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A Comparison of Nasal Nitric Oxide Measurement Modes

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Dear Editor

Nasal nitric oxide (nNO) is currently a recommended screening tool for primary ciliary dyskinesia (PCD), a rare disease with chronic sinupulmonary issues. Nasal NO levels are significantly lower in PCD compared to healthy controls[1], making it an ideal screening test. More recent publications suggest nNO can even be used in the diagnosis of PCD when paired with a consistent phenotype[2]. As with any testing method, standard protocols are necessary to achieve reliable results. We present an important issue related to nasal NO testing methods.

In an article entitled *Standardizing Nasal Nitric Oxide Measurement as a Test for Primary Ciliary Dyskinesia*, Leigh and colleagues present a standard operating procedure (SOP) for measuring nasal nitric oxide (nNO) using the Ecophysics CLD 88 SP measuring system (Dürnten, Switzerland) and establish a disease specific cut-off of < 77 nL/min, with a sensitivity of 0.98 and specificity of >0.999 for detecting PCD[1]. As part of this standard protocol, participants achieve palatal closure by exhaling through their mouth into a disposable cardboard resistor or party favor. This results in a steady state nNO sampling with a stable plateau value. During the measurement, gas is aspirated at a constant rate through a sampling line with a disposable foam olive inserted into one nostril at a time with the other nostril open to ambient air. An acceptable maneuver includes a 20 second exhalation with a steady NO plateau for 3–10 seconds using the "offline NO test" mode. The device operator observes the NO tracing in real-time and chooses an acceptable NO plateau based on set criteria. The operator directly measures the plateau value. The average concentration of nNO in parts per billion (ppb) is multiplied by the sampling flow rate (typically 0.33 L/min on the

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Ecophysics CLD 88 SP measuring system) to calculate the nNO production in nanoliters per minute (nL/min). Acceptable plateau values must be reproducible, with at least two measurements in each nostril within 10% of each other. Though this method uses “offline NO test” mode, the sample is collected and analyzed in real-time.

At our center, we perform nNO testing with the Ecophysics CLD 88 SP measuring system and the “offline” technique described by Leigh and colleagues. However, Ecophysics has recently developed “online” software for nNO testing that is interactive with the test subject using an incentive “smiley face” image on the screen to cue exhalation force and duration. This software is used with a flow head, versus a cardboard resistor, to provide resistance for palatal closure and the Denox 88 NO scrubber to provide NO-free air if needed. Using the automated software with this “online” method, the default setting for an acceptable NO plateau is 4 seconds with a 10% variance to satisfy the plateau requirements. Once these criteria are met, the software automatically stops the test, measures the plateau and moves on to the next maneuver.

The ATS/ERS guidelines for measurement of nNO in adults and children outline the importance of velum closure and a constant sampling flow rate from the nares[3], however do not further specify methods. These recommendations simply state “any method that reliably closes the velum is acceptable[3]”. Our objective was to evaluate if the Ecophysics flow head and “online” software provided similar nNO results compared to the cardboard resistor and “offline” protocol outlined by Leigh and colleagues. We hypothesized there would be no significant difference between the two methods as both achieve palatal closure.

IRB approval was obtained and consent signed prior to enrollment. Patients referred to Pediatric Pulmonology at Riley Hospital for Children for suspected PCD underwent nNO testing using the Eco Physics CLD 88 SP measuring system. Participants performed both “online” and “offline” nNO testing maneuvers and completed 3 accurate and reproducible measurements in each nare with each method. In the “online” method, the plateau was automatically measured by the software. In the “offline” method, the plateau was determined manually by the operator. In both modes, participants obtained at least a 3 second plateau, and the measurement in ppb was multiplied by the flow rate of 0.33L/min to obtain final nNO measurements in nL/min. Clinical data was collected by retrospective chart review. Statistical testing was conducted using SPSS Version 24. Nasal NO values were compared using Wilcoxon signed-rank test.

Fifty participants completed the two methods, 40% male, median age at testing 12.1 years (range 4.1–64.1). The most common presenting symptom was cough (76%), followed by nasal congestion (50%), sinusitis (46%) and pneumonia/bronchitis (46%). Of the group, 4 (8%) had definite PCD by ciliary ultrastructural defect, 6 (12%) had possible PCD (nNO <77nL/min and consistent phenotype) and the remaining 40 (80%) were classified as undefined/other diagnosis (TABLE I). Spirometric indices were calculated using GLI reference equations[4]. For “online” testing, median nNO was 170.9 nL/min (range 5.7–531.1) and for “offline” testing, median nNO was 184.5 nL/min (range 6.2–586.2), $p<0.0001$.

The difference between nNO measurements using the “online” nasal NO test mode and flow head compared to the “offline” NO test mode and cardboard resistor was statistically significant, with the “online” values being lower. The differences in these values may be because the “online” software default for an acceptable NO plateau is only 4 seconds with a 10% variance. Once these criteria are met, the software automatically stops the test. We found the “online” acquisition terminates after an average of 8.9 seconds (SD 2.2), which in our experience is too short to reach the maximum NO value. In the “offline” method, participants exhaled an average of 17.6 seconds (SD 5.7). With the “offline” method, participants exhale longer, allowing them to reach a full plateau and approach residual volume, which further minimizes dilution of nNO with airflow from the lower airways. Both methods use the same sampling flow rate and provide adequate mouth pressure for velum closure, and thus are likely not causing the difference we demonstrate.

Clinically, the difference in measured nNO levels with each method is quite important. For patients with nNO values near the suggested diagnostic cut-off of 77 nL/min, this difference in nNO values could lead to false positive results. Thus, the Genetic Disorders of Mucociliary Clearance Consortium (GDMCC) recommends using the “offline” method with the cardboard resistor in both adults and children[1]. Since the disease specific cutoff of 77 nL/min was also derived using the “offline” nNO measurement method, it seems prudent to continue using this methodology until studies validate a similar nNO cutoff value using the “online” method. This finding highlights the importance of using a standardized approach across centers, especially as more widespread use of nNO is performed for PCD diagnosis.

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TABLE I

Demographics

Demographics	**n=50**
Male	20 (40)
Age at testing (years)†	12.1 (4.1–64.1)
FEV_1 % predicted‡	91.7 (25.6)
FEV_1 z-score‡	−0.66 (2.1)
†Median (range), ‡Mean (SD)	
Presenting symptoms (most common findings)	
Cough	38 (76)
Daily cough	22 (58)
Nasal congestion	25 (50)
Pneumonia/bronchitis	23 (46)
Sinusitis	23 (46)
Rhinorrhea	17 (34)
Unresponsive asthma	17 (34)
Neonatal respiratory distress	9 (18)
Situs inversus totalis	5 (10)
Nasal ciliary biopsy	
Normal ultrastructure	11 (22)
Outer dynein arm defect	2 (4)
Central pair defect	2 (4)
PCD determination	
Confirmed PCD	4 (8)
Probable PCD	6 (12)
Other diagnosis/undefined	40 (80)

Values are mean (SD) or median (range) for continuous variables and frequency (%) for categorical variables