Assessing small airways disease

To the Editors:

In their excellent study of the effect of small particle corticosteroids on small airway involvement in asthma, COHEN *et al.* [1], along with LAHZAMI and KING [2] in the accompanying lead editorial [2], decry the complexity associated with current measurements of small airways function. Those authors stress the desirability of finding simpler methods to assess small airways dysfunction.

A simple method of assessing smaller airways obstruction is easily available and could be used retrospectively. In contrast to the mean forced expiratory flow between 25 and 75% of forced vital capacity (FVC; $FEF_{25–75\%}$), which measures the mid-portion of exhalation ending at nearly the same time as the forced expiratory volume in one second (FEV_1) in these subjects, the $FEV_3/FVC\%$ or $(1\text{-}FEV_3/FVC)\%$ are excellent measures of small airways function. They measure the fraction of volume exhaled near the end of a forced exhalation, *i.e.* from airspaces and airways with the longest time constants [3, 4]. However, because they are ratios (as are FEV_1/FVC and $FEF_{25–75\%}$) they are not ideal measurements of airway responsiveness to bronchodilators. Rather, pre- and post-absolute volumes, such as FEV_1, FEV_3 and FEV_6, should be compared to assess bronchodilator effect. Presumably, if there is a small airways bronchodilator effect in the ciclesonide-treated group, the increase from pre- to post FEV_3 (ΔFEV_3) or FEV_6 (ΔFEV_6) should exceed that of pre- to post-FEV_1 (ΔFEV_1). For example, if the ΔFEV_1 was 150 mL and the ΔFEV_3 and ΔFEV_6 were also 150 mL, the dominant change was in the larger airways. If the ΔFEV_1 was 150 mL and the ΔFEV_3 and ΔFEV_6 were 200–250 mL, there was also an important change in the smaller airways. These simple measurements would objectively disclose whether the smaller airways were directly affected by the ciclesonide.

It would be of interest and importance if COHEN *et al.* [1] and other authors would retrospectively or prospectively measure and report these findings to see whether these simple, quick and inexpensive measures are useful in evaluating drugs that modify small airways obstruction.

J. Hansen
Medicine, Harbor-UCLA Medical Center, Torrance, CA, USA.

STATEMENT OF INTEREST

None declared.

REFERENCES

1 Cohen J, Duoma WR, ten Hacken NHT, Vonk JM, Oudkerk M, Postma DS. Ciclesonide imporves measures of small airway involvement in asthma. *Eur Respir J* 2008; 31: 1213–1220.
2 Lahzami S, King GG. Targeting small airways in asthma: the new challenge of inhaled corticosteroid treatment. *Eur Respir J* 2008; 31: 1145–1147.
3 Hansen JE, Sun X-G, Wasserman K. Discriminating measures and normal values for expiratory obstruction. *Chest* 2006; 129: 369–377.
4 Hansen JE, Sun X-G, Wasserman K. Ethnic- and sex-free formulae for detection of airway obstruction. *Am J Respir Crit Care Med* 2006; 174: 493–498.

DOI: 10.1183/09031936.00088908

From the authors:

J. Hansen describes an interesting method for assessing small airways dysfunction, namely *via* the bronchodilator effects on forced expiratory volume in three seconds (FEV_3) and FEV_6, as compared with the effects on FEV_1. As they are derived from flow–volume manoeuvres, these parameters are indeed simple to obtain, low-cost, show acceptable repeatability [1, 2] and may reflect relevant changes in small airways obstruction. We therefore retrospectively analysed the FEV_3 and FEV_6 values and compared the treatment effects of ciclesonide on FEV_3 and FEV_6 to FEV_1 in our study population [3]. To assess whether the changes in FEV_1, FEV_3, FEV_6 and forced vital capacity (FVC) after treatment with ciclesonide were indicative of small airway changes, we correlated them with the changes in methacholine-induced air trapping on expiratory computed tomography scans, another method of assessing small airways function.

Table 1 demonstrates the changes after treatment in FEV_1, FEV_3, FEV_6 and FVC. The ciclesonide-induced change in FEV_6

TABLE 1 Changes in forced expiratory volume in one second (FEV_1), FEV_3, FEV_6 and forced vital capacity (FVC) after treatment with ciclesonide or placebo

	Ciclesonide	Placebo	p-value
Subjects n	9	7	
ΔFEV_1			
%	18.1 (6.4–31.2)#	-0.7 (-1.9–8.6)	0.003
mL	550 (263–825)	-25 (-67.5–205)	
ΔFEV_3			
%	11.8 (7.9–14.6)¶	-0.3 (-1.3–6.7)	0.002
mL	500 (360–590)	-15 (-55–205)	
ΔFEV_6			
%	8.6 (2.6–11.4)	-0.9 (-1.9–5.6)	0.038
mL	375 (150–568)	-40 (-77.5–185)	
ΔFVC			
%	6.9 (4.8–10.2)	-1.2 (-1.8–2.8)	0.002
mL	380 (210–538)	-55 (-75–92.5)	

Data are presented as median (interquartile range), unless otherwise stated. In the ciclesonide arm, three subjects failed to reach 6 s of exhalation. Between-treatment differences were tested using the Mann–Whitney U-test and within-ciclesonide differences (%) were tested using the Wilcoxon signed rank test. #: $p<0.05$ *versus* ΔFEV_3, ΔFEV_6 and ΔFVC; ¶: $p<0.05$ *versus* ΔFEV_6.

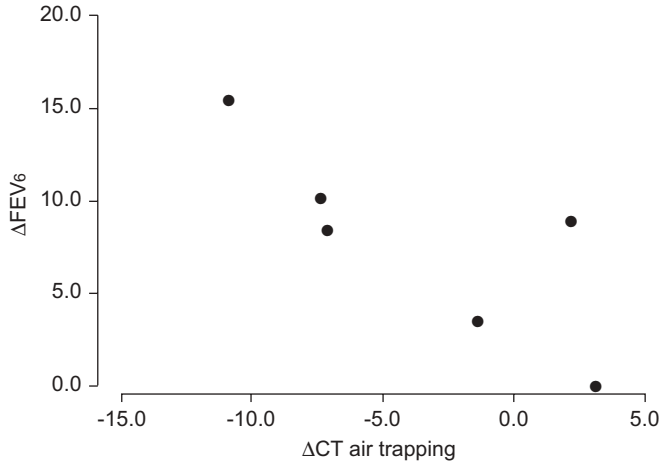

FIGURE 1. Correlation between ciclesonide-induced change (%) in expiratory lung volume on computed tomography (CT) scan and forced expiratory volume in six seconds (FEV_6). rho= -0.83, p=0.04.

(375 mL) did not exceed that of the FEV_3 (500 mL) and FEV_1 (550 mL). This was an unexpected finding as, according to the hypothesis of J. Hansen, it indicates worsening of small airways function. However, a beneficial effect on small airways function is very likely, and this seeming paradox may be explained as follows. Improved small airways function significantly contributes to the first part of the forced expiration and thus importantly improves FEV_1. As the lungs become relatively more deflated during the later phase of exhalation, a lower alveolar wall tension and a higher peripheral airway resistance lead to a relatively lower airflow and thus, relatively less improvement in FEV_3 and FEV_6 (in favour of FEV_1). The significant correlation between ciclesonide-induced changes in FEV_6 (but not FEV_1 or FEV_3) and air trapping on expiratory computed tomograph scan (fig. 1) is in line with this explanation.

We thank our colleagues J. Hansen for making us aware of this seeming paradox.

J. Cohen, N.R. Douma, N.H.T. ten Hacken and D.S. Postma
Dept of Pulmonology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

STATEMENT OF INTEREST

A statement of interest for D.S. Postma can be found at www.erj.ersjournals.com/misc/statements.shtml

REFERENCES

1 Kainu A, Lindqvist A, Sarna S, Sovijärvi A. Intra-session repeatability of FET and FEV_6 in the general population. *Clin Physiol Funct Imaging* 2008; 28: 196–201.
2 Bellia V, Sorino C, Catalano F, *et al*. Validation of FEV_6 in the elderly: correlates of performance and repeatability. *Thorax* 2008; 63: 60–66.
3 Cohen J, Douma WR, ten Hacken NHT, Vonk JM, Oudkerk M, Postma DS. Ciclesonide improves measures of small airway involvement in asthma. *Eur Respir J* 2008; 31: 1213–1220.

DOI: 10.1183/09031936.00101508

A possible role for Epstein–Barr virus infection in COPD?

To the Editors:

We read with interest the paper by McManus *et al.* [1], which appeared in a recent issue of the *European Respiratory Journal*. It is indeed tempting to suggest a role for latent viral infections in the development of chronic obstructive pulmonary disease. Epstein–Barr virus (EBV) infection has been associated with several medical conditions, as pointed out by those authors. However, relatively little is known about the role of EBV in chronic pulmonary conditions. Our research group focuses on the role of EBV infection in pulmonary conditions such as pleural effusion [2] and unexplained parenchymal disease [3].

We would like to make some comments on the study by McManus *et al.* [1]. The authors did not establish the serostatus of the patients and controls included in the study. This could be of importance because the control group had a significantly lower age compared to the study group. The proportion of subjects with a positive EBV serostatus is positively associated with age.

Another point of concern is the possible contamination of sputum samples with EBV DNA present in saliva. EBV loads in saliva can be very high [4]. Even though sputum was separated from saliva it could be helpful to measure the EBV load in sputum and determine the correlation between saliva and sputum results for EBV PCR.

A third possible confounder could be the presence of B-cells in sputum. McManus *et al.* [1] argue that EBV DNA PCR is indicative of viral replication; however, the PCR used cannot differentiate between DNA derived from active viral replication or latent infection. B-cells are known to harbour EBV in the latency phase. Determination of the number of B-cells in the sputum could have revealed whether these cells contribute to the relatively high levels of EBV in the study group.