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Effects of ageing and smoking on pulmonary computed tomography scans using parametric response mapping

To the Editor:

Chronic obstructive pulmonary disease (COPD) is an obstructive lung disease often caused by cigarette smoke, and characterised by inflammation and abnormalities of the large and small airways (*i.e.* those with an internal diameter <2 mm), as well as by alveolar destruction (emphysema). Recent evidence suggests that small airway disease precedes emphysema [1] and, therefore, it may be useful to identify the presence and extent of small airway disease and emphysema in early COPD, or preferably, even before the onset of disease.

Parametric response mapping (PRM) is a novel technique to analyse pulmonary computed tomography (CT) scans in order to quantify the extent of small airway disease (PRM^{fSAD}), emphysema (PRM^{Emph}) and parenchymal disease (PRM^{PD}), the latter reflecting increased attenuation of normal lung parenchyma [2, 3]. We aimed to evaluate the PRM technique in a cohort of well-characterised, respiratory-healthy subjects with a wide age range. As smoking and ageing are both risk factors in the development of COPD [4], we hypothesised that 1) an older age is associated with more PRM^{fSAD}, PRM^{Emph} and PRM^{PD}, and 2) current smoking is associated with more PRM^{fSAD}, PRM^{Emph} and PRM^{PD}. Finally, we investigated the association between PRM measurements and pulmonary function measurements.

We selected current smokers and never-smokers older than 18 years, without respiratory symptoms and with no history of respiratory diseases. In addition, they had normal pulmonary function, defined as a post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio above the lower limit of normal, no bronchial hyperresponsiveness and reversibility of FEV_1 to salbutamol <10% of the predicted value.

Spirometry (FEV_1, FVC, FEV_1/FVC and forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$)), body plethysmography (residual volume (RV), total lung capacity (TLC) and RV/TLC) and methacholine provocation tests were performed according to international guidelines [5, 6]. Transfer factor of the lung for carbon monoxide corrected from haemoglobin (T_{LCOc}) adjusted for alveolar volume (V_A) was measured using the single breath-holding technique, and small airway resistance (resistance at 5 Hz (R_5) minus resistance at 20 Hz (R_{20})) and reactance at 5 Hz (X_5) were measured by impulse oscillometry. We considered $FEF_{25–75\%}$, $FEF_{25–75\%}$/FVC, RV/TLC, $R_5–R_{20}$ and X_5 as small airway measurements.

Thin-slice (*i.e.* 75-mm) pulmonary CT scans were made at full in- and expiration (RV). PRM was performed to quantify PRM^{fSAD}, PRM^{Emph} and PRM^{PD} as percentage of total lung volume, as described previously [2, 3]. We applied linear regression analyses to assess associations between both age and smoking, and PRM^{fSAD}, PRM^{Emph} and PRM^{PD}, adjusted for sex. Next, we performed linear regression analyses to assess the associations between pulmonary function tests and PRM measurements, adjusted for age, sex, smoking status and height.

CT scans of 49 current smokers and 47 never-smokers were available for analyses; median age was 40 years (interquartile range (IQR) 22–53 years), 56% of subjects being males. The mean±SD FEV_1 in the study population was 108±12% predicted, FEV_1/FVC was 80±6% and median smoking history among current smokers was 16 pack-years (IQR 4–30 pack-years).

A higher age was significantly associated with more PRM^{fSAD}, PRM^{Emph} and PRM^{PD}, independently of smoking and sex (table 1). Current smoking was significantly associated with more PRM^{PD}, but not with more PRM^{fSAD} or PRM^{Emph}, independently of age and sex.

We investigated whether pulmonary function tests were associated with PRM measurements and found that a lower FEV_1/FVC was significantly associated with more PRM^{fSAD}, independently of age, sex, smoking status and height (table 1). In addition, higher RV/TLC, lower T_{LCOc}/V_A and lower $FEF_{25–75\%}$/FVC were significantly associated with more PRM^{fSAD} and PRM^{Emph}. $R_5–R_{20}$ was significantly and negatively associated with PRM^{fSAD}, but not with PRM^{Emph}. PRM^{PD} was not associated with pulmonary function tests.

TABLE 1 Linear regression analyses of the association between age, current smoking and pulmonary function tests and parametric response mapping (PRM)

	PRM^{fSAD}	PRM^{Emph}	PRM^{PD}
Age years[#]	**0.06** (0.04–0.08)**	**0.05** (0.03–0.06)**	**0.01* (0.00–0.01)**
Current smoking[¶]	−0.14 (−0.65–0.37)	−0.42 (−0.89–0.05)	**0.24* (0.03–0.44)**
Pulmonary function tests[+]			
FEV_1 L	0.18 (−0.47–0.83)	0.27 (−0.33–0.86)	−0.17 (−0.43–0.09)
FEV_1/FVC %	**−0.06** (−0.12–−0.01)**	−0.05 (−0.10–0.00)	0.01 (−0.01–0.03)
$FEF_{25–75\%}$ $L \cdot s^{-1}$	−0.28 (−0.62–0.06)	−0.19 (−0.50–0.13)	0.01 (−0.13–0.15)
$FEF_{25–75\%}$/FVC s^{-1}	**−2.29* (−3.84–−0.75)**	**−1.73** (−3.17–−0.29)**	0.33 (−0.32–0.98)
RV L	**3.65** (0.19–7.11)**	**1.01 (−0.40–2.42)**	−0.44 (−4.72–3.83)
TLC L	**0.56** (0.12–0.99)**	**0.53** (0.13 –0.93)**	−0.11 (−0.29–0.07)
RV/TLC %	**0.11* (0.04–0.17)**	**0.08** (0.01 –0.14)**	0.01 (−0.02–0.04)
T_{LCOc}/V_A $mmol \cdot min^{-1} \cdot kPa^{-1} \cdot L^{-1}$	**−1.97** (−3.55–−0.39)**	**−1.62** (−3.08–−0.16)**	0.36 (−0.29–1.01)
$R_5–R_{20}$ $kPa \cdot L^{-1} \cdot s^{-1}$	**−6.59** (−12.2–−0.92)**	−4.84 (−10.11–0.43)	0.41 (−0.19–2.76)
X_5 $kPa \cdot L^{-1} \cdot s^{-1}$	4.92 (−3.51 –13.35)	5.02 (−2.72–12.76)	−0.62 (−4.04–2.80)

Data are presented as β (95% CI). PRM values were normalised by natural-logarithmic transformation. PRM^{fSAD}: extent of small airway disease; PRM^{Emph}: extent of emphysema; PRM^{PD}: extent of parenchymal disease; FEV_1: forced expiratory volume 1 s; FVC: forced vital capacity; $FEF_{25–75\%}$: forced expiratory flow at 25–75% of FVC; RV: residual volume; TLC: total lung capacity; T_{LCOc}: transfer factor of the lung for carbon monoxide correction for haemoglobin; V_A: alveolar volume; R_5: resistance at 5 Hz; R_{20}: resistance at 20 Hz; X_5: reactance at 5 Hz. [#]: adjusted for sex and smoking status; [¶]: adjusted for sex and age; [+]: adjusted for age, sex, smoking status and height. Bold indicates statistically significant values. *: p<0.05; **: p<0.01.

We tested whether PRM^{fSAD} and PRM^{Emph} contributed independently to pulmonary function measurements by including PRM^{fSAD} and PRM^{Emph} in regression models with FEV_1/FVC, $FEF_{25–75\%}$/FVC, RV/TLC % predicted, TLC % predicted, T_{LCOc}/V_A % predicted and $R_5–R_{20}$, alternately, as outcome parameters. More PRM^{fSAD} was significantly associated with lower FEV_1/FVC (β=−0.57, p<0.05), lower $FEF_{25–75\%}$/FVC (β=−0.02, p<0.01) and higher RV/TLC % predicted (β=1.13, p<0.05), independently of PRM^{Emph}.

Our study investigated individuals without objective lung disease according to lung function tests and history. The results show that an older age is associated with more extensive small airways disease, as well as more extensive emphysema and parenchymal disease of the lungs, as measured with PRM. In addition, current smokers had more extensive parenchymal disease than never-smokers, independently of age. The more small airway disease and emphysema were present, the higher were RV/TLC values, and the lower T_{LCOc}/V_A and $FEF_{25–75\%}$/FVC values, even in these respiratory healthy subjects. Interestingly, more small airway disease was independent of the extent of emphysema associated with higher RV/TLC % predicted, lower $FEF_{25–75\%}$/FVC and lower FEV_1/FVC values.

An important finding was the elevated levels of PRM^{fSAD}, PRM^{Emph} and PRM^{PD} with increasing age. Ageing of the lung is related to decreased lung elasticity and increased RV due to collapsibility of the small airways [7, 8]. We were able to visualise these physiological alterations by using PRM to distinguish between small airway disease, emphysema and parenchymal disease. It has been previously shown that an indirect measurement of small airways disease (*i.e.* air trapping measured on an expiratory CT scan) increases with age in respiratory-healthy subjects [9]. However, a limitation of such an indirect measurement is that it cannot distinguish air trapping due to emphysema from air trapping due to small airway disease. Furthermore, it is well established that measurements of emphysema on CT scans increase with ageing both in smokers and nonsmokers (never-smokers and ex-smokers), which our findings support [10–12].

We found that current smokers had significantly more PRM^{PD} than never-smokers, independently of age. Parenchymal disease is defined as increased parenchymal density upon inspiration and it could be suggested that more PRM^{PD} in current smokers reflects an inflammatory process. This hypothesis is supported by a previous study from our group among haematopoietic cell transplant recipients showing that more PRM^{PD} is associated with pulmonary infection [3]. No differences in PRM^{fSAD} and PRM^{Emph} were found between current and never-smokers. This could be due to a lack of sensitivity of PRM or due to the deliberate accrual of smokers with normal pulmonary function. An alternative explanation may be that PRM^{PD} "masks" underlying PRM^{fSAD} and PRM^{Emph} among current smokers.

Finally, more PRM^{fSAD} and more PRM^{Emph} were found to be associated with higher RV/TLC values and lower T_{LCOc}/V_A and $FEF_{25–75\%}$/FVC values, even in this respiratory-healthy population. This is in line

with previous studies reporting that air trapping and emphysema on CT scans correlate with worse pulmonary function [2, 13–15]. To our surprise, we found a higher $R5–R20$, *i.e.* more small airway dysfunction, to be associated with less PRM^{fSAD}. It is difficult to explain this unexpected finding but it may result from the very small range of $R5–R20$ values in our healthy population (IQR 0.00–0.05 $kPa \cdot L^{-1} \cdot s^{-1}$). Of specific interest is that more PRM^{fSAD} was associated with worse pulmonary function independently of PRM^{Emph}. Since it was previously suggested that small airways disease precedes emphysema [1], we speculate that early changes in pulmonary function are better reflected by PRM^{fSAD} than PRM^{Emph}, suggesting that an increase in PRM^{fSAD} may be the first sign of pulmonary pathology.

A limitation of the study is the lack of histological samples (*i.e.* peripheral airway biopsies or lung tissue) for direct comparison with the PRM measurements in order to validate PRM^{fSAD}, PRM^{Emph} and PRM^{PD}. Furthermore, CT scans are accompanied by radiation exposure, which impedes the application of PRM on a large scale; therefore, future studies are needed to identify subsets of subjects who will benefit from the PRM technique.

In conclusion, our findings show that PRM is a promising tool to characterise early pulmonary alterations in the lungs even without clinical symptomatology, by distinguishing small airway disease, emphysema and parenchymal disease. Future studies are required to assess its role in predicting or phenotyping lung diseases.

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Parametric response mapping can distinguish small airway disease, emphysema and parenchymal disease on pulmonary CT http://ow.ly/Neuw6

Ilse M. Boudewijn[1,2], Dirkje S. Postma[1,2], Eef D. Telenga[1,2], Nick H.T. ten Hacken[1,2], Wim Timens[2,3], Matthijs Oudkerk[4], Brian D. Ross[5,6], Craig J. Galbán[5,6,7] and Maarten van den Berge[1,2,7]
[1]Department of Pulmonary Diseases, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. [2]University of Groningen, University Medical Center Groningen, Groningen Research Institute for Asthma and COPD, Groningen, The Netherlands. [3]University of Groningen, University Medical Center Groningen, Department of Pathology and Medical Biology, Groningen, The Netherlands. [4]University of Groningen, University Medical Center Groningen, Department of Radiology, Groningen, The Netherlands. [5]Department of Radiology, University of Michigan, Ann Arbor, MI, USA. [6]Center for Molecular Imaging, University of Michigan, Ann Arbor, MI, USA. [7]Both authors contributed equally.

Correspondence: Maarten van den Berge, University of Groningen, University Medical Center Groningen, Department of Pulmonary Diseases (AA11), PO Box 30.001, 9700 RB Groningen, The Netherlands. E-mail: m.van.den.berge@umcg.nl

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References

1 McDonough JE, Yuan R, Suzuki M, *et al.* Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med* 2011; 365: 1567–1575.
2 Galban CJ, Han MK, Boes JL, *et al.* Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. *Nat Med* 2012; 18: 1711–1715.
3 Galban CJ, Boes JL, Bule M, *et al.* Parametric response mapping as an indicator of bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2014; 20: 1592–1598.
4 Buist AS, McBurnie MA, Vollmer WM, *et al.* International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 2007; 370: 741–750.
5 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
6 Crapo RO, Casaburi R, Coates AL, *et al.* Guidelines for methacholine and exercise challenge testing – 1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000; 161: 309–329.
7 Dyer C. The interaction of ageing and lung disease. *Chron Respir Dis* 2012; 9: 63–67.
8 Janssens JP, Pache JC, Nicod LP. Physiological changes in respiratory function associated with ageing. *Eur Respir J* 1999; 13: 197–205.
9 Lee KW, Chung SY, Yang I, *et al.* Correlation of aging and smoking with air-trapping at thin-section CT of the lung in asymptomatic subjects. *Radiology* 2000; 214: 831–836.
10 Gevenois PA, Scillia P, de Maertelaer V, *et al.* The effects of age, sex, lung size, and hyperinflation on CT lung densitometry. *AJR Am J Roentgenol* 1996; 167: 1169–1173.
11 Wang Q, Takashima S, Wang JC, *et al.* Prevalence of emphysema in individuals who underwent screening CT for lung cancer in Nagano prefecture of Japan. *Respiration* 2001; 68: 352–356.
12 Camiciottoli G, Cavigli E, Grassi L, *et al.* Prevalence and correlates of pulmonary emphysema in smokers and former smokers. A densitometric study of participants in the ITALUNG trial. *Eur Radiol* 2009; 19: 58–66.

13 Matsuoka S, Kurihara Y, Yagihashi K, *et al.* Quantitative assessment of air-trapping in chronic obstructive pulmonary disease using inspiratory and expiratory volumetric MDCT. *AJR Am J Roentgenol* 2008; 190: 762–769.
14 Bommart S, Marin G, Bourdin A, *et al.* Relationship between CT air-trapping criteria and lung function in small airway impairment quantification. *BMC Pulm Med* 2014; 14: 29.
15 Schroeder JD, McKenzie AS, Zach JA, *et al.* Relationships between airflow obstruction and quantitative CT measurements of emphysema, air-trapping, and airways in subjects with and without chronic obstructive pulmonary disease. *AJR Am J Roentgenol* 2013; 201: W460–W470.

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