



Published in final edited form as:

*Otolaryngol Head Neck Surg.* 2015 July ; 153(1): 88–93. doi:10.1177/0194599815581832.

## Prevalence and Severity of Dysphonia in Patients with Cystic Fibrosis: A Pilot Study

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### Abstract

**Objective**—To assess the prevalence and severity of dysphonia in patients with cystic fibrosis sinusitis. We hypothesized that patients with CF sinusitis, compared with 2 control groups, would have higher self-reported prevalence of dysphonia and greater severity of dysphonia, according to patient-reported outcome measures as well as auditory-perceptual evaluation by expert listeners.

**Study Design**—Cross-sectional comparative pilot study.

**Setting**—Academic tertiary care clinic.

**Study Participants and Methods**—Analysis included 37 study participants: 17 patients with CF sinusitis, 10 healthy individuals, and 10 patients with non-CF sinusitis. All participants completed the 10-item Voice Handicap Index (VHI-10) questionnaire and provided voice samples. On all samples, 6 blinded speech-language pathologists independently performed auditory-perceptual evaluation, using Consensus Auditory-Perceptual Evaluation of Voice. To assess severity of sinonasal symptoms, we used the 20-item Sinonasal Outcome Test (SNOT-20). Standard parametric and nonparametric statistical analysis was performed.

**Results**—The differences between the 3 groups in prevalence of abnormal VHI-10 scores were not statistically significant. SNOT-20 scores were similar in the 2 sinusitis patient groups. VHI-10 scores were highest in patients with CF sinusitis, intermediate in patients with non-CF sinusitis, and lowest in healthy individuals ( $P = .005$ ). Auditory-perceptual evaluation demonstrated greater overall severity of dysphonia in patients with CF sinusitis compared with the 2 control groups ( $P = .0005$ ).

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This article was presented at the 2014 AAO-HNSF Annual Meeting & OTO EXPO; September 21–24, 2014; Orlando, Florida.

### Author Contributions

**John Willis**, study design, data acquisition, analysis, and interpretation, draft and critical revision of manuscript, final approval; **Deirdre D. Michael**, study design, data acquisition, analysis, and interpretation, critical revision of manuscript, final approval; **Holly Boyer**, study design, data interpretation, critical revision of manuscript, final approval; **Stephanie Misono**, study conception, design, data analysis and interpretation, draft and critical revision of manuscript, final approval.

### Disclosures

**Competing interests:** None.

**Conclusions**—Cystic fibrosis sinusitis appeared to be associated with worse vocal function as measured by patient self-report as well as auditory-perceptual evaluation of voice compared with patients with non-CF sinusitis and healthy controls. Further investigation in this area is warranted.

### Keywords

dysphonia; cystic fibrosis; sinusitis; chronic sinusitis; voice handicap; auditory-perceptual

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In the United States, cystic fibrosis (CF), an autosomal recessive disease, affects about 1 in 3200 whites and is the most common fatal hereditary disorder in that group. The disease results from a defective chloride ion transporter, the CF transmembrane conductance regulator (CFTR). The movement of chloride ions across cell membranes is an important regulator of intracellular water transport. In CF, exocrine glands in the upper airway are affected, resulting in reduced chloride and water flux outside of the cell. This reduction causes abnormally thick mucus, inadequate epithelial hydration, and subsequent tissue damage. Pulmonary manifestations of CF include progressive pulmonary fibrosis, restrictive lung disease, and eventual death.<sup>1</sup>

In the otolaryngology clinic, patients with CF are commonly seen with sinus disease. Abnormally thick nasal secretions can lead to chronic sinus tenderness, nasal polyposis, and purulent nasal drainage. More than 70% of patients with CF have chronic rhinosinusitis; 18% have nasal polyposis.<sup>2</sup> Histologically, patients with CF have submucosal gland hyperplasia and altered mucin production.<sup>3</sup>

The literature on the effects of CF on the human vocal folds is limited. The epithelial layers of the vocal fold contain multiple ion transport systems that regulate mucosal hydration and affect pliability. Multiple cellular receptors contribute to ion and water gradients and thus determine the hydration status of the human vocal fold. Receptors include sodium channels, sodium-chloride-potassium transporters, water aquaporins, and the CFTR receptor.<sup>4</sup>

In ovine vocal fold epithelium, large alterations in transmembrane currents were seen with the application of CFTR stimulators and inhibitors.<sup>5</sup> This finding gives reason to believe that a defective CFTR, such as in human patients with CF, could lead to altered fluid homeostasis in the vocal fold epithelium and to resultant hoarseness, or dysphonia. Recently, Lourencxo et al<sup>6</sup> showed that patients with CF lung disease demonstrated greater dysphonia on auditory-perceptual evaluation and acoustic analysis compared with healthy individuals. However, to our knowledge, no studies to date have assessed dysphonia in patients with CF while considering the potential role of sinusitis.

The objective of this pilot study was to assess the prevalence and severity of dysphonia in a sample of patients with CF sinusitis compared with 2 control groups: (1) healthy individuals and (2) patients with non-CF sinusitis (ie, those with sinusitis who did not have a known diagnosis of CF).

We hypothesized that patients with CF sinusitis would have higher self-reported prevalence of dysphonia and greater severity of dysphonia, according to patient-reported outcome measures as well as auditory-perceptual evaluation by expert listeners.

## Materials and Methods

### Patients

After obtaining institutional review board approval (IRB 1208M18302), we identified adult patients presenting with chronic sinusitis—with and without CF—at the Department of Otolaryngology clinic at the University of Minnesota Medical Center. Patients were considered to have chronic sinusitis if they had at least 2 of the following symptoms for more than 3 months: nasal congestion/obstruction, postnasal drainage, facial pain/pressure, or reduced sense of smell and taste, with either endoscopic or computed tomography (CT) evidence of mucosal abnormality.<sup>7</sup> Enrollment occurred from April to June 2012 and was conducted by the first author in a consecutive fashion on days he attended clinic. During their clinic visit, patients were approached and asked for their consent to participate in data collection for our study. Exclusion criteria included known diagnosis of laryngeal pathology or previous laryngeal surgery. For one of our control groups (healthy individuals), we recruited adults from among the staff members and otolaryngology residents within the Department of Otolaryngology.

### Data Collection

From all study participants, we collected basic demographic information. For our 2 patient groups (those with CF sinusitis and those with non-CF sinusitis), we used a questionnaire and, for verification, the electronic medical record to obtain their medical history, including medications, previous surgeries, diagnosis of gastroesophageal reflux disease (GERD), smoking status, and use of inhalant therapeutics. No medical record review was performed for the healthy individuals to avoid violating their privacy, but the same questionnaire was presented to all participants. To assess the general degree of sinonasal symptoms, we asked all study participants (including healthy individuals) to complete the 20-item Sinonasal Outcome Test (SNOT-20) with a total test score range of 0 to 100.<sup>8</sup>

To assess dysphonia, we used both subjective and objective measures. To measure dysphonia-related handicap, we asked all study participants to complete the 10-item version of the well-established Voice Handicap Index (VHI-10) questionnaire.<sup>9</sup> A total score of 11 or higher was defined as abnormal with a total test score range of 0 to 40.<sup>10</sup>

We also obtained voice samples. We asked study participants to sustain the vowels /a/ and /i/ at comfortable pitch and loudness for as long as possible and to then read each of the 6 Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V) sentences.<sup>11</sup> To record the voice samples in the patient examination room, we used a linear PCMM10 recorder (Sony Corporation, Tokyo, Japan) with a head-worn microphone (Shure Corporation, Niles, Illinois). Immediately after recoding, we previewed the audio files to ensure adequate loudness. Recordings were preserved as a single file, converted to .wav format, and then burned to a compact disk. Then, voice samples were presented, in random order, to 6 blinded, experienced speech-language pathologists who independently scored the samples, using the CAPE-V scale (0–100 mm) for overall severity, roughness, breathiness, and strain.<sup>12</sup> Given the relatively young age of many of our study participants, we also assessed vocal fry (which is not part of CAPE-V).<sup>13</sup>

## Statistical Analysis

Because of the small sizes of the study groups, we used the Fisher exact test to compare baseline demographic and clinical characteristics. Age, VHI-10, and SNOT-20 data were normally distributed and were therefore assessed using 1-way analysis of variance (ANOVA) with *t* testing of pairwise comparisons if significance was reached with ANOVA. Some subsets of CAPE-V data were found not to have a normal distribution, and therefore all CAPE-V data were analyzed nonparametrically using Kruskal-Wallis testing followed by Mann-Whitney rank-sum testing of pairwise comparisons for group comparisons that reached significance. Interrater reliability of the expert listeners for the auditory-perceptual evaluation was measured with intraclass correlation coefficients.<sup>14</sup> Confidence intervals were presented for normally distributed variables; median was presented for CAPE-V. Confidence intervals were not calculated for nonparametric distributions due to small sample size.<sup>15</sup>

## Results

Our analysis included 37 study participants: 17 patients with CF sinusitis, 10 healthy individuals, and 10 patients with non-CF sinusitis. (A total of 38 study participants were enrolled, but 1 patient with non-CF sinusitis was excluded because of incomplete data.) Demographic and clinical characteristics of the 37 study participants are presented in Table 1. Most study participants identified as white. Gender distribution was similar among all 3 groups. The only statistically significant difference between the groups was age distribution: the mean age of patients with CF sinusitis (30.4 years) and healthy individuals (31.3 years) was similar, but patients with non-CF sinusitis (41.9) were about 10 years older ( $P = .03$ ).

In all groups, the rate of smoking was low. In the patient groups, the frequency of previous sinus surgery was higher than in the healthy individuals group ( $P < .001$ ). Use of inhaled tobramycin was higher in patients with CF sinusitis ( $P < .001$ ) and use of inhaled steroids was higher in both patient groups than in healthy controls ( $P < .001$ ). The rate of GERD diagnosed by pH probe or esophagram was low in all groups, whereas patient-reported acid reflux was higher in patients with CF sinusitis than in the comparison groups. These differences were not statistically significant.

The prevalence of abnormal VHI-10 was 41% in the CF group, 20% in the non-CF sinusitis group, and 0% in the healthy individuals group; these differences between the 3 groups did not reach statistical significance. Severity of self-reported voice handicap was relatively low across groups, but the difference between mean VHI-10 scores across the groups (Table 2) was significant ( $P = .005$ ).

Auditory-perceptual evaluation revealed some differences between the 3 groups (Table 2). Raters observed greater overall severity in patients with CF sinusitis compared with the 2 control groups ( $P = .0005$ ). Values for breathiness ( $P = .06$ ), roughness ( $P = .09$ ), and strain ( $P = .08$ ) were also higher (ie, worse) in patients with CF sinusitis, but differences did not reach statistical significance. There was no difference in vocal fry between the 3 groups ( $P = .99$ ). Intraclass correlation coefficients for interrater reliability ranged from 0.71 to 0.80.

We also assessed sinonasal quality of life. The highest (ie, worst) SNOT-20 scores were reported by patients with non-CF sinusitis (mean, 39.1) compared with patients with CF sinusitis (33.9) and healthy individuals (5.2) ( $P < .0001$ ; Table 2).

Pairwise comparisons of VHI-10 scores revealed that VHI-10 scores were similar between patients with CF and non-CF sinusitis ( $P = .31$ ) but significantly worse than in healthy individuals ( $P = .001$ ). VHI-10 scores were also worse in patients with non-CF sinusitis than in healthy individuals ( $P = .02$ ). Pairwise comparisons of CAPE-V scores showed that overall severity on auditory-perceptual voice ratings was greater in patients with CF sinusitis than in either patients with non-CF sinusitis ( $P = .005$ ) or healthy individuals ( $P = .006$ ) and that patients with non-CF sinusitis were comparable to healthy individuals in this assessment ( $P = .17$ ). Pairwise comparison of SNOT-20 scores demonstrated that patients with CF and non-CF sinusitis scored comparably on sinonasal-related quality of life ( $P = .47$ ), but both groups were markedly worse than healthy individuals ( $P < .0001$  and  $P = .0001$ , respectively).

## Discussion

We observed greater severity of patient-reported voice handicap as well as worse overall severity on auditory-perceptual evaluation of voice in patients with CF sinusitis (compared with 2 control groups, patients with non-CF sinusitis and healthy individuals). Pairwise comparisons across the groups for VHI-10 scores suggested that subjectively, both patients with CF and non-CF sinusitis perceived a voice-related handicap that was greater than in healthy individuals. However, on auditory-perceptual analysis, CF sinusitis voice samples were rated worse than non-CF sinusitis voice samples, which were not significantly worse than healthy voice samples. Taken together, these results suggest that patients with CF sinusitis had worse vocal function than healthy individuals on both subjective (VHI-10) and objective (CAPE-V) measures. Patients with CF sinusitis were worse than patients with chronic sinusitis only on the objective (CAPE-V) measures. Non-CF chronic sinusitis appeared to influence patient report of voice-related handicap but was not associated with worse auditory-perceptual ratings. Thus, although sinonasal symptom severity and voice-related handicap were comparable between the 2 groups with sinusitis, the patients with CF sinusitis appeared to have worse objective ratings of dysphonia.

Our findings support the limited existing literature on dysphonia in patients with CF. Lourencxo et al<sup>6</sup> demonstrated significantly lower vocal intensity, a significantly lower harmonic to noise ratio, and significantly increased levels of jitter and shimmer on acoustic analysis in their patients with CF (compared with healthy controls). They also observed higher scores in CF patients for roughness, breathiness, and asthenia on GRBAS (Grade, Roughness, Breathiness, Asthenia, Strain) evaluation. Lourencxo et al did not observe greater strain. Although we did not detect a statistically significant difference in subdomains of the CAPE-V ratings in this pilot study, future studies with larger enrollment are needed.

In light of literature suggesting that sinusitis could be associated with dysphonia in the general population, we sought to compare voice findings among patients with CF vs non-CF sinusitis, in addition to a second control group of healthy individuals.<sup>16,17</sup> Our objective in

taking this approach was to determine whether severity of dysphonia might be explained by severity of sinusitis.

Contrary to our hypothesis, we did not observe a statistically higher prevalence of dysphonia (as reflected by VHI-10 scores) in patients with CF compared with patients with non-CF sinusitis and healthy individuals. One possible explanation is that our sample sizes in this pilot study were too small to detect a difference. At the time of study planning, no prevalence estimates were available to drive sample size determination. Based on our findings to date that 41% of the patients with CF, 20% of the patients with non-CF sinusitis, and 0% of the healthy control patients had an abnormal VHI score, 1-way ANOVA would give a power of 0.19 for the comparison across 17 patients with CF, 10 patients with chronic sinusitis, and 10 healthy controls. Thus, this pilot study was underpowered to detect differences in prevalence. Another possibility is that patients with a major medical problem such as CF might be less bothered by a voice disturbance, because competing health issues might take precedence. The impact of a potentially life-threatening comorbidity in the CF group may influence VHI scores in a way that is difficult to predict. Nonetheless, our patients with CF sinusitis *did* have more severe (ie, worse) VHI-10 scores than did healthy individuals. Although their mean VHI-10 score was below the cutoff for abnormal, suggesting that voice-related handicap is not universal in patients with CF (and perhaps accounting for the fact that we observed differences in severity but not prevalence), our findings do suggest concern about vocal function, even in these patients with competing medical challenges.

We observed auditory-perceptual differences in overall severity, with patients with CF sinusitis having worse ratings than those with non-CF sinusitis and healthy individuals. The literature on voice problems associated with sinusitis is limited, even though many patients subjectively report a relationship.<sup>17</sup> Our findings indicate that chronic sinusitis alone does have some impact on self-reported vocal handicap, but a significant impact on auditory-perceptual quality was not seen. Further investigation would help to clarify this issue.

Auditory-perceptual ratings can be influenced by knowledge of patient history,<sup>18</sup> but raters in this study were blinded and voice samples presented in random order. A potential for minor bias was introduced by the slightly different mean ages in our 3 groups, but this bias was likely to be conservative, because dysphonia is more common with increasing age.<sup>19</sup>

The most critical limitation of our pilot comparison study was its small sample size. Other limitations include lack of laryngoscopy and pulmonary function data, which we would like to include in future studies. Although decreased expiratory force and undiagnosed vocal fold pathologies in patients with CF could potentially contribute to objective worsening of voice parameters, Lourenço et al<sup>6</sup> did not observe significant differences in laryngoscopy findings between their CF and control groups. Assessment of cough severity, which could also influence voice outcomes, would be useful. Another potential confounder of our results could be the use of inhaled medications. Finally, the use of a nonpatient healthy individuals group may introduce bias. For this pilot study, due to the older age of most patients seen in the adult ear, nose, and throat (ENT) clinic and the potential impact of age and other ENT comorbidities (such as head and neck cancer or severe hearing loss) on vocal function/

subjective perception, we used a nonclinical healthy group. In future studies, we aim to recruit healthy patients through other clinics to reduce this potential bias.

Despite these limitations, CF sinusitis appeared to be associated with differences in vocal function as measured by patient self-report as well as auditory-perceptual evaluation of voice compared with patients with non-CF sinusitis and healthy controls. Differences in vocal fold hydration based on defective CFTR receptors in the vocal fold epithelium could be at least partially responsible for these findings. Examination of changes in vocal function and laryngeal health following targeted CF treatment (such as lumacaftor and ivacaftor, which restore CFTR function) would allow us to learn more about the role of the CFTR in laryngeal function.

Because dysphonia itself can have a significant impact on quality of life, provider awareness of the potential for voice problems in this patient population is important.<sup>20</sup> We urge the timely identification of patients who would benefit from referral for expert laryngeal examination and/or speech therapy.

## Conclusions

This pilot study demonstrated both subjective and objective differences in vocal function among patients with CF sinusitis (compared with patients with non-CF sinusitis and healthy individuals). Non-CF sinusitis was associated with greater subjective report of voice-related handicap but not with worse auditory-perceptual measures compared with healthy individuals. Further work is needed to elucidate the pathophysiology of these differences, as well as the effect they might have on quality of life in patients with CF.

## Acknowledgments

Brenna Finley, MPH, Kathryn Banks, BA, and Patricia Fernandes Boettner, DDS, MS, assisted with data management and research preparation and coordination. We thank Mary Knatterud, PhD, for her editing assistance and our expert listeners Sharyl Samargia, PhD; Bruce Poburka, PhD; Sara Oberg, MA, CCC-SLP; Lisa Butcher, MA, CCC-SLP; and Jesse Hoffmeister, MS, CCC-SLP, for their expertise.

**Sponsorships:** None.

**Funding source:** Lions Research Foundation Grant and NIH UL1TR000114.

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Table 1

Demographic and Clinical Characteristics.<sup>a</sup>

	P Value						
	CF (n = 17),	Non-CF Sinusitis (n = 10)	Healthy Individuals (n = 10)	Overall Comparison	CF vs Non-CF Sinusitis	Non-CF Sinusitis vs Healthy	CF vs Healthy
Gender, No. (%)				.87			
Male	9 (53)	4 (40)	6 (60)				
Female	8 (47)	6 (60)	4 (40)				
Age, y				.03	.03	.03	.83
Mean (SD)	30.4 (12.6)	41.9 (13.4)	31.3 (2.9)				
Range	18–58	22–62	28–37				
Race, No. (%)				.91			
White	17 (100)	10 (100)	8 (80)				
Nonwhite	0 (0)	0 (0)	2 (20)				
Medical characteristics, No. (%)	n = 17	n = 10	n = 9 (missing, n = 1)				
Current tobacco use	2 (12)	1 (10)	0 (0)	.79			
Previous sinus surgery	13 (76)	8 (80)	0 (0)	<.001	.99	<.001	<.001
Inhaled transoral steroid use	13 (76)	5 (50)	0 (0)	<.001	.22	.03	<.001
Inhaled gentamicin use	2 (12)	0 (0)	0 (0)	.49			
Inhaled tobramycin use	10 (59)	0 (0)	0 (0)	<.001	.003	1.0	.004
Patient-reported acid reflux	10 (59)	3 (30)	4 (44)	.30			
Diagnosed GERD	1 (6)	1 (10)	2 (22)	.99			

Abbreviations: CF, cystic fibrosis; GERD, gastroesophageal reflux disease; SD, standard deviation.

<sup>a</sup>Fisher exact test ( $3 \times 2$ ) was used to compare across groups for binary data; analysis of variance (ANOVA) was used for continuous data. For age, 1-way ANOVA was followed by the Student *t* test for pairwise comparisons. For medical characteristics, the Fisher exact test ( $2 \times 2$ ) was used for pairwise comparisons.

**Table 2** Voice Handicap Index, Auditory-Perceptual Evaluation, and Sinonasal Outcome Test Measures.<sup>a</sup>

	CF (n = 17)	Non-CF Sinusitis (n = 10)	Healthy Individuals (n = 10)	Overall Comparison	p Value		
					CF vs Non-CF Sinusitis	Non-CF Sinusitis vs Healthy	CF vs Healthy
VHI-10, mean score (SD) [95% CI]	7.94 (5.06) [5.34–10.5]	5.4 (4.9) [2.45–9.35]	1.7 (2.1) [0.19–3.21]	.005	.31	.02	.001
CAPE-V score, mean (SD) [median], mm Overall severity (R = 0.78)	28.7 (9.70) [29.3]	19.3 (4.98) [18.9]	15.7 (7.0) [15.3]	.0005	.005	.17	.006
Breathiness (R = 0.71)	9.74 (8.24) [9.5]	7.20 (4.62) [7.25]	2.93 (1.96) [2.5]	.06			
Roughness (R = 0.80)	21.7 (12.6) [18.7]	16.5 (6.64) [14.8]	12.9 (6.9) [12.3]	.094			
Strain (R = 0.77)	19.2 (10.7) [16.2]	11.0 (4.03) [11.8]	11.28 (4.62) [10.3]	.08			
Glottal fry (R = 0.78)	15.7 (11.6) [13.7]	15.6 (11.3) [14.8]	15.4 (10.4) [14.4]	.99			
SNOT-20, mean score (SD) [95% CI]	33.9 (16.8) [24.9–42.8]	39.1 (19.9) [24.9–53.3]	5.20 (5.35) [1.37–9.03]	<.0001	.47	.0001	<.0001

Abbreviations: CAPE-V, Consensus Auditory-Perceptual Evaluation of Voice; CF, cystic fibrosis; R, intraclass correlation coefficient for raters; SD, standard deviation; SNOT-20, 20-item Sinonasal Outcome Test; VHI-10, 10-item Voice Handicap Index.

<sup>a</sup>Comparisons were performed using 1-way analysis of variance followed by the Student *t* test for pairwise comparisons of VHI-10 and SNOT-20, as well as for CAPE-V using Kruskal-Wallis followed by the Mann-Whitney rank-sum test for pairwise comparisons.