REVIEW
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Significance of the pulmonary function test for the diagnosis of subglottic stenosis: a systematic review

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ABSTRACT

Objective: Subglottic stenosis is diagnosed on the basis of clinical presentation and flexible laryngoscopy findings and confirmed by direct laryngobronchoscopy. Other adjunct diagnostic methods have been proposed, including the pulmonary function test. This study aimed to systematically review the existing literature on the parameters of the pulmonary function test in patients with subglottic stenosis in order to provide clinicians with evidence-based information about its diagnostic utility.

Methods: We searched the Medline, PubMed, Scopus, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, and ProQuest dissertation databases for prospective or retrospective studies of adults diagnosed with subglottic stenosis, who underwent the pulmonary function test preoperatively. The data were collected by 2 independent authors who also assessed the quality of each study.

Results: Of the 479 studies identified, only 1 article met our inclusion criteria; the study included 42 patients with 251 pulmonary function test measurements (preoperative, n=45; postoperative, n=206). The mean peak expiratory flow and expiratory disproportion index before intervention were 3.19 L/s and 73.8, respectively, and those after intervention were 5.49 L/s and 44.9, respectively.

Conclusion: Available evidence suggests that the pulmonary function test alone, without airway visualization, is an unreliable method for diagnosing subglottic stenosis. However, it may be a useful adjunctive diagnostic tool to indicate subglottic stenosis, with an expiratory disproportion index value of 54 and a peak expiratory flow value of 4.4 L/s as presumptive cut-off diagnostic values. The pulmonary function test may also be useful postoperatively to monitor disease progress during follow-up.

Keywords: Laryngotracheal stenosis, pulmonary function test, respiratory function test, spirometry, subglottic stenosis

Introduction

Subglottic stenosis (SGS) is a part of the spectrum of laryngotracheal stenosis (LTS) disorders and is characterized by variable degrees of airway obstruction. It is a rare, progressive inflammatory condition manifested by fibrotic narrowing of the airway at the level of the subglottis (1-4). Multiple etiological factors, including trauma, neoplasia, infections, systemic inflammatory disorders, and idiopathic and congenital anomalies, have been described in the literature (1, 4). Additional comorbidities, such as laryngopharyngeal reflux, were suggested to contribute to disease pathogenesis, although this remains somewhat controversial (5-7). Obesity and diabetes are other comorbid conditions that alter the inflammatory profile, thus affecting the ability to heal after an injury (8).

A clinical diagnosis of SGS is made on the basis of the patient's history and physical examinations, including office-based flexible laryngoscopy. The diagnosis is confirmed with direct laryngobronchoscopy (DLB), which is considered the reference standard method (9, 10). Other diagnostic modalities that may aid diagnosis with varying degrees of sensitivity and specificity include plain radiography (11), acoustic reflection techniques (12), pulmonary function tests (PFTs) (13), flexible bronchoscopy (9, 10) computed tomography, high-resolution imaging with multiplanar reconstruction (9, 10, 14, 15) virtual bronchoscopy (10, 16) computational fluid dynamics (17-20), and magnetic resonance imaging (21, 22). Suspecting SGS when patients present

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with a suggestive clinical picture and performing DLB are likely the most useful method to avoid misdiagnosis. Unfortunately, approximately 33%-37% of patients with SGS are initially suspected of pulmonary diseases, such as bronchial asthma, particularly those of idiopathic etiology (23-25). Some of these patients could be subjected to unnecessary treatments with potentially grave consequences owing to progressive airway narrowing before the diagnosis of SGS is made (26-31). This scenario might be more common for patients living in rural areas that lack the facilities for airway evaluation. Therefore, finding a reliable, simple, widely available, and noninvasive tool that can aid in the diagnosis to enable prompt referral to higher specialized centers will minimize misdiagnosis in such patients.

In the early 1970s, the PFT was proposed as an adjunctive method that can assist in diagnosing upper airway obstruction and differentiate it from other pulmonological pathologies (32, 33). It is an excellent tool for evaluating patients with stenosis because of its low cost, availability, and noninvasive nature (34, 35). Compared with computed tomography and magnetic resonance imaging, which primarily visualize the structural component of stenosis, the PFT is a physiological test that assesses the effects of airway stenosis on airflow and the patient's actual respiratory function. Multiple PFT measurement parameters have been studied in patients with airway obstruction. Flow-volume loops, forced expiratory volume in 1 second (FEV1) divided by peak expiratory flow (PEF) rate (PEFR), forced expiratory flow (FEF50%) divided by forced inspiratory flow (FIF50%), FIF50%, and FEV1 divided by forced expiratory volume in 0.5 seconds have been investigated and correlated with upper airway obstruction (32, 33, 35-37), but none has been confirmed to be of high diagnostic value for SGS. The gradual change in PFT parameters with regard to the degree of stenosis over time and in response to surgical airway expansion interventions has been observed in several studies (13, 36, 38-42). The Cotton-Myers grading system, which is based on the total percentage of stenosis (grade I: 0%-50%, grade II: 51%-70%, grade III: 71%-99%, and grade IV: 100%), was usually used for correlation with PFT parameters to assess the improvement after surgery.[43] Whereas some studies found inspiratory-based parameters (forced inspiratory volume in 1 second and peak inspiratory flow [PIF]) to be a more accurate measure of airway stenosis degree (44, 45), other studies have reported expiratory-based parameters (PEF and expiratory disproportion index [EDI]) to be more useful with higher sensitivity and specificity (13, 46, 47).

Main Points:

- A pulmonary function test (PFT) is an adjunct diagnostic tool that could assess the degree of airway obstruction and monitor patient progress during follow-up. Using PFT without airway visualization cannot be relied on to establish a diagnosis of subglottis stenosis (SGS).
- PFT can be of value to support the diagnosis in patients with a highly suggestive clinical picture, especially in centers that lack facilities for airway visualization.
- An expiratory disproportion index of 54 and peak expiratory flow value of 4.4 L/s with obstructive-type volume loops could be used as indicative parameters for SGS.

In 2013, Nouraei et al. (13) showed that the EDI is a highly sensitive and specific tool that can differentiate LTS from lower airway pathologies with an optimal diagnostic threshold. The EDI was defined by the authors as the ratio of the FEV1 (in liters) to the PEF (in liters per second) multiplied by 100. In another study investigating treatment-related changes in the airway caliber in patients with LTS, Nouraei et al. (42) found that the change in the area under the curve for the flow-volume loop divided by forced vital capacity (FVC) is superior to the PEF and total peak flow (TPF). The PEF, TPF, and FEV1/PEF ratio are reportedly relatively sensitive and specific measures for monitoring disease progression (46, 47). Tasche et al. (39) showed in a single case report of a patient with acquired SGS who underwent repeated PFT measurements that a decrease in the PIF was associated with worsening of airway symptoms, and this was reversed after surgical intervention. More recently, Henes et al. (22) found a good correlation between the cross-sectional area of stenosis measured on magnetic resonance images with both inspiratory and expiratory values of PFT and reported improvement in these measures after treatment.

On the basis of the findings of previous studies, PFT can be an excellent, noninvasive, widely available adjunct diagnostic tool that can especially be utilized in centers that lack facilities for airway evaluation. Having a reference number for PFT parameters that indicate a diagnosis of SGS will help ensure prompt management and referral to a specialized center. Because of heterogenicity among reported studies and the absence of a clear consensus for PFT cut-off values that can be utilized to reliably diagnose upper airway obstruction, we performed a systematic review of the literature to determine the role of the PFT in the diagnosis of SGS. We also aimed to determine the PFT parameters that would be more suggestive of SGS and would better reflect the disease severity.

Methods

Search Strategy

The Medline, PubMed, Scopus, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, and ProQuest dissertation databases were searched using keywords, subject headings, and Medical Subject Headings. The search was completed on February 15, 2019. We used 2 sets of keywords, including Laryngostenosis AND Respiratory Function Tests, Subglottic AND stenosis AND Spirometry, Subglottic stenosis AND Respiratory function test, and Subglottic stenosis AND Pulmonary function test to identify all the previously published studies that investigated the role of the PFT for diagnosing SGS. The search was adapted to each database, and no limitations were applied during the online search. The reference lists of the identified studies were searched manually for additional related papers. All references were imported to an online reference manager (RefWorks 2.0, ProQuest, Ann Arbor, MI, USA). A repeated search using the same strategy was performed on February 1, 2020, and it revealed the same results in addition to 1 new study.

Inclusion and Exclusion Criteria

We included human studies published in English with longitudinal prospective or retrospective designs investigating adult patients (aged >18 years) with confirmed diagnoses of SGS by DLB in which the PFT was performed and reported with anthropometric data (age, height, and weight) within a period of 3 months before they underwent diagnostic confirmation by DLB. We excluded single case reports, expert opinion/narrative reviews/letters, and studies on participants with multilevel stenosis or pulmonological or neuromuscular disease.

Selection of Included Articles

The titles and abstracts of all articles extracted from the primary search were screened after removing duplicates. The full texts of relevant papers were reviewed for eligibility by 2 authors independently. Disagreements between the reviewers were resolved by consensus and adjudication by a third senior author.

Data Extraction and Quality Assessment

A total of 2 independent reviewers extracted the data from the included studies. An Excel (Microsoft Excel for Mac version 16.19, 2018) datasheet was used for data collection. The collected variables included the author names, publication year, study design, sample size, participants' age and sex, the diagnostic method for SGS, PFT protocol, PFT parameters reported in each paper, and whether or not tracheostomy was performed.

Quality assessment was performed by 2 independent reviewers. The revised Quality Assessment of Diagnostic Accuracy Studies 2 tool (48) was used to assess the quality of the included studies. Each study was assessed for the risk of bias and applicability in the following 4 main domains: patient selection and sampling, use of PFT as an index test, use of DLB as the reference standard test, and flow of patients through the study. A flow diagram was created for each study, and signaling questions were piloted and tested by the 2 authors and used for quality assessment after an agreement between the 2 authors by consensus and adjudication by a third senior author.

Statistical Analyses

Microsoft Excel for Mac, version 16.19, 2018, was used for the statistical analyses. The descriptive statistics of the variables and qualitative analysis are reported. A meta-analysis was not performed because of the lack of studies that provided PFT values for diagnosis.

Results

Our electronic search retrieved 478 articles; 2 additional articles were included from the manual reference search. A total of 109 duplicated articles were removed. We then screened the titles and abstracts of the remaining 371 papers and excluded another 342 articles because they were clearly irrelevant (n=262) or were case reports (n=9), nonhuman studies (n=2), or written in languages other than English (n=69). The full texts of the remaining 29 papers were obtained (Figure 1) (49).

After a review of their full texts, 14 articles were excluded because they were irrelevant. Of the remaining 15 studies, we excluded 14 articles with flaws that made them unfit for inclusion on the basis of our criteria (e.g., no stratification of results according to SGS subgroups and insufficient data on patient demography and anthropometry) (Table 1).

Eventually, only 1 study was eligible for inclusion in this systematic review. The quality of the included study is presented in Table 2,

Table 1. Studies excluded after a full-text review

No.	Author	Year	Reason for exclusion
1	Ingelstedt and Jonson	1966	Not related
2	Empey[36]	1972	No SGS reported
3	Shim et al.	1972	No SGS reported
4	Miller and Hyatt[35]	1973	No SGS reported
5	Yernault et al.[33]	1973	No SGS reported
6	Hyatt	1975	No SGS reported
7	Roncoroni et al.	1975	Not related
8	Ejnell et al.	1984	Not related
9	Hoijer et al.[45]	1991	Multiple pathologies in the patient sample without data stratification
10	Czaja and Mccaffrey[12]	1996	Experimental study on cadavers
11	Wassermann et al.	1999	No stratification of data according to patient subgroups
12	Hautmann et al.	2000	Experimental study on healthy volunteers
13	Nouraei et al.[40]	2007	Experimental study on healthy volunteers
14	Nouraei et al.	2008	No PFT data reported
15	Nouraei et al.	2008	No stratification of data according to patient subgroups
16	Nouraei et al.	2013	No stratification of data according to patient subgroups
17	Nouraei et al.13	2013	Not a longitudinal study
18	Nouraei et al.42	2014	No stratification of data according to patient subgroups
19	Tasche et al.39	2015	Single case report with repeated measurements
20	Martinez Del Pero et al.	2014	PFT not reported; no stratification of demographic data according to subgroups of patients with SGS
21	Pullens et al.44	2015	No stratification of data according to patient subgroups
22	Kraft et al.38	2015	PFT performed for a subgroup of patients without basic demographic data
23	Soldatova et al.	2016	No demographic data reported for patients with SGS
24	Franco et al.	2017	No PFT data reported
25	Cheng et al.	2017	No PFT parameters reported
26	Naunheim et al.	2017	No PFT data reported
27	Abdullah et al.47	2019	No demographic data reported for patients with SGS
28	Tie et al.50	2019	PFT performed for a subgroup of patients without basic demographic data

PFT: Pulmonary function test; SGS: Subglottic stenosis

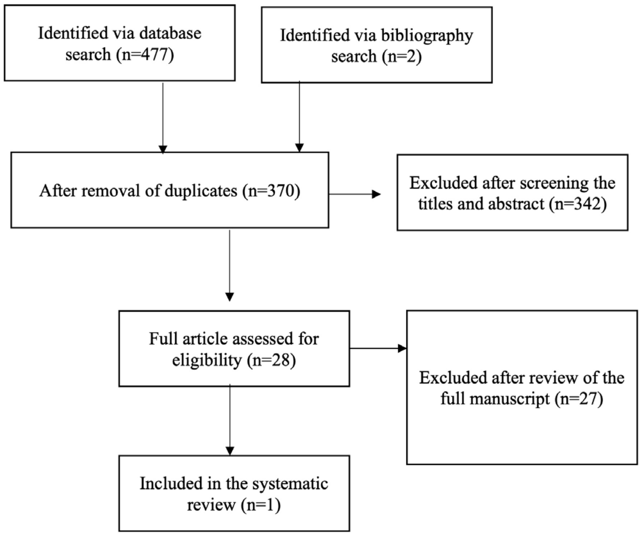

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection

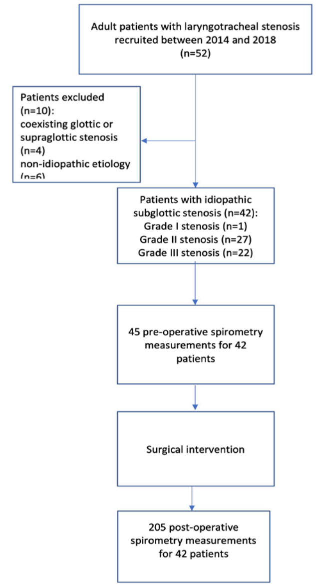

Figure 2. Flow chart of the included study

Table 2. Quality assessment of the included study as assessed by the QUADAS-2 tool

	Risk of bias				Applicability concerns		
Study	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Carpenter et al.[46]	?	O	O	O	O	O	O

The question mark (?) indicates unclear risk, O indicates low risk, and X indicates high risk
QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies 2

Table 3. Basic demographics and pulmonary function test parameter values of patients in the included study

							Before intervention			After intervention		
Study	No. of SGS patients	Age (years)	Height (cm)	Weight (kg)	Tracheostomy status	PFT protocol	No. of PFTs conducted	Mean PEF (L/s)	Mean FEV1/ PEF (s)	No. of PFTs conducted	Mean PEF (L/s)	Mean FEV1/ PEF (s)
Carpenter et al.46	42	Mean 51.5, range (32-72)	Mean 163.2, range (150-180)	Mean 89.4, range (59-182)	Excluded	Spirometry	45	3.19	73.8	206	5.49	44.9

FEV1: Forced expiratory volume in 1 second; PEF: Peak expiratory flow; PFT: Pulmonary function test; SGS: Subglottic stenosis

and the basic demographic data and PFT values of the patients are presented in Table 3. In a retrospective study of 42 patients with idiopathic SGS (grade I [n=1], grade II [n=27], and grade III [n=22]) (Figure 2), Carpenter et al. (46) reported mean PEFs for Cotton-Myer grades I, II, and III lesions as 5.6 (95% confidence interval [CI]: 5.4-5.9), 4.1 (95% CI: 3.7-4.5), and 3.0 (95% CI: 2.5-3.4) L/s, respectively. The mean EDIs for grades I, II, and III lesions were 44.6 (95% CI: 41.7-47.5), 62.2 (95% CI: 58.2-66.1), and 77.9 (95% CI: 73.2-82.5), respectively. The mean TPFs for grades I, II, and III lesions were 9.3 (95% CI: 8.8-9.8), 7.0 (95% CI: 6.4-7.6), and 5.1 (95% CI: 4.4-5.8) L/s, respectively (46).

Discussion

In the 1 eligible study that met our criteria (46), a total of 3 PFT parameters (PEF, TPF, and EDI) were reported to be indicative of SGS. The authors reported an EDI cut-off value of 54 with a sensitivity and specificity of 80.6% and 80.4%, respectively, which indicates the presence of airway obstruction that required surgical intervention. Similarly, they reported a PEF cut-off value of 4.4 L/s (264 L/min) with a sensitivity and specificity of 84.4% and 82.0%, respectively, and a TPF cut-off value of 7.4 L/s (444 L/min) with a sensitivity and specificity of 86.4% and 78.0%, respectively, requiring surgical intervention. Carpenter et al. (46) similarly noted that the PEF, EDI, and TPF were associated with disease severity with regard to the stenotic grade without an overlap between the different grades. Their study also compared the preoperative PFT parameter values with the postoperative parameter values after airway expansion procedures. The preoperative PEF value of 3.19 (95% CI: 2.94-3.43) L/s increased to 5.49 (95% CI: 5.14-5.84) L/s postoperatively, with a mean percentage change of

79.0% (95% CI: 64.6-93.4%). For EDI, the mean preoperative and postoperative values were 73.8 (95% CI: 68.2-78.6) L/s and 44.9 (95% CI: 42.1-47.7) L/s, respectively, with a mean percentage change of 37.5% (95% CI: 33.9-41.1%). These findings indicate that the PFT may be valuable for monitoring the degree of improvement in a patient's condition after a surgical expansion procedure and may be aiding follow-up by identifying the patients who develop airway stenosis recurrence that might require repeated intervention.

Several studies have been published with various reported methods and end points of PFT measurements for monitoring SGS. Kraft et al. (38) retrospectively reviewed 25 patients with SGS who underwent at least 1 balloon dilation and compared the pre and postdilation PFT parameters within 8 weeks after intervention. Among them, for the 17 patients with available PFT parameters, the authors found that the values of PEF, PIF, FEV1/PEF ratio, and FIF50% were significantly different after balloon dilation. During follow-up, a linear relationship was noted between time and both PEF and FEV1/PEF ratio (p=0.0307 and p<0.001, respectively) with differing slope patterns among patients. The PIF and FIF50% generally decrease as the time from surgery increases, but a linear relationship could not be established (38). However, the study did not specify a cut-off point for any PFT parameter that could indicate the presence of airway obstruction. That study also reported the changes in PFT parameters after surgical airway intervention. The pre and post-treatment PEF was 3.89 L/s and 6.67 L/s, respectively, with a median percentage change of 56.7% (p<0.001). The pre and postoperative FEV1/PEF ratios were 0.82 and 0.39 (equivalent to EDI of 82 and 39), respectively, with a median percentage change of 56.0% (p=0.001). These findings are in line with those reported by Carpenter et al. (46), which support the use of the PFT in monitoring patient progress after surgical intervention and during follow-up.

A recently published study by Tie et al. (50) examined the relationship between spirometry and SGS. All the PFT parameters used (PIF rate [PIFR], PEFR, EDI, and FEV1/FVC ratio) significantly differed from the baseline measurements after surgical intervention in the included sample (*n*=12). The PIFR was found to be an excellent indicator of the need for surgical intervention among patients with SGS with a reported sensitivity of 85% and specificity of 83%. The authors reported a cut-off value of 2.10 L/s. The mean pre and postoperative PIFR values were 1.77 L/s and 2.75 L/s, respectively, and they indicated a good response and improvement after treatment. Similarly, the study revealed PEFR to be a good indicator for the need for surgical intervention with a sensitivity of 70% and a specificity of 77% and reported a cut-off value of 2.5 L/s. The mean pre and postoperative PEFR were 2.51 L/s and 4.58 L/s, respectively. The EDI was found to be less specific (sensitivity of 80% and specificity of 62%), with a cut-off value of 75-78. The FEV1/FVC ratio was still less sensitive (sensitivity of 55% and specificity of 85%) with a reported cut-off value of 0.61.

Abdullah et al. (47) investigated the pre and postballoon dilatation changes in the values of FEV1; PEF; FEV1/PEF; FEF25, 50, and 75; and the maximum mid-expiratory flow in 19 patients with varying degrees of SGS. Significant postoperative changes were reported in all indices and ratios after balloon dilatation. The authors noted that no parameters correlated with the severity of SGS according to the Myer-Cotton grading system. However, the mean FEV1/PEF ratio was found to be >10 mL/L/min (equivalent to EDI of 60) in all grades. The authors concluded that this ratio might assist in diagnosis but does not reflect SGS severity. Other spirometry ratios and parameters (actual PEF, actual FEV1, actual predicted PEF, and actual predicted FEV1) did not correlate with different grades of SGS. These findings are contradictory to those reported in previous studies that assessed the association between PFT parameters and SGS severity. This discrepancy in results might be due to the small sample size used in this study.

Nouraei et al. (13) retrospectively reviewed 156 patients with LTS compared with 3,033 healthy subjects and 5,003 patients with other obstructive airway diseases and examined the PEF, FEV1, EDI, and FVC values. A total of 20 of the 156 patients with LTS were diagnosed with isolated SGS, in which 35 PFT measurements were reported. The authors reported high sensitivity and specificity of EDI as a test to differentiate between stenotic and nonstenotic cases. They claimed that an EDI cut-off value of 50 was suggestive of LTS with a sensitivity of 95.9% and a specificity of 94.2%. A higher EDI was found to be indicative of more severe stenosis, with values >75 indicating significant anatomical obstruction requiring surgical intervention. The mean PFT parameters were as follows: FEV1, 2.17 L; FVC, 3.15 L; and PEFR, 3.1 L. The authors recommend a flow-volume loop for patients with EDIs >50 to differentiate between fixed and variable obstructions or between intrathoracic and extrathoracic obstructions and to complete the assessment with DLB, if necessary.

To our knowledge, this is the first systematic review to investigate the role of PFT in the diagnosis of SGS. Our results indicate that there is insufficient evidence to support the use of PFT as a diagnostic tool for SGS because of the lack of consistent PFT values that can be relied on for diagnosis. Furthermore, because of the limited number of studies reporting on PFT values that can be used for diagnosis, a meta-analysis could not be conducted.

We found that many of the previously published studies have various methodological flaws. One of the major issues is a lack of a clear definition of the disease, which makes the study population questionable. In addition, the basic demographic data and comorbidities that might affect the PFT values were neither reported in detail nor stratified in different disease-specific subgroups to aid the extraction of useful data. Moreover, the PFT was performed with different protocols, and the method used was generally not specified.

Conclusion

The PFT is a noninvasive and widely available tool that could be utilized as an adjunctive diagnostic tool to assess the degree of airway obstruction. We advocate that it be used pre and postoperatively in patients with SGS to monitor patient progress during follow-up. Currently, on the basis of the available evidence, using the PFT alone without airway visualization techniques cannot be relied on to establish a diagnosis of SGS. However, it can be of value as an adjunctive diagnostic tool in patients with a highly suggestive clinical picture with an EDI of 54 and PEF value of 4.4 L/s as the presumptive cut-off points, with volume loops suggestive of the presence of upper airway stenosis. Such a tool would be of particular use in rural healthcare centers that do not have the required facilities for airway assessment. However, this conclusion is based on the findings of 1 study. Further studies are needed to confirm the role of PFT in the diagnosis and predictive prognosis of SGS.

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