REVIEW

Report of a workshop: quantitative computed tomography scanning in longitudinal studies of emphysema

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Report of a workshop: quantitative computed tomography scanning in longitudinal studies of emphysema. J.D. Newell Jr, J.C. Hogg, G.L. Snider. ©ERS Journals Ltd 2004.

ABSTRACT: It has been reported that quantitative computed tomography (CT) scanning of the lungs showed decreased progression of emphysema in a randomised clinical trial in patients with severe α_1 -antitrypsin (α_1 -AT) deficiency receiving monthly intravenous augmentation therapy with human α_1 -AT. Comparable results were not obtained using rate of decline of forced expiratory volume in one second.

Accordingly, the Alpha-1 Foundation convened a workshop to explore the feasibility of using quantitative CT data as a primary outcome variable in trials of drugs for treating α_1 -AT deficiency.

This report reviews the following: the principles for the use of modern CT scanners for quantifying emphysema; the methods and data on validation by comparison with measurements of severity of emphysema in inflation-fixed specimens of lungs; and the possibility of decreasing radiation dosage from CT to make it safe and ethically possible to use CT in longitudinal studies.

The workshop concluded that it is feasible, safe and ethically possible to use computed tomography in longitudinal studies of emphysema. It recommended that the primary end-point should be a significant shift in the 15th percentile of lung density.

Eur Respir J 2004; 23: 769–775.

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Keywords: α_1 -Antitrypsin deficiency, computed tomography, emphysema, trials of therapy

Received: April 24 2003

Accepted after revision: January 19 2004

This workshop was funded by the following organisations: AlphaNet, American Red Cross, Aventis Behring LLC, Bayer Corporation, Grifols, Ono Pharmaceuticals USA and Roche Bioscience.

Severe α_1 -antitrypsin (α_1 -AT) deficiency is a genetic disorder that may result in the development of emphysema and chronic airflow obstruction (α_1 -AT-chronic obstructive pulmonary disease (COPD)), which usually begins in the 4th decade of life, in contrast to the much later onset of usual COPD. There are ~6,000 individuals with known α_1 -AT-COPD in the USA. Emphysema progresses more rapidly and has a worse prognosis than in usual COPD [1].

The therapy of α_1 -AT-COPD is identical to that for usual COPD, except for the use of weekly intravenous augmentation therapy with concentrated human α_1 -AT (Prolastin®; Bayer Healthcare, Research Triangle Park, NC, USA). At present, there is insufficient Prolastin to treat all patients for whom the drug has been prescribed. A number of α_1 -AT preparations and other antiprotease drugs are currently under development for administration by inhalation, as well as by intravenous infusion. The rate of decline of forced expiratory volume in one second (FEV1) has been the most widely used outcome variable to show clinical efficacy in treatments for COPD.

SCHLUCHTER *et al.* [2] made power estimates from data of the National Heart Lung and Blood Institute Registry of patients with severe deficiency of α_1 -AT. Using subjects with initial FEV1 35–49% predicted, biannual spirometry obtained over 4 yrs and adjustment for noncompliance would require 147 subjects per treatment arm to detect a difference in FEV1 decline of 23 mL·yr⁻¹ or a 28% reduction in rate of decline. The expense and difficulty in recruiting enough α_1 -AT-deficient participants into such a study are formidable.

DIRKSEN *et al.* [3] reported the results of a double-blind trial of α_1 -AT augmentation therapy in 26 Danish and 30 Dutch exsmokers with severe α_1 -AT deficiency and moderate emphysema (FEV1 30–80% pred). Patients were randomised to either α_1 -AT (250 mg·kg⁻¹) or albumin (625 mg·kg⁻¹) infusions at 4-week intervals for ≥ 3 yrs. The degree of emphysema was quantified annually by the 15th percentile point of the lung density histogram derived from computed tomography (CT). The loss of lung density measured by CT, mean $\pm$ SEM was 2.6 $\pm$ 0.41 g·L⁻¹·yr⁻¹ for placebo as compared with 1.5 $\pm$ 0.41 g·L⁻¹·yr⁻¹ for the α_1 -AT infusion group ($p=0.07$). Power analysis showed that this protective effect would be significant in a similar trial with 130 patients. In contrast, calculations based on annual decline of FEV1 showed that 550 patients would be needed to show a 50% reduction of annual decline.

These data suggested that rate of progression of emphysema in serial CT examinations could provide a tool for doing intervention trials on fewer subjects over a shorter period of time than using rate of decline of FEV1. Accordingly, a workshop was convened under the auspices of the Alpha-1 Foundation on February 2–3, 2001, to explore the current state of knowledge on the use of CT imaging for the quantification of emphysema. The primary goal of the workshop was to facilitate the development of a consensus on the critical parameters for performing multicentre, randomised, double-blind interventional studies using changes in CT indices of emphysema over time as the primary

outcome variable. New information published since the workshop has been incorporated into this report.

Background

Emphysema

Pulmonary emphysema is defined as "abnormal permanent enlargement of air spaces distal to terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis" [4]. The lesions are described in terms of the pulmonary acinus. Centriacinar emphysema (CAE), which predominates in the upper lungs, is associated with inflammation in the terminal airways with dilatation and destruction of the respiratory bronchiole and adjacent airspaces. Panacinar emphysema (PAE) uniformly affects all airspaces in the acinus and tends to predominate at the lung bases. The identification of emphysema presupposes knowledge of normal airspace size, which varies considerably with height, weight, sex and the degree of lung inflation. This creates problems in separating fully expanded normal lung from mild emphysema, and makes it difficult to detect the transition from health to disease.

Emphysema in usual COPD may be relatively pure CAE or PAE, but is more often a mixture of both forms of emphysema [5]. The emphysema in α_1 -AT-COPD is predominantly PAE. The increase in respiratory airspace size and decrease in tissue that occurs in emphysema causes the density (weight per unit volume) to decrease. Therefore, measurements of lung tissue density made using the CT scan should be able to provide qualitative and quantitative estimates of emphysema. Although CT can identify CAE and PAE [6–8], the emphasis in the workshop was on quantifying the initial severity of emphysema and changes in its severity over time, regardless of the anatomic type of emphysema.

Computed tomography imaging of the lungs

X-ray CT passes an x-ray beam through an object to obtain multiple one-dimensional line integrals, or projections, of the object. An inverse radon transform is performed on the one-dimensional line integrals to produce a true two-dimensional axial image of the object at a particular level. Multiple two-dimensional axial images are then stacked on top of each other to produce a true three-dimensional image of the scanned object [9].

Image acquisition

Computed tomography scanner geometry. Simply described, a CT scanner consists of a rotating x-ray tube and detector array that are 180° apart. Continuous rotation is achieved by placing the x-ray tube, the x-ray detector array and the associated electronics into a large metal cylinder that rotates inside a slightly larger metal cylinder. A large round aperture is located between the x-ray tube and the x-ray detector array. The patient is placed on a table that is precisely positioned inside the aperture between the rotating x-ray tube and the x-ray detector array.

The newest multidetector spiral CT scanners (MDCT) have more than one row of detectors rotating around the patient. Multiple images are obtained per 360° rotation. In the case of a four detector row MDCT, four transverse images of nominal slice thickness can be obtained per 360° rotation [9]. Current four row MDCT, depending on the manufacturer,

can obtain four 1 mm or four 1.25 mm images of nominal slice thickness of both lungs in a single breath-hold, 25–30 s; eight row MDCT scanners achieve this in 10 s and 16 row MDCT can achieve this in 5 s. MDCT has shown excellent repeatability of measurement of emphysema in patients scanned 2 weeks apart [10].

X-ray tube scanning parameters. Typically, the peak voltage (kVp) across the x-ray tube, which determines the maximum energy of x-ray photons that are produced, is 120–140 kVp. Energies <120 kVp increase the radiation dose for a given noise level in the image. Changing the kVp also changes the contrast scale of the images [10–14]. The use of an x-ray tube current of >160 milliamperere-seconds (mas) adds little to CT image quality and increases the radiation dose in proportion to the increase in mas [15].

Pitch (p) is defined as the speed of table movement (d), in mm per complete 360° rotation of the x-ray tube and detector, divided by the product of detector rows (M) and nominal slice thickness (S), as follows:

$$p = d / (M * S) \quad (1)$$

A single-detector spiral CT scanner that has the x-ray tube rotating through 360° in 1 s, a table speed of 10 mm per rotation of the x-ray tube and an image slice thickness or collimation of 10 mm will have a pitch of 1. If the table speed is increased to 20 mm per rotation of the x-ray tube, the pitch will be 2. The advantage of increasing the pitch from 1 to 2 is that radiation dose is reduced by up to one half with no increase in noise level [9]. Increasing the pitch more than 2 in spiral CT scans causes gaps in sampling of the object in the longitudinal (z) axis, [9, 14, 16].

The term collimation refers to the thickness of the x-ray beam as it impinges on the x-ray detector, and in the case of a four row MDCT, the data-set can produce four transverse images of nominal slice thickness. For a given kVp and mas the noise in the image goes up as the collimation decreases. Excellent results have been obtained in the quantitative CT assessment of emphysema using 1, 7, 8 or 10 mm collimation, [11–14, 17–23]. Acquiring single axial transverse images at noncontiguous regular intervals reduces the dose [18]. Spiral CT examinations provide contiguous acquisitions of the lung data. Slice widths less than the width of the original detector cannot be achieved [9]. A recent study reported excellent quantitative CT results in emphysema using a multidetector spiral CT scanner that simultaneously obtained four 2.5-mm thick axial images [10].

Image reconstruction. The reconstruction process can be adjusted to change the final image characteristics. For example, a low spatial-frequency algorithm provides optimal image contrast at the expense of spatial resolution. A high spatial-frequency algorithm provides high spatial resolution at the expense of contrast resolution. The standard algorithms are halfway between these two extremes. The standard algorithm has been used predominantly in studies using 10 mm collimation and the high spatial resolution algorithm has been used primarily in studies using 1 mm collimation. The projection or raw ray data can be reconstructed using any reconstruction algorithm [9]. KEMERINK *et al.* [24] stated "...we found negligible influence of zoom factor and reconstruction filter, with the exception of the ultra high resolution filter in case of extremely low lung density". The workshop agreed that the standard reconstruction algorithm should be used to avoid the errors described by KEMERINK *et al.* [24] with the ultra high resolution filter. In addition, KEMERINK *et al.* [25] emphasised that in order to compare CT histogram parameters from different CT scan acquisitions,

sample volumes of $\geq 8 \text{ mm}^3$ size should be used. The actual sample volume is a function of collimation, in plane resolution, and reconstruction filter. Sample volumes of $>8 \text{ mm}^3$ were more accurate in determining lung density than smaller sample volumes. This is especially important if the scans were going to be acquired using different collimations and reconstruction filters. The workshop agreed that all CT scans should be acquired in such a fashion as to enable the reconstruction of image data with larger slice thicknesses, *i.e.* $\geq 7 \text{ mm}$, and with a standard reconstruction filter or a better customised filter that might further optimise the determination of lung density or other important image measurements. This would mean acquiring scans with a sample volume of $\geq 10.15 \text{ mm}^3$, using the data in KEMERINK *et al.* [25].

Using an experimental porcine model, good correlations were reported between gravimetrically and CT-determined lung density using 1, 3, 7, and 10 mm collimations and both standard and high resolution reconstruction algorithms [26]. The investigators suggested that 7 mm collimation using a standard reconstruction algorithm may be optimal for quantifying lung density.

Lung volume. The lungs can be scanned near total lung capacity (TLC), or at functional residual capacity. Patients can be coached to breath-hold at the desired lung volume or a spirometer may be used to confirm the exact lung volume during CT examination. Most studies using quantitative CT have not used spirometry [11, 17–22, 23, 25]. A recent study concluded that spirometrically controlling lung volumes did not improve the repeatability of quantitative CT scanning in assessing the amount of emphysema [12]. There is controversy in the literature as to whether expiratory [27, 28] or inspiratory [19] CT scanning correlates better with physiological measures of emphysema. Workshop members agreed that scanning as close to TLC as possible without spirometry is acceptable.

Intravenous contrast media. Theoretically, intravenous contrast medium should not be used in the assessment of emphysema, since the contrast medium increases x-ray attenuation in the lung parenchyma. In a small study, COXSON *et al.* [23] found that the presence of intravenous contrast media increased lung density from -810 HU to -832 HU. The high precision and accuracy necessary in longitudinal quantitative CT assessments of emphysema, *i.e.* a change as low as $1.1 \text{ HU}\cdot\text{yr}^{-1}$, clearly makes the use of intravenous contrast media contraindicated. The clear consensus of the workshop participants was that intravenous contrast media should not be used in studies of CT lung densitometry.

Image analysis

Qualitative analysis. GODDARD *et al.* [29] developed a semiquantitative, subjective method to assess emphysema; it depended on low attenuation and vascular disruption on individual CT images of the lung. BERGIN and colleagues [30, 31], using Goddard's method, correlated semiquantitatively analysed CT images with the corresponding inflation-fixed, barium-impregnated specimens; they showed that CT accurately distinguished among panacinar, centriacinar and distal acinar emphysema. These and other reports using similar techniques confirmed good correlations among the distribution and severity of emphysema and physiological and pathological findings [29–32].

Quantitative analysis. GOULD *et al.* [33] reported the first successful application of a quantitative CT technique that correlated well with pathological evidence of emphysema.

They used two 13-mm thick axial images of the lung made 6 and 15 cm below the sternal notch, with a single-slice scan time of 15 s in 45 patients who subsequently had a lobe or lung resected for lung cancer. Histograms were derived from the pooled data of these two images. The modal CT attenuation value and the value of the 5th percentile of the histogram correlated well with a morphometric index measured on lung sections, the surface area of respiratory airspace walls per unit lung volume ($p < 0.0001$).

MULLER *et al.* [34] developed a density mask that identified the CT voxels deemed to represent emphysema in a histogram. They studied the proportion of voxels < -900 , -910 and -920 and found that the proportion of voxels < -910 HU correlated best with both anatomically measured emphysema and pulmonary function measures. They and others showed that this method only identified emphysematous airspaces that were $\sim 5 \text{ mm}$ in diameter or larger [34]; a threshold of -856 HU detected milder forms of emphysema [23].

KINSELLA *et al.* [35] used the density mask technique with a threshold value of -910 HU to show that there was good correlation between pulmonary function tests and quantitative CT evidence of emphysema. Many subsequent reports confirmed good correlations of histogram-derived, quantitative CT techniques with lung function tests and pathological evidence of emphysema [36–41].

BANKIER *et al.* [13] compared the density mask technique with a threshold value of -950 HU and the qualitative measure developed by GODDARD *et al.* [29]. In 62 consecutive patients, subjective grading of emphysema showed less agreement with macroscopic pathology ($r = 0.439\text{--}0.505$, $p < 0.5$) than the objective quantitative CT technique ($r = 0.555\text{--}0.623$, $p < 0.001$).

Phantoms for computer tomography scanner calibrations

Air and water phantoms should be used to calibrate CT scanners on a daily basis to maintain the accuracy of values on a given scanner. Anthropomorphic phantoms are also available to evaluate the ability of a CT scanner to accurately measure evidence of emphysema.

Central data analysis

The National Emphysema Treatment Trial (NETT) [42], a multicentre, multi-year randomised controlled trial of the relative efficacy of medical therapy *versus* lung volume reduction surgery in patients with advanced emphysema, has developed an Image Analysis Center (IAC) at the University of Iowa. The IAC is collecting, archiving and analysing CT image data from the 17 NETT centres across the USA. The CT data is transmitted to the centre over the internet, using transfer protocols that deal successfully with data security, patient confidentiality, image archiving and transfer of analysis results to the study-coordinating centre. To date, $>4,000$ files have been transferred and $>1,900$ have been analysed. The authors are confident that other centres can duplicate this effort.

Computer tomography radiation dose

It is evident that if CT is to be used to evaluate severity of emphysema in longitudinal studies, the radiation dose to research participants must be as low as possible without

compromising data quality. CT examinations in 1994 in Germany made up 4.2% of the total number of radiological examinations but contributed 37.8% of the entire effective radiation dose to the German population [9]. Similar results have been reported in the UK, where it is estimated that CT makes up 4% of the total radiological examinations and contributes 40% of the effective radiation dose to the population [43, 44].

Recent estimates of the effective radiation dose to the chest for a typical CT examination range 8.9–10.9 mSv [45]. The recommended annual radiation dose level for biomedical research studies of intermediate risk range is 1–10 mSv [10].

STOLK *et al.* [10] using a four row multi-detector CT scanner, scanned 10 patients with emphysema on two occasions, 2 weeks apart. Scanning parameters were 140 kV, 20 mas, 4×2.5 mm collimation and effective slice thickness of 2.5 mm. Lung density was measured as the 15th percentile point and the relative area of the lungs below -910 HU. The repeatability of both measurements was excellent with an estimated CT dose per examination of 0.7 mSv for a chest of 30 cm length.

In a study still in progress, DIRKSEN *et al.* [46] evaluated the reproducibility of CT lung density in 25 subjects with α_1 -AT deficiency and 25 current smokers with usual COPD. Low-dose, multislice CT were done 2 weeks apart at three different radiation doses (40, 20 and 10 mas). Images were reconstructed using three different algorithms (low, medium and high spatial resolution). High noise levels rendered the 10 mas data uninterpretable. There was good reproducibility of both the 20 and 40 mas data, which was independent of the reconstruction algorithm used. The standard deviation of CT density at the 15th percentile was 2–4 HU.

It thus appears that MDCT scanners can be used to measure emphysema in longitudinal studies at radiation doses that fall well within the recommended intermediate-risk research standard of 1–10 mSv [10]. These doses are also well below the annual background radiation dose of 2.4 mSv in Germany and 3.0 mSv in the USA [9].

Combining quantitative histopathological and computed tomography methods for the assessment of emphysema

The CT number in HU's, measured in each three-dimensional voxel of the CT image, can be converted to density by adding 1,000 to the measurement and dividing the summed value by 1,000. The specific volume is the inverse of density and can be converted to the volume of gas per gram of lung tissue by subtracting the specific volume of gas-free lung tissue from the specific volume of gas-containing lung tissue [47, 48]. When this value is expressed as a %TLC it provides precise information on the degree of lung expansion in that sample of lung. An analysis of the distribution of these values can be used to establish the volume of lung that is expanded beyond normal TLC. Histological analysis of the tissue can be used to confirm that the over-expanded tissue contains emphysematous lesions.

CRUZ-ORIVE and WEIBEL [49] introduced a robust cascade sampling design where the volume of the fixed inflated lung specimen is used as a reference for subsequent quantitative analysis of the histology of lung tissue and airspace. The realisation that the CT scan provides the tissue and airspace components of the reference volume used in this sampling cascade allowed this powerful technique to be applied to studies of patients undergoing lung resection. This approach has shown that the CT-determined lung volume can be linked to histologically measured surface area/volume ratio using the

following equation [23]:

$$\text{surface area/volume}(\text{cm}^2 \cdot \text{mL}^{-1}) = e^{6.84 - 0.32 \text{ ml gas/gram tissue}} \quad (2)$$

This allows both surface area:volume and total internal surface area of the lung to be estimated from the CT scan. The estimates of lung internal surface correlated with measurements of diffusing capacity made in the same subjects before and after lung volume reduction surgery [11, 23]. A subsequent study showed that the cigarette smoke-induced inflammatory response is amplified in the alveolar tissue and airspace of patients with advanced emphysema compared to patients with similar smoking habits but normal lung function [50].

These advanced methods described above will permit careful comparison of existing methods with newer methods to analyse CT images for the presence and severity of emphysema. The main purpose of these methods in longitudinal studies is as a means of accurately, anatomically validating new techniques of analysing CT data as they come along.

Clinical significance of computed tomography indices of emphysema

CT indices of emphysema reflect lung anatomy and provide the best possible measure of emphysema severity in life. It follows that change in emphysema severity can *per se* be used to evaluate an important facet of the natural history of COPD; that is, change in rate of progression of emphysema is useful as an outcome measure in interventional trials of usual or α_1 -AT-COPD. However, it is also reasonable to ask what clinical significance progression of emphysema severity might have.

A number of cross sectional studies [14, 31, 32, 51] have shown moderate, statistically significant, inverse correlations between CT measures of severity of emphysema and both FEV1 and carbon monoxide diffusing capacity. For FEV1, the coefficient of correlation (*r*) ranged -0.41–-0.57; for diffusing capacity, *r* was higher, ranging -0.54–-0.65.

DOWSON and colleagues [52–54] showed in a longitudinal study of PI*Z patients with emphysema that there was a parallel relation between progression of emphysema as determined in CT and rate of decline in FEV1, diffusing capacity and health-related quality of life (HRQL). The same authors in a cross-sectional study of 28 α_1 -AT-deficient patients, showed a significant relationship between CT-determined severity of emphysema and both HRQL and FEV1. From these studies it is clear that CT indices of emphysema severity relate significantly to diffusing capacity, FEV1 and HRQL and therefore to the adverse clinical effects of COPD.

Workshop recommendations on use of computed tomography in longitudinal studies

General conclusions

The workshop attendees agreed that CT imaging of the lungs is sufficiently developed to justify recommending its use in longitudinal studies designed to elucidate the natural history of emphysema in usual or α_1 -AT-COPD and to assess new therapeutic interventions to attenuate or reverse the course of emphysema. Preliminary evidence suggests that CT has greater power in demonstrating the effect of an intervention on slowing progression of emphysema than

decrease in the rate of decline of the FEV₁. With appropriate setting of spiral multidetector CT scanners the radiation dose to study participants can be made low enough to be acceptable for a longitudinal study.

Computed tomography imaging

The workshop attendees agreed on the essential elements for designing longitudinal studies using CT imaging of emphysema at the present time. Many of these recommendations may need to be revised as the technology continues to improve.

Computed tomography image acquisition

The time between CT imaging should be optimised based on the anticipated onset of benefit from the drug being studied. For a 2-yr study, imaging at baseline, 12, 18 and 24 months seems reasonable.

The patient should be coached to take in a full inspiration so that CT images are made as close to TLC as possible. Spirometry during the CT examination is not required.

Contrast media should not be administered because this directly changes CT-determined lung density.

The kVp and mas are two very critical parameters that greatly influence the image quality and radiation dose. The peak X-ray tube kilovoltage should be set between 120–140 kVp. Lower kilovoltages are not recommended because they have not been verified in existing quantitative studies and a lower kilovoltage will significantly alter the attenuation coefficients obtained by the CT scanner. Furthermore, lower kVp will increase the effective radiation dose to the patient. Although the majority at the workshop preferred that the tube current should be set between 80–100 mas, concern about radiation dose caused some to prefer tube currents as low as 20 mas in order to provide adequate signal:noise in the images and to avoid unnecessary radiation exposure. The final decision on kVp and mas selection should be investigated before the study begins using a lung phantom representing normal and emphysematous lungs. The phantom results should verify that the dose used for the study is adequate to provide reliable quantitative measures of emphysema while keeping the radiation dose as low as possible. If only measures of lung density are required recent research suggests that 140 kVp and 20 mas may be adequate for accurate results with an expected effective radiation dose to the subject of 0.7 mSv [44].

The recommended detector collimation is 1–1.25 mm for a four row multidetector CT scanner. The recommended pitch is the equivalent of 1.5 on a single detector spiral CT scanner. Multidetector CT scanners should be used to obtain data with 1–1.25 mm collimation with the four detector row MDCT scanners. This will enable both thin and thick images for data analysis. The scan time may be as long as 27 s for a 30 cm chest using an early model of the GE Lightspeed Qxi four row multi-detector CT scanner (General Electric Medical Systems, Waukesha, WI, USA). Such long scan-times may exceed breath hold times and may require imaging the chest using two breathholds to collect a full set of images. Newer scanners having 8, 10 or 16 rows of detectors achieve complete thoracic CT study times of ≤ 12 s.

Preliminary data suggest that more accurate measurements of density and weight are obtained from 7 mm slice thickness image data calculated from thinner collimated projections. The 1–1.25 mm collimated data is better for more advanced texture analysis.

It is recommended that imaging be done using state-of-the-art multislice, subsecond spiral CT scanners. Serial examinations on study subjects should be done on the same CT scanner over time. One model of one manufacturer's machine is recommended for all studies on any single study participant. Where multiple models of CT scanners must be used, there should be demonstration of equivalent spatial and density resolution.

Scanners used in longitudinal studies should be capable of storing reconstructed image data and the raw unreconstructed X-ray projection data on a removable, high-density storage medium, such as magnetic optical disks, which can be transmitted to a data analysis centre.

An advanced CT phantom of the thorax should be developed and circulated to each study centre to carefully validate the scanner's performance before study onset and after significant scanner upgrades during the course of the study. A simplified phantom should be used by each centre to verify scanner performance prior to each CT examination.

Computed tomography image analysis

A central data analysis centre should be established before the study begins. Digital image data, including if possible raw, unreconstructed, X-ray projection data, should be transferred by magnetic-optical disks on the internet to the central data analysis centre. Including the unreconstructed projection data will enable all data to be reconstructed in the same way using optimised back-projection kernels for producing the best images for quantitative analysis. Such a centralised image reconstruction workstation has been developed (W. Kalender, Professor and Chairman of the Institute of Medical Physics, University of Erlangen-Nuremberg, Erlangen, Germany), and it is recommended that this system or something similar be evaluated for such purposes. It is anticipated that new back-projection kernels will be invented and will benefit all patients with emphysema over time. It was agreed that the primary end-point should be a significant shift in the 15th percentile of lung density.

Suggestions for future research

Advanced methods of tissue characterisation, such as fractal analysis (one method of image clustering) and the more comprehensive adaptive multiple features method should be explored [55]. Reproducible quantitative computed tomography image analysis techniques should be developed that expose the patient to the lowest possible radiation dose. Lung computed tomography phantom and computer-based lung simulation programs should be sought that provide ways to develop and verify new quantitative computed tomography image analysis techniques for the assessment of emphysema.

Acknowledgements. Conference participants: J.C. Hogg (University of British Columbia), J. Newell (National Jewish Medical and Research Center), M.L. Brantly (University of Florida College of Medicine), M. Cosio (McGill University/Royal Victoria Hospital), H. Coxson (University of British Columbia), F. de Serres (Alpha-1 Foundation Board of Directors), A. Dirksen (Gentofte University Hospital), R. Fallat (California Pacific Medical Center), P. Alain Gevenois (Universite Libre de Bruxelles), D.S. Gierada (Washington University School Medicine), J. Goldin (UCLA Medical Center), E. Hoffman (University of Iowa), J. McCormick (FDA-Office of Orphan

Drug Development), N. Gerard McElvaney (Royal College of Surgeons in Ireland), P.J. Mergo (University of Florida College of Medicine), R. Meyer (US Food & Drug Administration-CDER), M. Mishima (University of Kyoto), Y. Nakano (University of British Columbia), S.D. Nightingale (DHHS-Office of Public Health & Science), L.R. Pierce (US Food & Drug Administration), R. Rogers (University of Pittsburgh), R.A. Sandhaus (Alpha-1 Foundation), R. Senior (Washington University School of Medicine), G.L. Snider (Boston VA Medical Center), J. Stocks (University of Texas Health Center), J. Stolk (Leiden University Medical Center), J.K. Stoller (Cleveland Clinic Foundation), G.M. Turino (Columbia University), P. Wagner (University of CA, San Diego), J.W. Walsh (Alpha-1 Foundation).

Industry scientific participants: V. Benn (Aventis Behring LLC), G. Bray (Baxter, Hyland Immuno), J.P. Caulfield (Roche Bioscience), D. Crockford (Profile Therapeutics, Inc.), S.H. Fox (GE Medical Systems), J. Humphries (Bayer Corporation), D. Ipe (Roche Global Development), H. Ishibashi (B.S., Ono Pharma USA Inc.), J. Ishikawa (Ono Pharma USA Inc.), N.D. Kennedy (American Red Cross), B. Peterson (Pfizer, Inc.), J.M. Rogers (Ono Pharmaceuticals USA), S. Rogy (Baxter Healthcare Corporation), V. Romberg (Aventis Behring LLC), D. Sundin (Pharm.D., AlphaOne Pharmaceuticals), S. Tong (Roche Bioscience), S. Tripathi, (Baxter, Hyland Immuno), C. Turner (CBER-FDA), M. Wright (Ono Pharmaceuticals), J.P. Yee (Roche Bioscience).

Staff support: S. Finn (Alpha-1 Foundation).

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