Same-day repeatability of fractional exhaled nitric oxide in severe asthma

To the Editor:

Fractional exhaled nitric oxide (F_{ENO}) is a single-breath test used in asthma diagnosis and management. Whilst a number of studies in mild to moderate asthma have demonstrated excellent repeatability of F_{ENO} by assessing intra-device reproducibility from consecutive blows [1–3], the reported between-session and diurnal variability have been inconsistent [4–9]. Asthma is a highly variable disease. The excessive diurnal variability in airflow obstruction is a marker for disease severity, poor control and mortality. Diurnal variability of F_{ENO} is also a predictor for poor asthma control [8]. We have demonstrated that F_{ENO} has a significant time-of-the-day difference with a median of 12 ppb between peak and trough readings within a 24-h cycle in stable mild/moderate asthma [10]; whether this same-day variation is clinically significant in the diagnosis and management of asthma remains unclear. F_{ENO} has been readily used in the monitoring of severe asthma, but its same-day reproducibility as a single-breath test is unknown in this group.

We investigated the same-day reproducibility of F_{ENO} as a single-breath test in patients with severe asthma.

Participants were recruited *via* Manchester Allergy, Respiratory and Thoracic Surgery Biobank (REC 15/NW/0409). Clinical data were recorded and baseline F_{ENO} measured (NIOX Vero; Aerocrine, Solna, Sweden) with a single blow between 08:00 and 09:00 h, before inhaled corticosteroids and other regular medications were administered under direct supervision. F_{ENO} measurements were then repeated at 1, 2, 4 and 8 h. Spirometry was performed after each F_{ENO} measurement. Food was provided at standard times by the hospital catering service. All study participants gave written informed consent.

Mean F_{ENO} ($F_{ENOmean}$) was defined as the mean of repeated measurements within the same subject. The intra-subject maximum difference (F_{ENOmax_diff}) was defined as the difference between the highest and lowest F_{ENO} value for each individual. $F_{ENOvariability}$ was calculated by the formula: $F_{ENOmax\_diff}/F_{ENOmean}$ and was presented as a percentage value.

Summary data are presented as median (interquartile range; IQR). Pearson's correlation (with bootstrapping) was used for comparisons of measurements (IBM SPSS 20). Missing data were excluded.

A total of 43 patients (age 50 (44–59) years, 25.6% male, two current smokers) completed the study. All participants were on British Thoracic Society step 4/5 treatment, with 30 (69.8%) on maintenance systemic corticosteroids and 27 (62.8%) on biological therapies for asthma. The majority (93%) had features of allergic sensitisation and/or serum/sputum eosinophilia. The median (IQR) daily dose of inhaled corticosteroids was 2000 (1600–2000) µg beclometasone dipropionate equivalent, with 75.0% (58.0–100.0%) adherence based on general practitioner prescription records. Participants had median (IQR) 1 (1–3) asthma exacerbations within the past 12 months, and 28 (65.1%) participants had previous admission to intensive care unit due to asthma. No participants had an acute exacerbation during the study period. The baseline forced expiratory volume within 1 s (FEV_1) was 59.5% (50.0–73.3%) of predicted.

11 F_{ENO} measurements were missing (all at the 8-h time-point), leaving 204 readings included in the analysis. The median (IQR) $F_{ENOmean}$ was 23.5 (12.8–47.4) ppb. Age, sex, use of biologics and oral corticosteroids, exacerbation rates and medication compliance were not significantly associated with $F_{ENOmean}$.

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Fractional exhaled nitric oxide (F_{ENO}) demonstrates marked same-day variation in patients with severe asthma, which may impact on clinical decisions. The same-day variability must be carefully considered when interpreting F_{ENO} as a single-breath test. https://bit.ly/38M1eJV

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F_{ENO} measurements at baseline were lower than those measured around midday (at 2-h and 4-h time points, with mean±SD difference of −3.7±7.9 ppb and −3.4±8.2 ppb; p<0.01). There was no significant difference in F_{ENO} before and after meals. The median (IQR) F_{ENOmax_diff} was 10.0 (4.0–15.0) ppb and $F_{ENOvariability}$ was 29.2% (17.9–54.7%). F_{ENOmax_diff} was correlated with $F_{ENOmean}$ (r=0.81, p<0.001) (figure 1), but not $F_{ENOvariability}$ (p=0.19). $F_{ENOmean}$ was not correlated with $F_{ENOvariability}$ (p=0.29). Patient demographics, use of medication and lung function were not significantly associated with $F_{ENOvariability}$ or F_{ENOmax_diff}.

In participants who had a $F_{ENOmean}$ of 50 ppb or more (n=10), the median (IQR) F_{ENOmax_diff} was 22.5 (14.3–55.3) ppb and $F_{ENOvariability}$ 21.9% (18.7–33.1%). In those who had $F_{ENOmean}$ of less than 50 ppb, the median (IQR) F_{ENOmax_diff} was 6.0 (3.0–11.5) ppb and $F_{ENOvariability}$ 33.1% (15.5–56.7%). 10 (23.3%) patients had F_{ENO} measurements that straddled 25 ppb or 50 ppb cut-off points within the same day.

$F_{ENOmean}$ did not show significant correlation to FEV_1 % predicted (p=0.31). The median (IQR) of FEV_1 % predicted maximum difference was 5.0% (2.0–13.0%) and FEV_1 % predicted variability (defined as (maximum−minimum)/mean FEV_1 % predicted) 8.7% (3.8–20.6%). Same-day variability in F_{ENO} was significantly greater than FEV_1 variability (p<0.001), but there was no significant correlation between the two (p=0.16).

We have shown that within-day variability of F_{ENO} in severe asthma is significant and clinically relevant. Consistent with this, SAITO *et al.* [8] had also demonstrated a similar amplitude of diurnal variation in F_{ENO} in patients with severe asthma, although that was not using a currently approved single-breath method. In our study, we measured F_{ENO} during clinical hours (between 08:00 h and 17:00 h) when the test is most commonly performed in the outpatient clinical setting in primary or secondary care. Whilst F_{ENO} measurements out of working hours may be useful in asthma management [8], they are not currently approved for home-based testing; indeed before this could happen further study would be required to describe variability over such extended time periods.

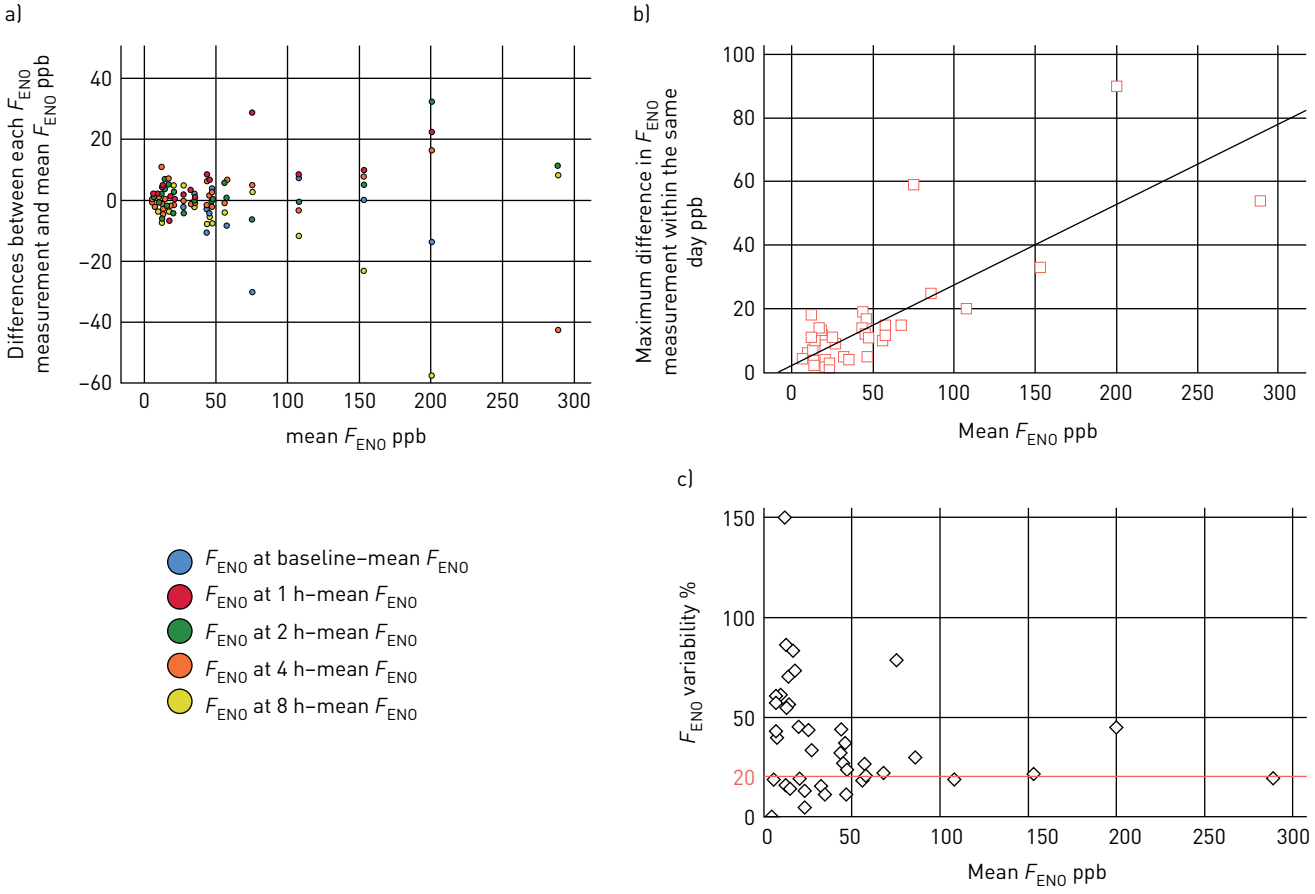

FIGURE 1 Same-day repeatability of fractional exhaled nitric oxide (F_{ENO}) in patients with severe asthma. a) The differences between individual F_{ENO} measurements taken at different time-points and mean F_{ENO}. b) Same-day F_{ENOmax_diff} increases with mean F_{ENO}. c) A significant proportion of patients had F_{ENO} variability of >20% within the same day.

Whilst diurnal variation in lung function and F_{ENO} are both predictive of poor asthma control [8, 11, 12], we did not demonstrate any significant correlation between these in our study. SAITO *et al.* [8] had previously demonstrated increased diurnal variability in F_{ENO} in uncontrolled asthmatics compared to those with well-controlled asthma, but no significant differences in the diurnal variability in peak flow. This may suggest that same-day variation in F_{ENO} is a more sensitive predictor for asthma control than lung function.

We note that a marginal reduction in F_{ENO} levels following spirometry manoeuvres has been reported, although not consistently [13, 14]. Nevertheless, the reduction in F_{ENO} returns to baseline within 1 h [13]. In our study, F_{ENO} was performed prior to spirometry at each time point, leaving a minimum of a 1-h gap between previous spirometry and F_{ENO} measurements.

There is a paucity of data to suggest what constitutes a minimal clinically important difference (MCID) in F_{ENO}, and the significant same-day variability adds further challenge to this. The most recent recommendations made by the American Thoracic Society (ATS) are now almost a decade old and the suggested MCID was based only on expert opinion [15]. A fall of >20% in F_{ENO} for values over 50 ppb, or 10 ppb for F_{ENO} less than 50 ppb, from one visit to the next were said to indicate treatment response [15]. Our study highlights that this suggested MCID and clinically relevant cut-off values in F_{ENO} must be considered with caution. Strikingly, 70% of those with a F_{ENO} more than 50 ppb and a third of those with F_{ENO} of less than 50 ppb in our study had met ATS-defined MCID in F_{ENO} within the same day. Further, almost a quarter of patients had F_{ENO} that straddled ATS-defined clinically relevant cut-off points (25 ppb and 50 ppb) within the same day, leading to potential misinterpretation in a significant proportion of patients. In the current study, we have demonstrated that a $F_{ENOmean}$ of 30 ppb has a same-day variability of 10 ppb (figure 1). More recently, HEANEY *et al.* [16] have demonstrated that a suppression of F_{ENO} by at least twice as much as suggested by the ATS guideline (−42% or more) in severe asthma patients with high F_{ENO} (⩾45 ppb) was associated with a significant improvement in both lung function and asthma control following treatment. This improvement was not observed in those who failed to reach the minimum F_{ENO} suppression (−42%), indicating that the MCID for positive treatment response may be much higher than previously suggested [15]. With the increasing use of F_{ENO} in the management of asthma, urgent research is needed to determine the MCID of F_{ENO} as a single-breath test, and the significant same-day, between-session variability of F_{ENO} must be carefully considered.

F_{ENO} demonstrates significant same-day variation in patients with severe asthma. This variation will have an impact on clinical decisions in some patients. Further studies are urgently needed to confirm the time-of-day effect of F_{ENO} and the impact on clinical use and interpretation of F_{ENO} in severe asthma.

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