B. M. Keller, A. P. Reeves, R. G. Barr, D. F. Yankelevitz, and C. I. Henschke. "Variation compensation and analysis of diaphragm curvature analysis for emphysema quantification on whole lung CT scans,"In *Medical Imaging 2010: Computer-aided Diagnosis*, N. Karssemeijer, R. M. Summers, eds., vol. 7624, pp. 762432, 2010.

http://dx.doi.org/10.1117/12.844012

# Variation Compensation and Analysis on Diaphragm Curvature Analysis for Emphysema Quantification on Whole Lung CT Scans

Brad M. Keller[a*], Anthony P. Reeves[b], R. Graham Barr[c], David F. Yankelevitz[d], and Claudia I. Henschke[d]

[a]Department of Biomedical Engineering, Cornell University, Ithaca, NY, USA;

[b]School of Electrical and Computer Engineering, Cornell University, Ithaca, NY, USA;

[c]Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY, USA;

[d]Department of Radiology, Weill Medical College of Cornell University, New York, NY, USA

## ABSTRACT

CT scans allow for the quantitative evaluation of the anatomical basis of emphysema. Recently, a non-density based geometric measurement of lung diaphragm curvature has been proposed as a method for the quantification of emphysema from CT. This work analyzes variability of diaphragm curvature and evaluates the effectiveness of a compensation methodology for the reduction of this variability as compared to the emphysema index. Using a dataset of 43 scan-pairs with less than a 100 day time-interval between scans, we find that the diaphragm curvature had a trend towards lower overall variability over emphysema index (95% CI: -9.7 to +14.7 vs. -15.8 to +12.0), and that the variation of both measures was reduced after compensation. We conclude that the variation of the new measure can be considered comparable to the established measure and the compensation can reduce the apparent variation of quantitative measures successfully.

**Keywords:** X-ray Computed Tomography, Computer-aided Diagnosis, Emphysema, Diaphragm, Curvature, Variation analysis

## 1. INTRODUCTION

Since the introduction of high-resolution, multi-row detector CT, radiologists have been able to view the anatomical basis of emphysema from CT scans. Emphysema is defined clinically as the destruction and breakdown of the alveolar air sacs in the lung. This creates what are known as emphysematous regions, or low-attenuation areas, of the lung parenchyma. Visually, emphysematous regions are described in CT as being regions of lung parenchyma that are of a significantly low density. This allows for a qualitative scoring of the extent to which an individual has emphysema present in the lungs. Computer-based scoring systems have been developed that extend this concept to allow for quantitative evaluation of emphysema from CT scans, with the majority of methods focusing on the use of density information as the primary index, either through relative area or distribution of regions of low-attenuation. The emphysema index, developed in 1988 by Müller,[1] is the most well known of all these measures.

One of the most useful purposes for scoring emphysema from CT is to measure and track the progression of disease. For a measure to be useful for the measurement of disease state change, it is beneficial to use measures which are inherently less variable. In this way, it becomes possible to equate changes in measurement with actual changes in disease state. However, there has been concern that the variation of emphysema index, and densinometric measurement of emphysema in general, over time would limit the usefulness in measuring disease progression. Measure variation has been attributed to multiple sources, including varying dose levels between scans,[2] variable inspiration levels,[3] and altered scan acquisition settings[4] Recently, it has been suggested that diaphragm curvature be used as a non-densinometric approach for evaluating the severity of emphysema present in a given patient,[5] as increasing emphysema severity has been associated with a flattening of the diaphragm. This effect is illustrated in figure 1. A non-density based approach for emphysema quantification would also have the benefit of avoiding some of the limitations noted above.

Medical Imaging 2010: Computer-Aided Diagnosis, edited by Nico Karssemeijer, Ronald M. Summers,
Proc. of SPIE Vol. 7624, 762432 · © 2010 SPIE · CCC code: 1605-7422/10/$18 · doi: 10.1117/12.844012

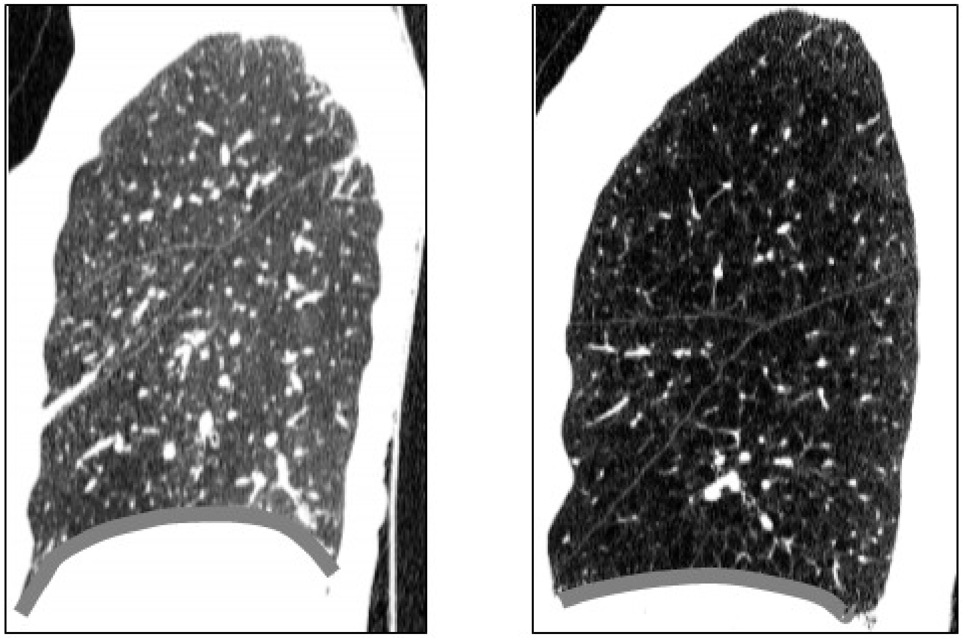

Figure 1. Sagittal projection of two right-lungs showing how increased emphysema relates to decreased lung curvature. Both images have identical window settings and have the diaphragm outlined by a thick, gray curve. Left) Healthy lung associated with higher diaphragm curvature Right) Emphysematous lung associated with low diaphragm curvature.

Previous work has shown that the diaphragm curvature estimates are as useful as emphysema index in quantifying COPD from CT scan.[6] While some work has been done on the analysis of emphysema index variation,[7,8] minimal work has been done in investigating diaphragm curvature variation. Therefore, the overall objective of this work was to compare the variation of emphysema index from low-dose, whole-lung CT scans on a number of short time-interval scan pairs with equivalent scan acquisition parameters (slice thickness and dose), in which true emphysema change would be expected to be negligible, and evaluate the effect of correction factors on both measures simultaneously.

## 2. METHODS AND MATERIALS

### 2.1 Generation of Emphysema Indicies

In order to generate the quantitative measures evaluated in this work, as well as the differences between the same indices in two subsequent scans, we first segment out the lung region from each scan-pair of whole-lung, low-dose CT scans using a standard algorithm. To minimize bias due to the low density volume in the major airways on density-based metrics, we further segment out the major airway structures (trachea, main bronchi, etc...) using a segmentation method as described by Lee et. al.[9] Two indices of emphysema were then computed for each scan within a pair, namely the emphysema index and the diaphragm extent ratio.

The emphysema index is the base measure of emphysema severity from whole lung CT scans. Developed in 1988 by Müller et. al.,[1] the emphysema index has become the most reported score in literature related to automated quantification of emphysema severity.[5,10–17] It also commonly refered to in the literature as low-attenuation ardea pecentage (LA%)[18] or relative area (RA).[19] As emphysema progresses, there is an increased amount of low-attenuation volume within the lung regions as a result of a relative increase in terminal airspace as compared to total lung volume. Given L as a set of pixels belonging to the lung region contained within a CT image, the emphysema index (EI) can then be calculated as

$$EI = \frac{|\{p_i\,:\,p_i \epsilon L,\; I(p_i) < T\}|}{|L|}$$

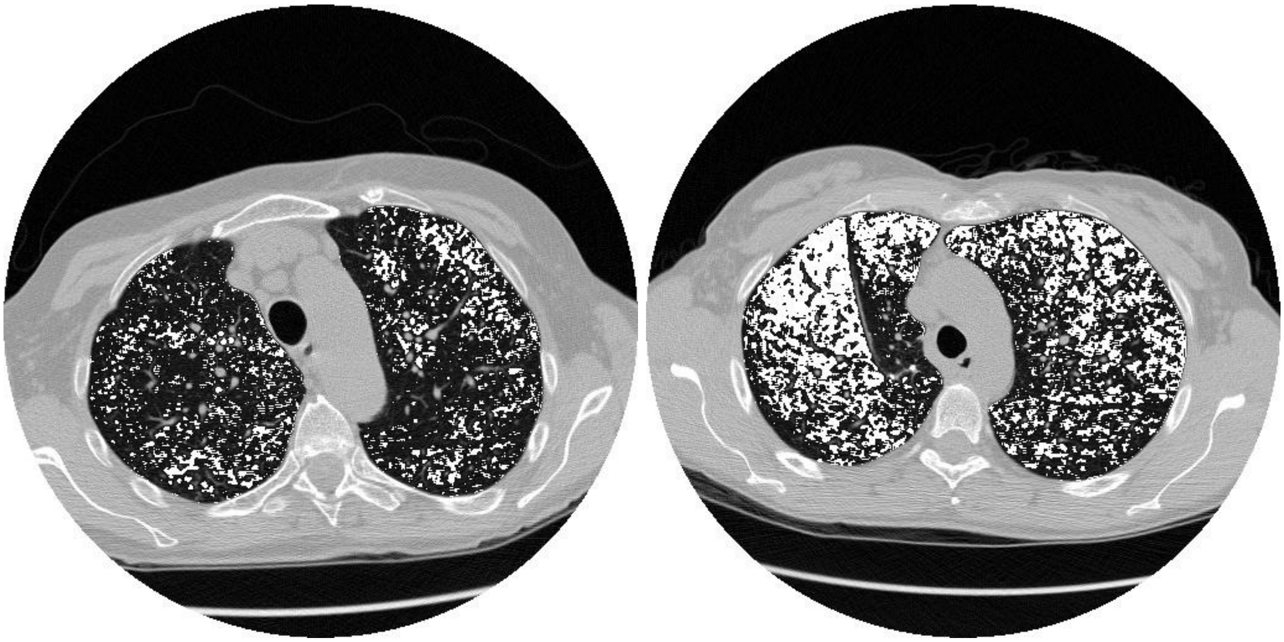

Figure 2. Calculation of Emphysema Index from CT Through Density Masking: Left) Axial slice depicting relatively mild emphysema. Right) Axial CT slice depicting relatively severe emphysema. Emphysematous regions in the lung region are shown in white.

where $I(p_i)$ is the density value of the pixel $p_i$ in the CT image being analyzed and $T$ is the density level below which a pixel is defined as being emphysematous. In this study, $T$ is set to -910 H.U. as this level is believed to encompass all regions in the lung parenchyma with some level of emphysema present. An example of emphysematous regions masked out in CT images for two levels of emphysema severity is provided in figure 2.

In order to compute the diaphragm curvature measure, we first segment out the diaphragm surface from the whole lung mask using an automated segmentation algorithm based on surface-normals as has been previously described.[6] Example segmentations of the diaphragm as acquired by this method are given in figure 3. To estimate diaphragm curvature, we computed both the height of the diaphragm[206] and width of the diaphragm normalized by height[6] as both have been shown to be useful in quantifying hyperinflation associated with emphysema. The height of the diaphragm is computed by calculating the z-extent of the segmented diaphragm surface. The coronal diaphragm extent ratio was then computed by calculating the maximal width of a projection of the diaphragm mask on the coronal plane and normalizing by the diaphragm height. As the computation is done on each of the two lung-diaphragm pairs in the image, a composite score is generated for the particular scan being analyzed by averaging the left and right lung scores into single, overall score. From this, the coronal diaphragm extent ratio can be computed by calculating

$$DER_C = \frac{\frac{CE_{Left}}{DH_{Left}} + \frac{CE_{Right}}{DH_{Right}}}{2}$$

where DERc is the diaphragm extent ratio in the coronal (x-axis) plane, CELeft and CERight are the coronal extents of the left and right diaphragms, respectively, and DHLeft and DHRight are the height of the left diaphragm and right diaphragm, respectively.

## 2.2 Evaluation of Emphysema Metric Variation

To quantify the variation of diaphragm curvature estimates as compared to emphysema index, 43 scan-pairs of whole-lung, low-dose CT scans comprised of 73 individual scans were analyzed using in-house developed software algorithms for lung segmentation and analysis. For each scan, the lung volume and height, as well as the emphysema index and diaphragm extent ratio in the coronal plane were computed. Then for each scan-pair the

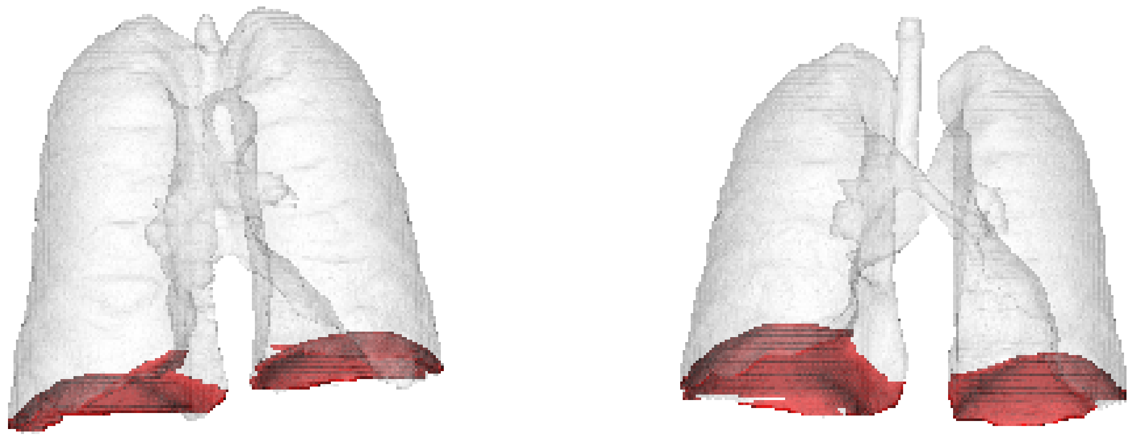

Figure 3. Segmentations of the diaphragm from whole lung CT using 3D visualization (Light-gray shading: Transparent light-shaded model of the lung, Heavy-shading: Extracted diaphragm)

absolute differences of the emphysema index and diaphragm extent ratio are computed, as well as the percent difference in volume and lung height. In order to account for the fact that the emphysema index and diaphragm score are on different scales, a linear transformation is performed on the scores to scale the two metrics into a standard 0-100 range.[8] For each of the two normalized metrics, the mean and standard deviation of the differences as well as the 95% confidence interval were computed and reported. A two-sample F-test is also performed to compare the two measures' variances and determine if there is any statistically significant difference between the two measures in terms of measure variation.

### 2.3 Variation Compensation of Emphysema Metrics

Compensation for change in emphysema scoring methods due to outside sources of variation is also considered in this work using a linear regression model for both the emphysema index and diaphragm extent ratios. As emphysema index is known to be effected by inspiration volume changes, this work seeks to evaluate the effectiveness of compensation for the reduction of the variation. Change in inspiration volume has been found to best correlated with emphysema index change, and thus is used as the compensation metric in this work. Empirically, we have also found inspiration volume change and change in lung height to correlate with the diaphragm extent ratio change, though to a more limited degree as compared to volume and emphysema index change. Therefore, both variation in inspiration volume and in lung height are used to correct for variation found. It should be noted that lung height differences was found to correlate extremely poorly with emphysema index, and thus is omitted from emphysema index compensation so as to not increase the variation by chance. To show the effectiveness of compensation, the mean and standard deviation of the differences as well as the 95% confidence interval are computed and reported for the two measures. Again, a two-sample F-test is also performed to compare two measures variances. Furthermore, two-sample F-test's are computed between the compensated and non-compensated measure

## 3. DATA

All scans used in this study were acquired at the Weill Medical College of Cornell University using a whole lung, low dose protocol at 120 kVp. Through retrospective selection, 43 short-time-interval CT scan-pairs across 28

Table 1. Variation of Emphysema Scores. The mean, standard deviation (SD) and 95% Confidence Interval are reported for normalized Emphysema Index (EI) and Diaphragm Extent Ratio (DERC).

| | Mean of Differences | SD of Differences | 95% Confidence Interval |
|---|---|---|---|
| EI | -1.98 | 7.55 | 15.8 - 12 |
| DE | -0.11 | 6.8 | -9.7 - 14.7 |

Table 2. Variation of Emphysema Scores after Compensation for Known Sources of Variation. The mean, standard deviation (SD) and 95% Confidence Interval are reported for normalized Emphysema Index (EI) and Diaphragm Extent Ratio (DERC).

| | Mean of Differences | SD of Differences | 95% Confidence Interval |
|---|---|---|---|
| EI | 0.26 | 6.42 | -11.8 - 10.9 |
| DE | 0.11 | 6.28 | -9.1 -12.9 |

cases were analyized in this work. All scans were acquired either on a GE Lightspeed Ultra, VCT, or Pro 16, with a 1.25 mm slice thickness. In order to analyze variation of the measures without variation due to change in disease state being, the scan-pairs were selected to have a mean time interval of less than 100 days (mean: 73 days, standard deviation: 24 days, max: 98 days, min: 21 days), as this would ensure relative stability of disease state.

## 4. RESULTS

The mean, standard deviation (SD) and 95% Confidence Interval for the emphysema index and the diaphragm extent ratio is given in table 1. In this work, we found that there is a trend towards smaller variation of the diaphragm extent ratio score than emphysema index prior to compensation, though this was not found to be statistacally significant (p=0.24). Table 2 shows the same statistics for the two measures computed after compensation. After compensation, the perceived trend is eliminated as the two measures are brought into better agreement and there was no statistical difference between the measures (p=0.44). What is interesting to note is the trend to decreasing variability for the compensated measures versus the non-compensated measures, although this was not found to be significant (p=0.12).

## 5. DISCUSSION

In this work we have found that, although not statistically significant, a trend exists for decrease variation in the diaphragm curvature measure as compared to the emphysema index. Using measures that are more repeatable is especially important in evaluating the progression of disease, so work has gone into the measurement of the variability of measures. As diaphragm curvature measurement has been proposed as a new quantitative metric for measuring emphysema progression, it is necessary to further evaluate the variability of the proposed measure.

As has been noted in other work and again seen in this work, the emphysema index can be see to be highly variable between two subsequent scans because of changes in inspiration volume, as well as being susceptible to changes in things such scan dose[2] and reconstruction algorithm.[4] However, this work shows that by compensating for known sources of variation, better estimation of true disease change can be obtained by requiring less of a difference in quantitative score to be seen in order to detect progression. This was found to be true for both the diaphragm curvature measure and particularly the emphysema index. This indicates that compensation is a useful technique and should be used to eliminate possible quantitative biases in emphysema measurements.

Linear regression was shown to be useful as a model of measure variability to in order to compensate for inspiration level changes, primarily with regards to the emphysema index. Although a simpler model, it was found to be useful in reducing the overall variability of emphysema index without the risk of over-fitting that more complex models would have on smaller datasets. This would be advantageous in larger studies that attempt to correlate emphysema index with other changes in image data.

An interesting point is that while compensation allowed for a slight reduction in variability of diaphragm curvature, it was not as large a reduction as was seen with the emphysema index. This is because lung curvature has been found to be relatively stable despite changes in lung volume,[21] though some variability can still be attributed to lung volume change. Although it was not the focus of this paper, it was noted that the highest variability in diaphragm curvature tended to come from a limited number of cases were the lung was found to have an uncommon morphometry, such as can be caused by a pleural effusion or partial lung resection. This is due to a limitation in the diaphragm segmentation algorithm which assumes as standard lung morphometry and orientation. Thus if the diaphragm surface is not effectively oriented downward, or the patient is angled in some manner, the algorithm is more likely to fail. As such, further improvements to the segmentation algorithm should be sought in order to account for these more difficult cases.

## 6. CONCLUSION

This work offered a detailed analysis of the variation of a new metric for emphysema quantification as compared to a standard measure. It was shown that there is a trend towards decreased variability in diaphragm curvature estimation versus emphysema index. Furthermore, a compensation methodology was presented that allowed for some correction of the variation within these measures. This allows for more accurate analysis of these measures in long term longitudinal studies of emphysema progression, where indication of true change in these measures is the most important indicator of disease state change.

## ACKNOWLEDGMENTS

This work was supported in part by NIH grant HL075476. Dr. Yankelevitz and Dr. Reeves are co-inventors on patents and other pending patents relating to evaluation of diseases of the chest including measurement of nodules. Some of these, which are owned by Cornell Research Foundation (CRF) are non-exclusively licensed to General Electric and they receive royalties from CRF pursuant to Cornell policy, which in turn is consistent with the Bayh-Dole Act. Dr Henschke is a co-inventor on patents and other pending patents relating to evaluation of diseases of the chest including measurement of nodules, some of which are owned by Cornell Research Foundation (CRF) are non-exclusively licensed to General Electric, but has divested herself of all financial or other interests.

## REFERENCES

[1] Müller, N. L., Staples, C. A., Miller, R. R., and Abboud, R. T., “"Density mask". An objective method to quantitate emphysema using computed tomography.,” *Chest* **94**, 782–787 (Oct 1988).

[2] Mishima, M., Itoh, H., Sakai, H., Nakano, Y., Muro, S., Hirai, T., Takubo, Y., Chin, K., Ohi, M., Nishimura, K., Yamaguchi, K., and Nakamura, T., “Optimized scanning conditions of high resolution CT in the follow-up of pulmonary emphysema.,” *J Comput Assist Tomogr* **23**(3), 380–384 (1999).

[3] Stoel, B. C. and Stolk, J., “Optimization and standardization of lung densitometry in the assessment of pulmonary emphysema.,” *Invest Radiol* **39**, 681–688 (Nov 2004).

[4] Boedeker, K. L., McNitt-Gray, M. F., Rogers, S. R., Truong, D. A., Brown, M. S., Gjertson, D. W., and Goldin, J. G., “Emphysema: effect of reconstruction algorithm on CT imaging measures.,” *Radiology* **232**, 295–301 (Jul 2004).

[5] Litmanovich, D., Boiselle, P. M., and Bankier, A. A., “CT of pulmonary emphysema–current status, challenges, and future directions.,” *Eur Radiol* **19**, 537–551 (Mar 2009).

[6] Keller, B., Reeves, A., Yankelevitz, D., Henschke, C., and Barr, R., “Emphysema quantification from CT scans using novel application of diaphragm curvature estimation: comparison with standard quantification methods and pulmonary function data,” in [*Proceedings of SPIE*], **7260**, 726032 (2009).

[7] Gietema, H. A., Schilham, A. M., van Ginneken, B., van Klaveren, R. J., Lammers, J. W. J., and Prokop, M., “Monitoring of smoking-induced emphysema with CT in a lung cancer screening setting: detection of real increase in extent of emphysema.,” *Radiology* **244**, 890–897 (Sep 2007).

[8] Keller, B., Reeves, A., Henschke, C., Barr, R., and Yankelevitz, D., “Variation of quantitative emphysema measurements from CT scans,” in [*Medical Imaging 2008: Computer-Aided Diagnosis. Edited by Giger, Maryellen L.; Karssemeijer, Nico. Proceedings of the SPIE*], **6915**, 69152I–69152I (2008).

[9] Lee, J. and Reeves, A., “Segmentation of the airway tree from chest CT using local volume of interest,” in [*Proc. of Second International Workshop on Pulmonary Image Analysis*], (2009).

[10] Gevenois, P. A., Vuyst, P. D., de Maertelaer, V., Zanen, J., Jacobovitz, D., Cosio, M. G., and Yernault, J. C., "Comparison of computed density and microscopic morphometry in pulmonary emphysema.," *Am J Respir Crit Care Med* **154**, 187–192 (Jul 1996).

[11] Madani, A., Maertelaer, V. D., Zanen, J., and Gevenois, P. A., "Pulmonary emphysema: radiation dose and section thickness at multidetector CT quantification–comparison with macroscopic and microscopic morphometry.," *Radiology* **243**, 250–257 (Apr 2007).

[12] Uppaluri, R., Mitsa, T., Sonka, M., Hoffman, E. A., and McLennan, G., "Quantification of pulmonary emphysema from lung computed tomography images.," *Am J Respir Crit Care Med* **156**, 248–254 (Jul 1997).

[13] Stolk, J., Dirksen, A., van der Lugt, A. A., Hutsebaut, J., Mathieu, J., de Ree, J., Reiber, J. H., and Stoel, B. C., "Repeatability of lung density measurements with low-dose computed tomography in subjects with alpha-1-antitrypsin deficiency-associated emphysema.," *Invest Radiol* **36**, 648–651 (Nov 2001).

[14] Madani, A., Keyzer, C., and Gevenois, P. A., "Quantitative computed tomography assessment of lung structure and function in pulmonary emphysema.," *Eur Respir J* **18**, 720–730 (Oct 2001).

[15] Zaporozhan, J., Ley, S., Eberhardt, R., Weinheimer, O., Iliyushenko, S., Herth, F., and Kauczor, H.-U., "Paired inspiratory/expiratory volumetric thin-slice CT scan for emphysema analysis: comparison of different quantitative evaluations and pulmonary function test.," *Chest* **128**, 3212–3220 (Nov 2005).

[16] Parr, D. G., Stoel, B. C., Stolk, J., and Stockley, R. A., "Validation of computed tomographic lung densitometry for monitoring emphysema in alpha1-antitrypsin deficiency.," *Thorax* **61**, 485–490 (Jun 2006).

[17] Kalender, W. A., Rienmüller, R., Seissler, W., Behr, J., Welke, M., and Fichte, H., "Measurement of pulmonary parenchymal attenuation: use of spirometric gating with quantitative CT.," *Radiology* **175**, 265–268 (Apr 1990).

[18] Lee, Y. K., Oh, Y.-M., Lee, J.-H., Kim, E. K., Lee, J. H., Kim, N., Seo, J. B., Lee, S. D., and Group, K. O. L. D. S., "Quantitative assessment of emphysema, air trapping, and airway thickening on computed tomography.," *Lung* **186**(3), 157–165 (2008).

[19] Parr, D. G., Dirksen, A., Piitulainen, E., Deng, C., Wencker, M., and Stockley, R. A., "Exploring the optimum approach to the use of CT densitometry in a randomised placebo-controlled study of augmentation therapy in alpha 1-antitrypsin deficiency.," *Respir Res* **10**, 75 (2009).

[20] Tanaka, R., Sanada, S., Okazaki, N., Kobayashi, T., Fujimura, M., Yasui, M., Matsui, T., Nakayama, K., Nanbu, Y., and Matsui, O., "Evaluation of pulmonary function using breathing chest radiography with a dynamic flat panel detector: primary results in pulmonary diseases.," *Invest Radiol* **41**, 735–745 (Oct 2006).

[21] Cassart, M., Hamacher, J., Verbandt, Y., Wildermuth, S., Ritscher, D., Russi, E. W., de Francquen, P., Cappello, M., Weder, W., and Estenne, M., "Effects of lung volume reduction surgery for emphysema on diaphragm dimensions and configuration.," *Am J Respir Crit Care Med* **163**, 1171–1175 (Apr 2001).