European Journal of Radiology 84 (2015) 1196–1201

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Regional bronchodilator response assessed by computed tomography in chronic obstructive pulmonary disease

Kaoruko Shimizu[a], Hironi Makita[a], Masaru Hasegawa[a], Hirokazu Kimura[a], Satoshi Fuke[a], Katsura Nagai[a], Takayuki Yoshida[a], Masaru Suzuki[a], Satoshi Konno[a], Yoichi M. Ito[b], Masaharu Nishimura[a,*]

[a] First Department of Medicine, Hokkaido University School of Medicine, N-15 W-7, Kita-Ku, Sapporo 060-8638, Japan
[b] Department of Biostatistics, Hokkaido University Graduate School of Medicine, N-15 W-7, Kita-Ku, Sapporo 060-8638, Japan

ARTICLE INFO

Article history:
Received 3 December 2014
Received in revised form 18 February 2015
Accepted 20 February 2015

Keywords:
Bronchodilation
Pulmonary function
Salmeterol/fluticasone propionate combination
Computed tomography

ABSTRACT

Background and objective: The reliability of CT assessment of regional bronchodilation is not universally accepted. In this study, using our proprietary 3D-CT software, we first examined airway inner luminal area (Ai) before and after inhalation of SFC in a group of COPD patients and then evaluated the same parameters for two sets of CT data obtained from clinically stable subjects with no intervention.
Methods: We conducted CT at deep inspiration and pulmonary function tests before and one week after inhalation of SFC in 23 COPD patients. As a non-intervention group, we used two sets of CT data obtained with one-year interval in another group of subjects who demonstrated stable pulmonary function ($n = 8$). We measured Ai at the mid-portions of 3rd to 6th generation in 8 bronchi of the right lung, a total of 32 identical sites before and after intervention.
Results: The average bronchodilation at all sites (ΔAi%: 28.2 ± 4.1 (SE)%) ($r = 0.65$, $p < 0.001$) and that of each generation significantly correlated with % improvement of FEV1 (ΔFEV1%), which increased from 1.40 ± 0.10 L to 1.58 ± 0.10 L. When subjects were classified into two groups in terms of mean ΔFEV1%, even the poor responders (ΔFEV1% <14% above baseline, $n = 13$) displayed significantly larger ΔAi% compared with the non-intervention group (19.1 ± 4.6% versus 2.1 ± 3.9%). Inter-observer variability for overall ΔAi% was within acceptable levels.
Conclusions: CT can reliably detect the regional bronchodilation in 3rd to 6th generation airways when ΔFEV1 is as small as 180 ml on average.
This study was registered in the UMIN Clinical Trials Registry (UMIN-CTR) system (http://www.umin.ac.jp/. No. UMIN 000002668).

1. Introduction

Recently, computed tomography (CT) has been extensively utilized to evaluate airway remodeling in bronchial asthma and chronic obstructive pulmonary disease (COPD) [1–7].

However, validation of the measurement of airway dimensions, such as airway wall area, particularly in smaller airways, has been challenging [8,9]. Airway inner luminal area (Ai) may not be suitable for assessment of airway remodeling because Ai varies with lung volume [10] and is likely affected by the balance of pressure inside and outside the airway wall [11]. Despite these physiological characteristics, Ai measurement might be superior to other CT airway indices from a couple of viewpoints. A technical merit of Ai is that it is unaffected by attachment of lung tissue and vessels, which would interfere with delineation of the outer lung edge, leading to potential errors in the measurement of airway wall parameters. Indeed, our previous study showed that the percentage predicted forced expiratory volume in 1 s (FEV1) correlates more closely with Ai than airway wall parameters in patients with COPD [12]. Furthermore, measurement of Ai provides accurate quantitative assessment of regional bronchodilation induced by bronchodilators.

We previously demonstrated the quantitative effects of tiotropium on the Ai of 3rd to 6th generation airways [13]. Since then, there have been several similar studies in which changes in airway dimensions, such as Ai and airway wall area, were quantitatively examined using CT following single and/or combined inhalation of tiotropium, salmeterol/fluticasone propionate,

* Corresponding author. Tel.: +81 11 706 5911; fax: +81 11 706 7899.
E-mail address: ma-nishi@med.hokudai.ac.jp (M. Nishimura).

http://dx.doi.org/10.1016/j.ejrad.2015.02.022
0720-048X/

budesonide/formoterol, and indacaterol for COPD [14–17]. However, there have been no studies which attempted to examine the reproducibility and variation of the measurement of Ai when CT scans were taken twice with no intervention.

In some previous studies, airway dimensions were measured in 3rd generation airways alone, whereas in other studies, the researchers were not sure whether they really measured the same sites for comparison [14–17]. Our proprietary software for 3D-CT has the ability to assess Ai in 3rd to 6th generation airways [10,12,13,18,19], and furthermore the dual screen system enables us to simultaneously compare identical sites using two sets of CT data.

In this study, using our proprietary 3D-CT software, we first attempted to examine the magnitude of bronchodilation before and after one-week inhalation of salmeterol/fluticasone propionate combination (SFC) in a group of COPD patients and then evaluated the same parameters for two sets of CT data obtained with one year interval from clinically stable subjects with no intervention.

2. Methods

2.1. Inhalation of salmeterol/fluticasone propionate combination

Patients with clinically stable COPD (M/F, 22/1; age, 52–84 y; mean ± SD, 70.1 ± 7.6 y; GOLD [20] Stage 2, $n = 6$, Stage 3, $n = 17$) were recruited at Hokkaido University Hospital between January 2010 and February 2011. All patients were either current or former smokers. We excluded patients with bronchial asthma, pulmonary fibrosis, pulmonary cancer, giant bullae, and severe diffuse and/or local bronchiectasis. All patients provided written informed consent to participate and the Ethics Committee for Human Research at Hokkaido University Hospital approved the study. This study was registered in the UMIN Clinical Trials Registry (UMIN-CTR) system (http://www.umin.ac.jp/. No. UMIN 000002668).

After the first visit, the subjects refrained from using any respiratory medication for one week.

At the second visit, for baseline measurement, lung CT followed by pulmonary function tests were performed if the subjects were clinically stable and had not taken any respiratory medication for the previous week. All participants commenced inhalation of SFC from the evening of the second visit and used SFC twice a day from the following day. On the seventh day after the second visit, patients inhaled SFC about 2–3 h before they again underwent lung CT and pulmonary function tests.

2.2. Computed tomography and airway analysis

A multidetector-row spiral CT scanner with a 64-detector array (Aquilion Multi, TSX-101A/6A; Toshiba Medical Systems, Tochigi, Japan) was used. The acquisition parameters were 120 kVp, 300 mA, 64 detector × 0.5-mm collimation, slice thickness 0.5 mm, 0.5 s/rotation, and helical pitch 41. The entire lung of each patient was scanned in the supine position at full inspiration. The length of the pixel size was approximately 0.625 mm. Raw data were transferred to the workstation and reconstructed into three-dimensional chest images (Virtual place Fujin raijin 310; AZE Ltd., Tokyo, Japan). The detailed process of CT data acquisition and reconstruction has been described previously [13,21]. Eight bronchi were selected in the right lung: apical (B1), posterior (B2), and anterior (B3) of the upper lobe, lateral (B4) and medial (B5) of the middle lobe, and anterior basal (B8), lateral basal (B9), and posterior basal (B10) of the lower lobe. We rotate the 3D images of the bronchi to find any bifurcation, one bronchus was randomly selected at each bifurcation. If the image of the bronchus was poor or one bronchus was obstructed, the other bronchus, up to the 6th generation, was selected. These measurements were done under the condition where the examiner was unaware of which one of the two CT data had been taken earlier or later. Then, Ai was measured at the midpoint between bifurcations, from the 3rd (segmental bronchus) to 6th generation of each airway, leading to a total of 32 measurement sites per subject. We used two screens, which allowed simultaneous assessment of images before and after inhalation, so that we could compare the same point of the same bronchi in both states in a given subject (Fig. 1). Average values of Ai per generation and per lobe were calculated for analysis.

We measured only airway inner luminal area and not the airway outer wall. The inner diameter (Di) was calculated as $2\sqrt{Ai}/\pi$, assuming that the airway lumen was a true circle. The degree of bronchodilation was expressed as % improvement of Ai (ΔAi%). To delineate the inner circle of each airway, one was allowed to make manual plots only when the automatically obtained outline of airway inner area was obviously out of contour.

Measurement of lung volume (LV) is described in the online data supplement.

2.3. Pulmonary function tests

A rolling seal type spirometer, CHESTAC-33 (CHEST M.I., Inc., Tokyo, Japan), was used.

More information is presented in the online data supplement.

2.4. Study on airway measurements at an interval of one year

We did not have genuine controls because we did not want subjects to undergo CT exams twice within one week without any treatment. Instead, we used data from participants in the Hokkaido COPD cohort study to determine the reproducibility of Ai when the data of pulmonary function tests did not show any significant change on two occasions. Following the Hokkaido COPD cohort study protocol [22], participants underwent CT exams yearly and respiratory function tests every 6 months. Eight pairs of CT data from moderate to severe COPD patients, obtained at an interval of 1 year during which the difference in FEV1 was < 50 ml, were available (M/F 8/0, age, 62–86 y, mean ± SD, 78.5 ± 8.2 y; GOLD Stage 2, $n = 3$, Stage 3, $n = 5$). The CT scanner and protocol for measurements of Ai were the same as in the subjects treated with SFC in the current study.

2.5. Inter-observer variability in the measurement of Ai

We examined the inter-observer variability in evaluation of bronchodilation with our methods using intra-class correlations (ICC). When the number of observers was two, null hypothesis was 0.1, alternative hypothesis was 0.8, and power was 0.9, the required number of data was calculated as 12 [23]. Then, 12 subjects were randomly selected to reflect the variability of the improvement in FEV1 from the subjects in the SFC study. Two respiratory physicians independently assessed Ai in these 12 patients.

2.6. Statistics

Data are shown as mean ± standard error of mean (SEM). We used paired Student's *t*-tests to analyze differences in mean values between baseline and post-bronchodilator values.

Relationships between quantitative variables were examined using the Spearman test.

Bland–Altman analysis and ICC between the two observers were used to assess reproducibility in ΔAi% at all sites, that is, the average value of 32 data points. For comparison, we classified SFC-treated subjects into two groups, using the mean value of ΔFEV_1, as good responders (ΔFEV_1 >14%) and poor responders (ΔFEV_1 <14%).