Aims and objectives

Purpose:

To evaluate the reliability of pulmonary quantitative measurements of multi-detector row computed tomography (MDCT) in low-dose settings with iterative reconstruction (IR).

Key Points:

# The TLC is a reliable parameter even in low-dose setting.

# The TLC, LAA%, LAAC, and Non-LAAC are stable in low-dose settings with IR.

# The LAA% and MLD are unreliable in low-dose setting without IR.

Introduction:

Multi-detector row computed tomography (MDCT) is a promising tool for 3-dimensional evaluations of the lung [1 on page ]. At present, a routine MDCT scan of the whole lung can be completed within one breath-hold, and the continuous nature of the data acquisition allows 3-dimensional volumetric scanning with detailed spatial resolution in isotropic voxels sub-millimeter in size (e.g., 0.625 x 0.625 x 0.625 mm). Such 3-dimensional data acquisition allows for both volumetric and densitometric analysis. As a result, the interest in such quantitative analysis has been growing among researchers in chest radiology, especially in the area of pulmonary function evaluation for chronic obstructive lung disease (COPD). Several technical and methodological issues have already been recognized in terms of how to optimize the quality of source data for chest CT images [2-11 on page ].

Many studies have looked at the accuracy of the image quality of chest CTs, using combinations of iterative reconstruction and low-dose techniques, optimizing CT parameters such as slice-thickness (mm), tube voltage (kVp: kilo-volt peak) and effective tube current time product (mAs: milli-ampere second) [1 on page ; 12-15 on page ]. It is well known that slice-thickness is an essential parameter that greatly affects the quality of MDCT data of the lung [2 on page ; 9 on page ; 11 on page ]. The intra-voxel pulmonary structures are averaged to produce a single CT number in the corresponding pixel. The thicker the slice, the more pulmonary structures are averaged to convert the voxel data, resulting in varied attenuation of the normal lung parenchyma. Other fundamental parameters include the combination of sufficient radiation-dose and reconstruction algorithm [12 on page ]. Maintaining radiation doses according to the "as low as reasonably achievable" (ALARA) policy is
considered to have improved the signal-to-noise ratio without increasing the tube voltage or effective tube current time product. Recent developments in iterative reconstruction (IR) algorithms provide better quality CT images at low-doses than former analytic reconstruction algorithms such as the filtered back projection (FBP) technique.

To the best of our knowledge, there have been few studies of how improvements in the image quality of low-dose chest CT with IR have affected pulmonary quantitative measurements, such as total lung capacity (TLC), mean lung density (MLD), and percent low-attenuation area (LAA%), as potential biological markers in vivo [13 on page ; 14 on page ]. The purpose of this study is to evaluate the reliability of pulmonary quantitative CT measurements in low-dose settings using the hybrid IR technique.
Methods and materials

A chest phantom

This study evaluated a commercially available chest phantom (LSCT001; Kyoto Kagaku, Kyoto, Japan) that has been widely used in Japan to research simulated nodular ground-glass opacities (GGOs) of the lung. The normal lung parenchyma is simulated using a composite of Styrofoam and hard urethane foam powders in a urethane-resin adhesive, and the targeted CT value is -900 HU. A total of 24 simulated GGOs with a targeted value of -800 HU were bilaterally distributed at the level of the lung apex, tracheal bifurcation, and base. The diameters of the simulated GGOs were 6, 8, 10, and 12 mm. The simulated normal lung parenchyma occupied a sufficient volume, compared to the GGOs, to perform a quantitative analysis. The chest phantom replicated an anthropomorphic thoracic architecture in the arms-raised position. The chest wall consisted of a substance radio-graphically equivalent to water and ribs, and the mediastinum and vertebral bones were of the same substance. It was not necessary to consult the ethical review board of our institution for this study.

MDCT scan protocols and reconstruction algorithms

All of phantom studies were performed using a 256-section MDCT system (Brilliance iCT, Philips Healthcare, Cleveland, Ohio, USA). Imaging parameters were as follows: tube voltage, 120 kVp; focal-spot size, small; detector collimation, 128 x 0.625 mm; beam pitch, 0.586; table speed, 93.76 mm per gantry rotation; scan field of view (FOV), 320 mm; slice-thickness, 2 mm and 0.625 mm. The slice-thickness of 2 mm was considered to be a typical high-resolution tomographic data setting; that of 0.625 mm, a typical 3-dimensional volumetric data setting. The effective tube current time product (mAs) was defined as 100 mAs for the standard-dose setting and 30 mAs for the low-dose setting. An automatic exposure control was added in each study. Three combinations of CT parameter settings were selected with the effective tube current time product and reconstruction algorithm as follows: 100 mAs for intermediate-dose using an FBP technique; 30 mAs for low-dose using an FBP technique; and 30 mAs for low-dose using an iterative reconstruction (IR) technique (iDose). The IR technique attempts to reproduce the noise power spectrum observed in images created with the FBP technique, which represents a standard chest radiology noise texture, and reduces the image noise via a compensatory factor of 0.71. This net factor of 1.0 implies approximate noise level equivalency between the low-dose setting with the IR technique and the standard-dose setting with FBP technique. The CT scanner stability was routinely assessed with quality check-ups using a water cylinder phantom.

Quantitative MDCT measurements of the chest phantom
All CT data sets were transferred to a commercially available workstation (Volume Analyzer, SYNAPSE-VINCENT, Fujifilm, Tokyo, Japan), which was equipped with an image analysis application for the lungs. Simulated airways and lungs were eliminated from the volumetric MDCT data of the chest by density thresholding (Figure 1); pulmonary quantitative measurements were then automatically produced, including total lung capacity (TLC), mean lung density (MLD), and percent low-attenuation area (LAA %). Additionally, we calculated low-attenuation area capacity (LAAC) and non-low-attenuation area capacity (Non-LAAC) with the following formulas: $\text{LAAC} = \text{TLC} \times (1 - \text{LAA} \%/100)$; $\text{Non-LAAC} = \text{TLC} \times \text{LAA} \%/100$.

The CT density numbers ranged in the histogram for each measurement as follows: from -1024 to -250 Hounsfield unit (HU) for TLC and MLD, from -1024 to -950 HU for LAA% and LAAC, and from -950 to -250 HU for Non-LAAC.

**Fig. 1**: An example of the workstation display (Volume Analyzer, SYNAPSE-VINCENT, Fujifilm, Tokyo, Japan) with effective tube current time product of 100 mAs, tube voltage of 120 kVp, FBP reconstruction, and slice-thickness of 2mm. (A) An axial CT image of the lung phantom; (B) an automatically extracted 2-dimensional image; and (C) an automatically extracted 3-dimensional volumetric image. The attenuation values range from -1200 to -250 HU for the extracted lung. All of phantom images were obtained using 256-section MDCT (Brilliance iCT, Philips Healthcare, Cleveland, Ohio, USA).
Statistical analysis of quantitative MDCT measurements

Results of the quantitative measurements were expressed as means ± the intermediate deviation of mean for the TLC, MLD, LAA%, LAAC, and Non-LAAC, with slice-thicknesses of 2 mm and 0.625 mm. The statistical differences between these measurements were determined by two-paired Student's t test between the standard-dose setting with effective tube current time product of 100mAs and low-dose setting of 30mAs, with or without IR. Differences with P < 0.05 were considered significant.

Visual assessment of pulmonary surface map

Pulmonary surface maps of the low-CT, numbered from -1200 to -800 HU in a 10-color overlay, were visually assessed by four chest radiologists (YM, TK, MY, and YY). Subjective quantification of each pulmonary surface map focused on the distribution of the red to yellow overlay, corresponding to the low-attenuation area (LAA) of from -1200 to -900 HU, with a wide range offset. The CT numbers of the estimated normal lung were visualized by a 10-color scale in the following order: red, brown, orange, yellow, light-green, dark-green, sky-blue, blue, indigo and violet, ranging from -950 to -800 HU. Typical LAA were prearranged in the right base of the chest phantom (Figure 2). Since there is no standard method to be referenced for 10-color overlays, we performed only a subjective assessment without visual scoring in this study.

Fig. 2: (A) An axial 2-dimensional image, and (B) a 3-dimensional surface map of simulated lungs are automatically extracted with a 10-colors scale in the following
order: red, brown, orange, yellow, light-green, dark-green, sky-blue, blue, indigo and violet, ranging from -1200 to -800 HU. Most of the lungs appear as green to blue. Both images were simultaneously generated from the MDCT data with effective tube current time product of 100 mAs, tube voltage of 120 kVp, a FBP reconstruction and slice-thickness of 2 mm.

References: Molecular imaging & diagnosis, Graduate School of Medical Sciences, Kyushu University - FukuokaJP
Results

The TLC was constant as a simple volumetric CT parameter. The TLC, LAA%, LAAC, and Non-LAAC were equivalent in the effective tube current time product of 100mAs with FBP and 30mAs with IR. The quantitative CT measurements are summarized in Table 1-A (2-mm slice thickness) and Table 1-B (0.625-mm slice thickness) as means ± intermediate deviation of mean for the TLC, MLD, LAA%, LAAC, and Non-LAAC. Reproducibility of the TLC, MLD, LAA%, LAAC, and Non-LAAC varied more at the low-dose than at the standard-dose setting at both slice thicknesses.

Table 1-A
Summery of quantitative CT measurements for the lung with slice-thickness of 2mm at different effective tube current time product and reconstruction algorithm

<table>
<thead>
<tr>
<th></th>
<th>100 mAs</th>
<th>30 mAs</th>
<th>30 mAs with IR</th>
<th>Difference 100 vs 30 mAs</th>
<th>Difference 100 vs 30 mAs with IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC (ml)</td>
<td>4939.87±0.12</td>
<td>4942.13±0.10</td>
<td>4939.43±4.19</td>
<td>2.3*</td>
<td>NS</td>
</tr>
<tr>
<td>MLD (HU)</td>
<td>-848.55±0.12</td>
<td>-850.23±0.31</td>
<td>-847.95±0.30</td>
<td>-1.7*</td>
<td>0.6*</td>
</tr>
<tr>
<td>LAA% (%)</td>
<td>2.43±0.05</td>
<td>6.15±0.14</td>
<td>2.43±0.10</td>
<td>3.72*</td>
<td>NS</td>
</tr>
<tr>
<td>LAAC (ml)</td>
<td>120.20±2.55</td>
<td>303.94±6.81</td>
<td>120.19±5.06</td>
<td>184*</td>
<td>NS</td>
</tr>
<tr>
<td>Non-LAAC (ml)</td>
<td>4819.66±2.53</td>
<td>4638.19±6.89</td>
<td>4819.24±7.64</td>
<td>-182*</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 2
References: Molecular imaging & diagnosis, Graduate School of Medical Sciences, Kyushu University - Fukuoka/JP
Table 1

References: Molecular imaging & diagnosis, Graduate School of Medical Sciences, Kyushu University - Fukuoka/JP

Using the low-dose setting of 30mAs with FBP, the MLD and Non-LAAC were considerably lower compared to 100mAs with FBP in both slice-thicknesses; meanwhile, the LAA% and LAAC were increased as mirror opposites. When the slice-thickness was 2 mm, there was no significant difference between the quantitative parameter at 30mAs with IR and 100mAs with FBP in the TLC, LAA%, LAAC, or the Non-LAAC; there was a slight difference in the MLD. The difference was significant enough to quantify the MLD, the LAA%, and the LAAC, even in the isotropic slice-thickness of 0.625 mm.

Pulmonary surface maps with 10-color overlays visualized subtle differences in the homogeneity of the low-attenuation area (Figure 3). Four chest radiologists announced almost the same impression about the distribution and uniformity of the 10-color overlay at the surface of the lung phantom.
Fig. 3: Three-dimensional surface maps of the lung phantom at different combinations of effective tube current time product and reconstruction technique are shown using CT data of slice thickness 2 mm (A) 100mAs with FBP; (B) 30mAs with FBP, and (C) 30mAs with IR. There is no significant difference in the color configuration, but subtle differences in color uniformity were observed in the prearranged low-density area at the base of the simulated lung. The color gradient of red to yellow, which represented CT numbers of about -1000 to -900 HU, was mostly apparent at the right lung base in the 3-dimensional surface maps with 100mAs with FBP (A). The low-attenuation area was most extensive at 30mAs with FBP (B). The extension of red within yellow was stabilized in the image at 30mAs with IR (C), similar to that at 100mAs with FBP.

References: Molecular imaging & diagnosis, Graduate School of Medical Sciences, Kyushu University - Fukuoka/JP
Conclusion

Discussion:

MDCT is a powerful diagnostic tool with regard to high scan speed, detailed spatial resolution, and reasonable, low-dose utilization of radiation exposure [1 on page 1]. A scan range of the whole lung can be completed within a breath-hold. Isotropic or near-isotropic spatial resolution in routine thin-slice CT exams enables 3-dimensional data sampling for quantitative analysis of the lung. However, such objective CT measurements continue to be underutilized in clinical settings due to unclear diagnostic value and lack of standardization of scanning parameters [2 on page 2]. Several quantitative CT measurements, such as TLC, MLD, and LAA%, are now automatically produced via commercially available workstations able to recognize whole lungs, trace the shapes of lungs, calculate histograms of CT numbers, and measure the lung area occupied by voxels included in the pre-calculated threshold of density.

The TLC, one of the fundamental CT measurements, allows reasonably objective quantification of the lung during inspiration. Since the development of MDCT, several quantitative pulmonary studies have addressed TLC during inspiration without the IR technique (Table 2) [3-7 on page 3]. The semi-automatic extraction methods for TLC usually include an upper density threshold of between -200 and -500 HU, i.e., the 15th percentile point, which is defined as a threshold range below 15% of all voxels in the lung [6 on page 6]. Recent reports on these automatic extraction methods using commercially available workstations have noted a reduction in operator-dependent variability [3 on page 3; 4 on page 4].

Kermerink et al. reported that the effect of the upper limit of the density-threshold, usually from -500 to -200 HU, was not substantial for the TLC of a chest phantom, with less than a 3.2% per 100 HU decrease in standard dose setting [7 on page 7; 8 on page 8]. They also reported that the differences were much smaller and probably more acceptable than for the other sensitive measurements of scanning protocols, such as MLD and LAA% [5 on page 5; 9 on page 9]. In our chest phantom study, the stability of the TLC proved satisfactory at both the standard-dose and low-dose setting. The minimal effect for the TLC is considered via the effective tube current time product or reconstruction algorithm.

Although TLC is strongly dependent on the degree of inspiration in vivo, the simulated stability of the measurement is a strong argument for the routine use of quantitative MDCT data. The utility of the TLC on volumetric CT during inspiration has been limited, but we should focus on the significant correlation between TLC and residual volume in the pulmonary function test (PFT) [7 on page 7; 10 on page 10; 11 on page 11; 16 on page 16].
Not only for routine CT exams, but also for paired inspiratory/expiratory or 4-dimensional volumetric CT, TLC should be recognized as a stable measurement for pulmonary quantitative CT analysis even in low-dose settings. The thicker the slice, the more pulmonary parenchyma are averaged to convert the voxel data; thus, the TLC on CT increases due to the partial volume effect. However, we found only a 10-ml difference between slice thicknesses of 0.625 mm and 2 mm, corresponding to 0.2% of the TLD of the simulated lung in our study.

The MLD is related to the degree of pulmonary inflation, as well as to pulmonary circulation in vivo. This measure has been reported to be a favorable predictor of pulmonary function [5 on page ; 6 on page ; 16-18 on page ]. The MLD is correlated with forced expiratory volume in the first second (FEV1), and the ratio of FEV1 to forced vital capacity (FEV1/VC) in the PFT, especially in a paired inspiratory/expiratory CT scan. The TLC on CT is significantly correlated with the MLD, demonstrating a mirror-opposite relationship [3 on page ; 5 on page ]. The reproducibility of the MLD as a densitometric measurement in the lung, which is estimated to be better than 2-3% in a standard-dose setting, is degraded with suboptimal results in low-dose settings with FBP [11 on page ]. In our chest phantom study, the MLD in effective tube current time product of 30mAs with FBP decreased 1.7 HU at slice thickness of 2 mm, and 0.5 HU at slice thickness of 0.625 mm compared to that in 100mAs with FBP. The adaptation of IR in effective tube current time product of 30mAs increased the MLD by 2.3 HU for the 2-mm slice thickness, and 1.5 HU for the 0.625-mm slice. The effect of IR reduced image noise while increasing the signals for the MLD in the simulated lung. The optimization of the IR, therefore, tips the balance in favor of quantitative analysis in the low-dose setting.

The LAA% has been defined as the percentage of voxels with lung density of less than thresholds of -950 HU (which are still acceptable for thin-slice CT data below 2 mm) [19 on page ; 20 on page ]. Muller et al. originally proposed the concept of LAA%, also called the "Density Mask" or the "Emphysema Index", with a threshold of -910 HU for the objective quantification of pulmonary emphysema [14 on page ; 21 on page ]. The LAAC was calculated sequentially from the LAA% and the TLC. The LAA% and the LAAC show remarkable dependency upon the scanning protocol, so that the simple reduction of effective tube current time product without IR brings about suboptimal results for these measurements. Mets et al. reported the considerable effect of IR, showing a significant change in LAA% at effective tube current time product of 30mAs among 83 subjects, who were at baseline current or former smokers between the ages of 50 and 75 years [13 on page ]. Comparable results of the LAA% and the LAAC were observed in our phantom study. The LAA% of 30mAs with an IR showed no significant difference to that of 100mAs with FBP, which has been considered the standard scanning protocol for chest CT. The LAA% should be optimized carefully with appropriate scanning protocols. The noise reduction via an IR effectively compensates for the low-dose setting in quantitative CT measurements, especially the LAA%, LAAC, and Non-LAAC. At a slice-thickness of 0.625 mm, the MLD, LAA%, and LAAC were
more varied and unstable than at 2 mm. We recommend a slice thickness of 2 mm for quantitative thin-slice CT in a low-dose setting with IR.

The Non-LAAC was calculated from the LAAC and the TLC. The density for the Non-LAAC ranged from -250 to -950 HU, which could be divided into two groups, "estimated normal lung (-800 to -950 HU)" and "estimated opacity" (-250 to -800 HU). "Estimated opacity" could be said to be a rephrase of "ground-glass opacity (GGO)", but with a smaller increase in density in which the definition of the margins of pulmonary vessels and airway walls appear subjectively to be preserved. Several researchers have addressed the density of localized-GGOs, including atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), micro-invasive adenocarcinoma (MIA), invasive adenocarcinoma (IA), and fibrosing pneumonia (FP), discovering ranges from about -100 to -800 HU [22-24 on page __] in a standard-dose setting with FBP. The recognition of such density ranges in localized-GGOs is important, because the contrast between normal lung and localized-GGOs affects the image quality of chest CTs in terms of both subjective interpretation and objective quantification of lungs. The density of lungs is relatively low and very homogeneous, consisting of air-filled spaces of about -950 to -1000 HU within nearly water-equivalent soft-tissue of about 0 HU, which needs the optimization of offset at air density and non-linear partial volume effect, or averaging from the surrounding structure of the lung parenchyma. In our prior phantom study, in terms of contrast to noise ratio (CNR) at 1-mm slice-thickness between simulated lungs and localized-GGOs, as well as the detectability of localized-GGOs, there was no significant difference between the low-dose setting at effective tube current time of 50mAs with IR and the standard-dose setting at 200mAs with FBP [15 on page __]. Similarly, there were no significant differences in Non-LAAC between 100mAs with FBP and 30mAs with IR.

We performed visual assessments using 10-color overlay for the 3-dimensional CT data with a density of less than -800HU, corresponding to "estimated air-space (less than -950 HU)" and "estimated normal lung (-950 HU to -800 HU)". Recently, Galban et al. adapted 3 colors to an overlay extraction (-1000 HU to -500 HU), e.g. red for emphysema (<-950 HU at inspiration), yellow for gas trapping (<-856 HU at expiration), and green for normal (approximately 700 HU), to determine breathing ability during an inspiratory and expiratory CT scan [25 on page __]. A variety of applications are expected to emphasize regions of interest using a recognizable color overlay in the low-density area of the lung, which is usually represented as black areas in a gray scale. In our experience, the superimposed 10-color overlay for areas with less than -800 HU provided not only an enhanced ability to assess lung CT image quality, but also allowed a more comprehensive interpretation of lung lesions with relatively low density, such as localized GGO, mosaic perfusion, air-trappings, or emphysema. We believe that use of color overlay to enhance density ranges of less than -800 HU could soon play a more important role in this era of the quantitative chest CT, as it can confirm the presence, extent, or activity of lung diseases viscerally. In our phantom study, the images at effective dose time product of
30mAs or 100mAs showed subtle differences in the balance of colors in the lung. The gradient of red to yellow, which represented CT numbers of about -1000 to -900 HU, was similar for the images created with 30mAs with IR and 100mAs with FBP.

The appropriate use of qualitative chest CT protocols in a low-dose setting for clinical indication requires further investigation. Since the first qualitative assessments in thin-slice CT with low-dose were reported, there has been no general consensus regarding minimal clinically acceptable scanning parameters for chest CT [12 on page; 26 on page]. Low-dose settings of less than 20mAs with FBP should be used carefully, because detectability of pulmonary nodules will be degraded. In our prior qualitative study using the same CT scanner, the detectability of localized GGO with a diameter of 6 mm in a chest phantom was significantly lower at 20 mAs with IR than at 100mAs with FBP [25 on page]. Acceptable low-dose settings with IR for chest CT should be optimized for both qualitative and quantitative assessment.

This study has potential limitations. First, our results were obtained from the typical settings of a single CT vendor, and could be altered by different de-noising levels and algorithms for IR. Further studies using other CT scanners with IR are warranted to see if they produce different results. Second, the effects of other scanning parameters, such as tube voltage, helical pitch modifications, high spatial-frequency kernels, automatic exposure controls, and imaging filters, were not evaluated. Third, a chest phantom study cannot fully emulate human lungs anatomically, and does not produce a motion artifact from the heart and lungs in vivo. However, the controlled environment of the phantom study can equalize confounding variables that would affect pulmonary quantitative measurements and can complement knowledge that may not be ethically reproducible in human subjects.

**Conclusion:**

In our chest phantom study, pulmonary quantitative measurements using MDCT data was reliable in a low-dose setting with a hybrid IR, as well as in a standard-dose setting with an FBP. Careful optimization is sufficient for CT measurements with an appropriate scanning protocol.
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References


