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Airspace Dimension Assessment (AiDA) for early detection of lung function impairment in the peripheral airways of firefighters

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Abstract

Introduction

Firefighters have increased risk of chronic respiratory disease. Standard clinical techniques used in medical checkups may not detect the earliest microstructural changes in peripheral airways. A new technique called Airspace Dimension Assessment (AiDA) has been shown to enable early detection of emphysema in chronic obstructive pulmonary disease. This method may be useful in the occupational setting to detect early pulmonary changes and enable prevention.

Aim

To evaluate whether AiDA detects changes in the most peripheral airways of firefighters.

Methods

AiDA, measuring the effective airspace radius (r_{AiDA}) and zero-second recovery (R_0), was used as a complement to other standardized lung function measures in 21 male firefighters and 16 age-matched male controls.

Results

There were significant differences in r_{AiDA} and R_0 between firefighters (mean r_{AiDA} 0.301 mm, standard deviation (SD) 0.024; mean R_0 0.336 arbitrary units, SD 0.116 and controls (mean r_{AiDA} 0.276 mm, SD 0.044; mean R_0 0.576 arbitrary units, SD 0.168), $p=0.03$ and $p<0.001$, respectively. Higher forced vital capacity was found in firefighters (mean 101% of predicted) than in controls (mean 93% of predicted; $p=0.03$). No significant differences were found with regard to either the ratio between forced expiratory volume in 1 second and forced vital capacity or forced expiratory volume in 1 second. The majority of firefighters had diffusing capacity for carbon monoxide, oscillometry and single-breath nitrogen washout values within the normal ranges.

Conclusion

AiDA parameters can provide information on early pulmonary peripheral changes that may not be seen with standard techniques used in screening of pulmonary function.

Introduction

Firefighters are exposed to smoke, dust, fumes and toxic substances that are known to contribute to the burden of respiratory disease [1]. Usually, it is not possible to accurately assess the concentration and types of hazardous substances produced during a fire [2] nor to completely protect against them with personal protection equipment [2]. Therefore, a regular physical exam including pulmonary function tests is required in firefighters to detect any pathological changes in the lungs that might lead to chronic disease and prevent them from performing their duties [3].

Several, but not all, studies have shown that development of respiratory symptoms and decline of lung function is more likely in firefighters than in the general population [4-6]. The inconsistent results may be due to different types and times of exposure to hazardous substances and different methods being used to measure lung function [6]. For example, in Sweden, the standardized lung function tests used in an annual medical checkup of firefighters is dynamic spirometry [7], which has low sensitivity to peripheral airway obstructions, air trapping, and emphysema.

Exposure during firefighting may affect the lungs, even after a relatively short time [8], but may not cause symptoms or be detected by the standard lung function test. The pathological process may start in the small airways, for which standard dynamic spirometry has limited sensitivity [9]. There are several other methods that can give information on peripheral lung involvement, including inert gas washout, impulse oscillometry (IOS), diffusing capacity for carbon monoxide (D_{LCO}), and computed tomography (CT), but all these methods have several limitations [10]. IOS is mainly established as a sensitive method to identify obstructive airway disease, D_{LCO} can be affected also by non-respiratory diseases, such as heart failure, while CT requires ionizing radiation and is expensive [11]. Therefore, there is a need for new diagnostic techniques that can overcome those limitations and detect early changes in the small airways that would enable avoidance of further exposure and hopefully prevent development of respiratory disease in firefighters [10, 12]. Few studies have focused on detection of small airway dysfunction in firefighters [13].

A recently developed method, Airspace Dimension Assessment (AiDA), has been shown to provide better and more sensitive information on the distal airspaces than current standard methods [14, 15]. AiDA is based on standardized measurements of lung deposition of inhaled nanoparticles and involves a series of breathing maneuvers (typically six), similar to the ones used for measuring D_{LCO}. The patients inhale a test aerosol containing a known, low concentration of inert and insoluble nanoparticles (particles diameter = 50 nm) that reach the distal airspaces, where they are deposited almost exclusively by diffusion. The concentration of remaining nanoparticles is measured in samples of exhaled air after different breath-holding times. The fraction of exhaled nanoparticles is compared with the inhaled concentration (the recovery, R) for each measurement. These data are used to create a decay curve of inhaled particles as a function of residence time in the distal lung, based on which airspace dimensions can be calculated [16]. Results are presented as an effective airspace radius (r_{AiDA}) and an extrapolated imaginary zero-second breath-hold recovery (R_0) [17]. The airspace radius (r_{AiDA}) is conceptually a root mean square distance between opposing surfaces in the distal airspaces and corresponds to models predicting the inner diameter of the distal airway generation and alveoli [17-19]. Previous studies have shown that r_{AiDA} corresponds to the extent of emphysema in patients with chronic pulmonary obstructive disease [20]. r_{AiDA} has also been shown to correspond to proton lung tissue density as quantified using standard pulmonary structural magnetic resonance imaging (MRI) and MRI with hyperpolarized gases (^{129}Xe DW-MRI) [16]. AiDA was shown to be repeatable and safe [20].

The aim of this study was to evaluate whether firefighters with long-term occupational exposure had small airway changes that could be detected using AiDA. The subjects were also evaluated through standardized pulmonary lung function testing.

Materials and methods

Study population

This cross-sectional study evaluated occupational groups associated with chronic impaired lung function. It comprised 21 firefighters with at least ten years' experience of fire extinguishing duties and 16 unexposed controls (office workers), all never smokers and without any history of chronic disease. The firefighters and controls were recruited locally and evaluated using AiDA and dynamic spirometry at the Uppsala University Hospital, Uppsala, Sweden, and the Malmö University Hospital, Malmö, Sweden, respectively, between 2020 and 2022. The firefighters were also evaluated with D_{LCO}, IOS and single-breath nitrogen (N_2) washout in order to characterize lung function in exposed subjects. The pulmonary function tests were performed in accordance with the American Thoracic Society and the European Respiratory Society standards [21]. Height and weight were measured at the time of the pulmonary function tests.

The evaluation of firefighters was approved by the Regional Ethical Review Board Uppsala (2020-03794) and the evaluation of controls was approved by the Regional Ethical Review Board in Lund (2018-361). Participation was voluntary and all participants provided written informed consent. The study was performed in accordance with the Declaration of Helsinki.

AiDA

AiDA was used to determine distal airspace radius, r_{AiDA}, and zero-second recovery, R_0. The AiDA setup and method has been described elsewhere [14, 17]. The subjects performed a series of deposition measurements of 50 nm nanoparticles at three breath-holding times (duplicates at each timepoint): 5 s, 7 s, and 10 s. Data were considered acceptable if the subjects performed at least four valid breathing maneuvers, no instrument errors were detected, and Pearson's correlation coefficient, r, between breath-hold time and log recovery was higher than 0.9, showing sufficient fit to model. The AiDA measurements were performed directly in connection with the clinical lung function tests. Measurements were performed with two different instruments (one in Uppsala for the study population and one in Malmö for controls). An intercomparison was performed with five bio-controls: the difference between the instruments was found to be 0.002 ± 0.017 mm (mean ± SEM) for r_{AiDA} and 0.23 ± 0.05 for R_0.

Standardized lung function methods

In all subjects, dynamic spirometry was performed using a Jaeger MasterScreen PFT (Vyaire, Mettawa, IL, US). A minimum of three acceptable tests was performed, with FEV_1 in liters, FVC in liters, FEV_1/FVC, and predicted values and z-scores for these variables being determined.

In the firefighters, D_{LCO} was measured with the single-breath technique, using a Jaeger MasterScreen PFT (Vyaire, Mettawa, IL, US) with a gas mixture of 0.3% carbon monoxide, 0.3% methane, and balance air. In this technique, we measured D_{LCO} (in mmol/min kPa) and % of predicted value. Oscillometry was performed using the Masterscreen IOS, with the average from at least two measurements recorded. Oscillometry measured respiratory mechanics such as airway resistance at 5 Hz (R5), resistance at 20 Hz (R20), the difference between 5 and 20 Hz resistance (R5 - R20), reactance at 5 Hz (X5), area of reactance (AX) and resonance frequency (f_{res}). The technique is based on oscillating pressure signals. Resistance is linked to the airway caliber and reactance is associated with elastance and inertance, showing lung heterogeneity [22]. z-scores were calculated based on the reference values presented by Vogel [23]. The single-breath nitrogen washout (N_2 SBW) was performed using the Exhalyzer D (Eco Medics AG), measuring the slope of the expirogram-derived phase III (SIII). The predicted N_2 SIII was calculated using an equation validated in a previous study (N_2 SIII=2.489+0.007*age+0.010*height) [24]. Next, z-scores were calculated using the residual standard deviation for the healthy population (0.3325).

Statistical methods

Statistical analysis was performed using STATA version SE 17 (StataCorp, College Station, TX, USA). Descriptive statistics are presented as means with standard deviations (SDs) and ranges. Differences between groups were determined using unpaired t-tests, chi-squared tests, or Fisher's exact tests (for values such as 5 or less), as appropriate. Lung function values are presented as absolute values, % of predicted values, z-scores, or lower limit of normal (LLN) or upper limit of normal (ULN) values based on the Global Lung Function Initiative's reference values. The differences between the results of the lung function tests (AiDA variables, % predicted FVC and FEV_1) in firefighters and controls are presented as boxplots. Relationships between AiDA parameters and dynamic spirometry, D_{LCO}, IOS, and N_2 SBW were evaluated using Spearman's correlation. Univariate linear regression was used to assess association between r_{AiDA} and age or weight. A p-value of less than 0.05 was considered statistically significant.

Results

Subject demographics

In all, we examined 21 male firefighters with 10–35 years' experience of fire extinguishing duties and 16 age- and gender-matched controls. The characteristics of the study population are presented in Table 1. All subjects had normal FEV_1/FVC % predicted value (above 0.7) and a similar proportion of subjects with FEV_1/FVC below LLN (z-score < -1.645) was found in both groups: 23.8% (firefighters) vs 18.7% (controls), p=0.71. No significant differences were found with regard to the proportion with FEV_1 and FVC under LLN: 9.5% firefighters vs. 25% controls, p=0.37, and 0% firefighters vs. 12.5% controls, p=0.18, respectively. No firefighters had D_{LCO} under LLN. Two firefighters had SBW N_2 over ULN (z-score > +1.645).

One firefighter had abnormal X5 (z-score > +1.645) and abnormal R5 (z-score < -1.645) values, Table 1.

Table 1. The characteristic of the study population.

	Firefighters (n=21)			Controls (n=16)			P-value
	Mean	SD	Range	Mean	SD	Range	
Age, years	48.71	9.59	30–62	47.06	11.57	31–67	0.64
Height (cm)	180.88	6.82	165.5–197	181.87	6.06	170–193	0.69
Weight (kg)	85.74	9.32	74–110	84.12	14.95	61–110	0.65
BMI (kg/m^2)	26.24	2.74	21.90–32.85	25.38	4.01	20.57–32.19	0.44
Years of fire extinguishing duties	24.43	8.64	10–35	NA	NA	NA	NA
FEV_1							
liters	3.92	0.81	2.92–5.95	3.75	0.73	2.83–5.07	0.50
% predicted	95.21	15.20	70.59–126.46	88.97	12.00	65.21–107.26	0.18
z-score	-0.32	1.16	-2.02–0.57	-0.84	0.94	-2.66–2.20	0.15
FVC							
liters	5.28	0.80	3.9–6.97	4.94	0.79	3.66–6.29	0.21
% predicted	101.14	10.51	82.09–119.67	93.00	11.35	69.09–108.05	*0.03
z-score	0.09	0.79	-1.27–1.56	-0.55	0.89	-2.42–0.67	*0.02
FEV_1/FVC							
%	0.79	0.02	0.77–0.84	0.79	0.02	0.76–0.82	0.72
% predicted	93.52	8.66	76.17–106.37	95.46	8.60	78.87–105.58	0.50
z-score	-0.73	1.01	-2.73–0.81	-0.51	1.03	-2.34–0.93	0.52
r_{AiDA} (mm)	0.301	0.024	0.25–0.34	0.276	0.044	0.21–0.34	*0.03
R_0 (arbitrary units)	0.336	0.116	0.18–0.58	0.576	0.168	0.22–0.75	*<0.001
D_{LCO}							
mmol/min kPa	10.01	1.15	8.24–13.3	NA			
% predicted	97.70	9.25	78.68–115.56	NA			
z-score	-0.16	0.62	-1.46–1.05	NA			
IOS							
R5 kPa*s*L^{-1}	0.28	0.10	0.17–0.64	NA			
z-score	-0.07	1.02	-1.16-3.62	NA			
X5 kPa*s*L^{-1}	-0.09	0.05	-0.027–(-0.04)	NA			
z-score	-0.85	0.54	-2. 8-(-0.25)	NA			
R20 kPa*s*L^{-1}	0.24	0.04	0.19–0.35	NA			
R5 – R20 kPa*s*L^{-1}	0.05	0.08	0.01–0.27	NA			
AX kPa *L^{-1}	0.36	0.74	0.04–3.51	NA			
Resonance	11.65	5.03	6.95–28.87	NA			

frequency, Hz				
SBW N_2				
SIII (% L^{-1})	0.92	0.42	0.39–2.07	NA
z-scores	-0.27	1.17	-1.79–2.59	NA

*Significant values.

Note: SD, standard deviation; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; R_{AiDA}, airspace radius; R_0, zero-second recovery. $D_{LCO,}$ diffusing capacity of lung for carbon monoxide; IOS, impulse oscillometry, and SBW N_2, single-breath nitrogen washout. R5, resistance at 5 Hz; R20, resistance at 20 Hz; X5, reactance at 5Hz; AX, area of reactance; SIII, slope of the expirogram-derived phase III. For one subject, SIII was missing. NA, not applicable.

Lung function in firefighters and controls

No significant differences in FEV_1, FEV_1/FVC, or predicted values were found between groups, Table 1 and Figure 1. There was a significant difference in FVC as a percentage of predicted values between groups.

The distal airspace radius r_{AiDA} in firefighters was significantly higher than that in controls. The zero-second recovery R_0 was significantly lower in the firefighter group than among controls, Table 1 and Figure 1.

Characteristics associated with AiDA measures

Univariate linear regression showed that r_{AiDA} increased with age (p-value= 0.003) and decreased with weight (p-value=0.046), Supplementary figure 1. There was significant association between r_{AiDA} and weight (p-value=0.02), and FEV1% predicted (p-value=0.04), FVC% predicted (p-value=0.003), FEV1/FVC% (p-value=0.01) in the Spearman correlation on the whole study population, Supplementary table 1.

Discussion

In this study we investigated whether firefighters with long-term occupational exposure had pathologies in the small airways that could not be seen with standardized lung function tests. We compared the pulmonary lung function in 21 firefighters and 16 controls. There was a significant difference in AiDA parameters including distal airspace radius r_{AiDA} and zero-second recovery R_0 between firefighters and controls. We found no significant difference in FEV_1/FVC and FEV_1 between the groups and all subjects had normal values of these parameters in the dynamic spirometry. However, firefighters showed significantly higher predicted FVC values than controls. In addition, we showed that the majority of firefighters had D_{LCO}, N_2, and IOS values within the normal range.

The results of this study showed that firefighters had significantly larger mean r_{AiDA} than controls, whose r_{AiDA} corresponded to previously reported values from healthy volunteers [14, 15, 20]. A previous study of subjects 50–64 years old from the Swedish general population (n=618; a sub-study in the Swedish CardioPulmonary bioImage Study, SCAPIS) found that larger r_{AiDA} corresponded to emphysema (enlargement of the distal airspace) [15]. Subjects with larger r_{AiDA} had signs of emphysema, detectable both visually and through density measurements in CT scans. In addition, greater r_{AiDA} was associated with airflow obstruction in dynamic and static spirometry [15]. In the current study, no firefighter had any signs of airflow obstruction in standardized lung function tests such as dynamic spirometry, D_{LCO}, and N_2 washout, and only one had abnormal IOS values. The mean r_{AiDA} in firefighters (0.30 mm) was lower than that in patients with emphysema in the previous study (mean 0.33 mm, range 0.27–0.52 mm), but significantly higher than that among controls in this study (mean 0.27 mm) and the previous one (mean 0.28 mm) [19]. This suggests an early change in the smallest airways of the firefighters.

Previous studies have shown that exposure to noxious smoke, dust, fumes and toxic substances that occurs under fire extinguishing stimulates an inflammatory response that may lead to small airway disease [25]. However, there is a long period during which the pathophysiological changes in the small airways may remain undetectable when using standardized lung function methods and the first early signs of chronic respiratory disease may not be seen. Injuries and changes in the small airways are the first stage in chronic respiratory disease [10, 12]. There are a limited number of methods in the clinical praxis that can detect the early mild changes in the distal airways, such as CT and MRI with hyperpolarized gases (^{129}Xe DW-MRI) [26].

We demonstrated that R_0 was significantly lower in firefighters than in controls. R_0 is suspected to be correlated with particle loss during the dynamic process of breathing and represents heterogeneity in the acini (the distal airways). However, interpretation requires further studies [16, 19, 27].

Similarly, to the previously mentioned study SCAPIS using AiDA on a larger Swedish population (n=695) aged 50–65 years, we found significant correlation between r_{AiDA} and percent predicted FVC and FEV1 in dynamic spirometry as well as several IOS indices [27].

In other studies, AiDA parameters were found to be correlated with results of ^{129}Xe DW-MRI [16] and CT of the lungs [15]. However, unlike AiDA, these techniques are expensive, time-consuming, and – in case of CT – associated with exposure to ionizing radiation [26].

We also showed that the firefighters had significantly higher FVC in relation to predicted values than the controls. A possible explanation for this might be the "healthy workers' effect," i.e., that people who have exercised during the lung growth phase are more likely to choose an occupation that requires being fit and strong [13]. As has been suggested in previous studies on firefighters [13], there might be a selection bias where firefighters with respiratory problems do not want to participate in research, as this could have a negative impact on their professional career.

We showed that r_{AiDA} increases with age. Lung tissue density correlates with age [15]. Elastic recoil in the lungs diminishes with age and it has been previously been shown that the distal airspace dimensions increase with age [28] and that airspace size increases with age in adults [29]. Lung tissue density differs between sexes, but the current study included only men. This was because the firefighter profession is dominated by men in Sweden (as it is worldwide) [30].

Although firefighting is a profession known to be heavily exposed to air pollution, previous studies focusing on early changes to smaller airways for this group are scarce. A study of 488 metropolitan firefighters from Australia showed oscillometry-detected pulmonary abnormalities in 8% with normal spirometry and in 19% with abnormal spirometry [13]. The addition of oscillometry to spirometry increased the probability of detecting peripheral airway dysfunction from 0.12 to 0.19 [13]. Another study showed no short-term effects on small airway dysfunction in wildland firefighters from Thailand exposed to air pollution when using spirometry, whereas AX changes seen in IOS between non-pollution and pollution periods were significantly higher in firefighters than in controls [31]. As oscillometry cannot distinguish between obstructive and restrictive conditions and has limited ability to detect small airway dysfunction, these results suggest that the use of complementary methods with a focus on the small airways may aid detection of pulmonary pathology.

One strength of AiDA is that it can readily be used outside a specialized hospital setting and involves neither radiation nor an image that needs interpretation. As regards the breathing pattern used, the respiratory flow rates during inhalation and exhalation have previously been shown to have minimal impact on the measurements [32]. The effective airspace radius r_{AiDA} has previously been shown to be relatively constant in healthy subjects and repeatable when measured over a period of 18 months in healthy subjects [32]. While AiDA measurements are based on inhalation of nanoparticles, this exposure has been shown to be very low. The subjects were exposed to 0.05% of the daily mass exposure and 0.60% of the daily particle number exposure seen in a comparatively clean urban setting [33]. Another strength of this study was that we used the AiDA method, which has already been validated and shown sensitivity to detect early emphysema [15].

However, like all experimental studies, our study has some limitations. One was that the firefighters and controls were examined at two different university hospitals with two different AiDA instruments. However, the two instruments were evaluated during the study through measurements on two bio-control subjects and showed good agreement. Therefore, we do not expect this to introduce any significant bias in our results. Another limitation is that the small sample size makes the results hard to generalize. Yet another limitation is that the exposure assessment of the firefighters was somewhat limited with regard to total accumulated exposure for each individual firefighter and use of protective gear over time. However, exposure assessment is always prone to uncertainty. Therefore, we opted for a simple measurement of years active as a firefighter, and hoped that this would give us an adequate assessment at a group level. In a previous study, r_{AiDA} was found to be correlated to smoking measured as pack-years [27]. A more detailed investigation of the link between the extent and type of occupational exposure in firefighters and AiDA measurements should be considered in future studies. Also, this study has an explorative character and a formal sample size was not estimated before its start. However, the results of this study encourage us to carry out further lung function studies of larger population of firefights and other occupational groups.

Conclusions

Our study indicates that AiDA can provide information on early pulmonary peripheral changes that may not be detected with standardized methods currently used in screening of pulmonary function. AiDA may be considered a non-invasive and relatively cheap technique for revealing respiratory abnormalities in occupational settings, as a complement to spirometry.

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Competing interests

Prof. P Wollmer and Assoc. Prof. J. Löndahl have a patent issued for a "Device and Method for pulmonary function measurements." The other authors declare no competing interests.

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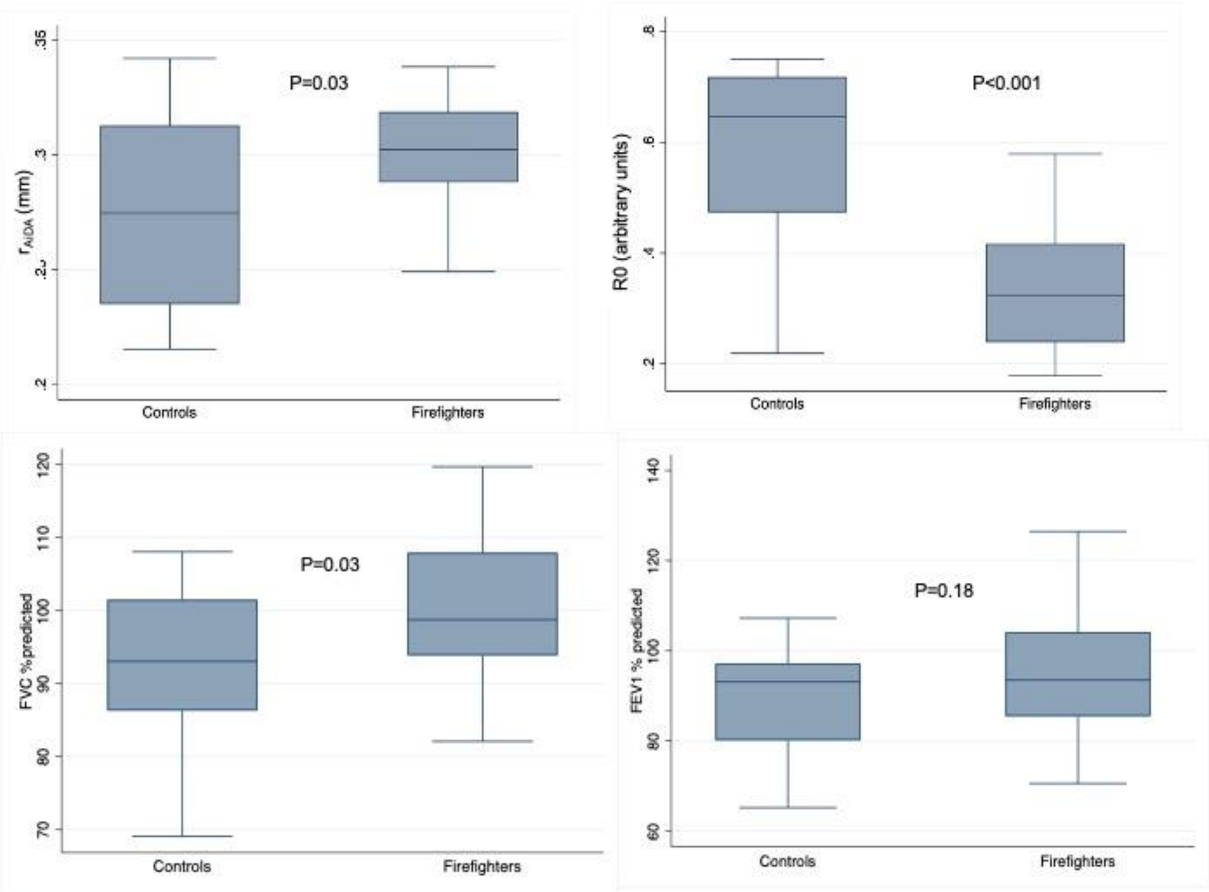
Figure capture:
Figure 1. Boxplot of the distal airspace radius, r_{AiDA} (mm), zero-second recovery, R_0 (arbitrary units), forced expiratory volume in 1 s (FEV_1) % predicted, and forced vital capacity (FVC) % predicted in firefighters and controls. The differences between the groups were measured using unpaired t-tests, with p-values presented.



Supplementary table 1. The relationship between the AiDA parameters (r_{AiDA} and R_0) and subject characteristics age, height, weight, FEV_1, and FVC for all subjects and additional lung function measurements D_{LCO}, IOS, and single-breath nitrogen (N_2) washout for the firefighter group. For one firefighter, SIII was missing.

	R_0		r_{AiDA}	
	Spearman's rho	P-value	Spearman's rho	P-value
Age	0.25	0.13	0.47	*0.003
Height	0.07	0.67	-0.25	0.13
Weight	-0.02	0.90	-0.38	*0.02
FEV_1	-0.23	0.17	0.06	0.73
FEV_1 %predicted	-0.13	0.42	0.34	*0.04
FVC	-0.08	0.62	0.14	0.42
FVC %predicted	0.03	0.84	0.47	*0.003
FEV_1/FVC %	-0.28	0.09	-0.41	*0.01
N_2, SIII	0.04	0.85	-0.23	0.32
D_{LCO}	-0.07	0.77	0.01	0.96
D_{LCO} %predicted	-0.07	076	0.09	0.69
R5	-0.06	0.78	-0.45	*0.04
R20	-0.04	0.84	-0.26	0.25
R5 - R20	0.02	0.91	-0.62	*0.002
X5	0.31	0.17	0.48	*0.03
AX	-0.22	0.34	-0.50	*0.02
Resonance frequency	-0.26	0.25	-0.45	*0.04

Supplementary figure 1. Association between airway radius (rAiDA) and age.