

# Signs of Hyperinflation and Ventilation Heterogeneity in Individuals With Severe Alpha-1-Antitrypsin Deficiency at the Age of 42

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**Background:** Severe alpha-1-antitrypsin deficiency (AATD) is a known risk factor for early development of emphysema and COPD. By the Swedish national screening program within the years 1972–74 a cohort of individuals with severe AATD (PiZZ) was identified and regularly followed up. The aim of this study was to investigate alveolar volume ( $V_A$ ) and the ratio  $V_A$ /Total lung capacity ( $V_A$ /TLC) for the detection of signs of hyperinflation and ventilation heterogeneity in PiZZ individuals compared with an age-matched control group (phenotype PiMM), randomly selected from the population registry.

**Methods:** All study participants underwent pulmonary function tests (PFT) including dynamic spirometry and total lung capacity (TLC), residual volume (RV), functional residual capacity (FRC) and alveolar volume ( $V_A$ ). They answered a questionnaire on smoking habits and symptoms. Quality of life was assessed by answering the Saint George's Respiratory Questionnaire (SGRQ).

**Results:** Fifty-six PiZZ and 66 PiMM individuals participated in the study. The PiZZ individuals had a significantly lower  $V_A$ /TLC ratio ( $p=0.004$ ) and significantly higher RV ( $p<0.001$ ) and RV/TLC ratio ( $p=0.001$ ) than the PiMM individuals. The 13 PiZZ ever-smokers had a significantly higher TLC ( $p=0.025$ ), RV ( $p=0.003$ ) and FRC ( $p=0.003$ ) and a significantly lower  $V_A$ /TLC ratio ( $p=0.006$ ) than the 24 PiMM ever-smokers. No significant differences in RV, TLC,  $V_A$ , and  $V_A$ /TLC ratio were found between the never-smoking PiZZ and PiMM individuals. The ratio RV/TLC was significantly higher in the PiZZ never-smokers than in the PiMM never-smokers ( $p=0.026$ ).

**Conclusion:** At the age of 42 the PiZZ ever-smokers have signs of hyperinflation and ventilation heterogeneity.

**Plain language summary:** Uneven airflow in the lungs, also called uneven ventilation is known as an indicator for lung disease. It can be analysed by measurement of alveolar volume and total lung capacity. The presence of uneven ventilation has not been investigated in individuals with severe Alpha-1-antitrypsin deficiency (shortened to AATD).

We invited 129 individuals from a known cohort with severe AATD to perform lung function tests. Furthermore, they answered questions about health, tobacco consumption and respiratory symptoms. To compare the results, we also invited a group of individuals without AATD and had them perform the same tests.

We found that individuals with severe AATD show signs of uneven ventilation, especially when they are or have been smoking.

Our results suggest that analysis of alveolar volume is a simple, safe and time-saving method for the early detection of lung disease in individuals with severe AATD.

**Keywords:** alpha-1-antitrypsin-deficiency, alveolar volume, hyperinflation, smoking

## Introduction

AAT is an important protease inhibitor that inactivates serine proteases such as neutrophil elastase in order to protect lung tissue from destruction.

The rare autosomal codominant genetic disorder severe alpha-1-antitrypsin (AAT) deficiency (PiZZ) is a well-known risk factor for early development of pulmonary diseases such as COPD and emphysema.<sup>1</sup> This genetic defect results in an accumulation of AAT in the hepatocytes and a decreased release into the circulation. Although knowledge about the natural history of AATD continues to improve, early diagnosis remains crucial for ensuring optimal patient care. Early diagnosis enables the identification and prevention of other risk factors for COPD development, such as smoking or occupational exposure to airway irritants.

During the Swedish national AAT screening project from 1972 to 1974, all 200,000 new-born children were screened for AAT deficiency (AATD) with the aim of estimating the prevalence of AATD in the Swedish population. A cohort of 127 PiZZ, 2 PiZnull, 54 PiSZ and 1 PiSnull children was identified and has been followed up regularly to study the natural course of AATD.<sup>2</sup>

Since the age of 30, an age-matched control group, randomly selected from the Swedish population registry, has been followed up in order to compare the results between the AAT-deficient individuals and the Swedish general population.<sup>3,4</sup> We have previously reported signs of hyperinflation and early signs of COPD at the age of 42 in individuals with severe AATD (PiZZ), especially in ever-smokers but also in never-smokers.<sup>5,6</sup>

In healthy individuals, the uniform distribution of minute volume minimizes the work of breathing and maximizes the efficiency of the lung as a gas exchanger. Previously published studies using imaging, nitrogen washout or the inert gas elimination technique have shown a non-uniform distribution of inspired gas, termed ventilation heterogeneity (VH). In these studies, VH was identified as an early marker of airflow limitation development in initial stages of COPD and thereby being a fundamental impairment of lung function.<sup>7</sup> In addition, in patients with manifest COPD, the uneven ventilation distribution is found to be a sensitive marker of early physiological impairment and disease progression.<sup>8,9</sup>

The VH can be assessed by physiological measurement of the ratio alveolar volume ( $V_A$ ) to total lung capacity (TLC) derived from plethysmography. Measurement of the diffusing capacity of carbon monoxide ( $D_{LCO}$ ) includes a measurement of  $V_A$ . The manoeuvre entails a forced inhalation of a gas mixture containing CO and a poorly soluble gas, commonly CH<sub>4</sub> (methane). The two gases are measured in an alveolar sample of exhaled gas and  $V_A$  is calculated from the dilution of CH<sub>4</sub>. Due to the forced inhalation, there may be heterogeneous distribution of the inhaled gas in the lung as a consequence of regional differences in time constants. In the calculation of  $V_A$ , airway dead space is subtracted, wherefore  $V_A$  is, in principle, always lower than total lung capacity (TLC) measured by body plethysmography. The difference will increase with ventilation heterogeneity. The ratio  $V_A$ /TLC has been studied mainly in smoking subjects with established COPD.<sup>10,11</sup> Recently,  $V_A$ /TLC has also been shown to be reduced in smokers with normal spirometry.<sup>12</sup> We are not aware of any such studies in subjects with AATD.

The aim of this study was to investigate if there are signs of ventilation heterogeneity by analysing  $V_A$  and TLC in individuals with severe AATD at the age of 42 and to study their relation to airflow obstruction.

## Methods

This was a prospective case-control study comparing lung function in individuals with severe AATD (PiZZ), identified by neonatal screening, with an age-matched control group randomly selected from the population registry.

## The Study Population

All individuals within the cohort were invited to participate in this follow-up study at the age of 42 years. The same 300 age-matched control subjects, who had earlier been randomly selected from the population registry, were invited to participate.<sup>3-5</sup>

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Regional Ethical Review Board of Lund, Sweden. All study participants gave their signed, informed consent.

## Pulmonary Function Tests and CT Scan

All pulmonary function tests (PFT) were performed at Skåne University Hospital, Malmö, Sweden. After bronchodilation with Terbutaline 1.5 µg the study participants underwent PFT including dynamic spirometry for measurement of vital capacity (VC), forced expiratory volume in one second (FEV<sub>1</sub>) and forced mid-expiratory flow (FEF<sub>25-75</sub>), body-plethysmography for measurement of TLC, residual volume (RV), functional residual capacity (FRC) and alveolar

volume ( $V_A$ ). Furthermore, they underwent measurement of diffusing capacity for carbon monoxide ( $D_{LCO}$ ) (Intramedic Masterscreen<sup>®</sup>, Sollentuna, Sweden). Measurement of airway resistance was performed by impulse oscillometry (IOS).

The PFT were performed according to the guidelines of American Thoracic Society/European Respiratory Society. The results of PFT are presented as percent of the reference values stipulated by the European Community for Steel and Coal.<sup>13</sup> The values of  $V_A$  and  $V_A/TLC$  and  $FEV_1/VC$  are presented as absolute values. The CT scan of thorax was performed at the Department of Radiology, Skåne University Hospital, Malmö, Sweden at full inspiration.

## Questionnaire

The participants answered a questionnaire concerning smoking habits (yes/no, duration of smoking, stopping age, numbers of cigarettes per day), self-estimated exertion capacity on the VAS (visual analogue scale). For the evaluation of quality of life, the study participants answered the Saint George's Respiratory Questionnaire (SGRQ) [0–100 points where high points indicate poor quality of life].<sup>14</sup>

## Statistical Analyses

The Statistical Package for the Social Sciences (SPSS), version 25, was used for the statistical analyses. Continuous variables were analysed with the parametric One-Way-ANOVA-test and post-hoc analysis according to Tukey. When comparing two groups, we used independent samples *t* test. Categorical variables are presented as frequencies and percentages. The Pearson Chi-square ( $\chi^2$ ) test was used to compare categorical variables. For correlation analysis, we used Pearson's bivariate correlation. A *p*-value <0.05 was considered as significant.

## Results

### The Study Population

The number of participants, their age and smoking habits are presented in Table 1.

The proportion of men was lower in the control group (phenotype PiMM) than in the PiZZ subjects. The proportion of smokers and the level of tobacco consumption was lower among the PiZZ subjects compared to PiMM, but the differences were not statistically significant.

### Pulmonary Function Tests and Analysis of Alveolar Volume, Oscillometry and Presence of Emphysema

The results of the pulmonary function tests, measurement of alveolar volume, oscillometry and presence of emphysema in the Pi subgroups are shown in Table 2.

**Table 1** Demographic Data of the Study Population

|                                    | PiZZ n = 56    | PiMM n = 66     | p-value |
|------------------------------------|----------------|-----------------|---------|
| Men, n (%)                         | 29 (52)        | 30 (46)         | NS      |
| Age (years)                        | 43 (41–45)     | 44 (43–45)      | NS      |
| Smoking habits                     |                |                 |         |
| Never, n (%)                       | 43 (77%)       | 42 (64%)        | NS      |
| Ever, n (%)                        | 13 (23%)       | 24 (36%)        | NS      |
| Pack years                         | 6.7 (0.5–16.5) | 11.8 (0.4–45.0) | NS      |
| Age at smoking stop, years (range) | 29.5 (15–40)   | 30.9 (16–42)    | NS      |

**Notes:** Data are presented as frequency (percentage), mean (range).

**Table 2** Results of Pulmonary Function Tests, Oscillometry and Presence of Emphysema in Pi Subgroups

|                                  | <b>PiZZ (n=56)</b> | <b>PiMM (n=66)</b> | <b>p-value</b> |
|----------------------------------|--------------------|--------------------|----------------|
| FEV <sub>1</sub> (% of pred)     | 107 (104–111)      | 111 (108–114)      | NS             |
| VC (% of pred)                   | 113 (110–117)      | 117 (114–120)      | NS             |
| FEV <sub>1</sub> /VC             | 0.78 (0.76–0.80)   | 0.78 (0.77–0.79)   | NS             |
| FEF <sub>25-75</sub> (% of pred) | 96 (89–103)        | 95 (89–101)        | NS             |
| TLC (% of pred)                  | 110 (106–114)      | 109 (106–111)      | NS             |
| RV (% of pred)                   | 111 (104–117)      | 98 (95–102)        | <0.001         |
| FRC (% of pred)                  | 116 (110–122)      | 106 (102–111)      | 0.008          |
| RV/TLC                           | 0.30 (0.29–0.31)   | 0.28 (0.27–0.29)   | 0.001          |
| V <sub>A</sub> (L)               | 6.5 (6.2–6.9)      | 6.3 (6.0–6.6)      | NS             |
| V <sub>A</sub> /TLC              | 0.91 (0.90–0.92)   | 0.93 (0.92–0.94)   | 0.004          |
| D <sub>LCO</sub> (% of pred)     | 95 (91–99)         | 98 (94–102)        | NS             |
| K <sub>CO</sub> (% of pred)      | 93 (88–97)         | 93 (89–97)         | NS             |
| R5Hz (kPa/(L/s))                 | 0.29 (0.27–0.31)   | 0.31 (0.30–0.33)   | 0.034          |
| R20Hz (kPa/(L/s))                | 0.27 (0.26–0.29)   | 0.30 (0.28–0.31)   | 0.035          |
| R5Hz- R20Hz (kPa/(L/s))          | 0.23 (0.20–0.26)   | 0.28 (0.26–0.30)   | 0.014          |
| Emphysema, n (%)                 | 7 (13%)            | 1 (2%)             | 0.015          |

**Notes:** Data are presented as means (95% CI) and frequency (percentage).

The PiZZ subjects had significantly higher mean RV ( $p<0.001$ ), FRC ( $p=0.008$ ), RV/TLC ratio ( $p=0.001$ ) and significantly lower V<sub>A</sub>/TLC ratio ( $p=0.004$ ) than the PiMM subjects. The values for airway resistance R5Hz, R20Hz and R5Hz-R20Hz were significantly lower in the PiZZ individuals compared to the PiMM individuals, [Table 2](#)

The number of individuals with emphysema confirmed by CT scans was significantly higher in PiZZ individuals compared to the controls ( $p=0.015$ ).

The results of the pulmonary function tests, measurement of alveolar volume, oscillometry and presence of emphysema in the smoking subgroups are shown in [Table 3](#).

**Table 3** Pulmonary Function Test Results, Oscillometry Results and the Presence of Emphysema in 56 PiZZ and 66 PiMM Individuals Stratified by Smoking Habits

|                                  | <b>Never-Smokers</b> |                    |                | <b>Ever-Smokers</b> |                    |                |
|----------------------------------|----------------------|--------------------|----------------|---------------------|--------------------|----------------|
|                                  | <b>PiZZ (n=43)</b>   | <b>PiMM (n=42)</b> | <b>p-value</b> | <b>PiZZ (n=13)</b>  | <b>PiMM (n=24)</b> | <b>P-value</b> |
| FEV <sub>1</sub> %               | 107 (103–111)        | 112 (108–116)      | NS             | 109 (97–121)        | 109 (104–114)      | NS             |
| VC (% pred)                      | 110 (106–114)        | 116 (112–121)      | NS             | 126 (119–133)       | 118 (113–124)      | NS             |
| FEV <sub>1</sub> /VC             | 0.79 (0.78–0.81)     | 0.79 (0.78–0.81)   | NS             | 0.72 (0.66–0.79)    | 0.76 (0.74–0.79)   | NS             |
| FEF <sub>25-75</sub> (% of pred) | 99 (91–106)          | 97 (90–104)        | NS             | 88 (70–106)         | 90 (79–101)        | NS             |

(Continued)

**Table 3** (Continued).

|                           | Never-Smokers    |                  |         | Ever-Smokers     |                  |         |
|---------------------------|------------------|------------------|---------|------------------|------------------|---------|
|                           | PiZZ (n=43)      | PiMM (n=42)      | p-value | PiZZ (n=13)      | PiMM (n=24)      | P-value |
| TLC (% pred)              | 107 (103–111)    | 108 (105–111)    | NS      | 122 (112–131)    | 110 (106–114)    | 0.025   |
| RV (% pred)               | 107 (102–111)    | 97 (93–102)      | NS      | 123 (99–148)     | 100 (95–106)     | 0.003   |
| FRC (% pred)              | 112 (107–117)    | 107 (101–113)    | NS      | 130 (110–150)    | 106 (99–112)     | 0.003   |
| RV/TLC                    | 0.30 (0.29–0.31) | 0.28 (0.26–0.29) | 0.026   | 0.31 (0.27–0.35) | 0.29 (0.27–0.30) | NS      |
| V <sub>A</sub>            | 6.5 (6.2–6.9)    | 6.3 (5.9–6.7)    | NS      | 6.6 (5.8–7.4)    | 6.1 (5.6–6.6)    | NS      |
| V <sub>A</sub> /TLC       | 0.92 (0.91–0.93) | 0.93 (0.92–0.94) | NS      | 0.89 (0.86–0.92) | 0.93 (0.92–0.95) | 0.006   |
| D <sub>LCO</sub> (% pred) | 97 (92–100)      | 99 (93–103)      | NS      | 90 (82–100)      | 96 (90–101)      | NS      |
| K <sub>CO</sub> (% pred)  | 95 (90–100)      | 93 (90–98)       | NS      | 85 (75–95)       | 92 (85–99)       | NS      |
| R5Hz (kPa/(L/s))          | 0.28 (0.27–0.30) | 0.31 (0.30–0.34) | NS      | 0.30 (0.26–0.35) | 0.32 (0.29–0.34) | NS      |
| R20Hz (kPa/(L/s))         | 0.27 (0.26–0.29) | 0.30 (0.28–0.32) | NS      | 0.28 (0.25–0.32) | 0.29 (0.27–0.31) | NS      |
| R5Hz-R20Hz (kPa/(L/s))    | 0.24 (0.20–0.27) | 0.29 (0.27–0.32) | NS      | 0.23 (0.16–0.30) | 0.27 (0.23–0.31) | NS      |
| Emphysema, n (%)          | 4 (9%)           | 1 (2%)           | NS      | 3 (23%)          | 0                | 0.014   |

**Notes:** Data are shown as mean (95% CI), frequency (percentage).

The ever-smoking PiZZ subjects had a significantly lower mean V<sub>A</sub>/TLC ratio (p=0.006) than the ever-smoking PiMM individuals. The mean TLC, RV and FRC were significantly higher in the ever-smoking PiZZ individuals compared to the ever-smoking PiMM individuals. The PiZZ never-smokers had a significantly higher RV/TLC ratio compared to the PiMM never-smokers. Among ever-smokers, the number of individuals with emphysema was significantly higher in PiZZ individuals compared to controls (p=0.014).

The results of the correlation between V<sub>A</sub>/TLC ratio, PFT results and symptoms are shown in Table 4. Among the PiZZ subjects the V<sub>A</sub>/TLC ratio was significantly correlated to FEV<sub>1</sub>/VC ratio, RV/TLC ratio, D<sub>LCO</sub>, K<sub>CO</sub>, SGRQ

**Table 4** Pearson Correlation Coefficient Between V<sub>A</sub>/TLC Ratio, Pulmonary Function Tests, Oscillometry and Symptoms

|                            | PiZZ n=56 |         | PiMM n=66 |         |
|----------------------------|-----------|---------|-----------|---------|
|                            | Rho-value | p-value | Rho-value | p-value |
| FEV <sub>1</sub> /VC       | 0.345     | 0.009   | 0.172     | NS      |
| FEF <sub>25-75</sub> (L/s) | 0.181     | NS      | 0.303     | 0.016   |
| RV/TLC                     | −0.464    | <0.001  | −0.593    | <0.001  |
| D <sub>LCO</sub>           | 0.371     | 0.005   | 0.272     | 0.027   |
| K <sub>CO</sub>            | 0.284     | 0.034   | 0.142     | NS      |
| R5Hz (kPa/(L/s))           | 0.151     | NS      | 0.158     | NS      |
| R20Hz (kPa/(L/s))          | 0.014     | NS      | 0.218     | NS      |

(Continued)

**Table 4** (Continued).

|                         | PiZZ n=56 |         | PiMM n=66 |         |
|-------------------------|-----------|---------|-----------|---------|
|                         | Rho-value | p-value | Rho-value | p-value |
| R5Hz-R20Hz (kPa/(L/s))  | 0.093     | NS      | 0.097     | NS      |
| SGRQ symptom            | −0.291    | 0.029   | −0.069    | NS      |
| SGRQ activity           | −0.421    | 0.001   | −0.094    | NS      |
| SGRQ impact             | −0.280    | 0.040   | −0.037    | NS      |
| SGRQ total              | −0.377    | 0.005   | −0.051    | NS      |
| Exertion capacity [VAS] | 0.282     | 0.041   | 0.239     | NS      |

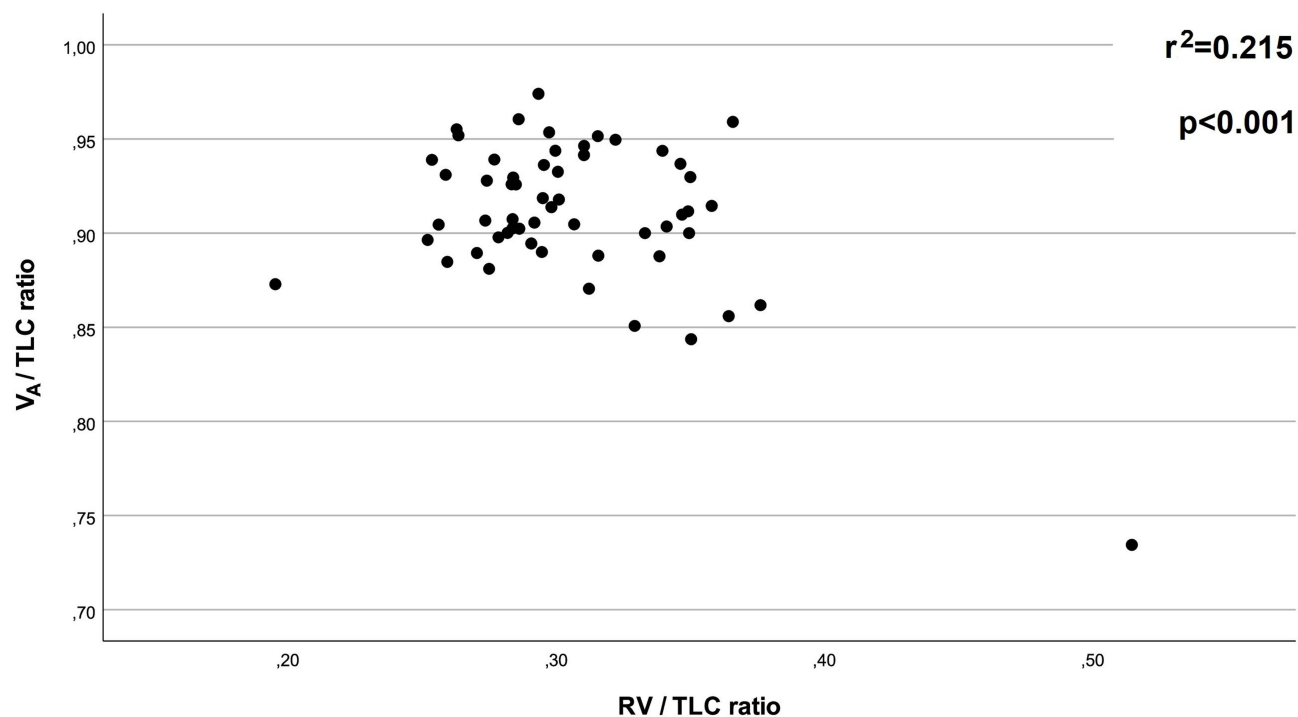
symptoms, activity, impact, total points and to self-estimated [VAS] exertion capacity. Among the PiMM individuals there was a significant correlation between  $V_A$ /TLC ratio and RV/TLC ratio, FEF<sub>25-75</sub> and  $D_{LCO}$ .

When we excluded two outliers (one PiZZ and one PiMM) using a box plot, there was a significant correlation between  $V_A$ /TLC ratio and  $D_{LCO}$ , SGRQ symptom and SGRQ total.

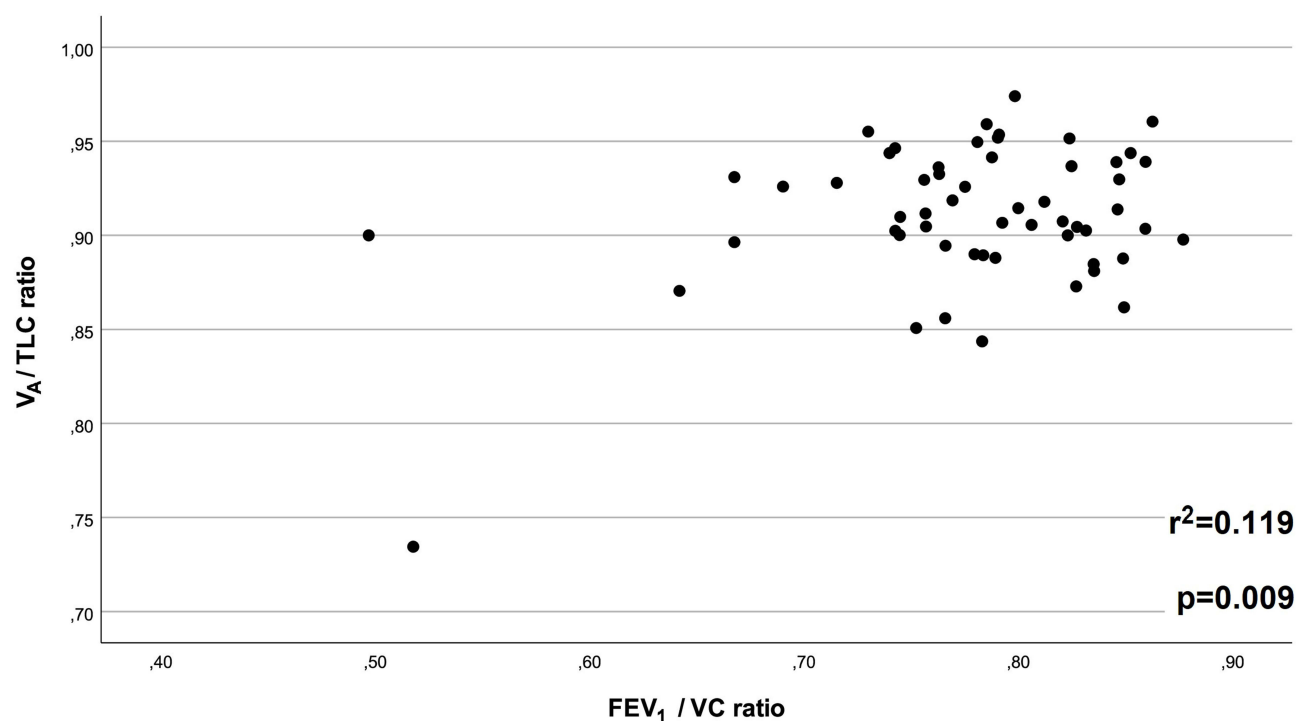
Figures 1–5 illustrate the correlation between the  $V_A$ /TLC ratio, PFT and symptoms.

## Discussion

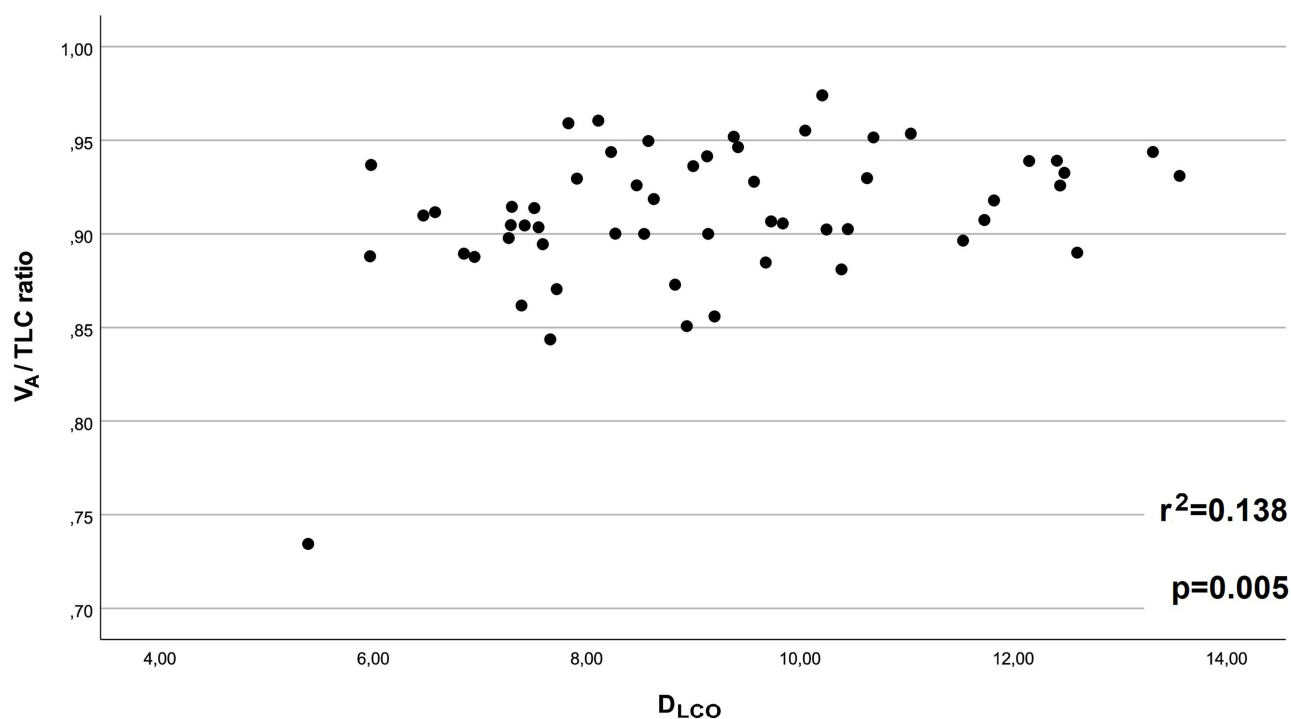
The results of this study demonstrate a significantly reduced  $V_A$ /TLC ratio in individuals with severe AATD (PiZZ) compared with the control group (PiMM). This finding may serve as an early indicator of ventilation heterogeneity in



**Figure 1** Relation between RV/TLC ratio and  $V_A$ /TLC ratio (PiZZ individuals).

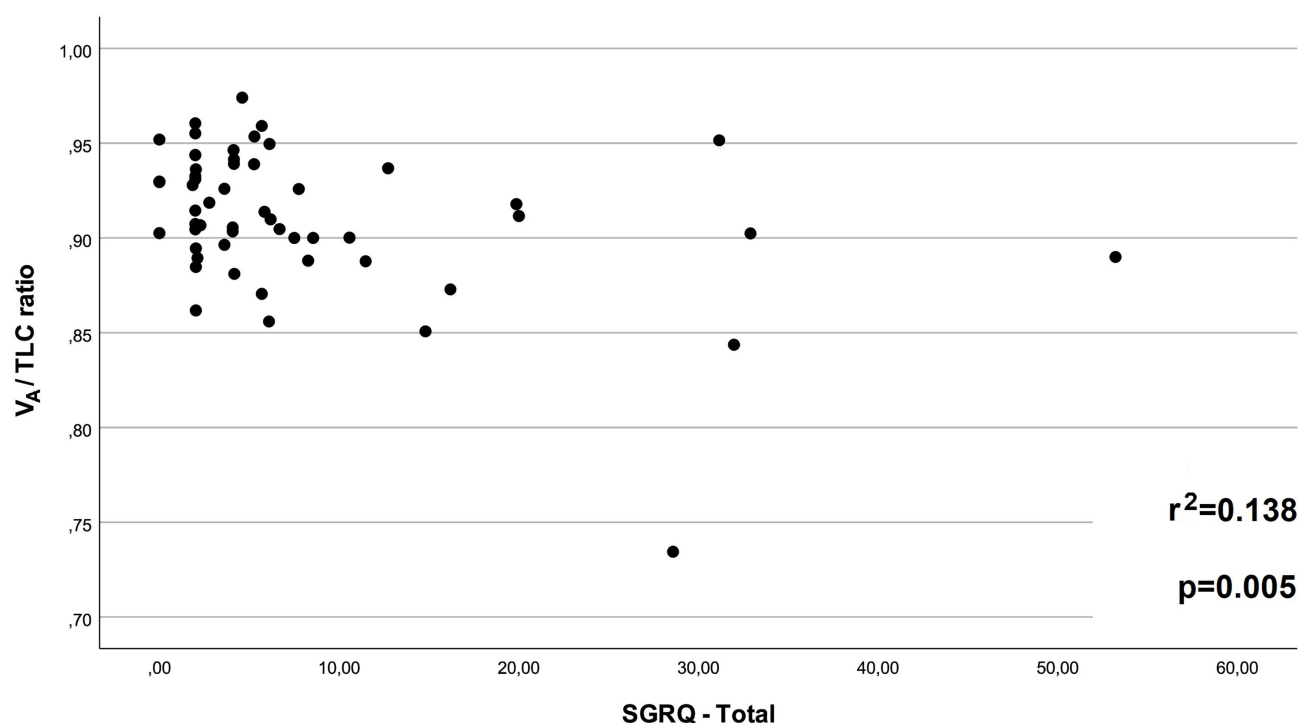


**Figure 2** Relation between  $FEV_1/VC$  ratio and  $V_A/TLC$  ratio (PiZZ individuals).

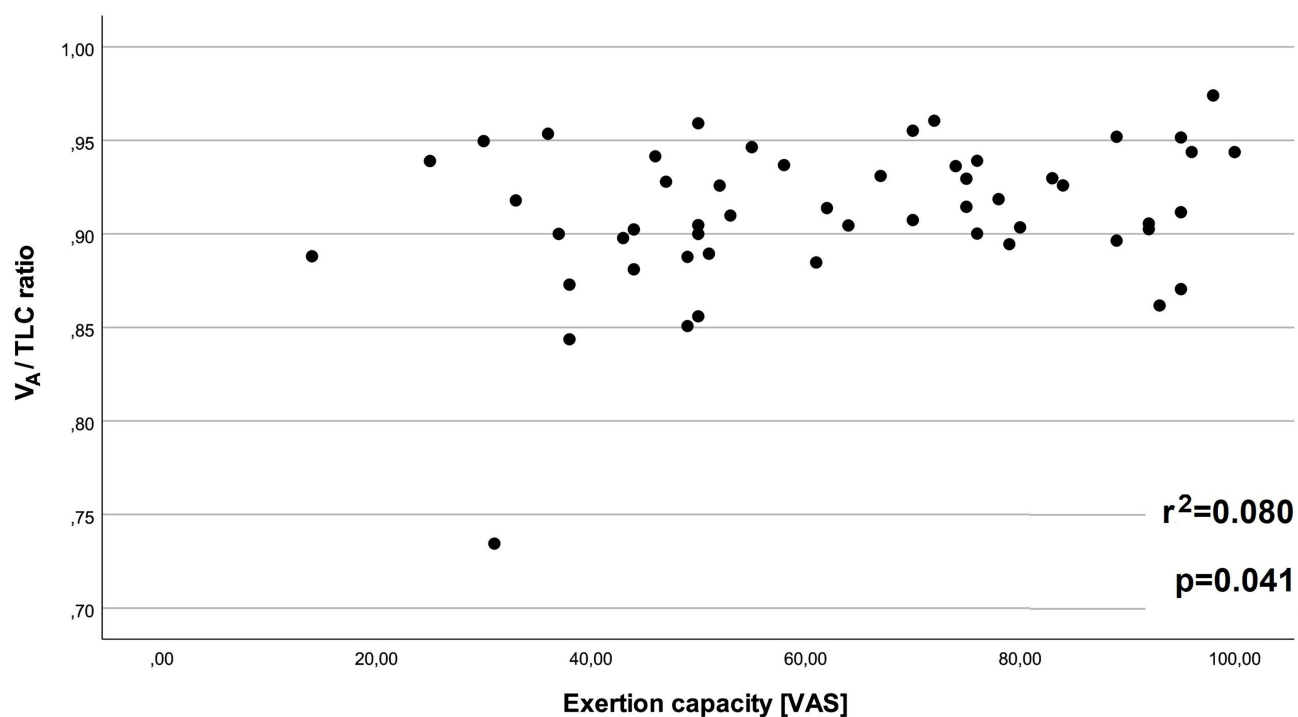


**Figure 3** Relation between  $D_{LCO}$  and  $V_A/TLC$  ratio (PiZZ individuals).

PiZZ individuals. Ever-smoking PiZZ individuals exhibited a significantly lower  $V_A/TLC$  ratio, as well as significantly higher TLC, RV, and FRC compared to the ever-smoking PiMM individuals. No corresponding differences were observed between never-smoking PiZZ and PiMM individuals. Additionally, a higher proportion of the PiZZ individuals



**Figure 4** Relation between SGRQ total and  $V_A/TLC$  ratio (PiZZ individuals).



**Figure 5** Relation between exertion capacity [VAS] and  $V_A/TLC$  ratio (PiZZ individuals).

exhibited emphysema on CT scans and had significantly lower airway resistance (R5Hz, R20Hz and R5Hz-R20Hz) compared to controls. To our knowledge, this study represents the first to investigate the  $V_A/TLC$  ratio in individuals with severe AATD.

The results of this study align with our previously published studies on lung function in the same cohort, which demonstrated early signs of COPD as early as age 38, characterized by an elevated RV.<sup>6</sup> Additionally, our prior findings indicated that, at age 42, a greater proportion of PiZZ individuals had an FEV<sub>1</sub>/FVC ratio below 0.7 compared to the PiMM individuals.<sup>5</sup> However, our earlier analysis of lung function at age 42 did not encompass the distribution of ventilation.

An explanation for ventilation heterogeneity in severe AATD may be attributed to collapse in the small airways. This is evidenced by individuals with the PiZZ phenotype displaying a notably higher RV compared to PiMM individuals as a further evidence for closure of small airways.

While a reduced FEV<sub>1</sub>/VC ratio is commonly employed for diagnosing airflow limitation, and FEV<sub>1</sub> (% of predicted) is utilized to gauge disease severity in COPD, our investigation did not show any significant differences in these spirometric parameters between PiZZ and PiMM individuals. In accordance with our previous studies the analysis of airway resistance by impulse oscillometry<sup>5</sup> exhibited significant differences between PiZZ and PiMM individuals. Oscillometry is considered to reflect heterogeneity in the lung. V<sub>A</sub>/TLC showed significant difference between PiZZ and control individuals among smokers, whereas oscillometry did not. This suggests that V<sub>A</sub>/TLC may be a more sensitive indicator of ventilation heterogeneity in this particular condition.

Interestingly, we observed a significant correlation between the V<sub>A</sub>/TLC ratio and patients' symptoms, as measured by the SGRQ, as well as their self-estimated exertion capacity using the VAS. This correlation underscores the potential of the V<sub>A</sub>/TLC ratio as an indicator of respiratory health and symptomatology in individuals with severe AATD.

In healthy subjects, V<sub>A</sub> closely matches TLC. A decreased V<sub>A</sub>/TLC ratio has been found in patients with "usual" COPD<sup>10,15</sup> as well as in ever-smokers without airflow obstruction.<sup>12</sup> In subjects with AAT deficiency, ventilation inhomogeneity has been studied with multiple breath nitrogen washout (N<sub>2</sub>-washout) technique.<sup>16</sup> However, N<sub>2</sub>-washout is time consuming and not available in all units for pulmonary function tests. Washout of Xenon-133 is another method for assessment of ventilation inhomogeneity. In this method the patients are exposed to radioactive irradiation, making it less commonly available. Measurement of V<sub>A</sub>/TLC ratio by body plethysmography is easy to perform because TLC and V<sub>A</sub> are obtained from routine pulmonary function test. Therefore, this method seems to be a promising, simple, safe, time-saving examination for early diagnosis of emphysema in individuals with severe AATD.

## Strengths

This cohort of subjects with severe AATD is the only existing of its kind. After identification at birth, the cohort has been followed up regularly, giving us a unique opportunity to investigate the natural course of this rare disorder.

## Limitations

This study has some limitations. One is the low number of participants which leads to weaker statistical power. Another point is that there are no established reference values for the V<sub>A</sub>/TLC ratio. For this reason, we only analyzed the absolute values.

## Conclusion

At the age of 42 PiZZ ever-smokers show signs of ventilation heterogeneity compared to PiMM ever-smokers. Our findings indicate the importance of suitable lung function testing in individuals with severe AATD including the measurement of static lung volumes. The early detection of hyperinflation and assessment of ventilation heterogeneity increases the possibility of an early diagnosis and thereby improved management of COPD in individuals with severe AATD.

## Abbreviations

AAT, Alpha-1-antitrypsin; AATD, Alpha-1-antitrypsin deficiency; CH<sub>4</sub>, Methane; COPD, Chronic obstructive pulmonary disease; D<sub>LCO</sub>, Diffusing capacity of carbon monoxide; FEV<sub>25-75</sub>, Forced mid-expiratory flow; FEV<sub>1</sub>, Forced expiratory volume in one second; FRC, Functional residual capacity; K<sub>CO</sub>, Diffusion capacity coefficient; PFT, Pulmonary function tests; R5Hz, Airway resistance at 5 hertz; R20Hz, Airway resistance at 20 hertz; RV, Residual volume; SGRQ, Saint Georges Respiratory Questionnaire; TLC, Total lung capacity; V<sub>A</sub>, Alveolar volume; VC, Vital capacity; VH, Ventilation heterogeneity.

## Data Sharing Statement

Due to the sensitive nature of individual personal data and study material, they cannot be made freely available.

## Ethical Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Regional Ethical Review Board of Lund, Sweden. All study participants gave their signed, informed consent.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study designs, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors took part in drafting, revising or critically reviewing the article, gave final approval of the version to be published. All authors have agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work.

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## Disclosure

Professor Per Wollmer reports personal fees from Chiesi Pharma, grants from Swedish Heart and Lung Foundation, outside the submitted work. The authors report no other conflicts of interest in this work.

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