Restrictive spirometric pattern and true pulmonary restriction in a general population sample aged 50 - 64 years

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Abstract

Background: There is low diagnostic accuracy of the proxy restrictive spirometric pattern (RSP) to identify true pulmonary restriction. This knowledge is based on patients referred for spirometry and total lung volume determination by plethysmography, single breath nitrogen washout technique or gas dilution and selected controls. There is, however, a lack of data from general populations analyzing whether RSP is a valid proxy for true pulmonary restriction. We have validated RSP in relation to true pulmonary restriction in a general population where we have access to measurements of total lung capacity (TLC) and spirometry.

Methods: The data was from the Swedish CArdioPulmonary bioImage Study (SCAPIS Pilot), a general population-based study, comprising 983 adults aged 50–64. All subjects answered a respiratory questionnaire. Forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) were obtained before and after bronchodilation. TLC and residual volume (RV) was recorded using a body plethysmograph. All lung function values are generally expressed as percent predicted (% predicted) or in relation to lower limits of normal (LLN). True pulmonary restriction was defined as TLC < LLN 5 defined as a Z score < −1.645, i.e. the fifth percentile. RSP was defined as FEV1/FVC ≥ LLN and FVC < LLN after bronchodilation. Specificity, sensitivity, positive and negative likelihood ratios were calculated, and 95% confidence intervals (CIs) were calculated.

Results: The prevalence of true pulmonary restriction was 5.4%, and the prevalence of RSP was 3.4%. The sensitivity of RSP to identify true pulmonary restriction was 0.34 (0.20–0.46), the corresponding specificity was 0.98 (0.97–0.99), and the positive likelihood ratio was 21.1 (11.3–39.4) and the negative likelihood ratio was 0.67 (0.55–0.81).

Conclusions: RSP has low accuracy for identifying true pulmonary restriction. The results support previous observations that RSP is useful for ruling out true pulmonary restriction.

Keywords: Validity, Restrictive lung disease, RSP, TLC, Reference values, SCAPIS

Introduction

True pulmonary restriction is synonymous with reduced total lung capacity (TLC) and is associated with a number of pathological conditions that either take up space in the thoracic cavity or restricts movements of the thoracic cage or diaphragm – for example interstitial lung diseases, pleurisy, lung edema, kyphosis, neuromuscular weakness and severe obesity. Measurements of TLC
require relatively sophisticated equipment such as a body plethysmograph, or helium or nitrogen gas analyzers [1, 2]. These measurements are usually done in specialized lung function laboratories. In recent years, TLC has also been measured using inspiratory and expiratory chest computed tomography [3].

Conversely, dynamic spirometry can be done at low cost. The procedure is simple and widely used, but does not measure TLC. Consequently, there is a need for a spirometric algorithm that identifies reduced TLC with high diagnostic accuracy. It has been suggested that low vital capacity in the absence of airflow limitation could be used as a proxy for true pulmonary restriction. The proxy restrictive spirometry pattern (RSP) has been defined as forced expiratory volume in 1 s (FEV$_1$)/forced vital capacity (FVC) ≥ 0.7 and FVC < 80% predicted [4]. Alternative definitions, based on the lower limit of normal (LLN), are becoming more widely used, and the most common of these is to define RSP as FEV$_1$/FVC ≥ LLN and FVC < LLN [2]. Slow vital capacity (SVC) is usually larger than the FVC [5]. Hence, it would also be of interest to define RSP using SVC instead of FVC.

We have identified five studies investigating RSP in relation to static lung volumes [1, 6–9]. All five studies were based on patients referred for spirometry and lung volume determination by plethysmography or gas dilution and selected controls. Generally, reduced TLC was defined as <LLN. The sensitivity of RSP ranged from 68 to 100% and the specificity from 61 to 93% depending chiefly on the chosen cut-off values for vital capacity.

Some general population studies report using RSP as a proxy for true pulmonary restriction [10–14]. However, the prevalence of true pulmonary restriction in these general population studies is unknown, as TLC was not measured. Further, the applied definitions of RSP varied with regard to whether results reflect measurements before or after bronchodilation and how the cut-off values were defined, for instance based on the LLN or on percentage of predicted normal values. There is a lack of data from general populations regarding whether RSP is a valid proxy for true pulmonary restriction. In other words, studies are lacking where persons in a random general population sample have been investigated with both dynamic spirometry and static lung volumes, TLC.

The RSP phenotype has been linked to diabetes, metabolic syndrome and increased mortality and RSP is probably capturing a different phenotype but overlapping group in relation to true pulmonary restriction, low TLC [2].

Hence, there is a need to perform a general population study examining the validity of the proxy RSP in identifying true pulmonary restriction. We have performed a validation study in a general population sample, for which we had access to measurements of TLC using body box, residual volume (RV), and dynamic spirometry before and after bronchodilation. Hence, we will have the possibility to validate RSP for indicating true pulmonary restriction.

**Material and methods**

Our data was from the pilot part of the Swedish CArdio-Pulmonary bioImage Study (SCAPIS Pilot), a Swedish general population-based study. For this initial pilot study, a randomly selected population sample of 2243 adults aged 50–64 years were invited to take part and 1111 agreed to participate [5, 15]. All persons answered an extensive respiratory questionnaire, including detailed items about smoking habits.

Dynamic spirometry, including FEV$_1$, FVC and slow vital capacity (SVC) was performed before and 15 min after inhalation of 400 μg of salbutamol using a nose clamp with the subject in a sitting position. All accepted exhalations had a duration of > 6 s and a plateau on the curve the last second of the exhalation. Static lung volumes, TLC and RV, were determined by body plethysmography based on two measurements recorded after bronchodilation. There were daily calibrations of pressure, volume and flow. All procedures were performed according to American Thoracic Society (ATS)/European Respiratory Society (ERS) standards [16]. There were daily volume controls of the spirometer. All beta-agonist were withheld the day of the investigation. A Jaeger Master Screen pulmonary function (PFT) system (Vyaire, Mettawa, Illinois, US) was used for all measurements. Predicted values of FEV$_1$, FVC and SVC were based on recently published local reference equations [17, 18]. Predicted values for TLC and RV were based on published equations [19]. For analysis of TLC, we additionally developed a local reference equation for TLC based on the never-smokers in the present study population without any respiratory symptoms (wheeze, dyspnea, chronic bronchitis) and without self-reported heart diseases. All lung function values are generally expressed as percent predicted (% predicted) or in relation to the LLN, using published locally equations [17, 18].

**Definitions**

True pulmonary restriction was defined as TLC < LLN described as a z score < −1.645 (i.e. a z score below the fifth percentile), using both the published equations of Quanjer et al., TLC < LLN$_{QUANJER}$ and the local equation TLC < LLN$_{GOTHENBURG}$ see “Statistics” [19].

Restrictive spirometric pattern (RSP) was in five different ways;

\[ \text{RSP}_{\text{LLN}} = \frac{\text{FEV}_1}{\text{FVC}} \geq \text{LLN} \text{ and FVC} < \text{LLN} \text{ after bronchodilation} \]
RSP0.7 = FEV1/FVC ≥ 0.7 and FVC < 80% predicted after bronchodilation [17, 18].

RSPpredil = FEV1/FVC ≥ LLN and FVC < LLN before bronchodilation [17, 18].

RSPLLNSVC = FEV1/SVC ≥ LLN and SVC < LLN after bronchodilation [17, 18].

RSP0.7SVC = FEV1/SVC ≥ 0.7 and SVC < 80% predicted after bronchodilation [17, 18].

Asthma was defined as an affirmative answer to an item about physician-diagnosed asthma [20]. Dyspnea was defined as a modified Medical Research Council (mMRC) breathlessness score ≥ 2 [21].

Smoking was categorized into current smokers, former smokers, and never-smokers. Former smokers were defined as those who had smoked for at least 1 year but who had not smoked during the past 12 months. In this analysis current smokers and former smokers were categorized as ever-smokers.

Statistics

All calculations were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). The local reference equation for TLC was computed by a linear regression model with height as a covariate, stratified by gender. The resulting equation for women was TLC = height (cm)*0.085 – 8.71, with residual standard deviation (RSD) = 0.56. For men the equation was TLC = height (cm)*0.102 – 10.93, with RSD = 0.83.

Specificity, sensitivity, positive and negative predictive values (PPV, NPV), positive and negative likelihood ratios (LR+, LR-) were calculated, and 95% confidence intervals (CIs) were calculated using exact methods. Post-test probabilities of disease after positive and negative tests were assessed [22]. We calculated the percentiles of FVC, and sensitivity and specificity of RSP LLN using increasing percentiles of FVC were plotted. Factors associated with disconcordance between true pulmonary restriction and RSP LLN and RSP LLNSVC were analyzed as follows:

| Age, gender, smoking habits, symptoms and lung function values in 983 subjects according to different definitions of restrictive spirometry pattern (RSP) and true pulmonary restriction defined as TLC < LLN |
|---|
| **Restrictive spirometric pattern (RSP)** | **True pulmonary restriction** |
| **FEV1/FVC ≥ LLN and FVC < 80%** | **TLC < LLN<sub>3</sub> (Quanjier)** | **TLC < LLN<sub>3</sub> (Gothenburg)** |
| **(RSP<sub>LLN</sub>)** | **N = 33 (3.4%)** | **N = 46 (4.7%)** | **N = 53 (5.4%)** |
| **FEV1/FVC ≥ 0.7 and FVC < 80% predilation (RSP<sub>0.7</sub>)** | **N = 31 (3.2%)** | **N = 33 (3.4%)** |
| **FEV1/FVC ≥ 0.7 and FVC < 80% predilation (RSP<sub>predil</sub>)** | **N = 33 (3.4%)** |
| **TLC < LLN<sub>3</sub> (Quanjier)** | **N = 33 (3.4%)** |
| **BMI (kg/m<sup>2</sup>)** | **29.3 (6.1)** | **29.8 (6.5)** | **29.2 (5.7)** | **28.8 (5.2)** | **28.6 (5.5)** |
| **Age (yrs)** | **57.0 (4.2)** | **57.9 (4.2)** | **56.8 (4.4)** | **56.8 (4.4)** | **56.9 (4.4)** |
| **Ever-smokers** | **n = 570 (58.0%)** | **n = 21 (63.6%)** | **n = 17 (54.8%)** | **n = 20 (60.6%)** | **n = 25 (54.5%)** | **n = 20 (48.8%)** |
| **Never-smokers** | **n = 417 (42.4%)** | **n = 12 (36.4%)** | **n = 14 (45.2%)** | **n = 13 (39.4%)** | **n = 25 (50.0%)** | **n = 39 (84.8%)** |
| **FEV1 (%) pred** | **76.1 (8.7)** | **75.7 (8.8)** | **78.8 (8.2)** | **82.9 (7.1)** | **84.4 (18.6)** |
| **FVC (%) pred** | **74.0 (6.6)** | **73.3 (6.3)** | **77.6 (7.3)** | **80.5 (17.7)** | **82.8 (19.2)** |
| **TLCQUANJER (%) pred** | **90.3 (7.7)** | **90.7 (8.2)** | **89.6 (7.4)** | **74.6 (8.5)** | **73.0 (8.6)** |
| **TLCGOTHENBURG (%) pred** | **84.9 (7.0)** | **85.9 (7.8)** | **84.1 (6.5)** | **77.5 (5.6)** | **77.8 (5.3)** |
| **RV (%) pred** | **99.2 (29.8)** | **99.9 (30.9)** | **100.4 (29.4)** | **84.5 (26.0)** | **82.6 (27.4)** |
| **Asthma** | **n = 93 (9.5%)** | **n = 3 (9.1%)** | **n = 2 (6.5%)** | **n = 3 (9.1%)** | **n = 4 (8.0%)** | **n = 4 (9.8%)** |
| **MRC ≥ 2** | **n = 51 (5.2%)** | **n = 5 (15.2%)** | **n = 5 (16.1%)** | **n = 5 (15.2%)** | **n = 4 (8.0%)** | **n = 5 (12.2%)** |
| **Diabetes** | **N = 165 (16.7%)** | **N = 8 (24.2%)** | **N = 7 (22.6%)** | **N = 7 (21.2%)** | **N = 11 (23.9%)** | **N = 11 (20.8%)** |
| **Myocardial infarction** | **N = 27 (2.8%)** | **N = 1 (3.1%)** | **N = 3 (10%)** | **N = 1 (3.0%)** | **N = 3 (6.7%)** | **N = 3 (5.7%)** |

Definition of abbreviations: BMI Body mass index, FEV1 Forced expiratory volume in one second, FVC Forced vital capacity, LLN Lower limit of normal, TLC Total lung capacity, RV Residual volume, MRC Medical Research Council.
odds ratios (OR), using multiple logistic regression. The variables age, body mass index, gender, smoking habits and RV were a priori selected as potentially associated with discordance.

**Results**

Of the 1111 subjects, 128 were excluded because of incomplete data on smoking and dynamic spirometry or missing TLC measurements, resulting in a final study population of 983 subjects. Descriptive data on age, gender, smoking, lung function, and prevalence of asthma and dyspnea is shown in Table 1. The prevalence of true pulmonary restriction, TLC < LLN, was 4.7% (n = 46), and when using our local equation, the prevalence of TLC < LLN was 5.4% (n = 53). The prevalence of RSP, RSPLLN, RSP0.7, and RSPPPREDIL was, 3.4% (n = 33), 3.2% (n = 31), and 3.4% (n = 23), respectively. When applying SVC, the prevalence of RSP and RSP0.7SVC was 2.1% (n = 21) and 1.8% (n = 18), respectively (Online Supplement Table S1).

The specificity, sensitivity, NPV and PPV, positive and negative likelihood ratio of RSP, RSP, RSP0.7, and RSPPPREDIL in relation to true pulmonary restriction, defined either according to Quanjer et al. or based the Gothenburg equation, are shown in Table 2. When applying the Quanjer equation, the sensitivity of identifying TLC < LLN was about 0.30 for all definitions of RSP. The highest sensitivity, 0.33, was in relation to RSP. All the RSP definitions has a high positive likelihood ratio, 17 to 24. With a pretest probability (prevalence) of true pulmonary restriction of 5.4%, a LR+ around 21 indicates a 50% post-test probability of true pulmonary restriction if presence of RSP. The negative likelihood ratios ranged from 0.67 to 0.71. A negative likelihood ratio around 0.70 means that there is a 40% post-test probability of true pulmonary restriction if there is no RSP. When applying the Gothenburg TLC equations to calculate predicted values the results were quite similar as compared to the Quanjer equation (Table 2). The sensitivity of identifying TLC < LLN was ranged from 0.32 to 0.36. A plot of increasing percentiles of FVC in the definition of RSP is shown in Fig. 1. Increasing the FVC from the 10th percentile to the 20th percentile increased the sensitivity from 0.55 to 0.80, with moderately decreased specificity. The max sensitivity and specificity was around 25th percentile of FVC.

When applying SVC, the specificity, sensitivity, NPV and PPV, positive and negative likelihood ratio of RSP and RSP0.7 in relation to true pulmonary restriction, defined either according to Quanjer et al. or based the Gothenburg equation, are shown in Table 3. Using SVC instead of FVC resulted in lower sensitivity and higher specificity, with no obvious differences between whether true pulmonary restriction was defined based on the Quanjer or the Gothenburg equation.

Body mass index was positively associated with discordance between RSP and true pulmonary restriction (OR 1.10, 95% CI 1.03–1.17) and residual volume was negatively associated (OR 0.96, 95% CI 0.94–0.97) (Table 4).

**Discussion**

The main result of the present study is that the sensitivity of RSP was fairly low in relation to true pulmonary restriction, whereas the specificity and NPV were high. The validity, sensitivity, and specificity were similar, regardless of which definition of RSP that was used. Finally, there was no difference between the pre- and post-bronchodilation results. Hence, we confirm previous results from referred-based populations, that RSP is
relevant for ruling out true pulmonary restriction, and RSP has low validity in identifying true pulmonary restriction.

This is, to the best of our knowledge, the first study of a general population sample, although in a narrow age interval, sample validating RSP in relation to true pulmonary restriction, based on measurements of TLC by body plethysmography. Our results confirm results from previous clinical studies indicating a high NPV for RSP used as a proxy. This means that spirometry with no sign of RSP makes it highly unlikely that the person has

Table 3 Validity of restrictive spirometric pattern using slow vital capacity (RSP_{LLNSVC} and RSP_{0.7SVC}) in relation to true pulmonary restriction

| Restrictive spirometric pattern (RSP) | True pulmonary restriction |
|-------------------------------------|----------------------------|
|                                     | TLC < LLN<sub>E</sub>      |
|                                     | (n = 46)                   |
|                                     | TLC < LLN<sub>E</sub>      |
|                                     | (n = 53)                   |
| RSP<sub>LLNSVC</sub> (n = 33)       | Value 95% CI               |
| Sensitivity                         | 0.24 0.13–0.39             |
| Specificity                         | 0.99 0.98–0.99             |
| PPV                                 | 0.52 0.30–0.74             |
| NPV                                 | 0.96 0.95–0.97             |
| LR+                                 | 22.4 9.2–31.5              |
| LR-                                 | 0.77 0.56–0.84             |
| RSP<sub>0.7SVC</sub> (n = 31)       | Value 95% CI               |
| Sensitivity                         | 0.22 0.11–0.36             |
| Specificity                         | 0.99 0.98–1.00             |
| PPV                                 | 0.56 0.31–0.78             |
| NPV                                 | 0.96 0.95–0.97             |
| LR+                                 | 25.4 10.6–61.5             |
| LR-                                 | 0.79 0.68–0.92             |

Definition of abbreviations: LLN Lower limit of normal; TLC Total lung capacity; CI Confidence interval

Table 4 Logistic regression model of factors associated with disconcordance regarding true pulmonary restriction and restrictive spirometric pattern (RSP). All included co-variates are presented in the table

| Co-variates | RSP<sub>LLN</sub> | RSP<sub>LLNSVC</sub> |
|-------------|-------------------|-----------------------|
| Age (yrs)   | 1.02 (0.95–1.09)  | 1.04 (0.97–1.12)      |
| Body mass index (kg/m<sup>2</sup>) | 1.10 (1.03–1.17) | 1.10 (1.02–1.18)      |
| Women vs. men | 0.58 (0.31–1.06) | 0.43 (0.22–0.84)      |
| Eversmoking (Yes/No) | 0.85 (0.47–1.55) | 0.62 (0.33–1.17)      |
| Residual volume (proc pred) | 0.96 (0.94–0.97) | 0.94 (0.93–0.96)      |

Definition of abbreviations: LLN Lower limit of normal, SVC Slow vital capacity, CI Confidence interval
The local equation did not add much to the results other than indicating that the published equation was suitable for our population. However, it has to be added that the present equations are not satisfactory as they are based on small populations. An equation for TLC and RV based on larger populations are highly warranted.

The main weakness of the present study is the small study sample. We have outlined 95% confidence interval around our estimates to be able to judge the reliability of our results. Another limitation is the narrow age interval 50–64 years, making the conclusions valid for this age group only. Selection bias may be a problem, as the participation rate was around 50%. In the current population chronic obstructive pulmonary disease and cardiovascular disease seem to have increased the participation, but we believe this has only marginally affected the validity of the estimates [27].

**Conclusion**

RSP has low validity for identifying true pulmonary restriction. We do not recommend using RSP in general population studies as a proxy for true pulmonary restriction. Our results support previous observations that RSP is useful for ruling out true pulmonary restriction.

**Supplementary information**

**Abbreviations**

CI: Confidence interval; FEV₁: Forced expiratory volume in one second; FVC: Forced vital capacity; LLN: Lower limit of normal; LR: Likelihood ratio; OR: Odds ratio; PREDIL: Prebronchodilation; RSD: Residual standard deviation; RSP: Restrictive spirometric pattern; RV: Residual volume; SCAPIS: Swedish CArdioPulmonary bioImage Study; SVC: Slow vital capacity; TLC: Total lung capacity.

**Authors’ contributions**

K.T., J.B., A.M., A-C.O., G.B. and B.B. jointly designed the study. G.B. and K.T. collected the data. K.T. and B.B. performed the statistical analyses. K.T. drafted the manuscript and all authors contributed to the final manuscript. The authors read and approved the final manuscript.

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**Availability of data and materials**

The data is available upon request to the corresponding author. All analyses requires a permission from a Swedish ethical committee. A detailed description of the database can be found at www.scapis.org.
Ethics approval and consent to participate
The study was approved by the Regional Committee of Ethics in Umeå, (2010/228-31), and all included subjects gave their written consent to participate in the study.

Consent for publication
Not applicable.

Competing interests
All authors have completed the Unified Competing Interest form att www.icmje/coiDisclosure.pdf and they do not have any conflict of interest to report.

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