Improved Lung Function after Sinus Surgery in Cystic Fibrosis Patients with Moderate Obstruction

Sabrina Khalfoun, MD1, Dmitry Tumin, PhD2, Maroun Ghossein, MD3, Meredith Lind, MD4, Don Hayes Jr, MD1, and Stephen Kirkby, MD1

Abstract

Objectives. Cystic fibrosis (CF) is characterized by infection and inflammation of the sinuses and respiratory tract. Functional endoscopic sinus surgery (FESS) is an option for patients with severe sinusitis. We sought to evaluate pulmonary function testing after FESS in pediatric and adult patients with CF.

Study Design. Retrospective chart review using data from all patients with CF who underwent FESS from January 2009 to July 2014.

Setting. Patients were from a single institution.

Subjects and Methods. Data were extracted for 181 patients and 320 surgeries. Lung function data, including the forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and FEV1/FVC, were retrieved within 1 year before and after surgery. Mixed-effects regression was used to compare FEV1 trajectories before and after surgery. The effect of surgery was stratified by presurgery FEV1 to compare patients with mild/no lung disease (FEV1 >80%) and moderate/severe lung disease (FEV1 <80%).

Results. Of the 181 patients reviewed, 131 with primary FESS had FEV1 data. Presurgery average age was 16 years (95% confidence interval [CI], 14.27-17.73), and FEV1 mean was 85% (95% CI, 81.02-88.98). There were 88 patients with FEV1 >80% and 43 patients with FEV1 <80%. For the entire cohort, lung function did not change related to FESS. Among patients with FEV1 <80%, FEV1 declined presurgery by 3.5% per year (95% CI, 6.1% to 0.8%; P = .010), which halted after surgery with these patients, then showing no subsequent change in FEV1 (95% CI, 0.9%-3.7%; P = .240). No benefit was identified for patients with FEV1 >80%.

Conclusion. Pulmonary function testing improved in patients with moderate/severe lung disease 1 year following FESS. This suggests FESS may benefit pulmonary outcomes.

Keywords
sinusitis, rhinitis, spirometry, quality of life

Cystic fibrosis (CF) is the most common genetic disease in the white population, occurring in approximately 1 in 3200 births.1 CF is caused by abnormal regulation of chloride ion transport through nonfunctioning or abnormally functioning cystic fibrosis transmembrane regulator (CFTR) protein that is present on the apical surface of cells located in airways, sinuses, sweat glands, the hepatobiliary tract, and the reproductive tract. Dysregulation of epithelial chloride ion transport leads to an imbalance of sodium and water transport and results in dehydrated and characteristically thick secretions.2 Progressive respiratory insufficiency is the primary cause of death, with significant morbidity related to sinus disease. Managing morbidity has become paramount in addition to the prevention of mortality.

Chronic sinusitis with bacterial colonization and nasal polyposis is almost universally present in patients with CF. Symptoms can range from decreased sleep quality to impaired taste and smell, leading to decreased quality of life.3,4 Even in patients with more mild pulmonary phenotypes, sinus disease can still be prominent.5,6 When medical therapies such as nasal steroids, nasal irrigation, and oral antibiotic courses fail, functional endoscopic sinus surgery (FESS) can be an adjunct for managing these symptoms.7,8

Several studies have demonstrated reports of improved symptoms following FESS either retrospectively or
prospectively through standardized quality-of-life measures.\textsuperscript{9-12} The literature is controversial regarding the benefit of FESS on lung function in general, and a gap exists for information on the pediatric population.\textsuperscript{10,13-16} Therefore, we sought to evaluate changes in pulmonary function testing after FESS in a large cohort of both pediatric and adult patients with CF. We hypothesized that there would be a gradual improvement in lung function after FESS. This was based on clinical observation as well as the unified airway theory and the idea that decreasing the upper airway bacterial burden would improve lower airway health and decrease bacterial colonization.\textsuperscript{17}

**Methods**

**Study Design and Population**

The study was approved by the Institutional Review Board of Nationwide Children’s Hospital, Columbus, Ohio (IRB10-00523). We performed a retrospective cohort study. We collected clinical data from all adult and pediatric patients with CF who underwent FESS from January 2009 to July 2014. Decision for surgical intervention was determined by a patient’s clinical symptoms and radiologic findings. FESS was performed by otolaryngologists using a standard endoscopic technique with concurrent polypectomy if nasal polyps were present. The extent of sinus surgery was determined by the individual surgeon, based on both sinus development and the presence of disease at the time of surgery. Patients undergoing both primary and revision FESS are included in the study. Otolaryngologists were both private and academic with longstanding experience with CF and our pulmonary group. Preoperative medical management included 1 week of oral and inhaled or intravenous (IV) antibiotics to cover respiratory pathogens cultured in the year prior to surgery with a focus on gram-negative bacteria and methicillin-resistant *Staphylococcus aureus* (MRSA). Prior respiratory cultures included those obtained from sputum, oropharyngeal (OP), or lower airway samples obtained at previous bronchoscopy. Postoperative care also included an additional week of the same antibiotic therapy (again systemic IV or oral/inhaled regimen) following surgery. Given patient and surgeon differences, there is not a standard practice at our institution regarding postoperative sinus care. Most patients receive either nasal saline spray or saline irrigations, depending on tolerance, on postoperative day 1. Those children who are on a nasal corticosteroid spray also typically restart it on postoperative day 1. Antibiotic and steroid nasal irrigations are not typically used at this institution except in select instances. Spirometry was performed by each patient at all quarterly clinic visits and at the end of a hospital admission for exacerbation. This was consistent over the time period studied. The number of specific times a patient performed spirometry varied for each patient in the cohort.

**Data Collection**

The collected data were compiled into a RedCap Database. For each patient, the earliest surgery during the study period was analyzed. If revision surgery was performed during the study period, only the data from the primary surgery were included. Patients were included in the analysis if they contributed data on pulmonary function both in the year prior to and in the year following their first FESS, with the exception of FESS performed after lung transplantation. Postsurgery observations were censored on the date a patient had undergone a second FESS, if applicable. Lung function data, including FEV1, FVC, and FEV1/FVC ratio, were retrieved for the time period from 1 year prior to surgery until 1 year after surgery. FEV1 and FVC were reported as a percentage of predicted normal, and FEV1/FVC ratio was reported as the raw value. Patients were classified according to the most recent available presurgery FEV1 as those with mild lung disease (FEV1 ≥80%) and those with moderate/severe lung disease (FEV1 <80%). We also examined the number of antibiotic courses and hospital admissions in the year before and the year following surgery in the overall study cohort.

**Statistical Analysis**

A mixed-effects regression model was fitted to predict FEV1 values with a random intercept at the patient level.\textsuperscript{18} FEV1 trajectories were modeled as a linear function of time before or after FESS and adjusted for patient age, sex, and genotype (F508del homozygous, F508del heterozygous, or other). The effect of FESS on the slope of patients’ FEV1 trajectories was assessed by comparing the time parameters (time until surgery, equaling 0 in the postsurgery period; time after surgery, equaling 0 in the presurgery period) using a Wald test. A statistically significant difference in the slopes, such as a change from declining FEV1 in the year before surgery to increasing FEV1 in the year after surgery, indicated a beneficial effect of FESS on pulmonary function. Differences in presurgery and postsurgery slopes of FEV1 trajectories were compared according to severity of presurgery lung disease by interacting the measure of lung disease severity with each of the time parameters. The multivariable model was fitted using cases with complete data on covariates. Stata/IC 14.2 (StataCorp LP, College Station, Texas) was used for all analyses, and $P < .05$ was considered statistically significant.

**Results**

Records for 320 surgeries performed on 181 patients over a period of 4.5 years were evaluated for inclusion in the study. The analytic data set was limited to 131 patients who met the inclusion criteria of primary FESS (exclusive of FESS performed after lung transplantation) with FEV1 data available in the year before and after surgery. At the time of first FESS, patient age ranged from 2 to 59 years (mean, 16 [95% confidence interval (CI), 14.27-17.73]; median, 14; interquartile range [IQR], 7-22). Other characteristics of this cohort are described in Table 1. The sex distribution was even with 66 females (50%) and 65 males (50%). In the study cohort, 75 (57%) were F508del homozygous, 38 (29%) were F508del heterozygotes, 2 patients (1%) had 1
Table 1. Characteristics of Patients with Cystic Fibrosis Prior to First Sinus Surgery (n = 138).

<table>
<thead>
<tr>
<th>Variablea</th>
<th>No/Mild Obstruction (n = 88)</th>
<th>Moderate/Severe Obstruction (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (95% CI)</td>
<td>13 (11.3-14.7)</td>
<td>21 (17.6-24.4)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>44 (50)</td>
<td>21 (49)</td>
</tr>
<tr>
<td>Genotype, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F508del homozygous</td>
<td>47 (53)</td>
<td>28 (65)</td>
</tr>
<tr>
<td>F508del heterozygous</td>
<td>28 (32)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (15)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>FEV1, mean (95% CI)</td>
<td>96 (92.6-99.4)</td>
<td>63 (58.1-67.9)</td>
</tr>
<tr>
<td>BMI, mean (95% CI)b</td>
<td>18 (17.2-18.9)</td>
<td>20 (18.8-21.2)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; FEV1, forced expiratory volume in one second.
*aContinuous variables assessed at the most recent available time point prior to surgery.
*bMissing data in 33 cases.

G551D mutation, and the others (5%) had varying other mutation combinations. The average presurgery FEV1 was 85% (95% CI, 81.0-88.98). There were 88 patients with mild/no lung disease and 43 patients with moderate/severe lung disease prior to FESS. Postsurgery FEV1 data were censored due to a repeat FESS within 1 year for 7 patients with mild or no lung disease and 4 patients with moderate/severe lung disease.

A total of 1536 FEV1 data points were included in the mixed-effects regression model. In Table 2, the model is shown with “mild or no lung disease” as the reference category, meaning that time parameters (time before surgery, time after surgery) reflect FEV1 change in the cohort with mild or no lung disease, and the interaction terms describe how FEV1 change before and after surgery is modified among patients with moderate or severe lung disease. Among patients with mild or no lung disease, FEV1 was stable in the year before surgery (95% CI, –0.7% to 3.7%; P = .176). These patients exhibited no change in FEV1 in the year after surgery (0.8%; 95% CI, –2.6% to 1.1%; P = .400). The Wald test comparing these 2 coefficients (P = .214) indicated that among patients with mild or no lung disease, the FEV1 trajectory did not meaningfully change after FESS.

By contrast, we observed significant modification of the FEV1 trajectory before FESS for patients with moderate or severe lung disease, as illustrated in Figure 1. In the year before surgery, FEV1 declined by 3.5% in this subgroup (95% CI, −6.1% to −0.8%; P = .010) and in the year after surgery, FEV1 exhibited no change (95% CI, 0.9%-3.7%; P = .240). Nevertheless, comparison of FEV1 trajectories before and after FESS using a Wald test of coefficients (P = .207) confirmed that FESS was associated with arresting the decline of FEV1 in the subgroup of patients with moderate or severe lung disease at the time of surgery. Among other covariates in the model, older age at FESS was associated with lower FEV1, but sex and genotype were not related to this outcome.

The median number of antibiotic courses before and after surgery did not change from a presurgery median of 3 (interquartile range [IQR], 2-4) to a postsurgery median of 3 (IQR, 1-4; P = .993 by signed-rank test). Similarly, there was no statistically significant change in the median number of antibiotic courses among patients with mild or no lung disease (presurgery median, 2 [IQR, 1-4]; postsurgery median, 2 [IQR, 1-4], P = .852) or patients with moderate/severe lung disease (presurgery median, 3 [IQR, 2-5]; postsurgery median, 4 [IQR, 2-5], P = .772).

Examining hospital admissions, we found that 54 of 131 (41%) patients did not require inpatient hospitalization for CF exacerbation in the year before or after surgery, and 36 patients (28%) were not hospitalized in the year prior but required hospitalization in the year following. Seventeen patients were hospitalized in the year prior to surgery but did not require hospitalization in the year following surgery, and 24 patients (18%) were admitted in both the year prior to and year following surgery. The overall need for inpatient hospitalization increased from 31% in the year before surgery to 46% in the year after surgery (P = .013 by McNemar’s test). In the group with mild or no lung disease, need for inpatient hospitalization remained similar before and after surgery (31% vs 39%; P = .223). The postsurgery

Table 2. Mixed-Effects Linear Regression of FEV1 (% Predicted) before and after Sinus Surgery (n = 131 patients, 1536 Observations).

<table>
<thead>
<tr>
<th>Covariatea</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time before FESS, yb</td>
<td>1.5</td>
<td>−0.7 to 3.7</td>
<td>.176</td>
</tr>
<tr>
<td>Time after FESS, yc</td>
<td>−0.8</td>
<td>−2.6 to 1.1</td>
<td>.400</td>
</tr>
<tr>
<td>Lung disease severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/mild</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>−3.4</td>
<td>−39.0 to −27.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Modification of time parameters in the moderate/severe disease groupd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time before FESS, y</td>
<td>−5.0</td>
<td>−8.4 to −1.6</td>
<td>.146</td>
</tr>
<tr>
<td>Time after FESS, y</td>
<td>2.2</td>
<td>2.6 to 1.1</td>
<td>.146</td>
</tr>
<tr>
<td>Age, y</td>
<td>−0.3</td>
<td>−0.6 to −0.1</td>
<td>.010</td>
</tr>
<tr>
<td>Male</td>
<td>−3.0</td>
<td>−7.6 to 1.7</td>
<td>.215</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F508del homozygous</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F508del heterozygous</td>
<td>−2.7</td>
<td>−8.2 to 2.8</td>
<td>.332</td>
</tr>
<tr>
<td>Other</td>
<td>2.0</td>
<td>−5.0 to 9.0</td>
<td>.579</td>
</tr>
<tr>
<td>Constant</td>
<td>98.2</td>
<td>94.0 to 102.5</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; FESS, functional endoscopic sinus surgery; FEV1, forced expiratory volume in one second.
aContinuous covariates are time varying.
bEquals 0 for FEV1 observations collected before FESS.
cEquals 0 for FEV1 observations collected after FESS.
dTime coefficients in the moderate/severe disease group are obtained by summing the modification factor and the corresponding time parameter in rows 1 to 2.
Due to FESS and one of the few that have shown lung function improvement in follow-up intervals in this retrospective cohort.

In sum, we demonstrated that FEV1 decline among patients with CF who have moderate to severe airway obstruction at the time of FESS stops and partially reverses in the year following surgery. It is important to recognize that some patients with CF may benefit from FESS with regard to pulmonary function. In addition to managing sinusitis symptoms and improving quality of life, FESS may stabilize lung function decline among these patients. Further prospective studies are needed to explore the effect of sinus surgery on clinical outcomes in CF, including the need for hospitalization, antibiotic courses, and growth parameters. Future investigation should also include evaluation of patient characteristics related to the need for revision sinus surgery or for better response to FESS.

**Discussion**

The clinical decision to perform sinus surgery in patients with CF remains a controversial one, but our study presents evidence to support its benefit in patients with CF with moderate to severe lung disease. Our analysis of pulmonary function tests demonstrated that FESS was associated with a halt and partial reversal of FEV1 decline among patients presenting for FESS with FEV1 <80%. This is the largest single-center study examining lung function change after FESS and one of the few that have shown lung function benefit among a group of patients with CF.13,17,19,20 Due to study design, we cannot identify causality of our findings but propose that these results may be due to FESS itself, leading to improvement in pulmonary function by reducing upper airway drainage and the mucopurulent secretion burden of the larger lower airways, thus reducing the bacterial colonization of the lungs.

Apart from FESS, other factors may have contributed to the improvement in lung function in the year following surgery. Our institution’s standard practice of 2 weeks of antibiotics surrounding surgery could be a component in the improvement in lung function in the year following surgery. Other institutions have also described use of perioperative antibiotic courses and without demonstration of improvement in lung function.14,19,20 As it has been demonstrated that FESS improves sinus symptoms such as headache, congestion, and sleep, it is possible our patients’ general quality of life improved following surgery.9,10,21 With improved sense of smell, perhaps patient appetite and thus body mass index would have improved over time, which has a known positive correlation with improved lung function in patients with CF. General well-being and improvement in sleep or headaches could possibly translate to better compliance with standard therapies such as airway clearance.

A halt in decline with subsequent reversal was only noted in those patients with FEV1 <80%. Perhaps part of their lower lung function was a higher mucous/secretion burden in part due to sinus drainage. This may have been a component of why surgery had a larger impact on the lung function of these patients. They were also starting with lower lung function to begin with and had more room for improvement than those patients starting with already normal lung function. However, in supplemental analysis, we also found this group also required more inpatient admissions with IV antibiotics after surgery compared to the presurgery period, and the contribution of this additional treatment to FEV1 is unclear.

Limitations of the study include retrospective analysis of data from a single institution, as well as not controlling for other potential confounders of increased pulmonary function after FESS. These could include inpatient hospitalization for pulmonary exacerbation and administration of antibiotics at the time of surgery. There were also insufficient patients with severe lung disease (FEV1 <50%) to definitively analyze outcomes of FESS in this subgroup. Last, we did not pursue a multivariable regression analysis of dichotomous outcomes (eg, need for hospitalization) due to the lack of standardization in follow-up intervals in this retrospective cohort.

In sum, we demonstrated that FEV1 decline among patients with CF who have moderate to severe airway obstruction at the time of FESS stops and partially reverses in the year following surgery. It is important to recognize that some patients with CF may benefit from FESS with regard to pulmonary function. In addition to managing sinusitis symptoms and improving quality of life, FESS may stabilize lung function decline among these patients. Further prospective studies are needed to explore the effect of sinus surgery on clinical outcomes in CF, including the need for hospitalization, antibiotic courses, and growth parameters. Future investigation should also include evaluation of patient characteristics related to the need for revision sinus surgery or for better response to FESS.

**Author Contributions**

Sabrina Khalfoun, study design, data collection and analysis, manuscript drafting and revision; Dmitry Tumin, study design, data analysis, manuscript drafting and revision; Maroun Ghossein, data collection, analysis, manuscript drafting and revision; Meredith Lind, study design, data analysis, manuscript drafting and revision; Don Hayes Jr, study design, data analysis, manuscript drafting and revision; Stephen Kirkby, study design, data analysis, manuscript drafting and revision.

**Disclosures**

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References


