Airspace dimension assessment with nanoparticles as a proposed biomarker for emphysema

H Laura Aaltonen,1,2,3 Madeleine Petersson Sjögren,4,5 Jonas K F Jakobsson,4,5 Hanna Nicklasson,1 Sandra Díaz,1,6 Francisco Sánchez Montiel,1,2 Sophia Zackrisson,1,2 Veronica Ideböhn,4 Gunnar Engström,7 Jakob Löndahl,4,5 Per Wollmer1,2

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 Biomaging 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±36 µm); OR per 10 µm: 1.16 (1.08–1.24, p<0.0001). 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 (DLCO), 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 (rAiDA) to be calculated.2,4 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 rAiDA differs between persons with and without CT-verified emphysema in an unselected population. We expected persons with enlarged, emphysematous airspaces to have larger rAiDA compared with non-emphysematous individuals. Secondary and tertiary aims were to determine whether subjects with emphysema suggested by lung function parameters have larger rAiDA 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.7 An exponential decay curve was fitted to the recovery values obtained at different breath-hold times, and the half-life (t1/2) was calculated. By solving the diffusion equation, rAiDA is obtained:

\[ r_{AiDA} = 2.89 \sqrt{\frac{D}{t_{1/2}}} \]

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...
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/m²)    | 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 | 47     | 4.9     | 1.1    | 3.9     | NS      |
| VC (% pred)    | 561    | 110     | 15     | 66–154  | 47     | 107     | 15     | 60–143  | NS      |
| FEV₁ (L)       | 561    | 3.1     | 0.70   | 1.55–5.35| 47      | 2.7     | 0.91   | 0.99–5.35| 0.006   |
| FEV₁ (% pred)  | 561    | 107     | 14     | 65–152  | 47     | 93      | 22     | 30–138  | <0.0001 |
| D_{LCO} (mmol min⁻¹ kPa⁻¹) | 530 | 8.12 | 1.61 | 4.47–14.66 | 45 | 7.16 | 2.20 | 4.56–12.82 | 0.006 |
| D_{LCO} (% 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/m²)    | 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)    | 492    | 110     | 15     | 60–154  | 40     | 112     | 13.2   | 78–139  | NS      |
| FEV₁ (L)       | 492    | 3.1     | 0.72   | 0.27–5.35| 40      | 3.45    | 0.95   | 0.99–5.08| 0.03    |
| FEV₁ (% pred)  | 492    | 106     | 15     | 46–152  | 40     | 103     | 22     | 30–139  | NS      |
| D_{LCO} (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_{LCO} (% 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    | NS      |
| 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; FEV₁, 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.
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, \( r_{\text{AiDA}} \), in subjects with mainly mild emphysema. Our results are in line with comparative methods \(^{7,9} \) (online supplemental S).

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 \( r_{\text{AiDA}} \) is not affected by specific airway generation, but corresponds to a mean of airspaces distal to generation 15–17. This may not apply in diseased airspaces and deposit there by diffusion. The \( r_{\text{AiDA}} \) 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.

The AiDA measurements cause a low exposure to nanoparticles, \( D_{LCOP} \) diffusing capacity for carbon monoxide; FEV\(_1\), forced expiratory flow in 1 s; LLN, lower limit of normal; NS, not significant; \( r_{\text{AiDA}} \) distal airspace radius measured with the AiDA method; RV-950 <7%.

| Emphysema present in CT, visual evaluation | N | Model 1 OR | Model 2 OR | Model 3 OR |
|-------------------------------------------|---|------------|------------|------------|
| Not present                               | 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\(_{CO}\) <2SD | 28 | 1.213 (1.137–1.318)** | 1.18 (1.09–1.29)** |
| 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 D\(_{CO}\) < 2SD and emphysema by CT cutoff RV-950 <7%.

*P<0.05. **p<0.01.

† That is, cough, phlegm, wheezing or dyspnoea.


discussion 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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ORCID iDs
H Laura Aaltonen http://orcid.org/0000-0002-4520-3229
Jakob Löndahl http://orcid.org/0000-0001-9379-592X

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