Correlation between Nasal Symptoms and Nasal Nitric Oxide at Baseline and while Humming

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Abstract: *Background*: Chronic rhinosinusitis (CRS) is important in asthma and chronic cough assessment. An accurate diagnosis of CRS based solely on symptoms and nasal endoscopy can be difficult. Sinus CT-imaging is usually recommended in patients with negative rhinoscopy. Nasal nitric oxide (nNO) levels obtained passively and while humming are decreased in sinusitis due to ostiomeatal complex blockage of paranasal sinus gas exchange by inflamed tissue. A nNO measurement is a potential point-of-care test (POCT) for CRS. The SinoNasal Outcome Test (SNOT-20) is a clinical tool to assess symptoms in CRS.

Objective: To evaluate if nNO levels provided objective information about CRS that would correlate with individual elements in the SNOT-20 and 6 additional CRS related symptoms. To examine these 26 symptom parameters for related clusters, and test correlation of the clusters with nNO measurements.

Methods: In 180 patients, basal and humming nNO level measurements, and 26 symptoms (SNOT-20 plus 6 added items) were collected. Hierarchical cluster analysis was applied to sort the data into clusters.

Results: The 26 questions grouped into 5 different clusters. 2 clusters contained questions that were most disease specific for sinonasal diseases in patients referred for subspecialty asthma and chronic cough evaluation. We demonstrated that nNO levels during humming, and the ratio between humming and basal nNO, correlated best with clusters 2 and 4.

Conclusion: Baseline and humming nNO measurements provide objective information about CRS. nNO measurements offers the potential of a POCT for objective assessment of CRS in patients presenting to a pulmonary clinic.

Keywords: Humming nitric oxide, Nasal biomarker, Nasal nitric oxide, SNOT-20 questionnaire, Nasal symptoms.

INTRODUCTION

Chronic rhinosinusitis (CRS) is a common disease that complicates the care of patients with asthma and chronic cough. It increases the risk of asthma exacerbations and hospitalizations. However, despite its frequent co-existence with asthma, clinical diagnosis at the point-of-care remains challenging [1]. While guidelines recommend screening for rhinitis and sinusitis in patients with asthma and chronic cough, the best way to accomplish this is unclear. In routine clinical practice, most providers base their diagnoses on clinical criteria, and order imaging sinus studies only when patients do not respond to treatment. Even with endoscopy, the diagnostic accuracy without sinus CT-imaging in patients without prior sinus surgery is <50% [2]. The expense, delay in definitive diagnosis, and potential for harm with antibiotics and corticosteroids argue for improving diagnosis with point of care testing (POCT); an example of which is office-based sinus CT-imaging.

One of the main problems confronting clinicians is that some of the symptoms assessed for diagnosing CRS do not correlate with objective findings [3, 4]. Office examination of the nasal passageway in non-ENT clinics is often limited to inspection of the immediate area of the nasal vestibule and nasal valve area with an otoscope and without the added benefit of decongestion; and flexible fiberoptic rhinoscopy has a <50% sensitivity in patients presenting with typical symptoms without prior sinus surgery [2]. Even in the post-operative setting, symptoms, endoscopies, and sinus CTs do not always track each other but rather provide complementary information [5]. Often times, a sinus CT scan test is required [6]. Concern has been raised about radiation exposure, serial tests, risk for children, and increasing health care costs from CT scans. In management of CRS as a chronic disease, serial sinus CTs during follow-up, diagnosis of recurrence, and assessing treatment outcomes is problematic.

Recently, the measurement of nasal nitric oxide (nNO), passively and during humming, was suggested as a possible screening tool for sinus disease [7]. The biological gas NO is produced mostly by the upper respiratory tract, in particular by the paranasal sinuses. It has been shown that patients with acute rhinosinusitis, nasal polyposis, cystic fibrosis, and primary ciliary dyskinesia have decreased levels of

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nNO [8-15]. An interesting physiological characteristic of nNO is that in healthy patients nNO levels increase dramatically while humming [16, 17]. This spike is thought to be the result of rapid gas exchange during humming between the paranasal sinus and the nasal cavity [18]. Therefore, a nNO measurement, taken while a patient is humming, has been considered an indirect marker for sinus ostium permeability. Recent studies have shown that patients with an obstructed ostiomeatal complex, including those with cystic fibrosis, nasal polyposis, and sinusitis, have decreased levels of humming nNO, compared with healthy controls [17, 19, 20]. Additionally, one of these studies indicated that the absence of an nNO peak during humming was associated with endoscopic findings suggestive of sinus ostial obstruction in patients with allergic rhinitis [19]. Nasal NO is measured by non-invasive techniques, which are less expensive than current diagnostic procedures.

Several questionnaires have been developed to screen and monitor patients with possible rhinitis and CRS [21]. One of the validated questionnaires in clinical use is the Sino-Nasal Outcome Test 20 (SNOT-20) [22, 23]. This instrument measures 4 domains with psychological function, sleep function, rhinological symptoms, and ear and/or facial symptoms [23, 24]. The score ranks the severity of the disease/symptoms. The SNOT-22 was developed to include 2 of the most important CRS symptoms, olfaction and nasal obstruction [24]. In order to have the most comprehensive assessment of potentially relevant symptoms, we assessed patients with the 22 questions in the validated SNOT-22 and added 4 questions from previous Otorhinolaryngology and Allergy Academy guidelines [8]. This resulted in 26 questions that all of the patients were asked to answer.

Prior to 2007, the diagnosis of CRS was made on the basis of symptoms. Since there was appreciable overlap of positive symptoms in patients without sinus inflammation, since 2007 the diagnosis of CRS also requires objective evidence of sinus inflammation with CT or endoscopy [25].

Some of the symptoms (e.g. olfaction, obstruction, drainage) have been found to more strongly correlate with the presence of inflammation of the sinuses (confirmed with CT) than others [26-28]. nNO measurements are another objective parameter that can reflect inflammation of the sinuses. There has not been a study of the relative strength of correlation of individual symptoms or symptom clusters with nNO measurement results. The purpose of this study is to evaluate whether nNO measurements also correlated with particular symptoms or symptom clusters (the same as found in the above studies), suggesting that these symptoms and the corresponding nNO measurement indicated the presence of sinus inflammation. If that was the case, this would support further studies to explore the use of nNO as an additional objective parameter option for assessment of the presence of CRS.

METHODS

Study Design

This is a retrospective study of consecutive patients referred for a fractional exhaled NO (FeNO) determination between May and October 2009. Only data from patients with research authorization on file was included in the analysis. The study was approved and performed in accordance with Mayo Clinic's Institutional Review Board. Electronic medical records were abstracted for demographic and clinical information.

Measurement of Nasal NO

The measurement of nNO output was performed according to the 1999 ATS/ERS recommendation with a Sievers Nitric Oxide Analyzer (NOA; Boulder, CO, USA). As per protocol for FeNO measurements, patients were instructed not to take any metered-dose inhalers or nebulizer-inhaled treatments within six hours of the scheduled appointment; to avoid food or alcoholic beverages two hours prior to testing and to avoid smoking and strenuous exercise for at least one hour prior to testing.

In brief, airflow through the nasal cavities was achieved by aspirating 50 ml/sec of air *via* one naris while the velum (soft palate) was closed. To close the velum, the patients exhaled through the oral device for measuring exhaled NO, thereby providing resistance and closing the soft palate. The sampling line was connected *via* the side port of a three way stopcock. The nasal cavities are aligned in series since air circulates from one naris to the other around the posterior nasal septum. The key element is the establishment of a constant transnasal flow rate to produce a washout phase followed by the establishment of a steady NO plateau seen in the profile of NO concentration in time. A nasal olive threaded with a catheter in the middle was used to

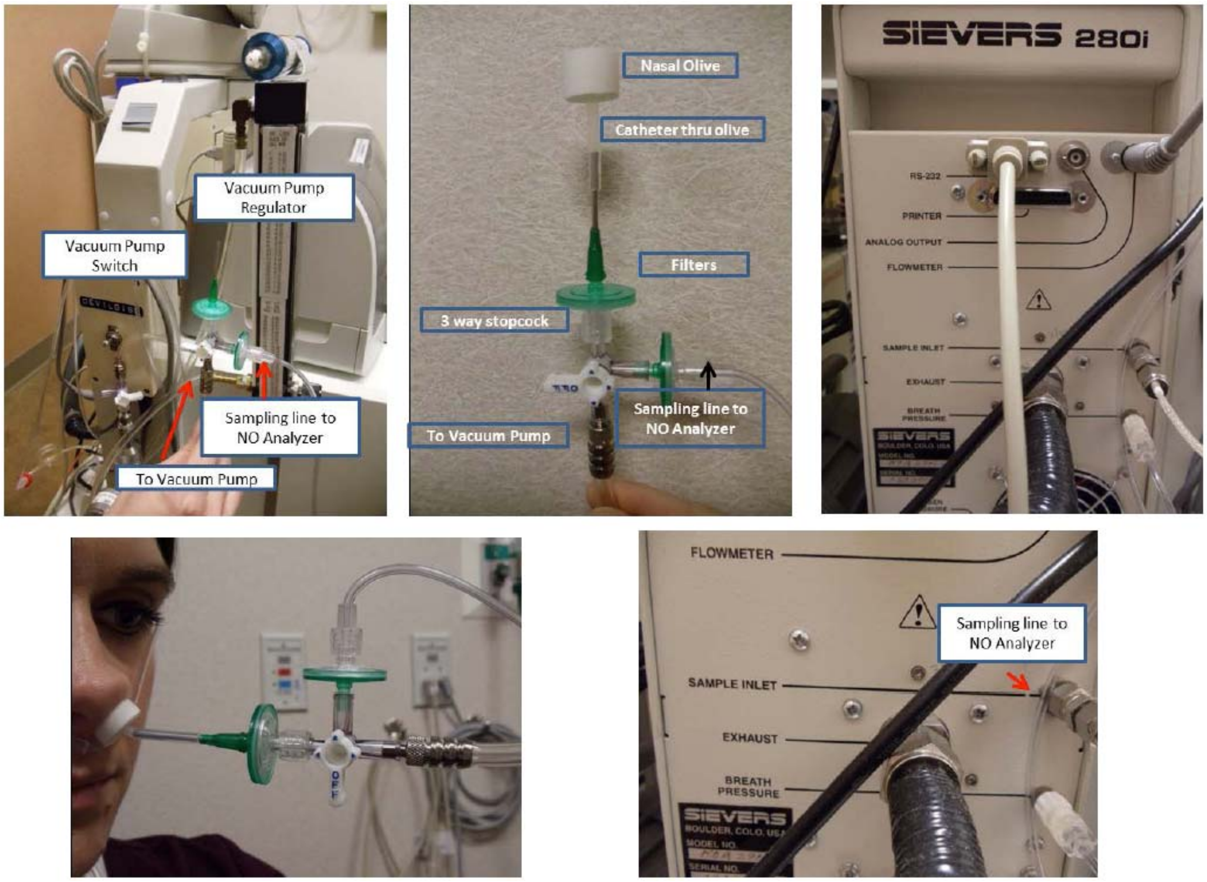

Figure 1: nNO set up.

One nasal olive with a central lumen is securely placed in one of the nares. An aspirating catheter is thread through the nasal olive and used to aspirate air from the nasal passage. Nitric oxide-free oxygen is provided to the other nares at 2L/min *via* nasal cannula and allowed to entrain air. The subject is seated and instructed on how to use a mouthpiece attached to a resistor. The subject inhales to total lung capacity, and exhales against expiratory resistance to close the velum. Concurrently, air from the nasal passages is aspirated at a constant 50 ml/s flow *via* the nasal olive by a suction pump. A three-way stopcock with filters attached is used to allow sampling of the aspirated air *via* a side port for the nNO analysis.

occlude one of the nostrils. The catheter was connected to a DeVilbiss vacuum pump set at 50 ml/sec. If the gauge was unable to maintain 50 ml/sec, the measurements were stopped, as this would be uncomfortable and indicated that the patient was too congested to be measured. Nitric oxide-free oxygen was provided to the contralateral nares *via* nasal cannula with one of the prongs left outside the nostrils (Figure **1**).

Measurement of Humming NO

After measurement of baseline nNO, the patients waited 4 minutes before beginning the humming portion of testing. The patients were instructed not to talk during the waiting period as the data can be affected significantly. During the waiting period, the nasal olive was disconnected from the sampling line to decrease condensation in the tubing. The contralateral naris continued to have NO-free oxygen *via* nasal cannula. After 4 minutes, the sample line was reconnected and patients were instructed to take a deep breath in and hum as long as they could. We ensured that patients sat quietly for 4 minutes before they performed additional humming maneuvers. To be acceptable, the data from at least 2 maneuvers had to be within 10% of each other.

Symptom Questionnaire

Nasal symptoms were assessed using a questionnaire which included the 20 questions of the SNOT-20, the 2 additional questions that were added in the SNOT-22, and 4 additional questions used by the Academies of Otorhinolaryngology and Allergy (Figure **2**) [8]. After the NO testing, patients were given the questionnaire to complete. Patients rated the severity of the 26 symptoms or social /emotional consequences of their CRS on a scale of 0 to 5, with 0 representing no problem, 1 representing a very mild problem, 2

Considering how severe the problem is when you experience it and how frequently it happens, please note each item below by marking an "X" in the column that best corresponds with how you are feeling.	No Problem	Very Mild Problem	Mild or Slight Problem	Moderate Problem	Severe Problem	Problem as Bad as it Can Be
	0	1	2	3	4	5
1. Need to Blow Nose						
2. Sneezing						
3. Runny Nose						
4. Cough						
5. Post-nasal Discharge						
6. Thick Nasal Discharge						
7. Ear Fullness						
8. Dizziness						
9. Ear Pain						
10. Facial Pain Pressure						
11. Difficulty Falling Asleep						
12. Wake Up at Night						
13. Lack of a Good Night's Sleep						
14. Wake up Tired						
15. Fatigue						
16. Reduced Productivity						
17. Reduced Concentration						
18. Frustrated/Restless/Irritable						
19. Sad						
20. Embarrassed						
21. Fever						
22. Nasal Obstruction/Blockage/Congestion						
23. Headache						
24. Decreased Sense of Smell						
25. Bad Breath (Halitosis)						
26. Dental Pain						

Figure 2: The 26-Symptom Questionnaire.

Our modified SNOT-20 questionnaire includes 6 additional questions (numbered 21 through 26) for the diagnosis of sinusitis. The 26-symptom questionnaire scores range from 0-5, with higher scores indicating a greater problem, as perceived by the patient. The total score is calculated as the mean item score for all 26 items.

representing a mild or slight problem, 3 representing a moderate problem, 4 representing a severe problem and 5 representing a problem as bad as it can be.

Statistical Analysis

The individual symptom scores were calculated as the mean among non-missing items, with higher scores indicating a greater severity. Hierarchical cluster analysis was used to place the 26 items into groups or clusters suggested by the data so that items in the same cluster were similar to each other and items in different clusters were dissimilar from each other. The assignment of items to clusters was performed by nearest component sorting, using alternating least-squares, and was restricted so that the clusters maintained a hierarchical tree structure. Total cluster scores were calculated as the mean among items contained in that cluster. A total symptom score was calculated as the mean for all of the 26 item scores.

Correlations between the individual symptom scores, cluster scores, and total score compared to age, gender, and nNO levels were evaluated using Wilcoxon rank sum tests and Spearman rank correlation coefficients. Spearman rank correlation coefficients can range from -1 to +1. The closer the correlation is to either of these extremes, the stronger the correlation between two continuous variables. Correlations close to 0 indicate weak correlations between two continuous variables. Positive (+) correlations indicate that the two variables tend to change in the same direction (e.g., when one variable increases, the other variable increases). Negative (-) correlations indicate that the two variables tend to change in opposite directions (e.g., when one variable increases, the other decreases). Statistical analyses were performed using the SAS software package (SAS Institute; Cary, NC) and p-values <0.05 were considered statistically significant.

RESULTS

Of the 180 patients who were referred for FeNO determination, 105 (58%) were females and 75 (42%) were males. The mean age was 57.1 years (median 58; range 20 – 90). Fifteen (8%) of the 180 patients had a prior clinical diagnosis of CRS. Responses to the 26 symptom items are summarized in Table **1**. The mean total symptom score was 1.21 (median 1.08; range 0 – 3.65). Eleven patients were missing a response to one item, four patients were missing a

Table 1: Summary of 26-Symptom Questionnaire Test for 180 Patients[a]

Symptom	Severity – Frequency (%)					
	0	1	2	3	4	5
Need to blow nose	64 (36)	38 (21)	38 (21)	32 (18)	7 (4)	1 (1)
Sneezing	72 (40)	53 (29)	24 (13)	24 (13)	5 (3)	2 (1)
Runny nose (*N=179*)	62 (35)	50 (28)	30 (17)	22 (12)	14 (8)	1 (1)
Cough (*N=178*)	33 (19)	19 (11)	31 (17)	36 (20)	37 (21)	22 (12)
Post-nasal discharge (*N=175*)	62 (35)	34 (19)	30 (17)	28 (16)	17 (10)	4 (2)
Thick nasal discharge (*N=179*)	94 (53)	31 (17)	27 (15)	14 (8)	12 (7)	1 (1)
Ear fullness (*N=179*)	97 (54)	28 (16)	29 (16)	19 (11)	6 (3)	0
Dizziness (*N=179*)	105 (59)	32 (18)	17 (10)	13 (7)	11 (6)	1 (1)
Ear pain	139 (77)	18 (10)	16 (9)	6 (3)	1 (1)	0
Facial pain pressure (*N=179*)	120 (67)	26 (15)	16 (9)	14 (8)	3 (2)	0
Difficulty falling asleep	75 (42)	22 (12)	22 (12)	41 (23)	14 (8)	6 (3)
Wake up at night (*N=179*)	42 (23)	31 (17)	24 (13)	44 (25)	29 (16)	9 (5)
Lack of a good night's sleep	46 (26)	33 (18)	24 (13)	32 (18)	36 (20)	9 (5)
Wake up tired	44 (24)	34 (19)	27 (15)	38 (21)	27 (15)	10 (6)
Fatigue (*N=179*)	43 (24)	27 (15)	32 (18)	36 (20)	30 (17)	11 (6)
Reduced productivity (*N=178*)	53 (30)	36 (20)	28 (16)	31 (17)	23 (13)	7 (4)
Reduced concentration (*N=179*)	73 (41)	36 (20)	29 (16)	23 (13)	15 (8)	3 (2)
Frustrated (*N=179*)	68 (38)	47 (26)	25 (14)	21 (12)	14 (8)	4 (2)
Sad	115 (64)	30 (17)	16 (9)	8 (4)	9 (5)	2 (1)
Embarrassed	131 (73)	28 (16)	7 (4)	9 (5)	4 (2)	1 (1)
Fever	157 (87)	15 (8)	5 (3)	3 (2)	0	0
Nasal obstruction	73 (41)	28 (16)	32 (18)	32 (18)	13 (7)	2 (1)
Headache (*N=179*)	90 (50)	46 (26)	16 (9)	17 (10)	7 (4)	3 (2)
Decreased sense of smell	102 (57)	30 (17)	18 (9)	16 (4)	7 (4)	7 (4)
Bad breath (*N=177*)	113 (64)	32 (18)	23 (13)	7 (4)	1 (1)	1 (1)
Dental pain	129 (72)	32 (18)	11 (6)	7 (4)	1 (1)	0

[a]Sixteen patients chose not to respond to every symptom.

response to two items and one patient was missing a response to three items.

Hierarchical Cluster Analysis of the 26 Symptom Items Yielded 5 Clusters

The hierarchical cluster analysis grouped the 26 symptom items into 5 clusters. Cluster 1 (labeled the sleep domain) included the following items; difficulty falling asleep, wake up at night, lack of a good night's sleep, wake up tired and fatigue. Cluster 2 (rhinological domain) included; need to blow nose, runny nose, post-nasal discharge, thick nasal discharge, nasal obstruction, and decreased sense of smell. Cluster 3 (Irritation/Reflex domain) included sneezing, cough, and bad breath. Cluster 4 (Ear/facial/dental fullness/pressure) included symptoms of ear fullness, ear pain, facial pain pressure, headache and dental pain. The psychosocial domain, or Cluster 5, symptoms included dizziness, reduced productivity, reduced concentration, frustrated, sad, embarrassed, and fever. The two squared correlations for each cluster are summarized in Table **2**. The first correlation is the squared correlation of the item listed with its own cluster (Own R^2). A higher Own R^2 value indicates a

Table 2: Results of Hierarchical Cluster Analysis of the 26-Symptom Questionnaire Items

Cluster 1	**Own R2***	**Next R2****
Difficulty falling asleep	0.70	0.26
Wake up at night	0.82	0.28
Lack of a good night's sleep	0.89	0.35
Wake up tired	0.85	0.42
Fatigue	0.68	0.50
Cluster 2		
Need to blow nose	0.70	0.23
Runny nose	0.61	0.27
Post-nasal discharge	0.72	0.19
Thick nasal discharge	0.67	0.16
Nasal obstruction	0.55	0.25
Decreased sense of smell	0.26	0.10
Cluster 3		
Sneezing	0.70	0.18
Cough	0.52	0.21
Bad breath	0.36	0.09
Cluster 4		
Ear fullness	0.56	0.22
Ear pain	0.71	0.13
Facial pain pressure	0.62	0.21
Headache	0.52	0.25
Dental pain	0.24	0.06
Cluster 5		
Dizziness	0.38	0.17
Reduced productivity	0.56	0.35
Reduced concentration	0.73	0.33
Frustrated	0.74	0.39
Sad	0.52	0.17
Embarrassed	0.42	0.11
Fever	0.19	0.12

***Own R2 is the** squared correlation of the item listed within its own cluster. The higher Own R^2 value indicates a stronger correlation of an item with other items in its cluster.
****Next R2** is the highest squared correlation with the next closest cluster. Lower Next R^2 values indicate that clusters are well-separated.

stronger correlation of an item with other items in its cluster. The second correlation is the highest squared correlation with the next closest cluster (Next R^2). Lower Next R^2 values indicate that clusters are well-separated.

Examining the Composition of within each Cluster as well as the Differences between Clusters

For all 26 symptom items, the Own R^2 values were higher than the Next R^2 values. Fever had the lowest squared correlation with its own cluster (0.19), along with a low squared correlation with the next closest cluster (0.12).

Examining the Importance of Individual Symptom Scores and Correlating Age and Gender with Cluster Scores and Total Symptom Score

In order to gauge the contribution of available parameters that would not be expected to reflect the degree of sinus inflammation, we checked for correlations of patient age and gender with the individual symptom cluster scores and total symptom score. These are summarized in a-Table **1** (appendix). The total scores from clusters 1 and 4 were significantly negatively correlated with age. For example, as age increased, scores associated with ear fullness and pain decreased (Spearman rank correlation coefficient -0.20; p=0.008). Cluster 1 scores were also significantly associated with patient gender. Females had higher scores associated with fatigue compared with males (median cluster 1 scores of 2.20 and 1.40, respectively; p=0.013).

NO Levels and Patient Age and Gender

Among the 180 patients studied, the mean baseline nNO level was 220.8 (median 217; range 24 – 532), the mean humming nNO level was 1529.1 (median 1250.5; range 28 – 7681) and the mean humming-to-baseline nNO ratio was 7.5 (median 5.2; range 0.6 – 165.6). Associations of patient characteristics with nNO levels are summarized in a-Table **2**. Humming nNO and humming-to-baseline nNO ratios were significantly negatively correlated with age. For example, as age increased, humming-to-baseline nNO ratio decreased.

Correlating nNO, a Nasal Biomarker, with the 26 Symptoms, 5 Clusters, and Total Symptom Score

Scores for correlation of the 26 individual symptom items, the clusters scores and the total symptom score with nNO levels are summarized in Table **3**. The symptoms of post-nasal discharge, thick nasal discharge, and decreased sense of smell were significantly, although weakly, negatively correlated with the three nNO measurements (baseline nNO, humming nNO and the ratio between the two). The cluster 2 total score, which contains these three symptoms, and nasal obstruction (which correlated with humming and ratio nNO) was similarly negatively correlated with humming nNO levels and the ratio between humming and baseline nNO. Additionally, we saw that ear fullness (in Cluster 4) was negatively correlated with two of the nNO measurements (humming nNO and the humming-to-baseline ratio). Though this was the only single item in cluster 4 that correlated with nNO, the total cluster 4 score also correlated with the same nNO measurements. Finally, the total score for the 26 symptoms was found to negatively correlate with humming nNO and the humming-to-baseline ratio, with a p-value of <0.05.

DISCUSSION

Our study showed that nNO measurements correlated with certain symptoms and cluster, but not all of the symptoms and clusters that have been used to assess CRS. In our study [26], that included reporting the symptoms that changed the most with successful quieting of the inflammation of CRS by a systemic steroid, it is interesting that 3 symptoms that changed the most were olfaction, nasal obstruction, and nasal drainage, all included in the 4 best of the significant, though weak, correlates in Cluster 2. The presence of correlation of nNO (baseline, humming, and ratio) with these parameters over the others suggests that it shows potential as an objective assessment of the presence of sinus mucosal inflammation. Nasal NO has been shown to be altered in patients with sinus disease such as allergic rhinitis, sinusitis, cystic fibrosis and primary ciliary dyskinesia [10, 29-32]. Additionally, it is known that nNO increases several fold with humming: a consequence of the oscillating sound waves produced during this maneuver resulting in an increase exchange of NO from the sinuses to the nasal cavity [16, 18, 33, 34]. In the presence of sinus disease confirmed by sinus CT there is a decrease of the humming nNO peak, suggesting that this test may be helpful for clinical use in the diagnosis of CRS disease. Additionally, recent data suggests that humming nNO increases after 2 weeks of oral steroid therapy in patients with CRS with nasal polyposis [35]. As a POCT, nNO measurements are inexpensive and minimally invasive with the potential to increase diagnostic accuracy in sino-nasal disease.

Table 3: Associations of Nasal Symptoms with nNO Levels

	Baseline	Humming	Ratio
	Spearman Rank Correlation Coefficient		
Cluster 1 score	**+0.06**	**-0.08**	**-0.11**
Difficulty falling asleep	-0.02	-0.10	-0.10
Wake up at night	+0.02	-0.05	-0.06
Lack of a good night's sleep	+0.04	-0.05	-0.07
Wake up tired	+0.08	-0.06	-0.10
Fatigue	+0.09	-0.11	-0.15*
Cluster 2 score	**-0.14**	**-0.21***	**-0.20***
Need to blow nose	-0.12	-0.07	-0.05
Runny nose	-0.12	-0.09	-0.07
Post-nasal discharge	-0.15*	-0.24*	-0.24*
Thick nasal discharge	-0.16*	-0.21*	-0.19*
Nasal obstruction	+0.02	-0.20*	-0.23*
Decreased sense of smell	-0.18*	-0.17*	-0.15*
Cluster 3 score	**+0.04**	**-0.11**	**-0.12**
Sneezing	+0.06	-0.00	-0.02
Cough	+0.03	-0.14	-0.16*
Bad breath	-0.05	-0.08	-0.06
Cluster 4 score	**-0.03**	**-0.16***	**-0.17***
Ear fullness	+0.04	-0.16*	-0.20*
Ear pain	+0.03	-0.08	-0.10
Facial pain pressure	-0.12	-0.14	-0.13
Headache	+0.04	-0.06	-0.07
Dental pain	+0.00	-0.05	-0.04
Cluster 5 score	**+0.11**	**-0.09**	**-0.14**
Dizziness	+0.03	-0.02	-0.04
Reduced productivity	+0.10	-0.12	-0.17*
Reduced concentration	+0.08	-0.07	-0.10
Frustrated	+0.11	+0.00	-0.05
Sad	+0.11	-0.07	-0.11
Embarrassed	+0.11	-0.00	-0.03
Fever	-0.02	-0.07	-0.06
Total 26-Questionnaire score	**-0.01**	**-0.18***	**-0.20***

*$p<0.05$.

The hierarchical cluster analysis of the 26 symptoms was able to group the different symptoms into five distinct clusters. The symptoms clustered reflecting domains in the area of Sleep, Rhinological, Irritation/Reflex, Fullness or pressure from Ear/Facial/Dental and Psychosocial. All clusters were well separated among each and at the same time they had a strong correlation within the symptoms of the same cluster. There were only a few exceptions in which the correlation within their group was not as strong; fever being the one with the least correlation within its group.

One would not expect age or gender to cause a difference in symptom domain or total symptom scores as noted by the lack of correlation between total symptom score and age or gender. However, when the score of each of the clusters was compared with age and gender, we found that Clusters 1 (Sleep domain) and 4 (Fullness of Pressure from Ear/Facial/Dental) correlated negatively with age. For instance, the older the individuals, the less likely that they will give a higher score for CRS causing sleep or pain issues. While the importance of these findings needs to be further evaluated, these observations may become important when trying to diagnose patients with sino-nasal disease in the office, as the response to questions about the effect of their condition on symptoms of pain or sleep may not accurately reflect the severity of the real disease. Additionally, it was also noticed that Cluster 1 (Sleep domain) was negatively correlated with gender, with females reporting higher scores for effect of their condition in causing fatigue than males. Again, this may be indicative that for certain symptom domains, age or gender could affect the results. Cluster 2, which had the multiple correlates with nNO, did not reflect such an effect from age or gender.

In our study, the rhinologic symptom cluster (Cluster 2) showed the stronger correlation with nNO levels, particularly while humming and when the ratio between humming to baseline was calculated. Interestingly, the symptoms of post-nasal discharge, thick nasal discharge, decrease sense of smell and nasal obstruction (cluster 2) negatively correlated with at least 2 nNO measurements. In Cluster 4, the single symptom of ear fullness, also negatively correlated with two of the parameters (humming nNO and the baseline-to-humming ratio) and this apparently brought the overall cluster score to a significant level of correlation with nNO. This data could indicate that Cluster 2 symptoms and ear fullness best reflect the presence of inflammation in sinus tissues. If that is the case, then these symptoms, combined with the other significant correlates of fatigue, cough, and reduced productivity (isolated symptoms from Clusters 1, 3, and 5 respectively) may be the most useful, combined with objective parameters such as nNO measurement (especially with humming and humming over basal nNO levels) as tools for screening for the diagnosis of CRS.

Levels of nNO while humming as well as the ratio of humming versus basal nNO may be a less expensive, low risk, objective tool for the diagnosis of CRS. It could be an alternative or supplement to CT scanning or endoscopic procedures. In our study, we have shown that some of the patient-reported symptoms may vary depending upon gender and age, providing further evidence that a broad compilation of symptoms may not be the optimal tool for assessing the presence of sinus inflammation. While further prospective studies are needed to evaluate and validate the use of nNO levels in the diagnosis of sino-nasal disease, our study provides further evidence of the potential usefulness of this additional objective test for the diagnosis of CRS.

Ultimately, the optimum role for the objective parameters of nNO, CT, endoscopy, tests on nasal secretions and tissue, will be found. Objective assessment, combined with the strongest subjective symptom correlates can further refine the diagnosis of CRS as well as the assessment of response to treatment.

CONCLUSIONS

Measurement of nNO levels while humming and the ratio of humming versus basal nNO provide objective information about CRS. The combination of these nNO measurements with some of the symptoms and clusters analyzed here may enhance the diagnostic accuracy of CRS and minimize the use of other more invasive and expensive tests. Therefore, nNO measurement offers the potential of a point-of-care test for objective assessment of CRS in patients presenting to a pulmonary clinic.

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SUPPLEMENTAL MATERIALS

The supplemental materials can be downloaded from the journal website along with the article.

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