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Airspace dimension assessment with nanoparticles as a proposed biomarker for emphysema

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ABSTRACT

Airspace dimension assessment with nanoparticles (AiDA) is a novel method to measure distal airspace radius non-invasively. In this study, AiDA radii were measured in 618 individuals from the population-based Swedish CArdiopulmonary BioImaging Study, SCAPIS. Subjects with emphysema detected by computed tomography were compared to non-emphysematous subjects. The 47 individuals with mainly mild-to-moderate visually detected emphysema had significantly larger AiDA radii, compared with non-emphysematous subjects (326±48 µm vs 291±36 µm); OR for emphysema per 10 µm: 1.22 (1.13–1.30, p<0.0001). Emphysema according to CT densitometry was similarly associated with larger radii compared with non-emphysematous CT examinations (316±41 µm vs 291 µm±26 µm); OR per 10 µm: 1.16 (1.08–1.24, p<0.0001). The results are in line with comparable studies. The results show that AiDA is a potential biomarker for emphysema in individuals in the general population.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) originates in the distal airspaces, causing chronic inflammation and irreversible airspace enlargement, emphysema. The emphysematous component of COPD can be diagnosed by CT, which may be poorly accessible, expensive and complicated by large interobserver variation in interpretation, especially at early stages of disease. Reduced diffusing capacity for carbon monoxide ($D_{L,CO}$), in the presence of airflow obstruction, is indicative of emphysema, but the method is not specific.[1]

We have suggested a simple method, airspace dimension assessment (AiDA), to determine distal airspace radius based on inhalation of nanoparticles. Nanoparticles deposit in the distal airspaces by diffusion, the probability being dependent on residence time in the lung and distance to an airspace wall. Measurement of deposition related to time allows the mean airspace radius (r_{AiDA}) to be calculated.[2–5] In a proof-of-concept study, a preliminary version of the method differentiated emphysema patients from healthy controls.[6]

The aim of this study was to determine if r_{AiDA} differs between persons with and without CT-verified emphysema in an unselected population. We expected persons with enlarged, emphysematous airspaces to have larger r_{AiDA} compared with non-emphysematous individuals. Secondary and tertiary aims were to determine whether subjects with emphysema suggested by lung function parameters have larger r_{AiDA} relative to non-emphysematous persons, and to investigate the role of comorbidities.

METHODS

The Swedish CArdioPulmonary bioImage Study (SCAPIS) is a national population-based study with 30 154 participants between 50 and 64 years of age. Our study was performed in a random sample of participants examined in Malmö, Sweden, between 2014 and 2016 (figure 1, online supplemental 1).

In AiDA measurements, the subjects inhaled 50 nm nanoparticles and held their breath for 5–10 s. Exhaled nanoparticles were measured from a sample at a volumetric lung depth of 1300 mL. The procedure was repeated six times. Particle recovery was calculated as the ratio between exhaled and inhaled concentration.[3] An exponential decay curve was fitted to the recovery values obtained at different breath-hold times, and the half-life ($t_{½}$) was calculated. By solving the diffusion equation, rAiDA is obtained:

$$r_{AiDA} = 2.89\sqrt{Dt}$$

where D is the diffusion coefficient given by the Stokes-Einstein equation.[2]

A chest CT was obtained and interpreted visually by one of four chest radiologists. A semiquantitative emphysema score with a maximum value of

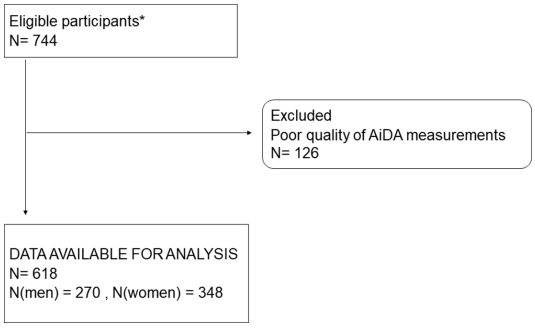

Figure 1 Exclusion chart. *Within the municipality of Malmö, Sweden, there were 51 061 registered inhabitants in the target age group in 2015. During the study time period, 4716 randomly selected individuals from the population registry were contacted, of which 50% (2358) participated. Of these, 744 randomly selected subjects underwent the AiDA measurements, corresponding to 1.5% of the target age population within the municipality. Please see online supplemental 1 for successful measurement criteria. AiDA, Airspace dimension assessment with nanoparticles.

18 was recorded (online supplemental 1). CT-derived total lung capacity by volumetric CT was calculated, and the percentage of voxels with a Hounsfield unit value below −950 (RV-950) was recorded. Emphysema was also defined quantitatively using two RV-950 percentage thresholds; >7% and >5%. Pulmonary function tests were performed according to American Thoracic Society and European Respiratory Society (ATS/ERS) standards.

RESULTS

Of the 744 subjects who underwent AiDA measurements, 618 were eligible for analysis (figure 1). The 47 persons with visually detected emphysema demonstrated an average emphysema score of 3.4±3.2, indicating mild-to-moderate disease. Most subjects had normal lung function, but some showed airflow obstruction. The r_{AiDA} was approximately normally distributed (online supplemental 3).

The persons with emphysema had a significantly larger r_{AiDA} compared with non-emphysematous subjects (tables 1A, B). By visual CT interpretation, the mean difference was 35 µm (95% CI 21 to 50 µm, p<0.0001). Findings were similar for emphysema defined by CT densitometry; mean differences were 25 µm (95% CI 11 to 36 µm, p<0.0001) and 37 µm (95% CI 15 to 59 µm, p<0.0001) for the 5% and 7% thresholds, respectively.

Dividing the r_{AiDA} into tertiles, we observed that with increasing radius, an increasing percentage of the subjects had emphysema and airflow obstruction. (online supplemental 4)

Logistic regression analysis was conducted using several definitions of emphysema and airflow obstruction (table 2). The radius was associated with increased OR with little effect of adjustments. No comorbidities caused significant differences in r_{AiDA} (online supplementals 1 and 2).

Table 1A Subject characteristics with and without visually detected emphysema

	Absent				Present				T-test
	N	M	SD	Range	N	M	SD	Range	P value
Age (year)	563	57.3	4.5	50–65	47	59.2	4.2	51–65	0.004
Weight (kg)	563	80	16	43–146	47	81	17	53–121	NS
Height (cm)	563	171	9	146–199	47	172	10	158–194	NS
BMI (kg/m^2)	563	27	5	17–45	47	27	4	18–36	NS
TLC (CTV) (L)	493	5.3	1.3	2.3–10.1	40	6.0	1.5	4.0–10.0	0.006
VC (L)	561	4.0	0.9	2.1–6.5	46	3.9	1.1	1.9–7.3	NS
VC (% pred)	561	110	15	66–154	47	107	16	60–143	NS
FEV_1 (L)	561	3.1	0.70	1.55–5.35	47	2.7	0.91	0.99–5.35	0.006
FEV_1 (% pred)	561	107	14	65–152	47	93	22	30–138	<0.0001
$D_{L,CO}$ (mmol min^{-1} kPa^{-1})	530	8.12	1.61	4.47–14.66	45	7.16	2.20	2.64–12.82	0.006
$D_{L,CO}$ (% pred)	526	91	13	54–170	43	81	20	29–134	0.001
RV −950 (%)	493	1.9	1.9	0–11	40	2.8	4.3	0–23	NS
Pack-years	517	9.9	12.8	0–86	44	27.6	16.0	0–66	<0.0001
r_{AiDA} (µm)	563	291	36	214–428	47	326	48	266–516	0.00001

Table 1B Subject characteristics with and without emphysema according to CT RV-950 cutoff >5%

	Absent				Present				T-test
	N	M	SD	Range	N	M	SD	Range	P value
Age (y)	492	57.4	4.5	50–65	41	57.5	4.7	50–65	NS
Weight (kg)	492	80	16	43–139	41	89	13	54–106	NS
Height (cm)	492	171	9	146–199	41	177	9	151–197	<0.0001
BMI (kg/m^2)	492	27	5	17–45	41	25	4	18–34	0.01
TLC (CTV) (L)	492	5.2	1.2	2.3–10.1	41	7.1	9.4	5.5–9.2	<0.0001
VC (L)	492	3.9	0.9	1.9–7.3	40	4.8	0.9	2.5–6.4	<0.0001
VC (% pred)	491	110	15	60–154	40	112	13.2	78–139	NS
FEV_1 (L)	491	3.1	0.72	0.27–5.35	40	3.45	0.95	0.99–5.08	0.03
FEV_1 (% pred)	491	106	15	46–152	40	103	22	30–139	NS
$D_{L,CO}$ (mmol min^{-1} kPa^{-1})	463	8.07	1.67	2.2–14.3	38	8.49	1.93	2.6–11.3	NS
$D_{L,CO}$ (% pred)	460	91	13	42–170	38	89	17	29–117	NS
RV −950 (%)	492	1.4	1.2	0–5	41	7.4	5.2	5–23	
Pack-years	453	10.5	14.2	0–86	38	10.1	14.8	0–54	NS
r_{AiDA} (µm)	492	291	36	214–516	41	316	41	239–412	<0.0001

AiDA, Airspace dimension assessment with nanoparticles; BMI, body mass index; TLC (CTV), total lung capacity measured by volumetric CT; D_{LCO}, diffusing capacity for carbon monoxide; FEV_1, forced expiratory flow in one second;NS, not significant; r_{AiDA}, distal airspace radius measured with the AiDA method; RV-950, the relative volume of voxels in lung parenchyma with a Hounsfield Unit value less than -950; TLC, total lung capacity; VC, vital capacity.

Table 2 r_{AiDA} logistic regression models; odds ratios (95% CIs) N=618

	N	Model 1 OR	Model 2 OR	Model 3 OR
Emphysema present in CT, visual evaluation	47	1.216 (1.134–1.303)**	1.209 (1.123–1.318)**	1.203 (1.184–1.311)**
Emphysema according to CT cut-off RV-950 >5%	41	1.157 (1.075–1.245)**	1.141 (1.054–1.235)*	1.146 (1.055–1.245)*
Airflow obstruction present according to FEV_1/VC <0.7	38	1.170 (1.088–1.258)**	1.166 (1.083–1.256)**	1.132 (1.044–1.227)*
Airflow obstruction present according to FEV_1/VC <LLN	36	1.196 (1.109–1.289)**	1.196 (1.107–1.292)**	1.162 (1.069–1.264)**
Emphysema suggested by $D_{L,CO}$ <2SD	28	1.213 (1.117–1.318)**		
Emphysema according to CT cut-off RV-950 >7%	18	1.019 (1.009–1.029)**		
Any respiratory symptom†	219	NS	1.051 (1.005–1.100)*	NS

Model 1, OR per 10 µm crude, unadjusted model. Model 2, with AiDA adjusted for age, sex, height and weight. Model 3, as Model 2 with additional adjustment for pack-years. Due to small N, models 2 and 3 are not given for emphysema suggested by $_{DL,CO}$ < 2SD and emphysema by CT cutoff RV-950 <7%.
*P<0.05.**p<0.01.
†That is, cough, phlegm, wheezing or dyspnoea.
AiDA, Airspace dimension assessment with nanoparticles; $D_{L,CO}$, diffusing capacity for carbon monoxide; FEV_1, forced expiratory flow in 1 s; LLN, lower limit of normal; NS, not significant; r_{AiDA}, distal airspace radius measured with the AiDA method; RV-950, the relative volume of voxels in lung parenchyma with a Hounsfield Unit value less than -950; VC, vital capacity.

DISCUSSION

This is the first study where distal airspace radii have been determined by nanoparticles in subjects with emphysema. In a previous study, we showed nanoparticle recovery at a single breath-hold time to be different between healthy subjects and patients with moderate to severe COPD. The present study in a population-based sample extends the information to calculation of distal airspace radius, r_{AiDA}, in subjects with mainly mild emphysema. Our results are in line with comparative methods[7–9] (online supplemental 5).

The small airways, <2 mm in diameter, have been suggested as the major site of early pathology in COPD. The repetitive toxic deposition stimulates an inflammatory response, repair and remodelling sequence, which later gives rise to a quantifiable airflow obstruction currently used as the diagnostic standard.[10] There is a long clinically silent period, where the pathophysiological changes do not result in airflow obstruction, and therefore the early stages of COPD often remain undiagnosed.[1] Also, spirometry alone will not differentiate between obstruction caused by airway narrowing and emphysema.

Due to their small size, nanoparticles traverse the distal airspaces and deposit there by diffusion. The r_{AiDA} in healthy volunteers is relatively constant at lung depths between 1000 and 2500 mL.[5] The r_{AiDA} cannot be taken to represent any specific airway generation, but corresponds to a mean of airspaces distal to generation 15–17. This may not apply in diseased airspaces with altered flow; further studies are needed.[5]

AiDA has similarities with $D_{L,CO}$, both being dependent on distribution of inhaled gas and diffusion within the airways. In contrast, AiDA is independent of transfer across the air-blood interface, haemoglobin concentration, recent smoking and altitude. The instrument is potentially simpler, as no compressed gases are needed. Compared with CT, the AiDA test is potentially easier and cheaper to administer. AiDA entails neither radiation nor an image that needs interpretation.

The AiDA measurements cause a low exposure to nanoparticles. The subjects were exposed to 0.05% of daily mass and 0.60% of daily particle number exposure in a comparatively clean urban setting.[11]

The study has several limitations. AiDA is a new technology, and we rely on a prototype of the apparatus. The proportion of measurements not fulfilling the technical criteria was high (online supplemental 1). This was mainly caused by the fact that at the beginning of the experiment, the particle concentration in the reservoir, and therefore, the inspired gas, was not uniform, resulting in several insufficient measurements. The subjects without emphysema in this study did not necessarily have normal lungs—a number of subjects had airflow obstruction. Due to the low number of subjects in the population with emphysema, the findings were not further analysed in subgroups according to disease severity, phenotype or presence of bullae. As emphysema and bronchial abnormalities frequently coincide in COPD, it is difficult to examine each phenotype on its own. Further studies on persons with predominantly airway involvement versus parenchymal disease phenotype are warranted, as well as studies to visualise where exactly the particles deposit.

We suggest AiDA is a potential biomarker for emphysema.[1] To validate the method, however, a diagnostic accuracy study in target populations should be conducted, and sensitivity and specificity calculated.

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Contributors PW, JL, GE, LHA and JJ participated in the experimental design. LHA, JJ, MPS, VI, FSM and SD participated in the data collection. All authors participated in the data analysis and interpretation. LHA prepared the first draft of the manuscript. All authors revised and approved the final version to be published. All authors are accountable for all aspects of the work.

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Competing interests PW and JL have a patent issued for the device used in the measurements. PW reports personal fees from AstraZeneca and Chiesi Pharma, outside the submitted work, SZ reports grants from Allmänna sjukhuset i Malmös stiftelse för bekämpande av cancer (Translation: Malmö general hospital's foundation for defeating cancer), and grants from Stiftelsen för cancerforskning vid onkologiska kliniken vid Universitetssjukhuset Malmö (Translation: Foundation for cancer research within the department of oncology in Malmö University Hospital) outside the submitted work.

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Online supplement 1: Method and Results

Material and Method

Study population

The study was conducted according to the Declaration of Helsinki. Local ethical board approval was obtained, and written informed consent was obtained from all participants. The study participants completed a questionnaire including medical history, symptoms, and smoking habits. See the questionnaire in Online Supplement 3.

Technical quality control

AiDA is a new technique, and the procedures for quality control are under development. In this study, breathing airflow monitor was set to zero before each measurement. The flow and particle size were calibrated monthly. Measurements performed on the same biocontrol individuals before, during, and after the study showed the r_{AiDA} measurements had a standard deviation below 7 µm. (5) Data were considered acceptable if 1) the subjects performed at least four valid breathing manoeuvres, 2) no instrumental errors were detected, and 3) the correlation coefficient, r, between breath-hold time and log recovery was higher than 0.9, showing sufficient fit to model.

Computed tomography (CT)

All chest CTs in this study were performed using the same multidetector-row scanner (Siemens Somatom Definition Flash; Siemens Healthineers, Forchheim, Germany) with a detector configuration of 128 × 0.6, tube voltage 120 kV (Care kV off), tube current modulation (CareDose 4D, ref mAs 30), pitch 0.9, rotation time 0.5 seconds. Images were acquired in full inspiration, and then reconstructed according to following kernels B31f, B20f, I30f (SAFIRE level 3), 0.6 mm slice thickness / 0.6 mm increment, as well as B35f 0.6 mm slice thickness / 0.4 mm increment. This protocol applied low radiation dose (Wang et al AJR 2014).

The images were assessed using syngo.via pulmo 3D software version VA. CT-derived total lung capacity TLC (CTV) was calculated as the volumetric sum of the CT voxels containing lung tissue at full inspiration. A density mask of -950 Hounsfield Units (HU) was applied. The percentage of voxels with a HU value below -950, termed relative volume, or RV -950, was applied. Emphysema was then defined using two different RV -950 percentage cutoff-values; > 7% or > 5%. Visually assessed emphysema was

defined by the Fleischner society's guidelines and recorded as present or absent. If present, a semiquantitative score was obtained as described by Goddard et al *Computed tomography in pulmonary emphysema. Clinical radiology 1982*; each lung was divided into an upper, middle and lower section, and for each section an emphysema score between 0 and 3 was assigned, where 0 represented no emphysema, 1 represented 0-25% emphysema, 2 denoted a 25-50% emphysema and 3 represented above 50% emphysema. The scores from each section were added together, yielding a maximum score of 18.

Statistics

Data were examined for skewness and kurtosis to test normality. Student's t-test was used to determine differences in in study variables between emphysematous and non-emphysematous subjects.

Three logistic regression models were used to investigate differences in r_{AiDA} odds ratios between emphysematous and non-emphysematous subjects, as well as between persons with and without airflow obstruction. Three different definitions of emphysema were used in the logistic regression: visually detected emphysema, RV -950 above 5% and RV-950 above 7%. Airflow obstruction was defined both according to GOLD criteria, as well as using a cut-off of $FEV_1/VC < 1.65$ SD, i.e. lower limit of normal. Lastly, a cutoff in $D_{L,CO}$ of -2SD was used. In model 1, each variable was considered alone without adjusting for other factors. In model 2, age, BMI and sex were accounted for. In model 3, age, BMI, sex as well as pack years were adjusted for.

Additionally, to avoid overfitting of the logistic regression models, we also used the residual method to adjust the AiDA values for confounding factors (Online supplement 1, Table 3). A multiple linear regression model was used. AiDA (dependent variable) was regressed on age, sex, height and weight (independent) and the residual values were saved. The residuals were normally distributed. In the next step, three logistic regression models were used to examine the relationships between r_{AiDA} and various definitions of emphysema, including CT, airflow obstruction and reduced $D_{L,CO}$. Model 1 was unadjusted. In model 2, residuals of AiDA (adjusted for age, height, weight and sex) were entered. were accounted for and in model 3, pack years was added to the model as a separate variable.

In each analysis, missing data were reported. Student's t-test was used to compare emphysema/airflow obstruction indices between included subjects and subjects excluded due to insufficient AiDA measurements. Student's t-test was also used to determine differences in r_{AiDA} with respect to the comorbidities listed under Online Supplement 3.

A p-value of less than 0.05 was considered statistically significant. The analyses were conducted using IBM SPSS (v. 24, 2016, Armonk, NY).

Study size

Past literature on AiDA is scarce. A power calculation was made based on data from a proof-of-concept study. Assuming a COPD prevalence of 10%, a sample size of 104 individuals is required (two-tailed $\alpha = 0.05$; $\beta = 0.2$) to establish sufficient power to prove a difference between emphysematous and non-emphysematous subjects. As the proof-of-concept study included subjects with advanced disease, and only mild emphysema was expected in a population-based sample, a sample size 5-6 times the above calculation was obtained.

Results

Supplement Table: –Logistic regression models of r_{AiDA} and measures of emphysema, with adjustments for covariates using the residual method. Odds ratios (95% confidence intervals) N=618

	N	Model 1 OR	Model 2 OR	Model 3 OR
Emphysema present in CT, visual evaluation	47	1.216 (1.134-1.303)**	1.209 (1.127-1.298)**	1.163 (1.082-1.249)**
Emphysema according to CT cutoff RV-950 > 5%	41	1.157 (1.075-1.245)**	1.135 (1.054-1.223) *	1.144 (1.057-1.237)*
Airflow obstruction present according to $FEV_1/VC < 0.7$	38	1.170 (1.088-1.258)**	1.163 (1.081-1.252)**	1.130 (1.047-1.219)**
Airflow obstruction present according to $FEV_1/VC <$ LLN	36	1.196 (1.109-1.289)**	1.192 (1.105-1.286)**	1.161 (1.073-1.255)**
Emphysema suggested by $D_{L,CO} <$ 2SD	28	1.213 (1.117-1.318)**		
Emphysema according to CT cutoff RV-950 > 7%	18	1.019 (1.009-1.029)**		
Any respiratory symptom‡	219	NS	1.055(1.008-1.104) *	NS

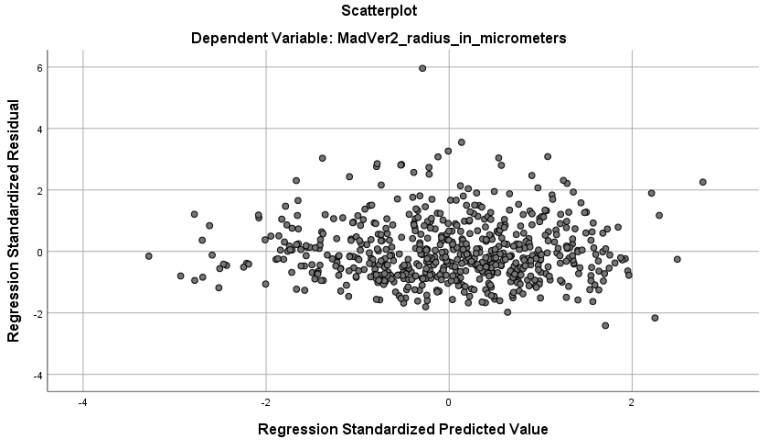
Model 1, odds ratio per 10 µm crude, unadjusted model. Model 2, with AiDA adjusted for age, sex, height and weight (residual method). Model 3, as Model 2 with additional adjustment for pack years.

Abbreviations: CT, computed tomography RV-950; the relative volume of voxels in lung parenchyma with a Hounsfield Unit value less than -950; FEV_1, forced expiratory flow in one second; VC, vital capacity; LLN, lower limit of normal; $D_{L,CO}$, diffusing capacity for carbon monoxide; r_{AiDA}, distal airspace radius measured with the AiDA method; NS, not significant, OR odds ratio.
*P<0.05
**P<0.0001

‡ I.e. cough, phlegm, wheezing or dyspnea

Due to small N, models 2 and 3 are not given for emphysema suggested by $D_{L,CO} <$ 2SD and emphysema according to CT cutoff RV-950
> 7%.

Supplement figure – Residual distribution



The persons excluded due to insufficient quality of AiDA measurements did not differ from the included with respect to age, FEV_1, $D_{L,CO}$ and RV-950.

Online Supplement 2: Questionnaire

Respiratory symptoms

In this paper, self-reported respiratory symptoms were defined as an affirmative answer to any of the following questionnaire items: “Do you cough even when you do not have a common cold?”, “Do you cough up phlegm, or experience mucus in your chest that you have trouble clearing, even when you do not suffer from a common cold?” “Do you experience wheezing or whistling in your lungs?”, “Do you experience shortness of breath when hurrying on level ground or walking up a slight incline?”, or “Have you ever suffered from shortness of breath severe enough to disturb your daily activities, or to force you to stay home from work?”

Comorbidities

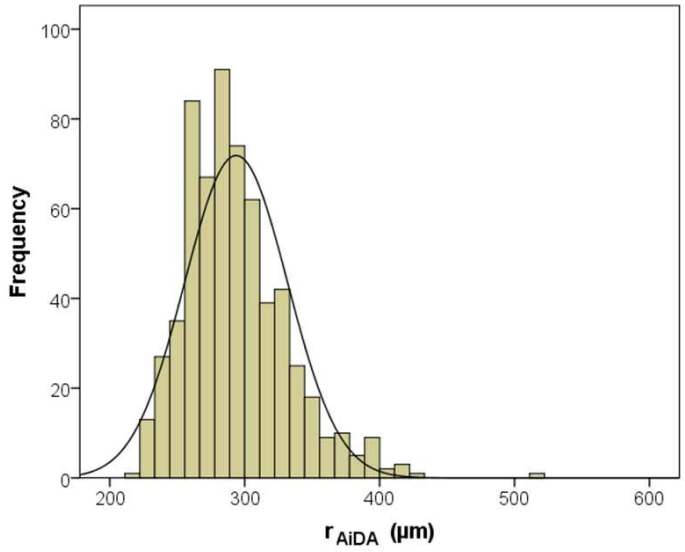
The subjects were given the following questions regarding their comorbidities.

Which of the following illnesses has a medical doctor diagnosed on you, or have been surgically treated for? (several alternatives can be chosen)

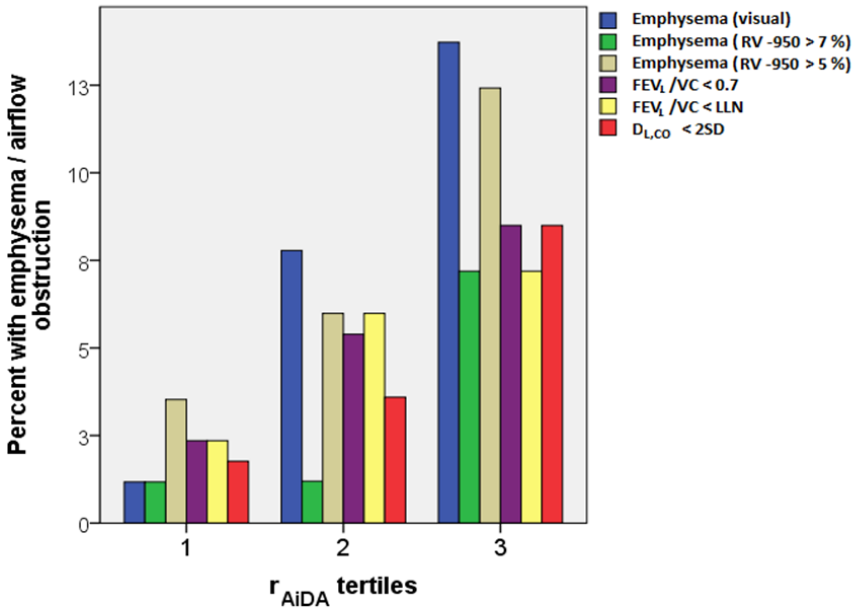
- Myocardiac infarct/a thrombus in the heart*
- Angina pectoris*
- Atrial fibrillation*
- Heart failure*
- Valvular heart disease*
- A bypass-operation or balloon dilatation of the coronary arteries*
- A procedure for treating stenosis caused by peripheral artery disease*
- A procedure for aortic aneurysm*
- Stroke/brain infarct/bleeding in the brain*
- High blood pressure
- High blood lipids / high cholesterol
- Diabetes
- Chronic obstructive pulmonary disease
- Asthma

- Tuberculosis
- Other lung disease
- Obstructive sleep apnea
- Gluten intolerance/coeliac disease
- Crohn's disease or ulcerative colitis
- Rheumatic disease
- Cancer
- None of the above

Cardiovascular disease other than hypertension is denoted by *



Online Supplement 3 - Frequency table of rAiDA with a normal distribution curve
The AiDA values were approximately normally distributed. There was one female outlier value with r_{AiDA} of 516 mm. This person had moderate emphysema on CT with a visual emphysema score of 8 (of 18). She had COPD stage 2 according to spirometric GOLD-criteria ($FEV_1/VC < 0.7$ and FEV_1 of 55% of predicted). She also had a $D_{L,CO}$ of 49% of predicted. This person was an active smoker with a >52 pack year smoking history. She also reported experiencing dyspnoea, cough, wheezing and increased phlegm.



Online Supplement 4: The percentage of subjects with different emphysema and airflow obstruction indices and $D_{L,CO}$ < 2 SD.
The subjects are divided into tertiles according to increasing r_{AiDA} values. For each variable, emphysema or outflow obstruction is considered either present or absent. The percentage of present findings per r_{AiDA} tertile are given.
$D_{L,CO}$ = diffusing capacity for carbon monoxide, SD = standard deviation, RV -950 = percent of voxels with an attenuation value below -950 Hounsfield Units, FEV_1 = forced expiratory flow in one second, VC = vital capacity, LLN = lower limit of normal, r_{AiDA} = distal airspace radius measured using Airspace Dimension Assessment with nanoparticles

Online Supplement 5: Distal airspace diameter measured by different methods

STUDY	Method	Site of measurement	Number of subjects	Average diameter, non-emphysematous lung	Average diameter, emphysematous lung	Comment
Tanabe 2017	Micro-CT	Lm	Controls N = 7 CLE N = 6 PLE N = 7	336 ± 37 µm	CLE: 766 ± 259 µm PLE: 698 ± 240 µm	
Woods 2006	^{3}He MRI	Lm	Controls N = 6 COPD N = 6	200 µm	410 µm	No SD given.
Kohlhaufl 1999	ADAM	Distal airspaces	Non-emphysematous N = 30 Emphysematous N = 20	330 ± 100 µm	840 ± 530 µm	
The present study	AiDA	Distal airspaces	Non-emphysematous N = 563 Emphysematous N = 47	582 ± 72 µm	652 ± 96 µm	Diameter = 2 x radius.

CT = computed tomography, CLE = centrilobular emphysema, PLE = panlobular emphysema, ^{3}He MRI = hyperpolarised helium magnetic resonance imaging, Lm = mean linear intercept, a measure of alveolar/acinar structures, ADAM = aerosol derived airway morphometry, AiDA = airspace dimension assessment with nanoparticles