

# Repeated Low-Dose Computed Tomography in Current and Former Smokers for Quantification of Emphysema

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**Objective:** To quantify different emphysema evolution in current and former smokers.

**Methods:** We retrospectively analyzed low-dose computed tomography scans from a lung cancer screening study of 59 current and 75 former smokers. The quantitative emphysema analysis was performed using a home-built software (YACTA version 0.9), yielding the parameters lung volume, emphysema volume (EV), emphysema index (EI), mean lung density, and 15th percentile.

**Results:** The baseline EV and EI were significantly different (median  $EV_{\text{former}} = 422$  mL vs  $EV_{\text{current}} = 249$  mL,  $P = 0.0003$ ; and median  $EI_{\text{former}} = 7.6\%$  vs  $EI_{\text{current}} = 4.1\%$ ,  $P = 0.0001$ , respectively). On the annual repeat scan, the median EI and EV for former smokers had decreased significantly ( $\Delta EI_{\text{former}} = -0.257\%$ ,  $P = 0.004$ ; and  $\Delta EV_{\text{current}} = -0.203$  mL,  $P = 0.020$ ), whereas there was no emphysema change in current smokers.

**Conclusions:** We were able to demonstrate different emphysema evolution in current versus former smokers; emphysema parameters decreased in the former smokers and remained stable in current smokers.

**Key Words:** emphysema, quantification, low-dose computed tomography

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Pulmonary emphysema is a frequently progressive destructive lung disease, related to air pollution and cigarette smoking in particular.<sup>1</sup> Both detection and assessment of its morphological extent are commonly performed with computed tomography (CT) of the chest.<sup>2</sup> Computed tomography, however, has not been established beyond mere descriptive assessment and non-standardized grading of emphysema, ranging from none to severe. Any attempts to further quantify the extent of emphysema, to relate emphysema to functional parameters, or to use CT for longitudinal comparisons and measurements have mostly failed. This is in part due to the low interobserver agreement between radiologists,<sup>1</sup> the lack of objective standards, and also the fact that the appearance of emphysema depends to a great extent on the CT data acquisition parameters.<sup>3</sup>

Cohort studies analyzing qualitative and quantitative emphysema parameters, however, have demonstrated to be useful in the assessment of emphysematous parenchymal features.<sup>4</sup> The standardized imaging protocol within a defined research protocol such as a lung cancer screening study offers a unique

opportunity to study the presence and evolution of emphysema in an at-risk group of individuals who have been scanned with identical parameters at repeat time intervals. As such, the purpose of our study was to assess changes in quantitative emphysema parameters derived from annual low-dose CT (LDCT) scans of the chest and furthermore to address whether differences in emphysema evolution can be resolved between former smokers and continuing smokers with ongoing damage of the lung parenchyma.

## MATERIALS AND METHODS

### Study Outline and Study Participants

In 2003, the Department of Medical Imaging at the Princess Margaret Hospital in Toronto became a member of the International Early Lung Cancer Action Project. Following their study protocol, we screen high-risk individuals 50 years or older, as defined by their past or current tobacco consumption ( $\geq 10$  pack-years). The study, as well as the retrospective analysis of the CT scans for emphysema quantification, was approved by our institutional review board. Study participants received a baseline LDCT, as well as (in the absence of any actionable findings) at least 1 repeat annual LDCT. Since September 2006, all screening CT scanning has been performed on the same CT scanner, with identical data acquisition parameters. We visually inspected 140 pairs of CT scans that were obtained with a time interval of at least 1 year and excluded those pairs of CT scans with obvious differences in patient positioning and breathing levels, anatomical differences, and with the presence of artifacts from motion or radiopaque structures both within the body (artificial valves, pacemaker/wires, osteosynthesis hardware) or outside the body (necklace, etc). We included 134 pairs of CT scans without any visually obvious differences in the chest and lung appearance for inclusion in the study.

### Demographics

The study population consisted of 59 current and 75 former smokers; demographics are summarized in Table 1. Among the nonsmokers, the median duration of quitting smoking before the baseline LDCT was 18 years (range, 1–25 years). The 2 populations did not differ in sex, age, and age at smoking onset, but there was a significant difference in the self-reported smoking history, which was considerably lower in the cohort of former smokers.

### CT Scans

All patients underwent repeat LDCT (50 mA, 120 kV) scanning on the same 4-slice scanner (GE LightSpeed QX/i; General Electric Medical Systems, Milwaukee, Wis). Scanner calibration for water was done once a month and on each day of active scanning for air. The repeat LDCT scans were obtained with time intervals ranging from 12 to 14 months (median, 12 months). All scans were obtained in a single breath-hold of approximately 30-second duration, in caudocranial scan direction (to minimize motion artifacts at the end of the breath-hold sequence) in helical

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**TABLE 1.** Demographics of the Group of Current and Former Smokers

	Male/ Female	Median Age (Range), y	Median Pack-Years (Range)	Median Age at Smoking Onset, y
Current	29/30	63 (52–78)	40 (10–60)	17.0
Former	29/46	64 (51–80)	26 (10–55)	17.5

mode, rotation time of 0.8 seconds, and an average dose-length product of 38.6 mGy-cm. Images were reconstructed with 1.25-mm slice thickness at a 50% increment, with a  $512 \times 512$  matrix. The soft kernel reconstructions were used for data postprocessing and emphysema quantification in this study.

### Emphysema Quantification

The stack of around 300 DICOM images per patients was exported and analyzed fully automatically in an unattended mode on a standard PC (1 GB RAM, Windows XP Professional, 2 GHz Pentium 4 processor) in around 9 minutes per study, depending on the amount of emphysema. The software used (YACTA version 0.9) combines different techniques for semi-automated segmentation such as region growing, threshold- and expert-based methods, and morphological analysis. Details can be found elsewhere,<sup>5,6</sup> but in principle, the software operates as follows: the in-house YACTA software is written in C++. No manual interaction was performed. First, automatic lung detection basing on feature recognition of the body and upper thresholding of  $-500$  Hounsfield units (HU) and N7 Boolean operators for detection of both lungs was performed. After recognition of a starting point in the trachea by feature recognition, a volumetric region-growth algorithm was applied to the tracheobronchial tree using an upper thresholding of  $-950$  HU as well as N27 and N7 Boolean operators for the exclusion of the airways down to the 6th to 10th generation. Three-dimensional dilatation and closing were applied to avoid hole in the segmented volumes. A threshold of  $-950$  HU was used with a noise correction for those voxels with a density between  $-910$  and  $-949$  HU that are surrounded by at least 4 voxels with a density of  $-950$  HU or less, applied to the lung parenchyma if necessary because of image noise.

From the CT analysis, the volume of the segmented lung volume (LV; in milliliters) of the segmented emphysema volume (EV; in milliliters), their ratio (pixel index, emphysema index [EI], in %), the volume of excluded tracheobronchial tree vol-

ume, mean lung density (MLD; in HU), and 15th percentile (15th) were calculated automatically. The 15th percentile is defined as the threshold value in Hounsfield units for which 15% of all lung voxels have a lower density value.

On all cases, emphysema analysis was performed both covering the entire lungs (Fig. 1) and limited to the upper lungs, lung apices to carina (Fig. 2). The limited analysis was performed to address the impact on workflow and to decrease processing time as well as to determine if EVs are affected by the increased level of noise often present in the lower portions of chest CT scans (Figs. 3 and 4). The limited analysis was conducted using the identical set of images edited in the YACTA DICOM image editor by selecting and manually deleting the images below the upper apex of the carina. The change in individual emphysema quantification was computed as the difference in EI (DEI) for each case, calculated by subtracting the EI measured on the baseline scan from the EI measured on the repeat scan, plotted against the mean of both EIs; overall  $\Delta$ EI is the sum of the individual  $\Delta$ EIs.

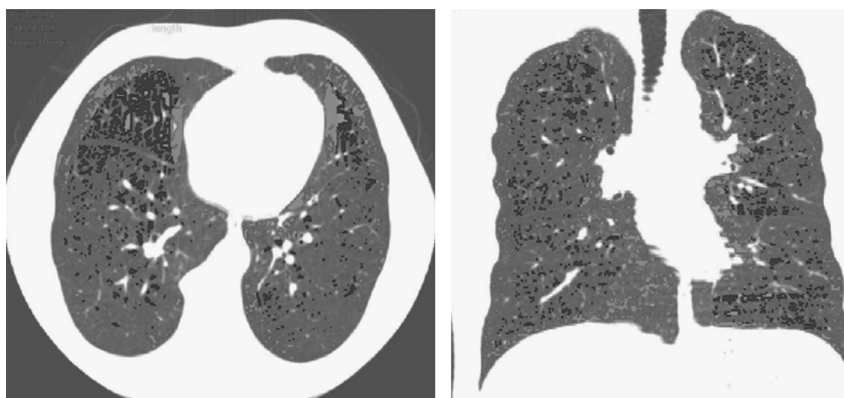
### Statistical Analysis

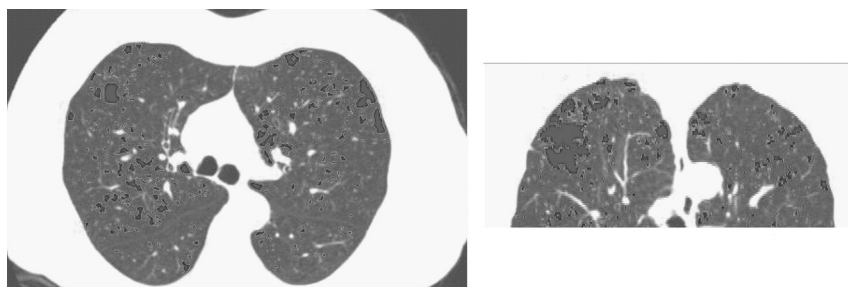
Data are presented as median  $\pm$  SE. Lung volume, 15th percentile, and MLD were compared between the 2 time points and between current and former smokers, using the Bland-Altman test<sup>7–9</sup>; percentage change; and Student *t* test (level of significance  $P < 0.05$ , after verification of normal distribution). The EI and EV were analyzed for interval change using the Bland-Altman test, percentage change, and Wilcoxon signed rank test<sup>10</sup> (level of significance  $P < 0.05$ ). Statistical analysis was conducted using Microsoft Excel 2007, and SPSS version 17.0 (SPSS Inc, Chicago, Ill).

### RESULTS

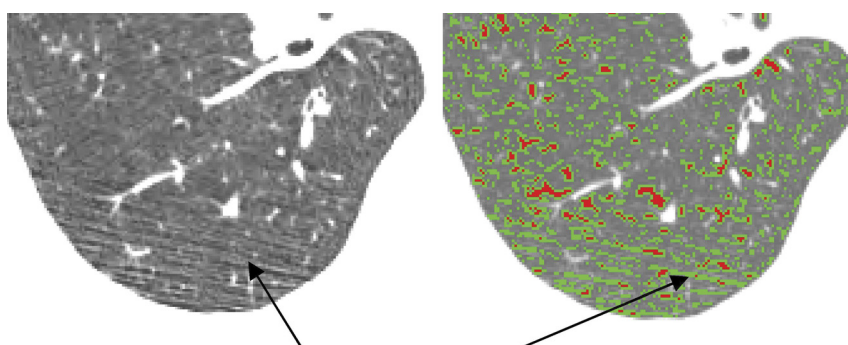
Average YACTA processing time per full-lung CT scan image stack was 1 minute 25 seconds. The baseline emphysema parameters in the 2 cohorts are summarized in Table 2. The quantitative analysis of the baseline scans showed considerably higher emphysema parameters in former smokers compared with the current smokers. Emphysema volume and EI were significantly different between the 2 groups ( $P = 0.005$  and  $P = < 0.000$ , respectively) as were the 15th percentile measurements ( $P = 0.006$ ). The difference in LV and MLD measurements between the 2 groups at baseline was not statistically significant ( $P = 0.06$  and  $P = 0.11$ , respectively).

The average YACTA processing time for the upper-lung CT image stack was 58 seconds. The baseline emphysema parameters are summarized in Table 3. The quantitative analysis

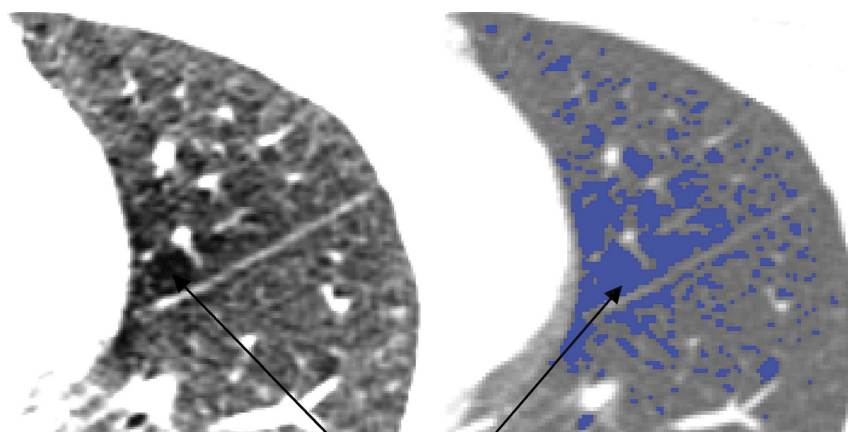
**FIGURE 1.** YACTA visual output of the emphysema quantification of the entire lung.



**FIGURE 2.** YACTA visual output of the emphysema quantification of the upper lung.



**FIGURE 3.** Beam hardening artifacts are seen in the right lower lobe and have been included in the emphysema quantification, represented as green lines on the figure created by the software. Areas of hardening artifact were detected as emphysema.



**FIGURE 4.** Pulsation artifacts are seen as low-attenuation areas in the paracardial parenchyma of the left lower lobe. They have been included in the emphysema quantification by the software, seen as blue areas on the image created by the software.

of the baseline scans continued to show greater emphysema parameters in former smokers compared with the current smokers. Emphysema volume and EI were significantly different between the 2 groups ( $P = 0.018$  and  $P = 0.001$ , respectively).

The average intraindividual difference in emphysema parameters between baseline and annual CT scan among current and former smokers is displayed in Table 4.

The median EI and EV for current smokers did not change significantly ( $\Delta EI$  [ $P = 0.860$ ] and  $\Delta EV$  [ $P = 0.714$ ]), whereas the EI and EV for former smokers decreased over the course of approximately 1 year. In the former smokers, EI and EV were statistically significantly different between the baseline scan and the annual scan  $\Delta EI$  ( $P = 0.009$ ) and  $\Delta EV$  ( $P = 0.020$ ). These results were reproducible when percentage change test was applied (current smokers EI median change = 0%, and EV median change = 0%; former smokers EI median change = -25% and EV median change = -16%). The LV, 15th, and MLD parameters show a similar trend in the group of former smoker and stability in the current smokers, but did not reach statistical significance.

The data from the analysis limited to the supracarinal lung region (Table 5) represent a tendency to emphysema improvement in former smokers over time, whereas there is no relevant change in the emphysema parameters of current smokers.

Restricting the analysis to the upper lungs, the baseline and annual EI and EV for current smokers were not significantly different ( $P = 0.179$  and  $P = 0.316$ , respectively). However, the EI and EV for former smokers were significantly different ( $P = 0.0002$  and  $P = 0.001$ , respectively). The median percentage change for current smokers EI was -6.2% and EV change = -0.4%. The former smokers' median percentage change for EI = -34% and EV median change = -35%. A graphical depiction of the variation in current and former smokers EI values can be seen in Figure 5. The same trends can be observed occurring in both the full-lung and limited-lung analysis.

There was no difference in total LV or upper LV between the baseline and follow-up scans; in smokers, the  $\Delta LV$  for the full-lung analysis was  $0.030 \pm 0.014$ , and for the upper-lung analysis,  $0.044 \pm 0.013$ ; in former smokers, the  $\Delta LV$  was  $0.033 \pm 0.049$  for the full-lung and  $0.037 \pm 0.018$  for the upper-lung analysis. A systematic difference was observed in the LV between the full-lung and upper-lung analysis in both current and former smokers.

## DISCUSSION

Using identical CT scanning parameters in annual intervals, we were able to demonstrate differences in the evolution of emphysema in current versus former smokers. Our analysis

**TABLE 3.** Emphysema Parameters Calculated by the Software From the Analysis of the Upper Lungs in Current and Former Smokers

	Current, Median $\pm$ SE	Former, Median $\pm$ SE	P
EI, %	4.5 $\pm$ 0.9	7.2 $\pm$ 0.8	0.018
EV, mL	78 $\pm$ 18	112 $\pm$ 13	0.001
LV, mL	1640 $\pm$ 89	1454 $\pm$ 40	NS
15th Percentile, HU	-916 $\pm$ 2.7	-925 $\pm$ 2.7	0.015
MLD, HU	-827 $\pm$ 2.9	-834 $\pm$ 3.5	NS

NS indicates not statistically significant.

showed a tendency toward decrease in emphysema parameters in the group of former smokers. These results were found when analyzing the entire lung or when limited to the upper lungs only.

Emphysema is commonly regarded as an irreversible destruction of the lung parenchyma.<sup>11</sup> As such, the fact that the EI in former smokers decreases over time does require further physiological explanation. We may hypothesize that some of the improvement is related to decreasing bronchiolitis after smoking cessation.<sup>12</sup> This would indicate that some of the voxels counted as emphysema in reality belong to air trapping. Our study is limited by additional functional information on the lung to further support this hypothesis, and this needs to be addressed in future studies, which should include expiratory scanning to address the presence of air trapping.

Of note, the cohort of former smokers had a significantly higher baseline EI than the current smokers, which surprisingly was not mirrored by a higher smoking history in this group. The smoking cessation might have been a result of the emphysema, as the subjectively recognized physical impairment by emphysema or a physical improvement during an incidental time of abstinence might have helped some of the former smokers to stop smoking. This baseline difference might influence our findings in the emphysema evolution, as it might be that more severe emphysema—as seen in the cohort of former smokers—has more “reversible” areas than the overall less pronounced emphysema in current smokers. However, some of the baseline difference in the smoking history might simply be artifactual (Figs. 3 and 4), as the smoking history is self-reported and the true extent of remote smoking might be remembered incorrectly. Our numbers are currently too small to support or reject any of

**TABLE 2.** Emphysema Parameters Calculated by the Software From the Analysis of the Full Lungs in Current and Former Smokers

	Current, Median $\pm$ SE	Former, Median $\pm$ SE	P
EI, %	4.1 $\pm$ 0.6	7.6 $\pm$ 0.7	0.005
EV, mL	249 $\pm$ 41	422 $\pm$ 43	0.005
LV, mL	5657 $\pm$ 172	5428 $\pm$ 133	NS
15th Percentile, HU	-915 $\pm$ 2.3	-925 $\pm$ 2.6	0.006
MLD, HU	-819 $\pm$ 3.0	-827 $\pm$ 3.8	NS

NS indicates not statistically significant.

**TABLE 4.** Changes in Emphysema Quantification Parameters From the Baseline to the Annual CT Scan, in Current and Former Smokers, Based on the Analysis of the Entire Lung

	Current, Median $\pm$ SE	P	Former, Median $\pm$ SE	P
$\Delta EI$ , %	-0.018 $\pm$ 0.082	0.860	-0.257 $\pm$ 0.082	0.009
$\Delta EV$ , mL	0.008 $\pm$ 0.085	0.714	-0.203 $\pm$ 0.084	0.020
$\Delta LV$ , mL	0.030 $\pm$ 0.014	NS	0.062 $\pm$ 0.018	NS
$\Delta 15th$ Percentile, HU	0.002 $\pm$ 0.002	NS	0.000 $\pm$ 0.002	NS
$\Delta MLD$ , HU	0.007 $\pm$ 0.003	NS	0.007 $\pm$ 0.002	NS

NS indicates not statistically significant.



**TABLE 5.** Changes in Emphysema Quantification Parameters From the Baseline to the Annual CT Scan, in Current and Former Smokers, Based on the Analysis of the Upper Lung

	Current, Median $\pm$ SE	<i>P</i>	Former, Median $\pm$ SE	<i>P</i>
$\Delta$ EI, %	$-0.009 \pm 0.106$	0.179	$-0.393 \pm 0.089$	0.0002
$\Delta$ EV, mL	$-0.064 \pm 0.107$	0.316	$-0.344 \pm 0.089$	0.001
$\Delta$ LV, mL	$0.044 \pm 0.013$	NS	$0.060 \pm 0.024$	NS
$\Delta$ 15th Percentile, HU	$0.001 \pm 0.002$	NS	$-0.003 \pm 0.002$	NS
$\Delta$ MLD, HU	$0.005 \pm 0.002$	NS	$0.004 \pm 0.002$	NS

NS indicates not statistically significant.

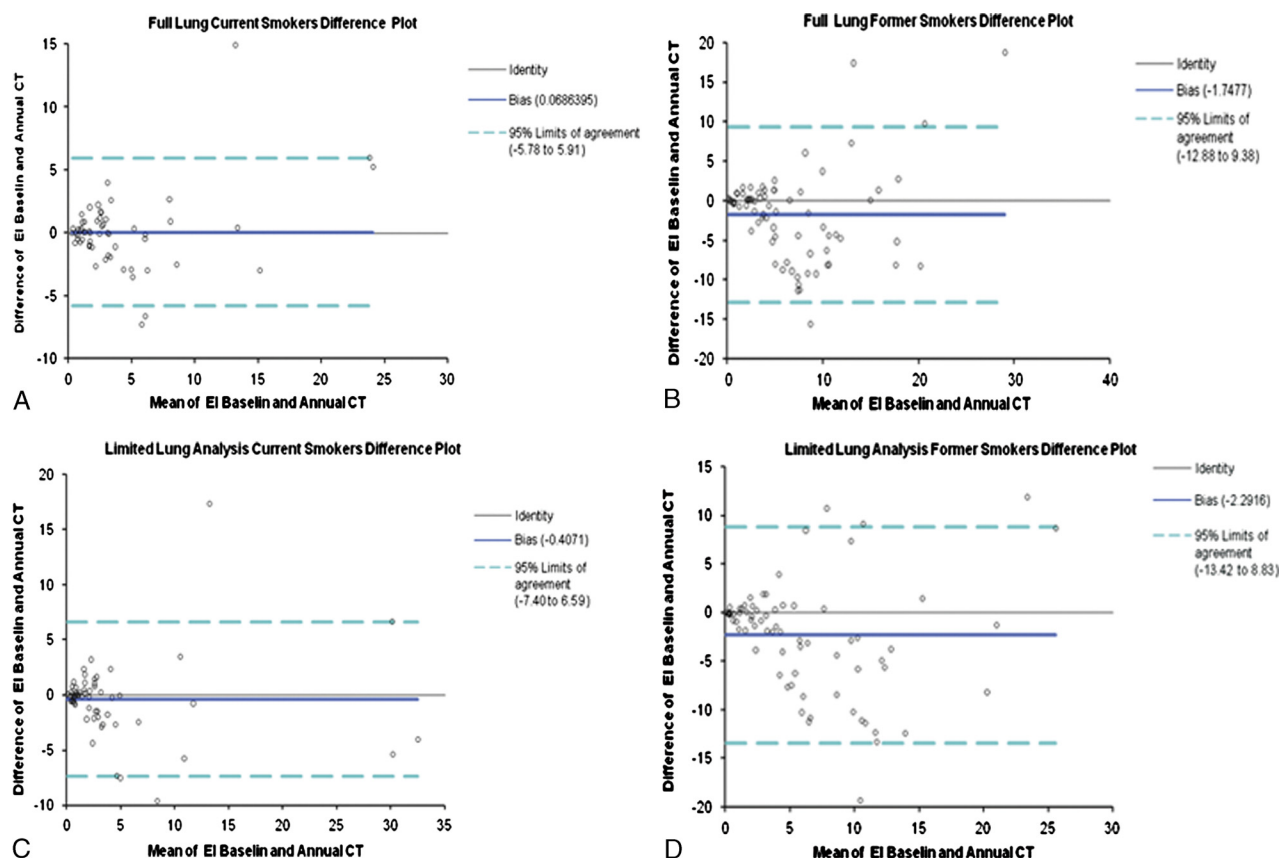
these hypotheses and will need to be addressed in further larger cohort analyses.

Even though our study design provides identical scanning parameters in annual intervals, which is required for emphysema comparison,<sup>13,14</sup> intraindividual variation is inherent. Reproducible emphysema quantification on a cohort level with substantial intraindividual variation has been documented before.<sup>9</sup> Parameters interfering with the reproducibility of emphysema measurements lie not only in methodological limitations and technological variations of the CT scanner, but mainly in phys-

iological variability of the patients and their lungs (eg, respiratory depth, patient positioning).<sup>15</sup> One potential way to address this is scanning in expiration rather than inspiration, which has been shown to better reflect pulmonary function test abnormalities than inspiratory scans.<sup>16</sup> The purpose of this study, however, was rather to evaluate the natural progression of a disease in a cohort of individuals with risk factors, thus averaging the intra-individual comparison.

The fact that the analysis can be limited to the upper lungs is helpful for future application when large numbers of CT examinations need to be processed in a timely fashion. The time saved by limiting the analysis was approximately 30 seconds per image stack, whereas manual deselection also requires time. That the results are consistent makes physiological sense because those lung areas that are mostly affected by smoking-related emphysema, that is, the upper lobes, are included in the analysis, and those areas that are most susceptible for artifacts from respiratory and cardiac motion are excluded, which should make the analysis more robust.

Our study is limited by the lack of correlation with pulmonary function parameters. Spirometry is not part of the lung cancer screening program and thus was not available in this retrospective study. Moreover, we analyze only the YACTA quantitative parameters. We did not perform a comparison of the quantitative YACTA assessment with radiologists' qualitative emphysema scoring. Not only is this difficult to achieve in a retrospective study, where the LDCT scans have been read by



**FIGURE 5.** Bland-Altman plots for current and former smokers' full-lung and limited-lung analysis. The plots depict the mean of the EI from the baseline and annual scans, plotted against the difference in EI from the baseline to annual scans. The bias is shown as a solid blue line; the limits of agreement are shown with a dashed line. A value above the upper limit or below the lower limit has a 95% likelihood to be a real progression or regression of emphysema.

several radiologists in a nonstandardized emphysema assessment. Visual grading is also compromised by low interobserver agreement,<sup>1</sup> which would make a radiologist's reading a very weak standard.

A software such as YACTA is a promising tool for monitoring disease progression over time and for monitoring the effect of treatment. Currently, patients with emphysema and COPD are followed up with spirometry and morphological imaging. Spirometry gives functional information on the entire lungs only, whereas the presented YACTA-based analysis yields information separately for each lobe. With such computer assisted detection systems, interventions such as smoking cessations can be monitored, and the effectiveness of new treatment strategies can be evaluated with better spatial resolution than pulmonary function parameters.

In summary, this study showed that emphysema quantification can resolve the difference in emphysema evolution in a cohort of current and former smokers and promises an understanding of the pathophysiology of smoking-related diseases. Further studies are planned, which will include expiratory scanning and correlation with spirometry.

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