

MATERIAL AND METHODS

Study design + participants

In this monocentric cross-sectional case-control study, subjects participating in a clinical trial (NELSON) were recruited between June 2009 and March 2012. NELSON is a Dutch-Belgian randomized lung screening trial which investigates whether 16-detector multi-slice computed tomography (CT) screening will decrease lung cancer mortality compared to no screening. Details of patient recruitment, inclusion and exclusion criteria are published elsewhere.[1] Briefly, all addresses of men and women (age 50-75 years) from 14 municipalities around Leuven (Belgium) were obtained (n=66,322) and 358 current or former smokers (age 50-75 years) responded to the questionnaires (general health, smoking exposure history, cancer history, etc.), met the eligibility criteria of the study, performed post-bronchodilator spirometry and were randomized into the CT screening or control group (no CT screening). From this study, 141 people (ex-) smokers agreed to participate of whom 62 subjects were identified as having spirometry proven COPD (cases) and 79 subjects did not have COPD (controls). Inclusion criteria of the study were age between 40 and 80 years, smoking history of at least 10 packyears and active smoking behavior till at least 10 years from the moment of enrollment. Patients were excluded if they had significant orthopedic or musculoskeletal problems which would interfere with their movement patterns, a recent diagnosis of cancer or respiratory disorders other than COPD (e.g. asthma). The study was approved by the local ethics committee (Medical Ethical Board of the University Hospitals Leuven, Belgium, approval number B32220096387) and all subjects provided written informed consent.

Study Procedures.

Symptoms of dyspnea, complete pulmonary function testing, physical exercise

testing, muscle force testing, and assessment of daily physical activity were assessed in all participants.

Symptoms of dyspnea

The modified Medical Research Council (mMRC) dyspnea scale rates the type and magnitude of dyspnea according to five grades (from mMRC 0 to mMRC 4) of increasing severity.[2]

Pulmonary function testing

Spirometric measurements (FEV₁, FVC), body plethysmographic measurements (inspiratory capacity (IC), functional residual capacity (FRC), residual volume (RV) and total lung capacity (TLC)) and single-breath diffusion capacity of the lung for carbon monoxide (T_{L,co}) were performed with standardized equipment (Whole Body Plethysmograph, CareFusion, Belgium) according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[3] Spirometric values were post-bronchodilator measurements, and all absolute values were expressed as percentage predicted of reference values.[4] Presence of COPD was defined by a post-bronchodilator FEV₁/FVC ratio <0.7 and post-bronchodilator FEV₁ was used to classify subjects into the appropriate GOLD (Global Initiative for Obstructive Lung Disease) stage according to the revised GOLD classification.[5] T_{L,co} was expressed as percentage of reference values.[6]

Physical exercise testing

Functional exercise capacity was determined by the six minute walking distance (6MWD).[7] Values were related to previously published reference values for the healthy Belgian population.[8] A symptom-limited incremental cycle ergometer test was conducted according to the ATS/ACCP statement on cardiopulmonary exercise testing to assess the maximal exercise capacity (VO₂ peak).[9] The values of peak

oxygen consumption (mean of last 30 seconds) were related to previously described reference values.[10]

Muscle force testing

Isometric quadriceps force (QF) was assessed with the subject seated on a dynamometer (Biodex Medical Systems, Inc., NY, USA), with the back straight, a 90° hip flexion and 60° knee flexion. Normal values had been previously reported.[11] Subjects performed 3 isometric maximal voluntary contractions for six seconds. The highest peak force value was used for analysis.

Assessment of daily physical activity

The SenseWear Pro Armband (BodyMedia, Inc., Pittsburgh, PA, USA) was worn for 7 complete (except during bathing and showering) and consecutive days to quantify physical activity. The device (85x54x20mm, 79g) is placed on the upper right arm and integrates information from a biaxial accelerometer with signals from non-invasive sensors measuring physical parameters such as changes in body temperature, near body ambient temperature, heat flux, and galvanic skin resistance. Together with individual characteristics including gender, age, height and body mass these variables are used to estimate energy expenditure (expressed as metabolic equivalents, METs) utilizing proprietary equations developed by the manufacturer. The number of daily steps, the daily time spent in moderate to vigorous physical activities (MVPA) and daily physical activity level (PAL, i.e. total energy expenditure divided by resting energy expenditure) were downloaded and analyzed using SenseWear Professional software 6.0. The time spent with an energy expenditure of >3 METS was considered as MVPA.[12] Total energy expenditure estimates of this activity monitor have been recently validated against the gold standard of doubly labeled water and indirect calorimetry in healthy adults [13] and patients with

COPD.[14, 15] A valid assessment was defined as at least 5 days (weekend days + at least 3 weekdays) of assessment during of at least 20 hours per day.[16]

Statistical analysis

Normal distribution was tested for all variables by a Kolmogorov-Smirnov test. Continuous variables were expressed as means with standard deviation (normal distribution) or as medians with interquartile range (skewed distribution). Categorical variables were expressed as proportions and testing between groups was done by a chi-square test. Comparisons between smoking controls and patients with COPD were performed by either a parametric (unpaired t-test) or non-parametric test (Wilcoxon-Mann-Whitney test). For the smoking control subjects the lower limit of normal was calculated as the value above which 90% of the control values were situated. The subjects with COPD below this lower limit of normal were defined as physically inactive.

Partial correlations in the subjects with (cases) and without COPD (smoking controls) were calculated to investigate whether any relationship existed between physical activity and lung function, muscle function or exercise capacity, after correcting for anthropometric variables (age, gender, weight and packyears) and season of assessment (daylight time, i.e. time from sunrise to sunset). Parameters of lung function (FEV_1 , FEV_1/FVC ratio, IC/TLC ratio, RV/TLC ratio, $T_{L,CO}$), muscle function (QF) and exercise capacity (6MWD and VO_2 peak) were divided into two categories by the median split method. After correcting for covariates (age, gender, BMI and season of assessment (daylight time)) physical activity levels (dependent variables) were compared between categories of dyspnea (mMRC), lung function, muscle function and exercise capacity by computing the least square means for the dependent variables using generalized linear models procedure. Finally, to investigate whether daily physical

activity is related to symptoms of dyspnea, lung function, muscle function and exercise capacity, a stepwise multiple regression analysis was performed in subjects with COPD, with age, gender, weight, packyears and daylight time (season) as potential covariates. All statistical analyses were performed with statistical software package SAS (version 9.3). The level of significance was 0.05 for all statistical tests.

Reference list

1. van Iersel CA, de Koning HJ, Draisma G, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). *Int J Cancer* 2007; **120**: 868-74.
2. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999; **54**: 581-6.
3. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005; **26**: 319-38.
4. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; **40**: 1324-43.
5. Vestbo J, Hurd SS, Agusti AG, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: GOLD Executive Summary. *Am J Respir Crit Care Med* 2013; **187**: 347-65.
6. Rosenberg E. The 1995 update of recommendations for a standard technique for measuring the single-breath carbon monoxide diffusing capacity (transfer factor). *Am J Respir Crit Care Med* 1996; **154**: 265-6.
7. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; **166**: 111-7.
8. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J* 1999; **14**: 270-4.
9. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003; **167**: 211-77.
10. Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis* 1985; **131**: 700-8.
11. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. *Am J Respir Crit Care Med* 1996; **153**: 976-80.

12. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc* 2007; **39**: 1423-34.
13. St-Onge M, Mignault D, Allison DB, Rabasa-Lhoret R. Evaluation of a portable device to measure daily energy expenditure in free-living adults. *Am J Clin Nutr* 2007; **85**: 742-9.
14. Rabinovich RA, Louvaris Z, Raste Y, et al. Validity of physical activity monitors during daily life in patients with COPD. *Eur Respir J* Published Online First: 8 February 2013. doi: 10.1183/09031936.00134312
15. Van Remoortel H, Raste Y, Louvaris Z, et al. Validity of Six Activity Monitors in Chronic Obstructive Pulmonary Disease: A Comparison with Indirect Calorimetry. *PLoS One* 2012; **7**: e39198.
16. Scheers T, Philippaerts R, Lefevre J. Variability in physical activity patterns as measured by the SenseWear Armband: how many days are needed? *Eur J Appl Physiol* 2012; **112**: 1653-62.