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Early Identification of Small Airways Disease on Lung Cancer Screening CT: Comparison of Current Air Trapping Measures

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Abstract
Background Lung cancer screening CT scans might provide valuable information about air trapping as an early indicator of smoking-related lung disease. We studied which of the currently suggested measures is most suitable for detecting functionally relevant air trapping on low-dose computed tomography (CT) in a population of subjects with early-stage disease.
Methods This study was ethically approved and informed consent was obtained. Three quantitative CT air trapping measures were compared against a functional reference standard in 427 male lung cancer screening participants. This reference standard for air trapping was derived from the residual volume over total lung capacity ratio (RV/TLC) beyond the 95th percentile of predicted. The following CT air trapping measures were compared: expiratory to inspiratory relative volume change of voxels with attenuation values between −860 and −950 Hounsfield Units ($RVC_{-860\ to\ -950}$), expiratory to inspiratory ratio of mean lung density ($E/I\text{-}ratio_{MLD}$) and percentage of voxels below −856 HU in expiration (EXP_{-856}). Receiver operating characteristic (ROC) analysis was performed and area under the ROC curve compared.
Results Functionally relevant air trapping was present in 38 (8.9 %) participants. $E/I\text{-}ratio_{MLD}$ showed the largest area under the curve (0.85, 95 % CI 0.813–0.883), which was significantly larger than $RVC_{-860\ to\ -950}$ (0.703, 0.657–0.746; $p < 0.001$) and EXP_{-856} (0.798, 0.757–0.835; $p = 0.002$). At the optimum for sensitivity and specificity, $E/I\text{-}ratio_{MLD}$ yielded an accuracy of 81.5 %.
Conclusions The expiratory to inspiratory ratio of mean lung density ($E/I\text{-}ratio_{MLD}$) is most suitable for detecting air trapping on low-dose screening CT and performs significantly better than other suggested quantitative measures.

Keywords Air trapping · Small airways disease · Computed tomography · Quantitative analysis

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Introduction

Substantial mortality reduction has been reported recently for computed tomography (CT)-based lung cancer screening, which raises high expectations [1, 2]. Lung cancer screening CT also may provide information on other smoking related diseases, such as chronic obstructive pulmonary disease (COPD), which is a growing healthcare issue [3]. COPD is characterized by chronic airflow limitation, largely caused by emphysema and small airways

remodeling [4]. Small airways disease precedes emphysematous destruction in the course of the disease [5] and might be used as an early marker of COPD. This early detection of the disease and subsequent intervention at an early stage is crucial and might prevent progression of COPD-related morbidity and mortality.

CT assessment of small airways disease in COPD has been an active area of research for the past years. After initial use of inspiratory large airway wall dimensions as a surrogate of small airways remodeling [6, 7], more recently the quantification of air trapping in expiratory CT scans has been used to evaluate small airways disease [8–12]. Options range from simple ratios of expiratory to inspiratory mean lung density [12] to absolute expiratory thresholds based on normal values of lung inflation [11] or complex threshold-based measures that try to correct for emphysematous components [8]. There is, however, no consensus yet about the most suitable quantification measure in the population of interest, i.e., with early-stage disease. Therefore, we studied which of the currently suggested measures is most suitable for detecting air trapping on low-dose CT in lung cancer screening participants.

Materials and Methods

This study was conducted as a side-study of the Dutch and Belgium Lung Cancer Screening Trial (NELSON trial-ISRCTN63545820) [13]. The lung cancer screening study was approved by the Ministry of Health of The Netherlands and the institutional ethical review board. Written informed consent was obtained in all screening trial participants.

Patient Selection

To study the small airways disease component of COPD in lung cancer screening setting, an expiratory acquisition was added to the screening protocol at our center. CT scanning and pulmonary function testing took place between July 2007 and September 2008. Participants in the lung cancer screening trial were aged 50–75 years, current or former heavy smokers (ceased smoking <10 years ago), with a smoking history of at least 16 cigarettes/day for 25 years or at least 11 cigarettes/day for 30 years (i.e., >16.5 pack years) [13]. A random sample of 447 participants received extensive PFT, including body plethysmography, on the same day as the CT scan. As a next step, we excluded the female subjects ($n = 18$) and the subjects who were imaged on a different CT scanner ($n = 2$). The final study population thus comprised 427 male current or former heavy smokers in a lung cancer screening setting.

CT Scanning

All CTs were performed without intravenous contrast injection, and obtained with 16 × 0.75 mm collimation (Brilliance 16P, Philips Medical Systems, USA). In our center, volumetric inspiratory CT and volumetric end-expiratory CT were obtained after standardized breathing instructions in all subjects. In the lung cancer screening trial, subjects weighing 80 kg or less were scanned with 120 kVp at 30 mAs for inspiratory acquisition and 90 kVp at 20 mAs for expiratory acquisition (total effective dose 0.98 and 0.27 mSv, respectively). In subjects >80 kg, this was 140 kVp at 30 mAs for inspiratory acquisition and 120 kVP at 20 mAs for expiratory acquisition (total effective dose 1.4 and 0.65 mSv, respectively). Axial images were reconstructed from lung bases to lung apices at a slice thickness of 1.0 mm at 0.7 mm increment, using a smoothed reconstruction filter (B-filter, Philips).

Pulmonary Function Testing (PFT)

PFT was performed with ZAN equipment (ZAN Messgeräte GmbH, Germany) and obtained according to European Respiratory Society (ERS) guidelines [14]. The RV/TLC (ratio of residual volume over total lung capacity) was used as reference, because this is a generally used method that allows in vivo assessment of air trapping. The predicted upper limit of normal for each subject was calculated as the 95th percentile by using the formula for adult males: $14.0 + 0.39*age + (1.64*\text{RSD})$ [15]. Cases with an RV/TLC above this 95th percentile were considered functionally abnormal and were assigned as air trapping positive.

Quantitative CT Assessment of Air Trapping

First, the lungs were automatically segmented from the chest wall, airways, and mediastinum using dedicated software [16]. Second, a noise reduction filter was applied to decrease the influence of noise on the quantitative measurements [17]. Last, CT air trapping was automatically quantified using three measures that are currently suggested in the literature.

Quantitative CT measure (1) $\text{RVC}_{-860 \text{ to } -950}$; the relative inspiratory to expiratory volume change of voxels with attenuation values from −860 to −950 HU [8]. For this measure, as described by Matsuoka et al. [8], new limited lung volumes are calculated for the inspiration and expiration CT by excluding the volume with HU-values below −950 to correct for pulmonary emphysema. Next, the difference between expiratory and inspiratory lung

Table 1 Demographic data and quantitative CT air trapping measurements of the study population

	$N = 427$
Age, year (mean ± SD)	61.8 ± 5
$\%FEV_1$, % (mean ± SD)	94.7 ± 16.3
FEV_1/FVC, % (mean ± SD)	70.3 ± 9.1
Airflow limitation[a], *n* (%)	175 (41)
Mild, *n* (%)	119 (68)
Moderate, *n* (%)	49 (28)
Severe, *n* (%)	7 (4)
RV/TLC, % (mean ± SD)	35.8 ± 8.3
Air trapping positive[b], *n* (%)	38 (8.9)
Quantitative CT air trapping	
$RVC_{-860\ to\ -950}$, % (median, P25–P75)	−57.9 (−67.3 to −44.3)
$E/I\text{-}ratio_{MLD}$, % (median, P25–P75)	84.3 (79.5–87.4)
EXP_{-856}, % (median, P25–P75)	6.5 (2.3–14.4)

$\%FEV_1$ = percent predicted of forced expiratory flow in one second; FEV_1/FVC = ratio of forced expiratory flow in one second over forced vital capacity; RV/TLC = ratio of residual volume over total lung capacity; $RVC_{-860\ to\ -950}$ = air trapping measure as change in relative lung volume with attenuation values from −860 to −950 HU between paired inspiratory and expiratory CT; $E/I\text{-}ratio_{MLD}$ = air trapping measure as expiratory to inspiratory ratio of mean lung density; EXP_{-856} = air trapping measure as percentage of lung voxels in expiratory CT with an attenuation value below −856 HU; GOLD = Global initiative for chronic obstructive pulmonary disease

[a] Airflow limitation is defined as FEV_1/FVC <70 %, classified as mild (FEV_1 >80 % predicted; GOLD 1), moderate (FEV_1 between 50 and 80 % predicted; GOLD 2), and severe disease (FEV_1 <50 % predicted; GOLD 3)

[b] Air trapping is defined as an RV/TLC above the 95th percentile

volume below −860 HU in the limited lung volume is expressed as $RVC_{-860\ to\ -950\ HU}$. This measure is thus calculated according to the formula *expiratory relative lung volume below* −860 HU—*inspiratory relative lung volume below* −860 HU, with relative lung volume below −860 HU defined as the lung volume between −860 and −950 divided by the total lung volume over −950 HU [8]. Increase in air trapping results in a higher $RVC_{-860\ to\ -950}$ value.

Quantitative CT measure (2) $E/I\text{-}ratio_{MLD}$; the expiratory to inspiratory ratio of mean lung density [12]. The expiratory mean lung density in HU is divided by the inspiratory mean lung density, and presented as percentage. Increase in air trapping results in a higher $E/I\text{-}ratio_{MLD}$.

Quantitative CT measure (3) EXP_{-856}; the percentage of lung voxels in expiratory CT with an attenuation value below the threshold of −856 HU [11]. This expiratory threshold of −856 HU is a conversion of 6.0 ml/g lung inflation in inspiration [18] and has been used previously in studies of asthmatic children [19]. Increase in air trapping results in a higher percentage of low-attenuation voxels.

Data Analysis

First, the three quantitative CT air trapping measures ($RVC_{-860\ to\ -950}$, $E/I\text{-}ratio_{MLD}$ and EXP_{-856}) were compared to each other by testing the areas under the receiver operating characteristic (ROC) curves for significant differences in performance [20]. As a next step, we determined the optimal cutoff value at highest sensitivity and specificity for the preferred quantitative CT air trapping method.

ROC comparison was performed with MedCalc v11.3.8.0 (Mariakerke, Belgium). All other analyses were performed with SPSS software v15.0 (SPSS Inc., Chicago, IL). A p value <0.05 was considered statistically significant. Subject characteristics and pulmonary function data are expressed as means with standard deviation. Quantitative CT measurements are expressed as median with 25th to 75th percentile.

Results

Demographic data on the 427 included male subjects are listed in Table 1. Thirty-eight (8.9 %) subjects had functionally relevant air trapping according to the RV/TLC reference, defined as a value over the 95th percentile of the predicted value.

Comparison of CT Air Trapping Measures

Medians with interquartile range of the three CT air trapping measures are presented in Table 1. The area under the ROC curve was 0.703 ($RVC_{-860\ to\ -950}$), 0.85 ($E/I\text{-}ratio_{MLD}$), and 0.798 (EXP_{-856}; Table 2; Fig. 1). The area under the curve was significantly larger for $E/I\text{-}ratio_{MLD}$ compared with both $RVC_{-860\ to\ -950}$ ($p < 0.001$) and EXP_{-856} ($p = 0.002$).

The optimal cutoff for $E/I\text{-}ratio_{MLD}$ to depict air trapping was at a ratio of 87.4 %. This cutoff assigned the correct status to 348 of the 427 subjects; an accuracy of 81.5 %, with a sensitivity of 81.6 % (31/38) and a specificity of 81.5 % (317/389).

Discussion

This study statistically compares the currently suggested quantitative CT air trapping measures and shows that the expiratory to inspiratory ratio of mean lung density ($E/I\text{-}ratio_{MLD}$) is the preferred quantitative CT measure to identify air trapping in a population of current and former heavy smokers in a lung cancer screening setting.

When comparing the two other quantitative CT air trapping measures to the $E/I\text{-}ratio_{MLD}$ in low-dose CT imaging, $RVC_{-860\ to\ -950}$ is clearly outperformed. The

Table 2 Area under the receiver operating characteristic (ROC) curve for the various quantitative CT air trapping measures

	AUC	Difference[a]
$E/I\text{-ratio}_{MLD}$	0.85	–
EXP_{-856}	0.798	0.05 (0.02–0.08)
$RVC_{-860\ to\ -950}$	0.703	0.15 (0.07–0.23)

Three quantitative CT measures were used to identify air trapping, defined as RV/TLC >95th percentile of the predicted value. The area under the ROC curve is significantly larger for $E/I\text{-ratio}_{MLD}$ compared to EXP_{-856} ($p = 0.002$) and $RVC_{-860\ to\ -950}$ ($p < 0.001$)

AUC area under the curve; *CI* confidence interval; $E/I\text{-ratio}_{MLD}$ = air trapping measure as expiratory to inspiratory ratio of mean lung density; EXP_{-856} = air trapping measure as percentage of lung voxels in expiratory CT with an attenuation value below −856 HU; $RVC_{-860\ to\ -950}$ = air trapping measure as change in relative lung volume with attenuation values from −860 to −950 HU between paired inspiratory and expiratory CT

[a] Absolute difference (95 % CI) compared with $E/I\text{-ratio}_{MLD}$

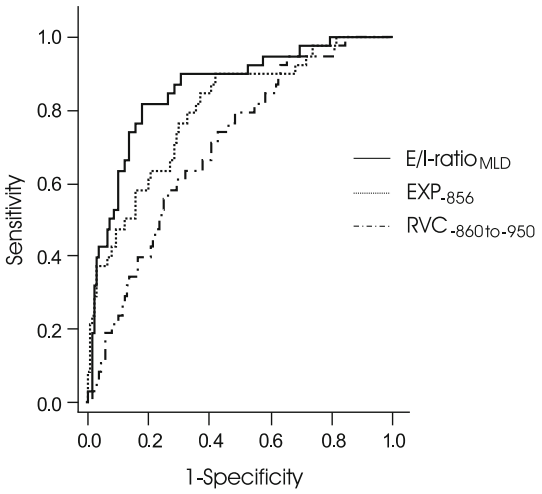

Fig. 1 Receiver operating characteristic (ROC) curves for the identification of air trapping in low-dose lung cancer screening CT scans by three currently suggested quantitative CT measures. Three quantitative CT measures were used to identify air trapping, defined as RV/TLC >95th percentile of the predicted value. It is shown that $E/I\text{-ratio}_{MLD}$ is significantly superior to EXP_{-856} and $RVC_{-860\ to\ -950}$ in the detection of air trapping. $E/I\text{-ratio}_{MLD}$ = air trapping measure as expiratory to inspiratory ratio of mean lung density; EXP_{-856} = air trapping measure as percentage of lung voxels in expiratory CT with an attenuation value below _856 HU; $RVC_{-860\ to\ -950}$ = air trapping measure as change in relative lung volume with attenuation values from −860 to −950 HU between paired inspiratory and expiratory CT

$RVC_{-860\ to\ -950}$ method was developed in a small population of subjects suffering from severe and very severe COPD [8]. When applied to a population of screening participants with absent or mainly low-grade disease, $RVC_{-860\ to\ -950}$ performed significantly worse than other measures for identifying air trapping. The percentage of lung voxels below −856 HU in expiration has been introduced more recently as a measure of air trapping in COPD research [11]. The absolute threshold of −856 HU originates from 6.0 ml/g lung inflation (i.e., lung inflation at normal TLC in inspiration [21]), and has previously been applied in inspiratory scans as a measure for mild emphysema in heavy smokers [18] and in expiratory scans as a measure for air trapping in asthmatic children [19]. The drawback of such a single threshold measure in a population of heavy smokers is that it does not compensate for the influence of possible emphysematous areas; i.e., it combines the low attenuation areas of air trapping and emphysema into one measure. The results of our study show that the single threshold EXP_{-856} measure has lower accuracy in the identification of air trapping in a screening population compared with the $E/I\text{-ratio}_{MLD}$. Besides the poorer performance, a single fixed threshold in expiratory CT may be less robust due to increased susceptibility to differences in scanning protocol and scanner type compared with a measure that combines inspiratory and expiratory data [22].

The present study reports a crucial step on the way of quantification and interpretation of air trapping in early-stage disease, which, in addition to CT quantification of emphysema, is of value for two reasons. First, it has been shown that CT assessment of air trapping and emphysema may reveal "hidden" disease in undiagnosed COPD patients who undergo chest CT screening [23]. This is promising because early intervention with smoking cessation is currently the only way to prevent progress of COPD-related morbidity and mortality. Second, COPD is a heterogeneous disease [24, 25]. Therefore, separate quantification of disease components might allow establishing morphologic phenotypes within this disease, which might help in the development of targeted research and therapy.

Our study has limitations. First, the quality of lung function testing as reference standard is limited. The reference standard used is not a direct measure of small airways remodeling, but a functional measure of small airways dysfunction (i.e., air trapping). Because this is an in vivo phenomenon, there is a lack of pathological evidence for the relationship between pulmonary function testing and small airways disease. Also, lung function testing is insensitive to mild abnormalities, which is expressed in the fairly low number of air trapping positive cases in our study. However, given the purpose of in vivo assessment of small airways disease in a lung cancer screening setting, RV/TLC is the most optimal reference standard and a widely acknowledged measure of small airways disease. Second, CT acquisitions were not spirometrically controlled, which would have guaranteed a standardized level of inspiration and expiration during scan acquisition. However, its absence strengthens the generalizability of the results, because spirometer-gated scanning is not widely used in lung cancer screening setting. Moreover, it has been reported that quantitative CT measurements in gated and ungated scanning are very closely

correlated [26]. Third, it is noted that the number of cases with functionally relevant air trapping (i.e., an abnormal RV/TLC) was limited to 38 due to the fact that the screening cohort comprises mainly subjects without or with only mild disease. Nevertheless, this is exactly the population of interest for early detection of smoking-related disease. Despite the fairly low number of cases, this number is generally believed to be sufficient to compare three determinants in diagnostic studies [27]. Last, our study population consisted only of male participants, which might limit the generalizability of our results.

In conclusion, the expiratory to inspiratory ratio of mean lung density (E/I-ratio$_{MLD}$) has an accuracy of more than 80 % for the detection of air trapping on low-dose screening CT and is significantly superior to other suggested quantitative measures.

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Conflict of interest The authors declared no conflicts for the work under consideration.

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