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Research letter

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

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To the Editor:

Fractional exhaled nitric oxide (FeNO) 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 FeNO by assessing intra-device reproducibility from consecutive blows (1-3), the 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 FeNO is also a predictor for poor asthma control (8). We have demonstrated that FeNO has a significant time-of-the-day difference with a median of 12 parts per billion (ppb) between peak and trough readings within a 24-hour cycle in stable mild/moderate asthma (10); whether this same-day variation is clinically significant in the diagnosis and management of asthma remains unclear. FeNO 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 FeNO as a single-breath test in patients with severe asthma.

METHOD

Participants were recruited via Manchester Allergy, Respiratory and Thoracic Surgery Biobank (REC 15/NW/0409). Clinical data were recorded and baseline FeNO measured (NIOX Vero, Aerocrine, Solna, Sweden) with a single blow between 0800-0900, before inhaled corticosteroids (ICS) and other regular medications were administered under direct supervision. FeNO measurements were then repeated at 1, 2, 4 and 8 hours. Spirometry was performed after each FeNO measurement. Food was provided at standard times by the hospital catering service. All study participants gave written informed consent.

Mean FeNO ($FeNO_{mean}$) was defined as the mean of repeated measurements within the same subject. The intra-subject maximum difference ($FeNO_{max\_diff}$) was defined as the difference between the highest and lowest FeNO for each individual. $FeNO_{variability}$ was calculated by the formula: $FeNO_{max\_diff}/FeNO_{mean}$ and was presented as %.

Summary data are presented as median [interquartile range (IQR)]. Pearson correlations were used for comparisons of measurements (IBM SPSS 20). Missing data were excluded.

RESULTS

Participants

A total of 43 patients [age 50 (44-59) yrs, 25.6% male, two current smokers] completed the study. All participants were on British Thoracic Society steps 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) mcg beclometasone dipropionate equivalent with 75.0 (58.0-100.0) % adherence based on GP prescription records. Participants had median (IQR) 1 (1-3) asthma exacerbation within the last 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 flow within one second FEV_1 was 59.5 (50.0-73.3) % predicted.

Eleven FeNO measurements were missing (all at the 8hr timepoint), leaving 204 readings included in the analysis. The median (IQR) $FeNO_{mean}$ was 23.5 (12.8-47.4) ppb. Age, gender, use of biologics and oral corticosteroids, exacerbation rates and medication compliance were not significantly associated with $FeNO_{mean}$.

Same-day repeatability of FeNO

FeNO measurements at baseline were lower than those measured around mid-day [at 2hr and 4hr timepoints, 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 FeNO before and after meals. The median (IQR) $FeNO_{max\_diff}$ was 10.0 (4.0-15.0)ppb and $FeNO_{variability}$ was 29.2 (17.9-54.7)%. $FeNO_{max\text{-}diff}$ was correlated with $FeNO_{mean}$ ($r=0.81$, $p<0.001$; figure 1), but not $FeNO_{variability}$ ($p=0.19$). $FeNO_{mean}$ was not correlated with $FeNO_{variability}$ ($p=0.29$). Patient demographics, use of medication and lung function were not significantly associated with $FENO_{variability}$ or $FeNO_{max\_diff}$.

In participants who had a $FeNO_{mean}$ of 50ppb or more (n=10), the median (IQR) $FeNO_{max\text{-}diff}$ was 22.5 (14.3-55.3)ppb and $FeNO_{variability}$ 21.9 (18.7-33.1)%. In those who had $FeNO_{mean}$ of less than 50ppb, the median (IQR) $FeNO_{max\text{-}diff}$ was 6.0 (3.0-11.5)ppb and $FeNO_{variability}$ 33.1 (15.5-56.7) %. Ten (23.3%) patients had FeNO measurements that straddled 25ppb or 50ppb cut-off points within the same day.

$FeNO_{mean}$ did not show significant correlation to $FEV_1\%pred_{mean}$ ($p=0.31$). The median (IQR) of $FEV_1\%pred_{max\_diff}$ was 5.0 (2.0 -13.0)% and $FEV_1\%pred_{variability}$ (defined as (maximum-minimum)/

FEV_1%pred $_{mean}$) 8.7 (3.8-20.6) %. Same day variability in FeNO was significantly greater than FEV_1 variability ($p<0.001$), but there was no significant correlation between the two ($p=0.16$).

DISCUSSION

We have shown that within-day variability of FeNO in severe asthma is significant and clinically relevant. Consistent with this, Saito *et al* had also demonstrated a similar amplitude of diurnal variation in FeNO in patients with severe asthma (8), although that was not using a currently approved single-breath method. In our study, we measured FeNO during clinical hours (between 0800-1700) when the test is most commonly performed in the outpatient clinical setting in primary or secondary care. Whilst FeNO 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.

Whilst diurnal variation in lung function and FeNO 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* had previously demonstrated increased diurnal variability in FeNO 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 FeNO is a more sensitive predictor for asthma control than lung function.

We note that a marginal reduction in FeNO levels following spirometry manoeuvres has been reported, although not consistently (13, 14). Nevertheless, the reduction in FeNO returns to baseline within an hour (13). In our study, FeNO was performed prior to spirometry at each time point, leaving a minimum of one-hour gap between previous spirometry and FeNO measurements.

There is a paucity of data to suggest what constitutes a minimal clinically important difference (MCID) in FeNO, and the significant same-day variability adds further challenge to this. The most recent recommendation made by the American Thoracic Society are now almost a decade old and the suggested MCID was based only on expert opinion (15). A fall of >20% in FeNO for values over 50ppb, or 10ppb for FeNO less than 50ppb, 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 FeNO must be considered with caution. Strikingly, 70% of those with a FeNO more than 50ppb and a third of those with FeNO of less than 50ppb in our study had met ATS-defined MCID in FeNO within the same day. Further, almost a quarter of patients had FeNO that straddled ATS-defined clinical relevant cut-off points (25ppb

and 50ppb) within the same day, leading to potential misinterpretation in a significant proportion of patients. In the current study, we have demonstrated that a $FeNO_{mean}$ of 30ppb has a same-day variability of 10ppb (figure 1). More recently, Heaney and colleagues have demonstrated that a suppression of FeNO by at least twice as much as suggested by ATS 2011 (-42% or more) in severe asthma patients with high-FeNO (≥45ppb) was associated with a significant improvement in both lung function and asthma control following treatment (16). This improvement was not observed in those who failed to reach the minimum FeNO suppression (-42%), indicating that the MCID for positive treatment response may be much higher than previously suggested (15). With the increasing use of FeNO in the management of asthma, urgent research is needed to determine the MCID of FeNO as a single-breath test, and the significant same-day, between-session variability of FeNO must be carefully considered.

CONCLUSION

FeNO 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-the-day effect of FeNO and the impact on clinical use and interpretation of FeNO in severe asthma.

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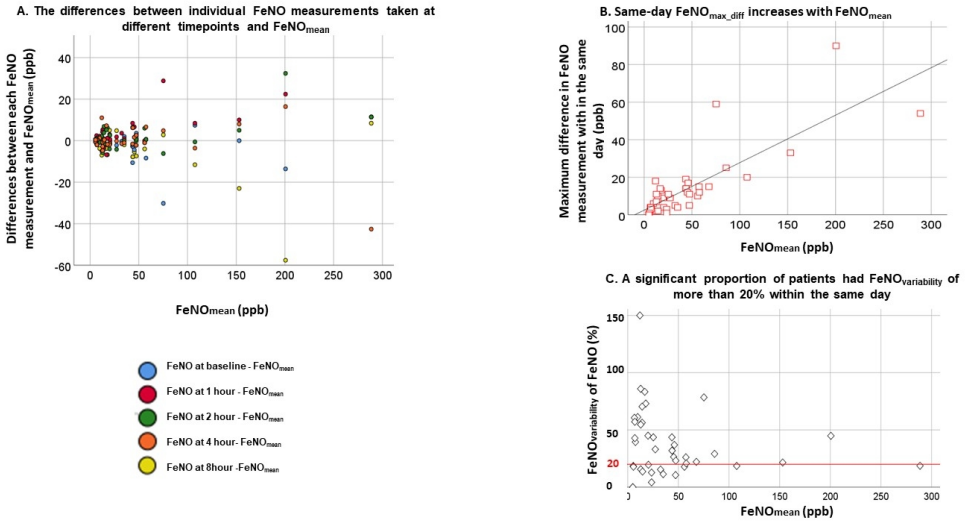

Figure 1. Same-day repeatability of FeNO in patients with severe asthma