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Establishing normative nasal nitric oxide values in infants

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ABSTRACT

Introduction: Primary ciliary dyskinesia (PCD), a disease of impaired respiratory cilia motility, is often difficult to diagnose. Recent studies show low nasal nitric oxide (nNO) is closely linked to PCD, allowing the use of nNO measurement for PCD assessments. Nasal NO cutoff values for PCD are stratified by age, given nNO levels normally increase with age. However, normative values for nNO have not been established for infants less than 1 year old. In this study, we aim to establish normative values for nNO in infants and determine their utility in guiding infant PCD assessment.

Methods and results: We obtained 42 nNO values from infants less than 1 year old without a history of PCD or recurrent sinopulmonary disease. Using regression analysis, we estimated the mean age-adjusted nNO values and established a 95% prediction interval (PI) for normal nNO. Using these findings, we were able to show 14 of 15 infant PCD patients had abnormally low nNO with values below the 95% PI.

Conclusions: In this study we determined a regression model that best fits normative nNO values for infants less than 1 year old. This model identified the majority of PCD infants as having abnormally low nNO. These findings suggest nNO measurement can help guide PCD assessment in infants, and perhaps other pulmonary diseases with a link to low nNO. With early assessments, earlier clinical intervention may be possible to slow disease progression and help reduce pulmonary morbidity.

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1. Introduction

Primary ciliary dyskinesia (PCD) is a disease of impaired respiratory cilia motility causing mucociliary clearance defects and high morbidity from recurrent sinopulmonary disease [1,2]. Unfortunately, currently one-third of PCD patients are not identified until adulthood, and with unrecognized disease comes a high risk of recurrent pulmonary infections that ultimately can progress to irreparable chronic respiratory impairment [3]. The diagnosis of PCD can be complex, and often involves a combination of different types of assessments that may include nasal or bronchial biopsies for cilia motion evaluation utilizing video microscopy as well as cilia ultrastructure analysis by electron microscopy (EM). However, nasal biopsies can be uncomfortable for patients and they can have variable quality that is not always suitable for cilia motion or EM analysis. In addition, not all PCD patients exhibit abnormal EM cilia ultrastructure. Genetic testing is also now feasible for PCD diagnosis, as nearly 30 genes have been identified to cause PCD [4]. Despite this nearly 30% of patients undergoing genetic testing fail to have a PCD causing mutation identified [4].

More recently, the measurement of nasal nitric oxide (nNO) has been shown to be useful for PCD screening, as PCD patients are observed to have nNO levels that are only 10–20% of normal, healthy controls [5,6]. Nasal NO values are detectable in neonates within hours of being born and measurements are relatively easy to

Abbreviations: PCD, primary ciliary dyskinesia; EM, electron microscopy; nNO, nasal nitric oxide; CHP, Children's Hospital of Pittsburgh of UPMC; MRI, magnetic resonance imaging; ppb, part per billion; CNMC, Children's National Medical Center; PI, prediction interval; LPL, lower prediction limit; CHD, congenital heart disease; CED, cranioectodermal dysplasia; CF, cystic fibrosis.

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obtain, reproducible, and noninvasive [7–9]. Several nNO sampling methods exist whereby a small sampling cannula is placed just into the naris and the amount of nNO being produced by the nasal sinuses is analyzed [10]. Many of these methods require patient cooperation to exhale against a resistance or phonate to close the velum during sampling. However, quiet tidal breathing has been validated in younger children unable to cooperate [7,8,11]. Nasal NO values obtained by such tidal breath sampling has shown good reliability, sensitivity, and high within-subject repeatability [11–14].

As methods for nNO measurement have become standardized, and nNO cutoff values established and validated for PCD, nNO is becoming a useful screening tool for PCD assessments [6,13,15,16]. The PCD level nNO cutoff values are stratified by age, given nNO levels normally rise with age. However, there is very little data on infant nNO values except for a few case reports. This is despite the fact that approximately 75% of patients with PCD have a history of neonatal respiratory distress syndrome, suggesting the need for early diagnosis and early intervention to slow disease progression [17–19]. In this study, we investigate and show the feasibility of establishing normative nNO values in children less than 1 year of age to guide infant nNO assessments.

2. Methods

2.1. Patient recruitment

With Institutional Review Board approval, we enrolled infants and young children (ages 0–13 months) from the Children's Hospital of Pittsburgh (CHP) of UPMC. Infants were presenting on an outpatient basis for either evaluation for, or follow-up from general surgical procedures, outpatient surgical procedures, as patients presenting for MRI imaging, or as healthy volunteers (Supplemental Table 1). Infants were not eligible if they had a diagnosis of PCD or history, signs, or symptoms of recurrent or chronic sinopulmonary disease. Infants were excluded if their underlying diagnosis was consistent with a defect associated with abnormal nitric oxide levels or ciliary dysfunction. Late-preterm infants (defined as 34–37 weeks post-conceptual age) were enrolled, but infants born prior to 34 weeks post-conceptual age were excluded [20].

2.2. Data collection

With parental written informed consent, nNO values were acquired using a CLD 88sp NO analyzer (Eco Physics AG, Ann Arbor, Michigan) according to established protocols [21]. All values were obtained via low continuous sampling suction at a rate of 0.3 L/min from each naris using a nasal olive sampling cannula during tidal breathing. Five peak values from each naris during 50 s of tidal breathing were averaged to yield a final value in nl/min [22,23]. Values in nl/min are equal to values in parts per billion (ppb) multiplied by the sampling flow rate in L/min (with standard sampling flow rates recommended between 0.25 and 3 L/min) [21]. To ensure consistency, a single investigator (OK) collected all the nNO values at CHP. Additional values were obtained from subjects using the same inclusion criteria and identical methods in a previous study at the Children's National Medical Center (CNMC) in Washington, D.C. (collected by coauthor LL).

2.3. Statistical analysis

The nNO values plotted against ages demonstrated increased variability with the larger nNO values in the older infants. Therefore, we applied a log transformation to the nNO values to normalize the distribution and then performed a regression analysis. A quadratic age effect was included in the model to explore the possible nonlinear age trend. The regression model coefficients were calculated by the least squares method and the associated prediction interval (PI) was generated to obtain the plausible nNO values from this study population. Statistical analysis was performed using the R statistical software, version 3.1.2.

3. Results

A total of 42 values were used in this study (Table 1). Ten of the 42 values were from CNMC, with the remaining 32 values obtained from CHP. Ages ranged from 8 to 459 days old (mean 151, median 91) and nNO values from 9.9 nl/min to 96.3 nl/min (mean 38.7 nl/min, median 30.6 nl/min) (Table 1). CHP patient characteristics included 19/32 males (59%) and 27/32 Caucasians (84%) (Supplemental Table 1). No patients had a diagnosis of PCD, cystic fibrosis, or situs abnormalities/heterotaxy.

The regression analysis showed that the quadratic age term was statistically significant ($p = 0.025$ using an F-test), suggesting a quadratic relationship between nNO and age. Thus, the nNO values increase more rapidly between 0 and 6 months of age, compared to 6–12 months of age. The log-transformation nNO values were

Table 1
Infant nNO values (CHP, CNMC).

# of values	Origin of value	Age (d)	nNO (nl/min)
1	CNMC	8	10.2
2	CNMC	10	9.9
3	CNMC	15	19.9
4	CNMC	18	18.6
5	CNMC	23	13.8
6	CNMC	24	11.7
7	CHP	24	19.0
8	CHP	30	13.4
9	CHP	36	23.5
10	CHP	41	16.6
11	CHP	47	23.5
12	CNMC	53	22.2
13	CHP	58	19.8
14	CHP	63	23.5
15	CHP	64	40.9
16	CHP	65	19.6
17	CHP	81	18.7
18	CHP	82	30.5
19	CHP	88	27.9
20	CNMC	90	23.1
21	CHP	91	34.1
22	CHP	91	48.5
23	CHP	98	23.9
24	CNMC	150	32.8
25	CHP	158	38.6
26	CHP	169	67.5
27	CHP	187	78.0
28	CHP	190	52.2
29	CHP	227	39
30	CHP	238	30.6
31	CHP	247	60.4
32	CHP	262	37.7
33	CHP	267	90.0
34	CNMC	270	33.4
35	CHP	283	75.9
36	CHP	301	30.4
37	CHP	322	42.3
38	CHP	335	69.5
39	CHP	343	77.7
40	CHP	364	81.5
41	CHP	373	79.1
42	CHP	459	96.3

Infant nNO values and ages obtained from Children's Hospital of Pittsburgh of UPMC (CHP) and Children's National Medical Center (CNMC).

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