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

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### 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<sup>fSAD</sup>), emphysema (PRM<sup>Emph</sup>) and parenchymal disease (PRM<sup>PD</sup>), 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<sup>fSAD</sup>, PRM<sup>Emph</sup> and PRM<sup>PD</sup>, and 2) current smoking is associated with more PRM<sup>fSAD</sup>, PRM<sup>Emph</sup> and PRM<sup>PD</sup>. Finally, we investigated the association between PRM measurements and pulmonary function measurements.

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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 $\pm$ SD  $FEV_1$  in the study population was  $108\pm12\%$  predicted,  $FEV_1/FVC$  was  $80\pm6\%$  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.

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<sub>1</sub>/FVC ( $\beta=-0.57$ ,  $p<0.05$ ), lower FEF<sub>25-75%</sub>/FVC ( $\beta=-0.02$ ,  $p<0.01$ ) and higher RV/TLC % predicted ( $\beta=1.13$ ,  $p<0.05$ ), independently of PRM<sup>Emph</sup>.

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<sub>25-75%</sub>/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<sub>25-75%</sub>/FVC and lower FEV<sub>1</sub>/FVC values.

An important finding was the elevated levels of PRM<sup>fSAD</sup>, PRM<sup>Emph</sup> and PRM<sup>PD</sup> 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<sup>PD</sup> than never-smokers, independently of age. Parenchymal disease is defined as increased parenchymal density upon inspiration and it could be suggested that more PRM<sup>PD</sup> 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<sup>PD</sup> is associated with pulmonary infection [3]. No differences in PRM<sup>fSAD</sup> and PRM<sup>Emph</sup> 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<sup>PD</sup> “masks” underlying PRM<sup>fSAD</sup> and PRM<sup>Emph</sup> among current smokers.

Finally, more PRM<sup>fSAD</sup> and more PRM<sup>Emph</sup> were found to be associated with higher RV/TLC values and lower  $T_{LCOc}/V_A$  and FEF<sub>25-75%</sub>/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  $R_5-R_{20}$ , *i.e.* more small airway dysfunction, to be associated with less PRM<sup>fSAD</sup>. It is difficult to explain this unexpected finding but it may result from the very small range of  $R_5-R_{20}$  values in our healthy population (IQR 0.00–0.05 kPa·L<sup>-1</sup>·s<sup>-1</sup>). Of specific interest is that more PRM<sup>fSAD</sup> was associated with worse pulmonary function independently of PRM<sup>Emph</sup>. 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<sup>fSAD</sup> than PRM<sup>Emph</sup>, suggesting that an increase in PRM<sup>fSAD</sup> 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<sup>fSAD</sup>, PRM<sup>Emph</sup> and PRM<sup>PD</sup>. 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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TABLE 1

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

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

Data are presented as  $\beta$  (95% CI). PRM values were normalised by natural-logarithmic transformation. PRM<sup>fSAD</sup>: extent of small airway disease; PRM<sup>Emph</sup>: extent of emphysema; PRM<sup>PD</sup>: extent of parenchymal disease; FEV<sub>1</sub>: forced expiratory volume 1 s; FVC: forced vital capacity; FEF<sub>25–75%</sub>: 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.

<sup>#</sup> adjusted for sex and smoking status

<sup>¶</sup> adjusted for sex and age

<sup>+</sup> adjusted for age, sex, smoking status and height. Bold indicates statistically significant values.

<sup>\*</sup> p<0.05

<sup>\*\*</sup> p<0.01.