1% and $\%DL_{CO}/V_A$ on the one hand and MRER and CT-based FLV on the other are shown in Table 1. Correlations of MRER or CT-based FLV with lifetime smoking exposure and pulmonary functional parameters were significant ($p<0.0001$). In addition, correlation coefficients of MRER with the lifetime smoking exposure or pulmonary functional parameters were slightly better than those of CT-based FLV. Detailed characteristics of the four clinical stage groups and the results of the statistical comparison of MRER and CT-based FLV for clinical stage classification are shown in Table 2. FEV_1/FVC%, FEV_1%, $\%DL_{CO}/V_A$ and MRER for each clinical group showed significant differences among each other ($p<0.05$). Lifetime cigarette smoking exposure and CT-based FLVs of the 'Smokers without COPD' and 'Mild COPD' groups showed significant differences with those of the 'Moderate COPD' and 'Severe or Very Severe COPD' groups ($p<0.05$).

Conclusion: O_2-enhanced MRI was found to be effective for smoking-related pulmonary functional loss assessment and clinical stage classification of smoking-related COPD as well as quantitative thin-section MDCT. Detailed correlation analysis of O_2-enhanced MR parameters and pulmonary function test results and power analysis of O_2-enhanced MR parameters for smoking-related COPD patients at all clinical stages demonstrated that assessment of the regional signal intensity changes due to inhalation of 100 % oxygen on O_2-enhanced MRI yielded maps that show correlation with not only airflow limitation in the lungs, but also with diffusing capacity.

Table 1. Correlations among Lifetime smoking exposure, pulmonary functional parameters, O_2-enhanced MRI and quantitative CT.

	MRER r (p value)	CT-based FLV r (p value)
Lifetime smoking exposure	-0.57 (p<0.0001)	-0.37 (p<0.0001)
FEV_1/FVC%	0.68 (p<0.0001)	0.52 (p<0.0001)
$\%FEV_1$	0.65 (p<0.0001)	0.57 (p<0.0001)
$\%DL_{CO}/V_A$	0.61 (p<0.0001)	0.48 (p<0.0001)

MRER: Mean relative enhancement ratio
CT-based FLV: CT-based functional lung volume
r: Correlation coefficient

Table 2. Characteristics and statistical results of O_2-enhanced MRI and quantitative CT for all groups.

	Smokers without COPD	Mild COPD	Moderate COPD	Severe or Very Severe COPD
Cases	40	40	40	40
Age (years)	62±13	62±12	62±11	62±10
me smoking exposure (pack years)	32±27	35±23.7	$62±22^{a,b}$	$79±43^{a,b}$
FEV_1/FVC% (%)	85.4±5.0	$65.0±3.9^{a}$	$51.1±9.6^{a,b}$	$37.3±12.0^{a,b,c}$
FEV_1 (%)	92.0±10.2	$84.8±4.9^{a}$	$64.4±12.0^{a,b}$	$37.7±7.1^{a,b,c}$
$\%DL_{CO}/V_A$ (%)	90.4±18.3	$78.5±13.8^{a}$	$65.0±15.0^{a,b}$	$47.8±13.6^{a,b,c}$
MRER	0.21±0.07	$0.16±0.04^{a}$	$0.13±0.04^{a,b}$	$0.09±0.04^{a,b,c}$
CT-based FLV	0.70±0.14	0.61±0.13	$0.50±0.16^{a,b}$	$0.43±0.18^{a,b}$

All values represent mean ± standard deviation.
MRER: Mean relative enhancement ratio
CT-based FLV: CT-based functional lung volume
[a]: Significant difference with 'Smokers without COPD' group ($p<0.05$).
[b]: Significant difference with 'Mild COPD' group ($p<0.05$).
[c]: Significant difference with 'Moderate COPD' group ($p<0.05$).

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