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The effects of dynamic hyperinflation on CT emphysema measurements in patients with COPD

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ABSTRACT

Objectives: Dynamic hyperinflation (DH) significantly affects dyspnea and intolerance to exercise in patients with chronic obstructive pulmonary disease (COPD). Quantitative computed tomography (QCT) of the chest is the modality of choice for quantification of the extent of anatomical lung damage in patients with COPD. The purpose of this article is to assess the effects of DH on QCT measurements.
Methods: The study sample comprised patients with Global initiative for Chronic Obstructive Lung Disease (GOLD) stages III and IV COPD referred for chest CT. We examined differences in total lung volume (TLV), emphysema volume (EV), and emphysema index (EI) determined by QCT before and after DH induction by metronome-paced tachypnea (MPT). Initial (resting) and post-MPT CT examinations were performed with the same parameters.
Results: Images from 66 CT scans (33 patients) were evaluated. EV and EI, but not TLV, increased significantly ($p < 0.0001$) after DH induction.
Conclusion: QCT showed significant increases in EV and EI after MPT-induced DH in patients with GOLD stages III and IV COPD. For longitudinal assessment of patients with COPD using QCT, we recommend the application of a pre-examination rest period, as DH could mimic disease progression. QCT studies of the effects of DH-preventive therapy before exercise could expand our knowledge of effective measures to delay DH-related progression of COPD.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health issue, despite its preventability and treatability [1,2]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging system has been adopted widely for the systematization of patients workup and therapeutic approaches. However, the symptoms and anatomical signs of COPD are known to be poorly correlated with forced expiratory volume during the first second (FEV1) [3].

Since the initial description of the pathophysiology of COPD during exercise [4,5], several studies have demonstrated that the degrees of intolerance to daily activities and impairment in quality of life are affected directly by dynamic hyperinflation (DH) [6–8]. The definition of DH is based on the increase in end-expiratory lung volume during and after exercise [9]. Patients with COPD, who have increased inspiratory drives at rest [10], have very limited potential for the expansion of inspiratory capacity in response to different levels of exercise; this situation leads to exertional dyspnea, blood oxygen desaturation, and oxidative stress damage [7,11].

Computed tomography (CT) of the chest is the modality of choice for the assessment of lung parenchyma and airway anatomy, and is well established for the assessment of anatomical lung damage caused by COPD [12,13]. Post-processing tools allow further analysis based on image segmentation according to the density [in Hounsfield units (HU)] of each voxel. By identifying voxels with densities less than −250 HU, the lungs can be isolated from other

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structures (e.g., mediastinum, diaphragm, and chest wall). The sum of the volume of lung (−250 HU) voxels informs the total lung volume (TLV), which can then be segmented by identifying voxels with densities of −950 to −250 HU (here defined as "normal voxels") and those with densities less than −950 HU ("emphysematous voxels"). The normal lung volume and emphysema volume (EV) are the sums of the volumes of normal and emphysematous voxels, respectively. This post-processing sequence of volume calculation based on the measurement of densities on CT images is termed quantitative CT (QCT) [14,15]. However, the effects of DH on QCT measurements have not been investigated. In this study, we aimed to assess the magnitude of changes in TLV, EV, and the emphysema index (EI) caused by DH.

2. Materials and methods

2.1. Subjects

Thirty-three patients with confirmed diagnoses of COPD (GOLD stage III or IV) who had been referred for chest CT participated in this study. Clinical diagnosis and GOLD staging of COPD were based on a relation FEV1/forced vital capacity <0.70 and FEV1 <50% (GOLD III) or <30% (GOLD IV) of the predicted value [16]. This group of patients was chosen to avoid radiation exposure of patients with GOLD stages I and II, who have longer life expectancies. The research followed the guidelines of the Declaration of Helsinki and was approved by the local ethical review committee (reference ISCMPA-25152713.0.0000.5335). Written informed consent was obtained from each patient at the time of CT referral and confirmed at the Radiology Department before the imaging examination.

2.2. Study design

Patients with GOLD stages III or IV, who had been referred for chest CT for any reason, were invited to participate in this individualized, longitudinal, observational study. Exclusion criteria were: (a) age <30 years; (b) presence of a pulmonary nodule >10 mm, lung mass, area of atelectasis, consolidation, ground-glass attenuation, or any other significant lung abnormality noted during the review of chest CT images before progression to the metronome-paced tachypnea (MPT) maneuvers required for the study; (c) unstable COPD signs or symptoms in the 6 weeks preceding CT examination; (d) risk of pregnancy or lactating status; (e) failure to provide consent; and (f) CT examination with contrast medium injection, which could impair the reproducibility of QCT measurements.

Patients were instructed to continue all usual medications, but to withhold short-acting beta2-agonists for 6 h and long-acting anti-cholinergic drugs or slow-release theophylline for 24 h before CT examination. Patients' compliance with these instructions was checked at the Radiology Department. The initial CT examination (CT1) was performed with the patient at rest, and the second examination (CT2) was performed after the induction of DH (Fig. 1). After

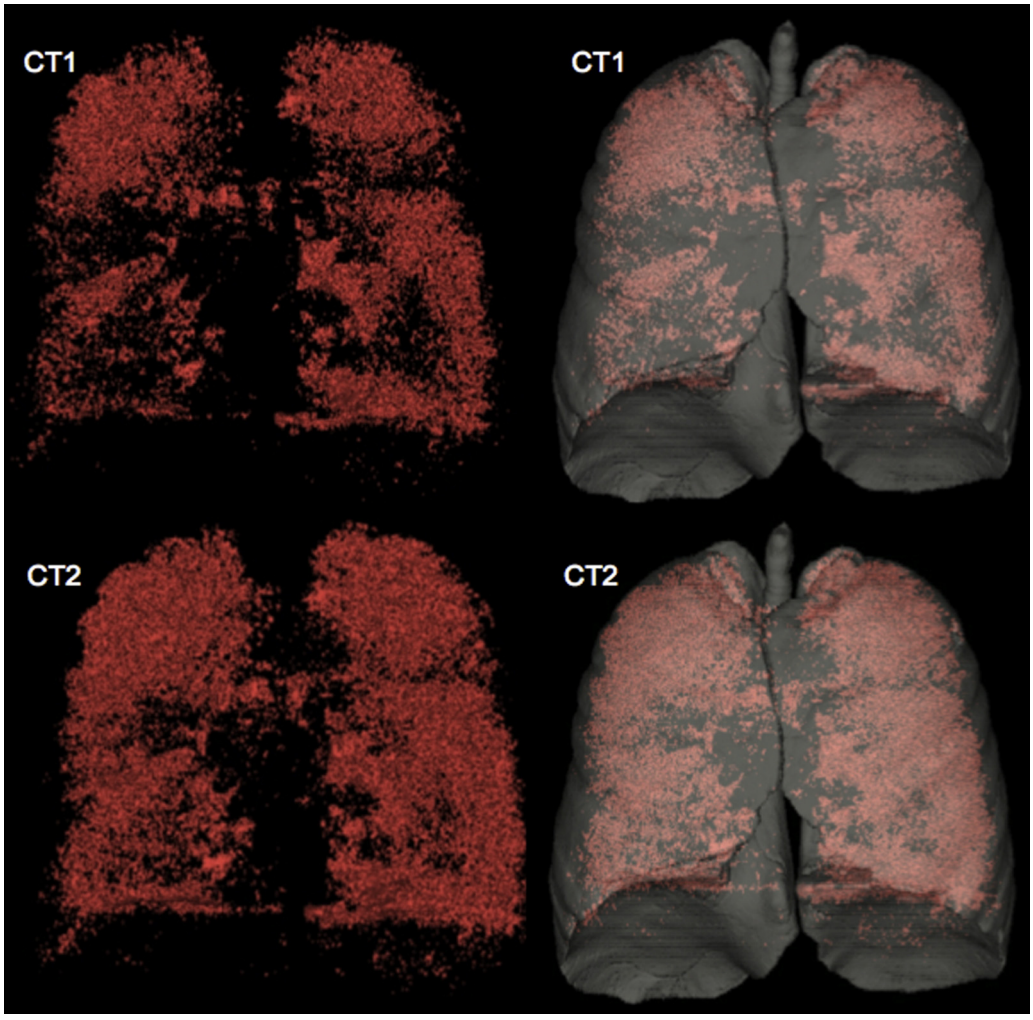

Fig. 1. Frontal three-dimensional reformatted computed tomographic (CT) images of the same patient before (CT1) and after (CT2) the induction of dynamic hyperinflation.

CT1, the images were checked for quality and to identify any abnormality that would result in the patient's exclusion from the study (as inclusion of intestinal gas). A radiologist, with 5 years of experience in thoracic radiology, performed this initial screening. When an exclusion criterion was identified, the examination was stopped and CT1 data were reported outside of the study. Otherwise, the patient was instructed to perform MPT, which involves the gradual increase of the respiratory rate in pace with a metronome until a rate of 40 breaths/min is sustained for 2 min, to induce DH. This method has shown good applicability in research protocols, and its use is valuable in patients who cannot walk or perform upper-limb maneuvers to induce DH [17]. MPT was performed at the CT scanner table immediately after confirmation of the absence of exclusion criteria on CT1 images.

2.3. Image acquisition and analysis

Images of the entire chest were acquired in two helical sequences using a commercially available 64-row multi-detector CT scanner (SOMATOM Sensation 64 Systems; Siemens Medical Systems, Forchheim, Germany). To minimize respiratory movement artifacts, helical scans were performed in the caudal–cranial direction, with the patient holding his/her breath at the end of a maximal inspiratory effort. Lung volumes were not monitored by spirometry, which has been shown to potentially increase radiation exposure without significantly improving the precision of the technique [18]. The CT parameters were: collimation, 32 × 0.6 mm (with *z*-flying focal spot, producing 64 overlapping 0.6-mm slices per rotation); rotation time, 0.33 s; pitch, 1.3; 120 kV; and 200 mAs. Dose modulation was allowed for optimization according to patient size and anatomical shape (automatic exposure control). Reconstruction was performed to produce contiguous 1.00-mm-thick axial images using a standard kernel (B20; Siemens Medical Systems). No edge enhancement or softening filter was used to avoid artificial alteration of the original attenuation values of some voxels captured by the CT detectors, especially at interfaces between air and vessels, bronchial walls, chest wall, or mediastinum. The CT scanner was calibrated periodically according to the manufacturer's recommendations, with the use of a calibration phantom, in order to minimize the potential beam hardening effect on QCT measurements. Raw data were registered on a scale ranging from −1024 to 3072 HU. All examinations were performed without the injection of intravenous contrast medium, and a data matrix of 512 × 512 was used.

TLV, EV, EI and mean lung density were quantified by QCT and according to previously published methods using Syngo InSpace4D software (Siemens Medical Systems) [14,15]. The value of EI was obtained by the division of EV/TLV. Following previous studies [19,20], we used a threshold of −950 HU to quantify emphysema (normal *vs.* emphysematous lung voxels) on CT images. The adequacy of segmentation was checked by matching the visual analysis of emphysematous areas with the corresponding density mask on axial images, and by displaying the segmented data rendered for three-dimensional images. Although some authors have suggested the inclusion of volume correction in emphysema measurements [21], we did not perform such adjustment to maximize the reproducibility of results.

2.4. Statistical analysis

Data were tabulated in Excel® (Microsoft Corporation, Redmond, WA, USA) and processed using this software and SPSS (ver. 14.0; IBM Corporation, Armonk, NY, USA). Descriptive statistics were calculated and correlation analysis was performed. Absolute values were expressed individually, but mean, median, minimum, and maximum values and standard deviations were also checked for each parameter. Paired *t*-test was used to analyze data, with a significance level of .05. A Bland–Altman plot was further built to explore the differences between the two TLV.

Table 1
Characteristic of the study sample ($n = 33$), including sex, age, smoking status, and pulmonary function and GOLD category by the time of computed tomography performance.

Mean age (years) (range)	70.3 (35–88)
Male gender (*n*) (%)	24 (72.7%)
Current smokers (%)	66.82
Pack-years, median (25th, 75th percentiles)	43.6 (30.8, 82.0)
Mean FEV_1%pred (SD)	26.6 (19.3)
Mean Dl_{CO} (SD)	3.8 (1.1)
GOLD category (%)	
Stage III	27.3
Stage IV	72.7

Dl_{CO}, single-breath diffusing capacity of carbon monoxide (mmol/min/kPa); GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV_1%pred, first-second forced expiratory volume, expressed as the percentage of the predicted value; SD, standard deviation.

3. Results

The study cohort comprised 24 (72.7%) men and 9 (27.3%) women with a mean age of 70.3 (range, 35–88) years who underwent a total of 66 CT examinations (two per patient). 24 (72.7%) patients had GOLD stage IV and 9 (27.3%) had GOLD stage III COPD. These and other demographic characteristics are summarized in Table 1.

Mean TLVs obtained before (6.98 L) and after (7.02 L) DH induction did not differ significantly ($p = 0.85$) (Fig. 2). In contrast, significant differences were observed between pre- and post-DH EV (700 *vs.* 910 mL) and EI (10% *vs.* 13%; both $p < 0.05$; Table 2, Fig. 3).

4. Discussion

The importance of assessing the presence of DH in patients with COPD is well recognized. Zafar et al. [22] recently found a strong correlation between DH and oxygen desaturation during a 6-min walking test, corroborating the evidence that DH contributes directly to the worsening of COPD signs and symptoms. Other authors have reported that DH-preventive medication improved dyspnea scores and quality of life parameters in patients with COPD [23]. Although correlations between QCT data and pulmonary function parameters have been investigated [14,15], this study was the first to examine the effects of DH on QCT parameters in patients with COPD. The observed lack of a change in TLV, despite the

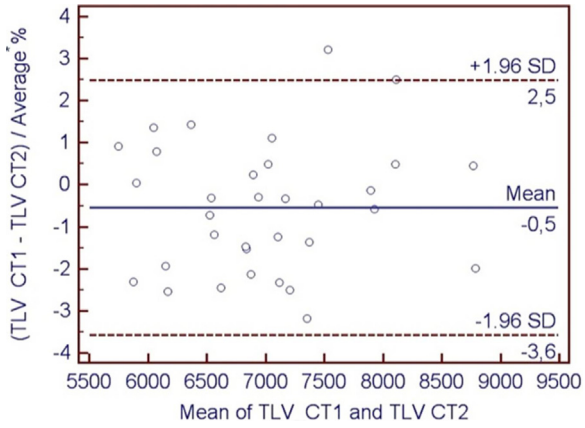

Fig. 2. Bland–Altman plot graphic comparing total lung volumes (TLVs), before (TLV1) and after (TLV2) dynamic hyperinflation induction. *Average = mean of all TLVs values in CT1 and CT2.

Table 2
Paired *t*-test results of quantitative computed tomography measurements before and after dynamic hyperinflation induction (CT1 and CT2, respectively).

	Mean	SD	Mean	SD	*P*	CI-95
TLV (ml)	6979.88	792.04	7016.70	783.47	0.85	−424 to 350
EV (ml)	700.30	119.61	910.18	128.21	<0.0001	−270 to −148
EI (%)	10.02	1.14	13.01	1.53	<0.0001	−3.65 to −2.32
MLD (SD)	−910	75	−918	93	0.77	−33.5 to 49.5

TLV, total lung volume; EV, emphysema volume; EI, emphysema index; MLD, mean lung density (Hounsfield units); *P*, *P*-value; CI-95, confidence interval of 95%; SD, standard deviation.

increase in EV, provides clear anatomical and functional evidence that the non-emphysematous parenchyma is further compressed by emphysematous areas in DH.

Different methods of DH induction have been described [7,11]. Castro et al. [24] recently showed that an arm cycle ergometer test induced DH to a greater degree than a diagonal arm exercise test. In the present study, we used MPT to induce DH because it was readily applied within the context of the examination and because it has demonstrated good reproducibility [3,17].

An understanding of the anatomical mechanisms and physiological consequences of DH in patients with COPD is important for the identification of protective measures that minimize the effects of exercise and other factors on the induction of DH. CT is the best *in vivo* method for the demonstration of anatomical changes in the lung parenchyma. QCT can provide physiological information, especially when examinations (e.g., inspiratory and expiratory scans) are performed before and after maneuvers that alter patients' physiological status [14], such as MPT to induce DH. Other QCT techniques for the quantification of lung volumes have also proven useful for assessing other cohorts of patients, such as those with obliterative bronchiolitis and candidates for living-donor lung transplantation [25,26]. QCT has also been demonstrated to be an objective method of assessment and outcome prediction in patients with COPD who are candidates for lung volume reduction surgery or endobronchial valve implantation [18,27]. Moreover, longitudinal studies have shown that QCT data are more accurate than FEV1 values for the determination of disease progression rates [28]. However, our data suggest that QCT studies in patients with COPD should be reasonably performed after a minimum period of rest, given that the influence DH exercises toward emphysema measurements could falsely indicate disease progression.

Mortality due to radiation-induced malignancy should always be considered when referring patients for imaging examinations entailing radiation exposure, especially fluoroscopy, CT, and positron emission tomography. This concern is greater in patients requiring frequent follow-up examinations. The patient's age and life expectancy carry great weight in consideration of the risk-benefit balance of such studies. The CT radiation dose can be reduced significantly by the selection of appropriate acquisition parameters, but such measures increase image noise, impacting image quality. Ultra-low-dose CT is of limited use in the assessment of emphysematous changes in the lungs. Image filters, dose modulation, iterative reconstruction and volume correction techniques may improve the quality of images obtained in ultra-low-dose examinations, facilitating visual image interpretation. However, these post-processing techniques have been shown to affect the accuracy of quantification, as they artificially change the Hounsfield values measured by the detectors; the extent of such alteration varies, depending on the nature of the tissue examined [29].

The limitations of our study include the examination only of patients with GOLD stage III or IV COPD, as DH is known to also affect patients with GOLD stage I or II COPD [6,22]. This choice was based on the life expectancy of this patient group, in consideration of the risk of death by radiation-induced malignancy. We also understand that the use of a fixed CT dose is preferable to the application of automatic exposure control parameters when performing QCT. However, we believe that our use of dose modulation was appropriate and necessary because the patients had been referred for CT for different clinical reasons. Finally, the beam hardening effect is reduced but not completely eliminated with the use of a calibration phantom, and additional techniques could have been applied to minimize its possible influence on the studied volumetric quantifications [30].

In summary, we observed by QCT that DH significantly increased the EV and EI without significantly altering the TLV. These results indicate that DH further compresses the remaining functional lung parenchyma, i.e., the portions of lung not yet destroyed by emphysema, within the same TLV. This can be partially confirmed by the non-significant variation in mean lung density values between CT1 and CT2 examinations. Further studies are needed to determine whether preventive measures minimize DH during exercise, thereby effectively maintaining pre-exercise ranges of EV and EI. As DH is a dynamic and reversible process, we would recommend patients referred for QCT quantification of emphysema to be allowed to rest before the examination to increase the

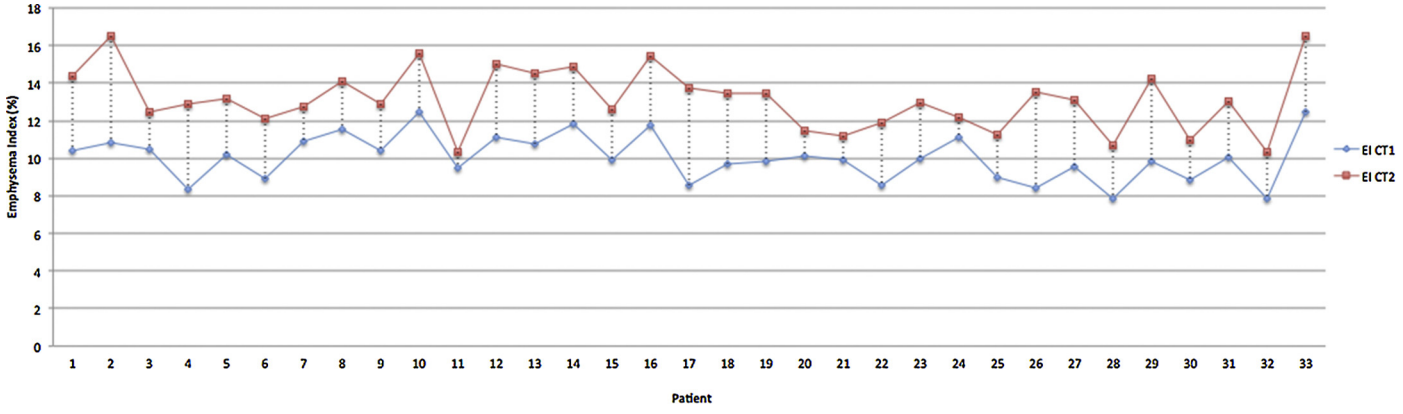

Fig. 3. Emphysema indices (EIs), expressed as percentages, before (EI1) and after (EI2) dynamic hyperinflation induction.

reliability and reproducibility of EV and EI values characterizing the extent of emphysema.

Conflict of interest

None of the authors have any conflict of interest to express.

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