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 (PRMfSAD), emphysema (PRMEmph) and parenchymal disease (PRMPD), 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 PRMfSAD, PRMEmph and PRMPD, and 2) current smoking is associated with more PRMfSAD, PRMEmph and PRMPD. 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 (FEV1)/forced vital capacity (FVC) ratio above the lower limit of normal, no bronchial hyperresponsiveness and reversibility of FEV1 to salbutamol <10% of the predicted value.

Spirometry (FEV1, FVC, FEV1/FVC and forced expiratory flow at 25–75% of FVC (FEF25–75%)), 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 (TLCOc) adjusted for alveolar volume (VA) was measured using the single breath-holding technique, and small airway resistance (resistance at 5 Hz (R5) minus resistance at 20 Hz (R20)) and reactance at 5 Hz (X5) were measured by impulse oscilometry. We considered FEF25–75%, FEF25–75%/FVC, RV/TLC, R5–R20 and X5 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 PRMfSAD, PRMEmph and PRMPD 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 PRMfSAD, PRMEmph and PRMPD, 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 FEV1 in the study population was 108±12% predicted, FEV1/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 PRMfSAD, PRMEmph and PRMPD, independently of smoking and sex (table 1). Current smoking was significantly associated with more PRMfSAD, but not with more PRMfSAD or PRMEmph, independently of age and sex.

We investigated whether pulmonary function tests were associated with PRM measurements and found that a lower FEV1/FVC was significantly associated with more PRMfSAD, independently of age, sex, smoking status and height (table 1). In addition, higher RV/TLC, lower TCO2/VA and lower FEF25–75%/FVC were significantly associated with more PRMfSAD and PRMEmph. Rs–R20 was significantly and negatively associated with PRMfSAD, but not with PRMEmph. PRMPD was not associated with pulmonary function tests.

We tested whether PRMfSAD and PRMEmph contributed independently to pulmonary function measurements by including PRMfSAD and PRMEmph in regression models with FEV1/FVC, FEF25–75%/FVC, RV/TLC % predicted, TCO2/VA % predicted and Rs–R20, alternately, as outcome parameters. More PRMfSAD was significantly associated with lower FEV1/FVC (β = −0.57, p < 0.05), lower FEF25–75%/FVC (β = −0.02, p < 0.01) and higher RV/TLC % predicted (β = 1.13, p < 0.05), independently of PRMEmph.

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 current, 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 TCO2/VA and FEF25–75%/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 FEF25–75%/FVC and lower FEV1/FVC values.

An important finding was the elevated levels of PRMfSAD, PRMEmph and PRMPD 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

### 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>Variable</th>
<th>PRMfSAD</th>
<th>PRMEmph</th>
<th>PRMPD</th>
</tr>
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<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>FEV1 L</td>
<td>0.18 (−0.47–0.83)</td>
<td>0.27 (−0.33–0.86)</td>
<td>−0.17 (−0.43–0.09)</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>−0.06** (−0.12–−0.01)</td>
<td>−0.05 (−0.10–0.00)</td>
<td>0.01 (−0.01–0.03)</td>
</tr>
<tr>
<td>FEF25–75% L·s⁻¹</td>
<td>−0.28 (−0.62–0.06)</td>
<td>−0.19 (−0.50–0.13)</td>
<td>0.01 (−0.13–0.15)</td>
</tr>
<tr>
<td>FEF25–75%/FVC s⁻¹</td>
<td>−2.29* (−3.84–−0.75)</td>
<td>−1.73** (−3.17–−0.29)</td>
<td>0.33 (−0.32–0.98)</td>
</tr>
<tr>
<td>RV L</td>
<td>3.65** (0.19–7.11)</td>
<td>1.01 (−0.40–2.42)</td>
<td>−0.44 (−4.72–3.83)</td>
</tr>
<tr>
<td>TCO2/VA mmol·min⁻¹·kPa⁻¹·L⁻¹</td>
<td>0.56** (0.12–0.99)</td>
<td>0.53** (0.13–0.93)</td>
<td>−0.11 (−0.29–0.07)</td>
</tr>
<tr>
<td>RV/TLC %</td>
<td>0.11* (0.04–0.17)</td>
<td>0.08** (0.01–0.14)</td>
<td>0.01 (−0.02–0.04)</td>
</tr>
<tr>
<td>TCO2/VA mmol·min⁻¹·kPa⁻¹·L⁻¹</td>
<td>−1.97** (−3.56–−0.39)</td>
<td>−1.62** (−3.08–−0.16)</td>
<td>0.36 (−0.29–1.01)</td>
</tr>
<tr>
<td>Rs–R20 kPa·L⁻¹·s⁻¹</td>
<td>−6.59** (−12.2–−0.92)</td>
<td>−4.84 (−10.11–0.43)</td>
<td>0.41 (−0.19–2.76)</td>
</tr>
<tr>
<td>Xs kPa·L⁻¹·s⁻¹</td>
<td>4.92 [−3.51–13.35]</td>
<td>5.02 [−2.72–12.76]</td>
<td>−0.62 [−4.04–2.80]</td>
</tr>
</tbody>
</table>

Data are presented as β (95% CI). PRM values were normalised by natural-logarithmic transformation. PRMfSAD: extent of small airway disease; PRMEmph: extent of emphysema; PRMPD: extent of parenchymal disease; FEV1: forced expiratory volume 1 s; FVC: forced vital capacity; FEF25–75%: forced expiratory flow at 25–75% of FVC; RV: residual volume; TLC: total lung capacity; TCO2: transfer factor of the lung for carbon monoxide correction for haemoglobin; VA: alveolar volume; Rs: resistance at 5 Hz; R20: resistance at 20 Hz; Xs: reactance at 5 Hz; §: adjusted for age, 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.
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 PRMPD than never-smokers, independently of age. Parenchymal disease is defined as increased parenchymal density upon inspiration and it could be suggested that more PRMPD 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 PRMPD is associated with pulmonary infection [3]. No differences in PRMFSA and PRMEmph 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 PRMPD "masks" underlying PRMFSA and PRMEmph among current smokers.

Finally, more PRMFSA and more PRMEmph were found to be associated with higher RV/TLC values and lower TLC/VA and FEF25–75%/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 PRMFSA. 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 L⁻¹ s⁻¹). Of specific interest is that more PRMFSA was associated with worse pulmonary function independently of PRMEmph. Since it was previously suggested that small airways disease precedes emphysema [1], we speculate that early changes in pulmonary function are better reflected by PRMFSA than PRMEmph, suggesting that an increase in PRMFSA 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 PRMFSA, PRMEmph and PRMPD. 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

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References
Accuracy of chest high-resolution computed tomography in diagnosing diffuse cystic lung diseases

To the Editor:

The diffuse cystic lung diseases (DCLDs) are a group of pathophysiologically heterogeneous processes characterised by the presence of multiple, thin-walled, air-filled spaces within the pulmonary parenchyma [1]. The differential diagnosis of DCLDs includes lymphangioleiomyomatosis (LAM), follicular bronchiolitis (FB), lymphocytic interstitial pneumonia (LIP), Birt–Hogg–Dubé syndrome (BHD), pulmonary Langerhans cell histiocytosis (PLCH), amyloidosis, light chain deposition disease, cystic metastases, infectious entities such as Pneumocystis, and other aetiologies [2]. Bronchiectasis and bullous changes seen in chronic obstructive pulmonary disease can also produce high-resolution computed tomography (HRCT) patterns that mimic the DCLDs.

The utility of HRCT in the diagnosis of LAM and differentiation from other DCLDs is not completely defined. According to the European Respiratory Society (ERS) guidelines, characteristic HRCT features along with a compatible clinical history are sufficient to confidently diagnose LAM, without the need for a tissue biopsy [3]. However, previously reported accuracy rates for diagnosing LAM based on HRCT findings may not be sufficient in an era when interventions with substantial risks are becoming available. Two prior studies have reported accuracy rates of 72–84% in diagnosing LAM based on imaging characteristics alone [4, 5]. The aim of our study was to determine the diagnostic accuracy of HRCT evaluation by radiologists and pulmonologists, at various levels of expertise, in patients with DCLDs presenting to referral centres.

We retrospectively obtained HRCTs from 89 patients referred to LAM Foundation Clinics at the University of Cincinnati (Cincinnati, OH, USA), Mayo Clinic Rochester (Rochester, MN, USA) and National Kinki-Chou Hospital (Osaka, Japan) for further evaluation of DCLDs. All scans were non-contrast HRCTs and only thin section (1–3 mm) images were employed in the analysis. Patient