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# A novel, noninvasive assay shows that distal airway oxygen tension is low in cystic fibrosis, but not in primary ciliary dyskinesia

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## Abstract

**Objectives:** Oxygen tension affects the biology of aerobic and denitrifying organisms. Using a novel, fast-response sensor, we developed a noninvasive procedure to measure $pO_2$ in distal human airways. We hypothesized that distal $pO_2$ would be low in cystic fibrosis (CF) airways.

**Materials and Methods:** We measured the fraction of expired oxygen ($F_{EO2}$) in real time using a fast laser diode analyzer in healthy subjects and in patients with CF, asthma, and primary ciliary dyskinesia (PCD). Subjects slowly exhaled to residual volume (RV), where the nadir of $F_{EO2}$ (NFO) was recorded. Values were compared to peripheral oxygen saturation ($S_aO_2$), expired $CO_2$ at RV, $FEV_1$, $FEV_1$/FVC, and $FEF_{25-75}$. We also measured the effect of supplemental oxygen on $F_{EO2}$.

**Results:** Seventy-four subjects completed the study. Seven additional subjects could not perform the maneuver. Mean (±SD) NFO values for controls ($n = 29$), CF patients ($n = 23$), asthma patients ($n = 15$), and PCD patients ($n = 7$) were 13.4 ± 1.1%, 12.4 ± 1.2%, 13.3 ± 1.1%, 14.4 ± 0.6%, respectively. NFO in CF was lower than in controls ($P = 0.0162$), and NFO in PCD was higher than in CF ($P = 0.0007$). Asthma results were heterogeneous. Oxygen caused a dose-dependent increase in NFO ($P < 0.0005$; $n = 3$; $r^2 = 0.91$). NFO values were positively associated with $FEV_1$ ($P = 0.0009$), $FEV_1$/FVC ($P = 0.0019$) and $FEF_{25-75}$ ($P = 0.0155$), but there was no association with $S_aO_2$.

**Conclusions:** Distal airway $pO_2$ is lower in CF than in controls. This may reflect absorption of oxygen in partially plugged acinar units, and/or increased epithelial oxygen consumption. Distal airway $pO_2$ can be precisely titrated to treat infections.

KEYWORDS
airway ecology, asthma, cystic fibrosis, hypoxia, primary ciliary dyskinesia

## 1 | INTRODUCTION

A new focus on airway anaerobic infection and colonization has emerged in concert with studies of the airway microbiome, particularly

Lori Mendelsohn and Christiaan Wijers have contributed equally to this work.

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in cystic fibrosis (CF) patients.[1–4] For example, there are regions of mucous in the CF airways that have profoundly low $pO_2$ as measured bronchoscopically. This has been attributed, in part, to increased $O_2$ consumption by CF airway epithelial cells.[3] Though controversial, chronic anaerobic infections are increasingly seen as damaging to the airway.[5–9] CF airway pathology classically begins in the distal airways.[10] We hypothesized that low $pO_2$ in the distal CF airways could be measured noninvasively, perhaps ultimately identifying risk for anaerobic or denitrifying infection.[11] Moreover, we hypothesized that nasal cannula oxygen would increase $pO_2$ to a measurable (and thus titratable) degree in the distal airway, potentially serving as an adjunctive therapy for patients with anaerobic distal airway infections.

Though integrated exhaled $O_2$ values are routinely measured to assess oxygen uptake in exercise physiology,[12] we were surprised that we could not identify any prior work measuring end-expiratory oxygen tension in health or disease. Therefore, we developed a novel system using a fast-response analyzer for continuous recording of $O_2$ and $CO_2$ tensions. We found that CF patients, overall, have lower exhaled $O_2$ than normal subjects at the residual volume (RV) nadir of fractional oxygen (NFO), at which $CO_2$ tension is >38 mmHg, and furthermore, that nasal cannula oxygen increases NFO linearly. Surprisingly, many asthma patients had low-normal NFO values as well, and primary ciliary dyskinesia (PCD) patients had higher levels. We believe these data have implications for understanding the complex ecology of the distal airway.

## 2 | MATERIALS AND METHODS

### 2.1 | Subjects

Subjects with CF[13], PCD[14] or moderate or severe asthma[15] were outpatients, 10 years or older, recruited from Rainbow's Pulmonology Clinic.[13–15] Healthy controls were volunteers from faculty, staff, or Case Western Reserve University students. Participants with a clinically documented disease exacerbation, intercurrent comorbid illness or hypoxia were excluded. This study was reviewed and approved by the University Hospitals Institutional Review Board. Informed consent and/or assent were obtained from all participants or their legal guardians, as applicable. We sought a minimum of 15 subjects in each disease category, but were unable to achieve this recruitment goal for PCD patients. As we consider this to be a pilot study, we chose to keep our sample sizes limited.

We specifically chose to investigate oxygen concentration in the distal airways of CF patients in order to corroborate past research findings of steep oxygen gradients.[3] Furthermore, we sought to investigate oxygen tension among PCD and asthma patients as, to our knowledge, there is no current literature describing this value among these disease groups. Healthy volunteers were recruited as controls.

### 2.2 | Experimental procedure

Oxygen, $CO_2$ and airflow were measured using an O2CPX Fast Laser Diode Oxygen Analyzer in series with a pneumotachometer and a $CO_2$ analyzer (Oxigraf, Mountain View, CA). Peripheral oxygen saturation ($S_aO_2$) was measured using pulse oximetry (Masimo SET, RadV). The experimental procedure was performed separately from spirometry testing.

Subjects were instructed to perform tidal breathing into a low-resistance, filtered mouthpiece for 10 s, then to hold their breath for 2 s at functional residual capacity before exhaling their expiratory reserve volume (ERV) slowly and steadily to RV. When they could no longer exhale, they took a deep inspiration. Attempts which did not achieve a concentration of >5% (>38 mmHg) $CO_2$ in exhaled air were rejected. Measurements were repeated in triplicate. At the outset, we did not know what to expect: these types of studies have not been previously reported. Therefore, our informed consent arbitrarily articulated three replicates. Surprisingly, these three replicates produced NFO values that were reproducible within 20% in 95% of all subjects, and within 10% in 85% of all subjects. The value recorded was the mean of the lowest recorded oxygen percentage in each trial. NFO was recorded when the fraction of exhaled $CO_2$ surpassed 5%, and also when the flow reached zero.

To investigate whether NFO could be increased with supplemental oxygen, three healthy subjects performed the procedure described above while receiving oxygen by nasal cannula at 0, 1, 2, 3, or 4 L/min after a 2 min exposure at each flow. Each participant completed three trials per flow rate.

### 2.3 | Spirometry

Spirometry was performed using a CareFusion spirometer according to ATS standards[16] for adults, and according to the standards adopted by the Cystic Fibrosis Foundation for children.

### 2.4 | Statistical analysis

Linear regression was used to model the relationship between NFO and $S_aO_2$, NFO and age, and NFO and $FEV_1$, $FEV_1$/FVC, and $FEF_{25-75}$ (percent predicted). Pearson correlation coefficients were used to determine associations between variables. Means of continuous variables were compared between disease groups and healthy subjects using Tukey's Honest Significant Difference test. A *P*-value of <0.05 was considered significant. The statistical analyses were carried out in JMP Pro 12 (SAS Institute Inc., Cary, NC).

## 3 | RESULTS

### 3.1 | Subjects

Seventy-four subjects, 10–61 years old, completed the study. There were 29 control subjects, 23 subjects with CF, 15 subjects with asthma and seven subjects with PCD (Table 1). No subjects had a pulmonary exacerbation or intercurrent illness, and all were normoxic (Table 1). Seven additional subjects (two CF, four asthma, and one control) were unable to perform the technique and were excluded from the analysis. No relationship was found between NFO and age among all subjects

**TABLE 1** Subject table

| | Healthy subjects | Cystic fibrosis | Asthma | Primary ciliary dyskinesia |
|---|---|---|---|---|
| N (M/F) | 29 (10/19) | 23 (14/9) | 15 (10/5) | 7 (3/4) |
| Mean age | 32.3 ± 12.0 | 26.2 ± 11.6 | 12.9 ± 2.7 | 14.9 ± 4.7 |
| Median age | 26 | 26 | 13 | 15 |
| Mean peripheral $O_2$ | 98.4 ± 1.8 | 97.1 ± 1.6 | 98.5 ± 1.0 | 97.1 ± 1.0 |
| Peripheral $O_2$ saturation range | 93-100 | 93-100 | 97-100 | 96-99 |

($P = 0.31$, $R^2 = 0.014$) or CF subjects in particular ($P = 0.21$, $R^2 = 0.073$); therefore, pediatric and adult CF patient data were analyzed together.

## 3.2 | Peripheral oxygen saturation and NFO

No relationship was found between NFO and $S_aO_2$ ($P = 0.21$, $R^2 = 0.0063$) (Figure 1).

## 3.3 | NFO in health and disease

Cystic fibrosis patients had significantly lower average NFO values than healthy subjects ($P = 0.0162$). The mean NFO in CF was 12.4 ± 1.23%, as compared to 13.40 ± 1.09% in healthy subjects (Figure 2). We found no difference in NFO values between asthma and CF patients ($P = 0.0907$), or between asthma patients and healthy subjects ($P = 0.997$). NFO for PCD (14.4% ± 0.59%) was significantly higher than CF ($P = 0.0007$), but not different from controls ($P = 0.145$) or asthma ($P = 0.154$).

We compared other parameters for measuring $F_{EO2}$ in addition to the absolute nadir. There was also a significant difference in mean $F_{EO2}$ between CF patients and healthy subjects at the time of the first consistent zero flow rate (12.6 ± 1.24%, 13.66 ± 1.06% $P = 0.012$), and there was a difference between CF and PCD (14.7 ± 0.64%, $P = 0.001$).

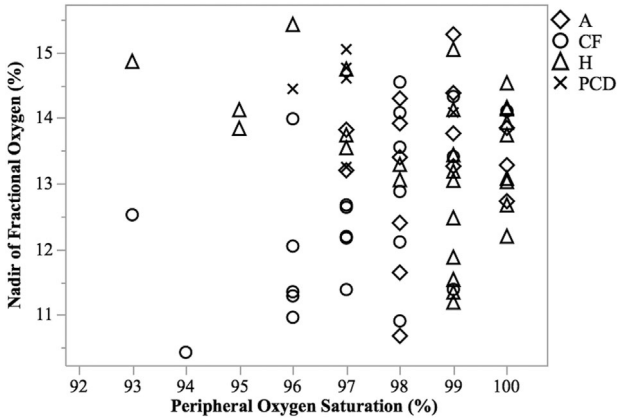


**FIGURE 1** Association between peripheral oxygen saturation and NFO was not statistically significant among all participants ($P = 0.21$, $R^2 = 0.0063$)

Using this method of evaluation, there were no other significant differences.

## 3.4 | Repeatability

Though we did not require repeatability, the three trials of all 29 control subjects were reproducible within 20% of one another, and most were reproducible within 10%. All but two CF subjects, 1 asthma subject and one PCD subject were reproducible within 20%. Intersubject coefficients of variation were 8.1% in controls, 9.8% in CF, 8.2% in asthma and 4.1% in PCD.

## 3.5 | NFO and lung function

When all groups were compared together, there was a positive association between $FEV_1$ and NFO ($P = 0.0009$, $R^2 = 0.24$) (Table 2, Figure 3). When compared individually, CF $FEV_1$ values were positively

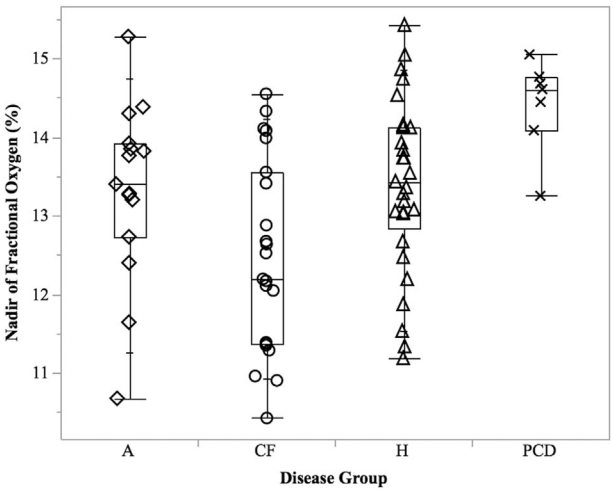


**FIGURE 2** Comparison of NFO between asthma patients (A), cystic fibrosis patients (CF), healthy subjects (H), and primary ciliary dyskinesia patients (PCD). There was a statistically significant difference in mean NFO between CF as compared to H (12.45% ±1.23, as compared to 13.40% ± 1.09, $P = 0.016$). There was a significant difference in mean NFO between CF and PCD (12.45% ±1.23, as compared to 14.4% ±0.59, $P = 0.0007$). There was no significant difference in mean NFO between A and CF, or A and PCD. There was no significant difference in mean NFO between PCD and H

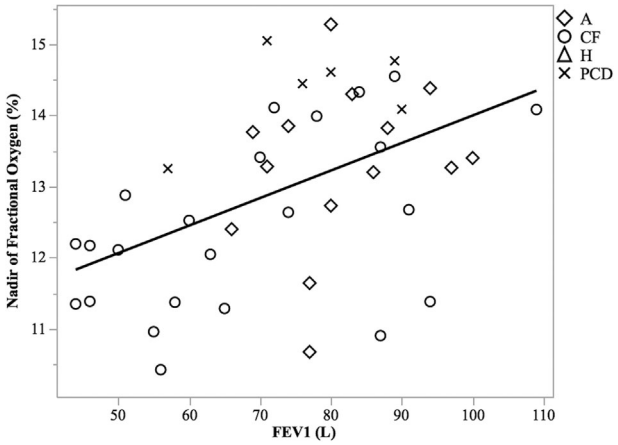


**FIGURE 3** There was a positive association between FEV1 and NFO among all disease groups ($P = 0.0009$, $R^2 = 0.24$)

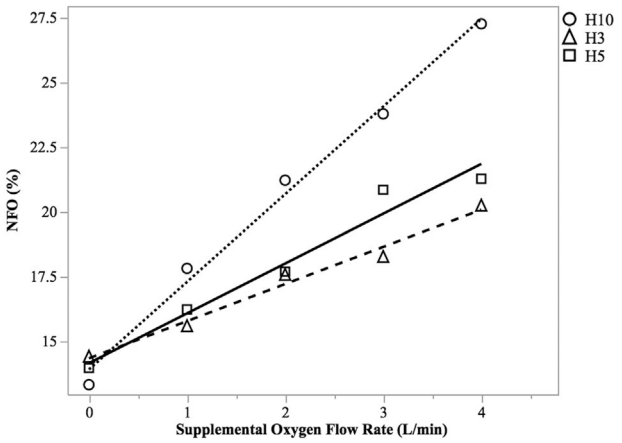


**FIGURE 4** Supplemental oxygen increased NFO in a dose-dependent manner in all three healthy subjects: H10, H3, and H5 ($P < 0.005$, $R^2 = 1.0$; $P < 0.005$, $R^2 = 0.98$; $P < 0.005$, $R^2 = 0.96$)

associated with NFO ($P = 0.014$, $R^2 = 0.26$); but asthma and PCD $FEV_1$ values were not associated with NFO ($P = 0.37$, $R^2 = 0.068$; $P = 0.30$, $R^2 = 0.26$) (Table 2). Similarly, when all groups were compared together, there was a positive association between $FEV_1$/FVC and NFO ($P = 0.0019$, $R^2 = 0.21$). $FEV_1$/FVC was positively associated with CF NFO ($P = 0.016$, $R^2 = 0.25$) and was not associated with asthma or PCD NFO ($P = 0.61$, $R^2 = 0.023$; $P = 0.33$, $R^2 = 0.24$) (Table 2). When all groups were compared together there was a positive association between $FEF_{(25-75)}$ and NFO ($P = 0.016$, $R^2 = 0.14$) (Table 2). However, when each disease group was evaluated individually, $FEF_{(25-75)}$ was positively associated with NFO only among CF patients ($P = 0.017$, $R^2 = 0.25$) and no NFO association was found among asthma or PCD patients ($P = 0.85$,$R^2 = 0.003$; $P = 0.71$, $R^2 = 0.053$) (Table 2).

### 3.6 | Effects of supplemental oxygen on NFO

Three healthy subjects, aged 23 to 60, received supplemental $O_2$ by nasal cannula at 0, 1, 2, 3, and 4 L/min. Their NFO was taken as the mean of three trials at each flow. The procedure was well tolerated by all subjects. Supplemental $O_2$ increased NFO values in a dose-dependent fashion in all three subjects, ($P = 0.0004$, $R^2 = 1.0$,; $P = 0.0009$, $R^2 = 0.98$,; $P = 0.0028$, $R^2 = 0.96$) (Figure 4). At 4 L/min of supplemental $O_2$, the fraction of exhaled oxygen did not exceed 28.4%.

## 4 | DISCUSSION

In this study, we introduce a novel, non-invasive measure: end-expiratory $F_{EO2}$. Surprisingly, we have not found any previous report measuring end-expiratory $F_{EO2}$ or NFO. The development of our technique was facilitated by the availability of a novel, fast laser assay (with a response time of <200 ms) to record the decay of $F_{EO2}$ between FRC and RV in real time. The results confirmed our hypotheses that distal airway $F_{EO2}$ is lower in CF than healthy controls, and that it increases measurably with nasal cannula $O_2$ treatment. However, we unexpectedly observed that many asthma patients had low NFO levels, and that PCD NFO levels were higher than CF. Notably, we also observed that age was not a determinant of NFO. These data may have a number of potential implications.

The low NFO levels in CF could be consistent with the increased $O_2$ consumption by the CF epithelium reported by Worlitzsch.[3] Nevertheless, we think additional mechanisms are relevant for three reasons. First, there was significant overlap between CF and controls. Second, many asthma patients had levels similar to those observed in the low CF range, despite likely having more normal CFTR function. Third, ventilation inhomogeneity was strongly suggested by the lack of association between NFO and peripheral oxygen saturation,

**TABLE 2** NFO and lung function

| | Healthy subjects | Cystic fibrosis | Asthma | Primary ciliary dyskinesia | All |
|---|---|---|---|---|---|
| NFO | 13.4 ± 1.1 | 12.4 ± 1.2 | 13.3 ± 1.1 | 14.4 ± 0.6 | 13.2 ± 1.2 |
| $FEV_1$ | N/A | 68.4 ± 18.7 | 81.6 ± 10.4 | 77.2 ± 12.3 | 73.9 ± 16.5 |
| $FEV_1$/FVC | N/A | 68.7 ± 10.2 | 79.3 ± 6.0 | 74.2 ± 10.6 | 72.9 ± 10.1 |
| $FEF_{25-75}$ | N/A | 45.2 ± 25.6 | 62.4 ± 19.8 | 50.2 ± 25.8 | 51.7 ± 24.5 |
| NFO vs $FEV_1$ | N/A | $R^2 = 0.26$ ($P = 0.0140$) | $R^2 = 0.068$ (ns) | $R^2 = 0.26$ (ns) | $R^2 = 0.24$ ($P = 0.0009$) |
| NFO vs $FEV_1$/FVC | N/A | $R^2 = 0.25$ ($P = 0.016$) | $R^2 = 0.023$ (ns) | $R^2 = 0.24$ (ns) | $R^2 = 0.21$ ($P = 0.0019$) |
| NFO vs $FEF_{25-75}$ | N/A | $R^2 = 0.25$ ($P = 0.017$) | $R^2 = 0.003$ (ns) | $R^2 = 0.053$ (ns) | $R^2 = 0.14$ ($P = 0.016$) |

consistent with classical ventilation/perfusion matching: if NFO reflected homogeneously low distal airway oxygen, systemic arterial saturation should be low. We hypothesize that the partial occlusion of airways, as recently demonstrated by hyperpolarized gas MRI and CT studies[17–20] results in regional alveolar hypoxia (the $O_2$ being low because alveolar gas is not readily refreshed during tidal breathing by atmospheric air). With forced expiration, slow emptying of these heterogeneous lung units located behind mucous plugs could account for low mixed $F_{EO2}$ at RV. This hypothesis could also account for higher oxygen levels in PCD, given the thinner mucous in these airways as compared to CF and asthma (ie, the defect is not in mucous secretion, but in transport of thin mucous). It could also account for the general relationship between airflow obstruction and NFO, thus suggesting that mucous plugs could be a major contributor to low NFO.

Either way, the data support relatively low $O_2$ tension in the distal CF airway. Whether or not these low distal $O_2$ concentrations are uniform and reflect epithelial metabolism[3] and/or mucous plugging, the data support prior evidence that anaerobic growth may be favored in the CF airway microbiome.[3,5–9] The anaerobes in the CF airway tend to be highly resistant to conventional antimicrobial treatment.[21] Our evidence that nasal cannula $O_2$ can increase distal airway levels modestly, below any level that would promote oxidative stress to the epithelium,[22] suggests the possibility that NC $O_2$ therapy could be used as an adjunct to antimicrobial therapy for anaerobic infections in the lung in CF and other conditions. Nevertheless, careful attention would be required to avoid providing extra $O_2$ to species whose growth would be favored.[23]

This technique may also have additional applications. Using elegant chest CT analysis, Dunican et al have recently shown that there is likely a mucous hyper-secreting phenotype of severe asthma with a tendency to have regional airway narrowing.[19] If this mucous plugging demonstrated by CT proves to be associated with NFO in subsequent studies, NFO measurement could be a simple way to identify this phenotype in the lung function lab. In adults with idiopathic bronchiectasis, NFO measurement may also be a helpful adjunct: if it is high, it might argue for a PCD diagnosis. However, these potential applications would certainly require further study.

Finally, distal airway $O_2$ tension is a piece of the complex puzzle of airway ecology. Direct[3,24–26] and indirect[25,27–30] measures have shown substantial differences in $O_2$ tension, $pCO_2$/pH and nitrogen oxide redox balance between control subjects, CF patients, asthma patients and PCD patients. Each of these groups' $O_2$, pH and nitrogen oxide levels, can affect, and be affected by the type of microbial colonization in an airway ecosystem.[8,11,15] Here, we show that the $pO_2$ in the distal airways may be low in asthma and CF, but not PCD. This observation raises several questions. First, is the asthmatic airway protected from infections (relative to CF) by having higher levels of nitrogen oxides or pH, or could there be anaerobic infections that exacerbate asthma, which have yet to be studied? Second, is bronchiectasis simply a condition caused by impaired mechanical clearance,[31] or does abnormal airway ecology behind a plug (low $pO_2$; low nitrogen oxide levels because of pulmonary or arterial circulation; low pH; alveolar flooding with uncleared mucus in PCD) contribute to an abnormal microbiome? Each of these possibilities would have therapeutic implications. Our NFO technique could help answer many of these questions.

The results of this study were limited by sample size. Fortunately, some subjects were able to perform the experimental procedure more consistently than others despite equal coaching and trials. The test proved reproducible, but future studies might be planned in which only measures within 10% of one another are accepted. Also, note that we did not have control childen, but the clear difference between results in asthma and PCD, despite similar ages, argues against age as a determinant of NFO values. This is the first study of its kind and is not a large population-based study: future research may expand on sample size.

In conclusion, using a noninvasive technique, we have demonstrated that the $O_2$ tension in the distal airways of patients with CF is significantly lower than in healthy subjects and PCD patients. Our findings raise questions regarding the physiology and airway ecology of CF and suggest new avenues of investigation. Furthermore, these results introduce the possibility of direct clinical application for this novel testing of NFO values in the evaluation of end expiratory $O_2$ tension for use in the management of CF patients.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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