Chapter 3

Effects of ageing and smoking on pulmonary CT scans, using Parametric Response Mapping

Ilse M. Boudewijn, Dirkje S. Postma, Eef D. Telenga, Nick H. T. ten Hacken, Wim Timens, Matthijs Oudkerk, Brian D. Ross, Craig J. Galbán*, Maarten van den Berge*

*shared last author

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To the Editor,

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

Parametric Response Mapping (PRM) is a novel technique to analyze pulmonary computed tomography (CT) scans in order to quantify the extent of small airways disease (PRM<sub>SAD</sub>), emphysema (PRM<sub>Emph</sub>) and parenchymal disease (PRM<sub>PD</sub>), the latter reflecting increased attenuation of normal lung parenchyma(2,3). We aimed to evaluate the PRM technique in a cohort of well-characterized, respiratory-healthy subjects with a wide age range. As smoking and ageing are both risk factors in the development of COPD(4), we hypothesized that 1) an older age is associated with more PRM<sub>SAD</sub>, PRM<sub>Emph</sub> and PRM<sub>PD</sub> and that 2) current smoking is associated with more PRM<sub>SAD</sub>, PRM<sub>Emph</sub> and PRM<sub>PD</sub>. 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<sub>1</sub>)/forced vital capacity (FVC) ratio above the lower limit of normal, no bronchial hyperresponsiveness and reversibility of FEV<sub>1</sub> to salbutamol <10% of the predicted value.

Spirometry (FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC and forced expiratory flow between 25-75% of FVC (FEF<sub>25-75</sub>)), 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 for haemoglobin (TLCOc adjusted for alveolar volume /VA) was measured using the single breath-holding technique, and small airways resistance (resistance at 5Hz (R<sub>5</sub>) minus resistance at 20Hz (R<sub>20</sub>)) and reactance at 5Hz (X<sub>5</sub>) were measured by impulse oscillometry. We considered FEF<sub>25-75</sub>, FEF<sub>25-75</sub>/FVC, RV/TLC, R<sub>5</sub>-R<sub>20</sub> and X<sub>5</sub> as small airways measurements.
Thin slice (i.e. 75-mm) pulmonary CT scans were made at full in- and expiration (RV). PRM was performed to quantify PRM\textsuperscript{SAD}, PRM\textsuperscript{Emph} and PRM\textsuperscript{PD} as percentage of total lung volume as described previously\cite{2,3}. We applied linear regression analyses to assess associations between both age and smoking, and PRM\textsuperscript{SAD}, PRM\textsuperscript{Emph} and PRM\textsuperscript{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), 56\% of subjects being males. The mean±SD FEV\textsubscript{1} in the study population was 108±12\% predicted, FEV\textsubscript{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\textsuperscript{SAD}, PRM\textsuperscript{Emph}, and PRM\textsuperscript{PD}, independently of smoking and sex (Table 1). Current smoking was significantly associated with more PRM\textsuperscript{PD}, but not with more PRM\textsuperscript{SAD} and PRM\textsuperscript{Emph}, independently of age and sex.

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

<table>
<thead>
<tr>
<th></th>
<th>PRM\textsuperscript{SAD}</th>
<th>PRM\textsuperscript{Emph}</th>
<th>PRM\textsuperscript{PD}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>0.06**</td>
<td>0.05**</td>
<td>0.01*</td>
</tr>
<tr>
<td>Current smoking §</td>
<td>-0.14</td>
<td>-0.42</td>
<td>0.24*</td>
</tr>
<tr>
<td>Pulmonary function tests*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV\textsubscript{1} (liters)</td>
<td>0.18</td>
<td>0.27</td>
<td>-0.17</td>
</tr>
<tr>
<td>FEV\textsubscript{1}/FVC (%)</td>
<td>-0.06**</td>
<td>-0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>FEF\textsubscript{25-75} (l/s)</td>
<td>-0.28</td>
<td>-0.19</td>
<td>0.01</td>
</tr>
<tr>
<td>FEF\textsubscript{25-75}/FVC ((l/s)/l)</td>
<td>-2.29*</td>
<td>-1.73**</td>
<td>0.33</td>
</tr>
<tr>
<td>RV (liters)</td>
<td>3.65**</td>
<td>1.01</td>
<td>-0.44</td>
</tr>
<tr>
<td>TLC (liters)</td>
<td>0.56**</td>
<td>0.53**</td>
<td>-0.11</td>
</tr>
<tr>
<td>RV/TLC (%)</td>
<td>0.11*</td>
<td>0.08**</td>
<td>0.01</td>
</tr>
<tr>
<td>TLCO\textsubscript{c}/VA (mmol/min/kPa/L)</td>
<td>-1.97**</td>
<td>-1.62**</td>
<td>0.36</td>
</tr>
<tr>
<td>R\textsubscript{5} - R\textsubscript{20} (kPa/l/s)</td>
<td>-6.59**</td>
<td>-4.84</td>
<td>0.41</td>
</tr>
<tr>
<td>X\textsubscript{5} (kPa/l/s)</td>
<td>4.92</td>
<td>5.02</td>
<td>-0.62</td>
</tr>
</tbody>
</table>

Data are presented as β (95\% confidence interval). PRM values were normalized by natural-logarithmic transformation. PRM\textsuperscript{SAD}: extent of small airways disease; PRM\textsuperscript{Emph}: extent of emphysema; PRM\textsuperscript{PD}: extent of parenchymal disease; FEV\textsubscript{1} = forced expiratory volume in 1 second; FVC = forced vital capacity; FEF\textsubscript{25-75} = forced expiratory flow between 25-75\% of FVC; RV = residual volume; TLC = total lung capacity; TLCO\textsubscript{c}/VA = transfer factor of the lung for carbon monoxide adjusted for alveolar volume and haemoglobin; R\textsubscript{5} = resistance at 5 Hz; R\textsubscript{20} = resistance at 20 Hz; R\textsubscript{5} - R\textsubscript{20} = difference between R\textsubscript{5} and R\textsubscript{20}; X\textsubscript{5} = reactance at 5 Hz; *adjusted for sex and smoking status; **adjusted for sex and age; *p<0.05; **p<0.01.
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 TLC/VA 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, TLCOc/VA% predicted and R$_5$-R$_{20}$ alternately, as outcome parameters. More PRM$^{fSAD}$ was significantly associated with lower FEV$_1$/FVC (Beta=-0.57, p<0.05), lower FEF$_{25-75}$/FVC (Beta=-0.02, p<0.01) and higher RV/TLC% predicted (Beta=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 airways disease and emphysema were present, the higher were RV/TLC values and the lower TLCOc/VA and FEF$_{25-75}$/FVC values, even in these respiratory healthy subjects. Of interest, more small airways disease was independently 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 were 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 visualize these physiological alterations by using PRM to distinguish between small airways 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 airways disease. Furthermore, it is well established that measurements of emphysema on CT scans increase with ageing both in smokers and non-smokers (never-smokers and ex-smokers) which our findings support(10-12).
We found that current smokers had significantly more PRM\textsuperscript{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\textsuperscript{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\textsuperscript{PD} is associated with pulmonary infection(3). No differences in PRM\textsuperscript{SAD} and PRM\textsuperscript{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 a normal pulmonary function. An alternative explanation may be that PRM\textsuperscript{PD} ‘masks’ underlying PRM\textsuperscript{SAD} and PRM\textsuperscript{Emph} among current smokers.

Finally, more PRM\textsuperscript{SAD} and more PRM\textsuperscript{Emph} were found to be associated with higher RV/TLC values and lower TLCO\textsubscript{c}/VA and FEF\textsubscript{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 $R_5-R_{20}$, i.e. more small airways dysfunction, to be associated with less PRM\textsuperscript{SAD}. 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/s). Of specific interest is that more PRM\textsuperscript{SAD} was associated with worse pulmonary function independently of PRM\textsuperscript{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\textsuperscript{SAD} than PRM\textsuperscript{Emph}, suggesting that an increase in PRM\textsuperscript{SAD} may be the first sign of pulmonary pathology.

A limitation of the study is the lack of histologic samples (i.e. peripheral airway biopsies or lung tissue) for direct comparison with the PRM measurements in order to validate PRM\textsuperscript{SAD}, PRM\textsuperscript{Emph} and PRM\textsuperscript{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 characterize early pulmonary alterations in the lungs even without clinical symptomatology, by distinguishing small airways disease, emphysema and parenchymal disease. Future studies are required to assess its role in predicting or phenotyping lung diseases.
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