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Follow-up of CT-derived airway wall thickness: Correcting for changes in inspiration level improves reliability

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ABSTRACT

Objectives: Airway wall thickness (AWT) is affected by changes in lung volume. This study evaluated whether correcting AWT on computed tomography (CT) for differences in inspiration level improves measurement agreement, reliability, and power to detect changes over time.

Methods: Participants of the Dutch-Belgian lung cancer screening trial who underwent 3-month repeat CT for an indeterminate pulmonary nodule were included. AWT on CT was calculated by the square root of the wall area at a theoretical airway with an internal perimeter of 10 mm (Pi10). The scan with the highest lung volume was labelled as the reference scan and the scan with the lowest lung volume was labelled as the comparison scan. Pi10 derived from the comparison scan was corrected by multiplying it with the ratio of CT lung volume of the comparison scan to CT lung volume on the reference scan. Agreement of uncorrected and corrected Pi10 was studied with the Bland-Altman method, reliability with intra-class correlation coefficients (ICC), and power to detect changes over time was calculated.

Results: 315 male participants were included. Limit of agreement and reliability for Pi10 was −0.61 to 0.57 mm (ICC=0.87), which improved to −0.38 to 0.37 mm (ICC=0.94) after correction for inspiration level. To detect a 15% change over 3 months, 71 subjects are needed for Pi10 and 26 subjects for Pi10 adjusted for inspiration level.

Conclusions: Correcting Pi10 for differences in inspiration level improves reliability, agreement, and power to detect changes over time.

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1. Introduction

Airway wall thickness (AWT) on chest computed tomography (CT) is a potential biomarker evaluating airway remodelling in for example chronic obstructive pulmonary disease (COPD), cystic fibrosis or asthma, as an addition to lung function tests [1–4]. As a result, a substantial number of studies assessed the most accurate way to measure airway wall dimensions. It has been shown that AWT measurements on CT can be used in the assessment of airway remodelling in COPD, however, it is still limited in its applicability.
due to the spatial resolution of CT and the lack of post-processing standards [5–9].

Performing a chest CT at two different moments in time inevitably leads to differences in levels of inspiration, reducing agreement and reliability of AWT measurements [10]. With sub-optimal inspiration AWT increases most likely due to a folding of the epithelium and basement membrane and thickening of the smooth airway muscle, that will result in changes in the luminal area [11–13]. This is particularly important when CT-derived AWT is used to evaluate disease progression or effects of therapy. Therefore, correction for variation in inspiration level between CT scans seems logical and could be beneficial when using AWT as an outcome measure in clinical studies [14]. Whether this truly improves agreement, reliability, and power to detect changes has not yet been determined. It has been shown that correcting for inspiration level in emphysema measurements lowers variability, which might suggest that this could be beneficial for AWT-measurements as well [14,15]. Hence, corrections for differences in inspiration level between CT scans could improve comparison of AWT measurements over time [16].

The aim of this study was to provide data on the reproducibility of CT-derived AWT before and after correction for lung volume differences between CT-scans. We evaluated the effect of correction on agreement, reliability, and power of AWT to detect changes over time. For this purpose, we used 3-month follow-up scans from a lung cancer screening trial.

2. Materials and methods

2.1. Participants

Participants were derived from the Dutch-Belgian Lung Cancer Screening Trial (Dutch acronym NELSON) [17]. Briefly, inclusion criteria for the NELSON trial were a smoking history of >15 cigarettes/day during >25 years or >10 cigarettes/day during >30 years. Former smokers should not have quit more than 10 years prior to inclusion in the study. Exclusion criteria were self-reported poor health status, the inability to climb two flights of stairs, a recent chest CT-scan, a history of cancer, or a body weight of more than 140 kg. The NELSON trial was approved by the Dutch Ministry of Health and the local institutional ethical review board, and is registered at www.trialregister.nl with registration number ISRCTN62545820 (IRB approval number 03/040). Written informed consent was obtained for all participants. For this particular sub study, only participants from the University Medical Center Utrecht were included who gave permission for their data to be used in side studies as well.

To evaluate the influence of inspiration level on AWT longitudinally, participants who underwent a short-term follow-up CT between April 2004 and August 2011 because of an indeterminate pulmonary nodule were included. Participants were included when the follow-up time was shorter than 100 days. CT scans were visually checked for the presence of interstitial pneumonia and participants were excluded when signs of pneumonia were present.

2.2. Image acquisition

Participants all underwent low-dose inspiratory volumetric CT scanning using a 16-slice CT scanner (Brilliance 16P or MX8000 IDT; Philips Healthcare, Best, The Netherlands). Data was obtained using 16 × 0.75 mm collimation (pitch = 1.3), without administration of intravenous contrast media injection. Participants weighing less than 80 kg were scanned with 120 kVp at 30 mAs, and participants weighing more than 80 kg were scanned with 140 kVp at 30 mAs. Slice thickness was 1.0 mm. Axial images were reconstructed with 0.7 mm increment by using a smooth reconstruction filter (B-filter; Philips Healthcare, Best, The Netherlands). Baseline and follow-up CT scans were performed with the same scanning protocol.

2.3. Airway wall thickness quantification

All low-dose CT scans were automatically analysed using CIRRUS Lung 15.02 (http://cirus.diagnijmegen.nl, Diagnostic Image Analysis Group, Nijmegen, The Netherlands; Fraunhofer MEVIS, Bremen, Germany). The lungs were segmented and lung volumes were recorded [18]. The airway lumen and its centerline were automatically segmented (Fig. 1A) [19]. Inner and outer wall boundaries were determined along the centerline in cross-sections perpendicular to the local airway dimension at a spacing of 1 mm, based on an intensity-integration approach (Fig. 1B) [20]. Cross sections obtained from the trachea, main bronchi, and bifurcations were automatically excluded, as well as cross-sections for which airway wall segmentation was determined to have failed. Airway wall borders were visually inspected in a random selection of cross-sections in each CT scan to verify correct segmentation. The square root of wall area was plotted against its internal perimeter for all segmented airways (Fig. 1C). Consequently, a regression line was drawn, from which the square root of wall area at an airway with an internal perimeter of 10 mm (Pi10) was derived [5]. Corrections of Pi10 for lung volume change are shown below.

2.4. Pi10 corrected for lung volume change

Corrected Pi10-values were calculated using the following equation:

\[ \text{Pi10}' = \text{Pi10}_{\text{comparison}} \times \frac{\text{Comparison CT lung volume}}{\text{Reference CT lung volume}} \]

with Pi10\_\text{comparison} and \text{Comparison CT lung volume} derived from the CT scan with the lowest CT lung volume (either baseline or follow-up) and the \text{Reference CT lung volume} derived from the CT scan with the highest achieved CT lung volume (either baseline or follow-up), resulting in Pi10 corrected for lung volume difference (Pi10\_').

2.5. Statistical analysis

Means and standard deviations (SD) were calculated for normal distributed values and medians and interquartile ranges for not normal distributed values. Normal distribution was visually checked with QQ plots. To provide data on intra-scan variability, Pi10 measurements were calculated twice in a random subset of 25 participants. Reliability was assessed using single measures two-way random intra-class correlation coefficients (ICCs).

The correlation between the difference in Pi10 from baseline to follow-up and the follow-up time in days was investigated with thePearson correlation coefficient. Additionally, correlations between the difference in inspiration depth and the difference in Pi10 were analysed. To evaluate agreement of uncorrected and corrected Pi10, differences in AWT were plotted against the mean of the paired AWT values by using the Bland Altman method. The limits of inter-examination agreement were defined as the mean difference ± 1.96 × SD. Reliability was assessed by using the single measures ICCs. Furthermore, a power analysis was performed based on a paired t-test (2-sided) with 90% power and an alpha of 5% (PASS 14.0, Kaysville, Utah, USA). All analyses were performed for Pi10 and Pi10 corrected for lung volume differences. To assess whether correcting Pi10 for lung volume differences is clinically relevant in terms of COPD diagnosis, logistic regression models were built with COPD based on baseline lung function tests as outcome.
A baseline model was created (including age, pack years, and smoking status), after which two models were created using the mean uncorrected Pi10 and the mean corrected Pi10. Diagnostic performance was assessed by calculating the area under the receiver operating characteristic (ROC) curve (i.e. C-statistic). Models were compared using the log-likelihood ratios test. Statistical analyses were performed with statistical software (SPSS 23.0, Chicago, Illinois, USA). Results are reported according to the GRRAS guidelines [21].

3. Results

3.1. Participants

A number of 349 male participants underwent a baseline and follow-up chest CT scan within 100 days. 25 participants were excluded because they had interstitial pneumonia. Five participants were excluded because of failures in the Pi10 measurements and four participants were excluded because of segmentation errors. This resulted in 315 participants eligible for analyses with a mean age of 61.9 ± 5.6 years. Median time between the two scans was 91 (84–91) days. Median smoking history was 38.7 (29.7–49.5) pack-years.

3.2. Intra-scan reliability

Pi10 was calculated twice in 25 participants. Mean ± SD Pi10 was the same in both calculations (both 2.47 ± 0.36 mm). There were no differences between both Pi10 measurements (0 ± 0 mm). ICC was excellent being 0.98 (0.96–0.99, p < 0.001).

3.3. Pi10 measurements at baseline and follow-up

On average there was no difference in Pi10 at baseline and at follow-up (2.43 ± 0.62 mm and 2.41 ± 0.59, respectively, p = 0.29). The mean difference between baseline and follow-up measurements was −0.02 ± 0.30 mm. No correlation was found between the difference in Pi10 from baseline to follow-up and the follow-up time in days (r = 0.05, p = 0.36). Mean lung volume was 6.9 ± 1.2 L for both baseline and follow-up scans.

When grouping the CT scans based on the achieved lung volumes during acquisition, the mean lung volume was significantly higher in the reference CTs compared to the comparison CTs (7.1 ± 2.1 and 6.7 ± 2.1, respectively, p < 0.001). Mean Pi10 on the reference CTs was significantly lower as compared to the comparison CTs (2.35 ± 0.57 mm and 2.49 ± 0.63 mm, respectively, p < 0.001). Mean difference was 0.14 ± 0.27 mm.

3.4. Agreement and reliability of Pi10

Median (Q1–Q3) absolute difference in CT lung volume between the reference CT and the comparison CT was 230 ml (110–460). The difference in Pi10 was significantly correlated with the difference in lung volume (r = 0.691, p < 0.001). After correcting Pi10 for lung volume differences between the reference and comparison CT there was no correlation present (r = −0.06, p = 0.29). Inter-examination reliability was good for uncorrected Pi10 with an ICC of 0.87 (0.85–0.90) and improved to 0.94 (0.93–0.95) for Pi10 corrected for lung volume differences. Limits of inter-examination agreement ranged from −0.61 to 0.57 mm for uncorrected Pi10 and from −0.38 to 0.37 mm for corrected Pi10. Mean difference for corrected Pi10 was 0.005 ± 0.19 mm. Bland-Altman plots are shown in Fig. 2.

3.5. Effect of volume correction on power of Pi10

Results of the power analysis are shown in Fig. 3. The sample size needed to detect, 10%, 15%, 20% or 25% change in AWT with a power of 0.90 decreased when Pi10 is adjusted for lung volume change. For example, to detect a 15% change in airway wall thickness over a period of 3 months, 71 participants are needed when using Pi10 without adjustments in order to reliably detect a 25% change in Pi10 with a power of 0.90, when using Pi10 corrected for lung volume, 26 participants have to be included.

3.6. Effect of volume correction on diagnostic accuracy

COPD diagnosis was based on baseline FEV1/FVC measurements. A baseline model was created and included age, pack years, and smoking status. Information on pack years was missing for one participant and consequently this participant was excluded from this analysis. The baseline model had a C-statistic of 0.598 (0.538–0.659). Adding the mean Pi10 value based on the baseline and follow-up measurements, this resulted in an improvement of the model with a C-statistic of 0.707 (0.652–0.763, p < 0.001), with a specificity of 66.4% and a sensitivity of 64.1%. Adding the mean Pi10 value after correction for lung volume differences, this resulted in a C-statistic of 0.716 (0.661–0.771), which was sig-
Because chest CTs are not acquired systematically at total lung capacity or another fixed inspiration level at the vast majority of institutions, correcting AWT measurements for inspiration level seems logical. This is especially true for use in longitudinal studies where comparison of Pi10 measurements is of importance. Our study showed that correcting Pi10 for changes in inspiration level improves reliability, agreement and power to detect change. Especially in participants who had large lung volume differences, correcting Pi10 has a great impact on agreement results. When correcting Pi10 for changes in lung volume, 0.38 mm becomes the cut-off to detect significant change because limits of agreement ranged from −0.38 to 0.37 mm. Hence, a change of 16% in Pi10 would be required to be able to identify thickening of the airway wall in a participant with a Pi10 of 2.4 mm. Transforming Pi10 back to airway wall thickness would mean that an actual change in AWT of 0.14 mm of an airway with an internal perimeter of 10 mm is needed in order to detect real change.

Although participants seemed to inspire quite constantly with a median difference in lung volume between two scans of 230 ml, our results showed that when using Pi10 to detect changes over time, correction for these lung volume changes on CT is feasible. The strong correlation between the difference in lung volume and the difference in Pi10 completely disappeared after correcting Pi10. Therefore, the impact of the inevitable difference in lung volume between scans on the variability of Pi10 has been accounted for entirely. Additionally, our results showed that correcting Pi10 for lung volume differences increases the power to detect change in Pi10 over time and improves diagnostic accuracy for COPD. Especially the improvement in specificity is important. If a patient does not inspire completely, lung volumes will be smaller and AWT will be thicker. In order to overcome possible over diagnosis based on AWT measurements, correcting for longitudinal change of lung volume seems therefore necessary.

Data on agreement and reliability of airway wall measurements is limited, since there are very few longitudinal studies of the airways [7]. Acknowledged problems that could arise in longitudinal studies are differences in X-ray dosage, subject position, and volume of inspiration. In this study, we showed that reproducibility of Pi10 derived from low-dose CTs is excellent and improved when correcting for differences in lung volume. Also, limits of agreement narrowed after this correction, resulting in a lower cut-off to differentiate variability from true change in Pi10. As such, the impact of positioning seems limited and a simple correction for differences in inspiration level seems to overcome the problem of getting different results.

Variation in inspiration level between CT acquisitions is common. This is inevitable because inspiration level is not routinely evaluated with spirometry gated CT. When evaluating Pi10 longitudinally, for example when evaluating treatment response, variation in inspiration level could lower the power to detect an effect [22,23]. A robust quantification method is therefore needed in order to compare measurements of airway remodelling. This is also of importance for instance in clinical studies such as genetic association studies [24,25]. Next to inspiration level, image reconstruction techniques are of great importance as well and change in reconstruction kernel might involve change in AWT measurements. Although in this study we utilized identical scanners and

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**Fig. 2.** Bland-Altman plots for Pi10 and Pi10 corrected for lung volume differences. The x-axes show the means of Pi10 of the baseline and follow-up scans; the y-axes show the differences between Pi10 at baseline and follow-up, expressed in mm. Mean differences are shown as a solid line; limits of agreement are shown as dashed lines. (a) Results for Pi10. Mean ± SD difference was −0.02 ± 0.30 mm and limits of agreement ranged from −0.61 to 0.57 mm. (b) Mean ± SD difference for Pi10 corrected for lung volume differences was 0.005 ± 0.19 mm and limits of agreement ranged from −0.38 to 0.37 mm.

Pi10: airway wall thickness at an internal perimeter of 10 mm.

**Fig. 3.** Estimates of sample sizes needed to detect significant changes in non-corrected Pi10 and Pi10 corrected for lung volume differences. Pi10: airway wall thickness at an internal perimeter of 10 mm.

Significantly higher than the model with uncorrected mean Pi10 (p < 0.001). Specificity improved to 68.1% and sensitivity improved to 65.9%.

**4. Discussion**

Because chest CTs are not acquired systematically at total lung capacity or another fixed inspiration level at the vast majority of institutions, correcting AWT measurements for inspiration level seems logical. This is especially true for use in longitudinal studies where comparison of Pi10 measurements is of importance. Our study showed that correcting Pi10 for changes in inspiration level improves reliability, agreement and power to detect change. Especially in participants who had large lung volume differences, correcting Pi10 has a great impact on agreement results. When correcting Pi10 for changes in lung volume, 0.38 mm becomes the cut-off to detect significant change because limits of agreement ranged from −0.38 to 0.37 mm. Hence, a change of 16% in Pi10 would be required to be able to identify thickening of the airway wall in a participant with a Pi10 of 2.4 mm. Transforming Pi10 back to airway wall thickness would mean that an actual change in AWT of 0.14 mm of an airway with an internal perimeter of 10 mm is needed in order to detect real change.

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reconstruction techniques, it is important to be aware of these other sources of variability [26].

The automatic PI10 measurements on CT were derived from airways up to approximately the 10th generation. This means that PI10 is based on measurements of bronchi including cartilage and bronchioles without cartilage. The cartilaginous tissue therefore limits extensibility of the larger airways. However, because not the entire airway is enclosed by cartilage, the airways have some extent of flexibility. This is well demonstrated by Brown and Mitzner who measured AWT during increasing air pressure in canine lungs [12]. They showed that during inspiration airways distend, but reach a maximum size quickly. This indicates that the large airways do not show a linear expansion during inspiration. Even though lumen distention may be more pronounced in more peripheral airways (i.e. without cartilage walls), these airways are not included in the current PI10 measurements. Although correcting PI10 as proposed in this study is based on a linear correction, changes in lung volume were limited and led to modest corrections of PI10 that will improve interpretation of changes in AWT. Nevertheless, future studies should focus on the actual relationship between changes in AWT and changes in lung capacity.

Our study has some limitations. In this study a low-dose CT protocol was applied which could result in masking of AWT changes by image noise. However, airway measurements on low-dose CT have been reported in several studies and can be used with the same approach as with high-dose CT [27,28]. In addition, because lung cancer screening is performed with low-dose CT it is of importance to have knowledge of the reproducibility in low-dose scans. Because of a shared risk for COPD, lung cancer screening participants are of special interest for a longitudinal evaluation of airway wall thickness. To evaluate inter-examination reliability of PI10, we selected participants with a follow-up time less than 100 days with the assumption that PI10 would not alter in this period due to disease progression. While to our knowledge, no important changes occurred in clinical condition and we did not find a correlation between the difference in PI10 and follow-up time, a follow-up CT examination directly after baseline would be more ideal to eliminate changes over time. We evaluated smoking or formerly smoking participants who were relatively healthy during the study period. Caution is therefore needed to extrapolate our results to a younger population, non-smokers or a population with more severe lung disease. Because of the initial design of the lung cancer screening trial, only males could be included in the present study.

In conclusion, we presented reproducibility and agreement results on AWT measured with PI10 and showed that correcting PI10 for changes in lung volume between scans increases reliability, agreement, and power to detect changes over time. Additionally, it improves diagnostic accuracy for COPD. Therefore, correcting PI10 for changes in lung volumes does seem to be beneficial for longitudinal evaluation.

Conflict of interest

Prof. Dr. H.J. de Koning reports grants from ZonMW and from KWF, during the conduct of the study; grants from Roche Diagnostics, non-financial support from Siemens Germany, other support from Roche Diagnostics, and LungCare outside the submitted work. Prof. Dr. J.-W.J. Lammers reports grants from TiPPharma and grants from EU during the conduct of the study. Prof. Dr. B. van Ginneken is co-founder of Thirona BV and reports grants from MeVis Medical Systems, grants from Toshiba, and grants from Delft Imagin Systems, outside the submitted work. Dr. E.M. van Rikxoort is co-founder and shareholder of Thirona BV and reports grants from the Netherlands Scientific Organisation (NWO) during the conduct of this study. Mr. J. Charbonnier is employee of Thirona BV. Dr. P.A. de Jong, Dr. O.M. Mets, Dr. J.-M. Kuhnigk, Dr. P. Zanen, Dr. R. Vliegenthart, Prof. Dr. M. Oudkerk, Dr. F.A.A. Mohamed Hoessein, Drs. E. Pompe have nothing to disclose.

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