Diagnosis of Laryngotracheal Stenosis From Routine Pulmonary Physiology Using the Expiratory Disproportion Index

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Objective/Hypothesis: The study's objective was to determine the utility of expiratory disproportion index (EDI), the ratio of forced expiratory volume in 1 second (FEV1) to peak expiratory flow rate (PEFR) (EDI = FEV1[3L]/PEFR[3L/s] × 100), in differentiating between laryngotracheal stenosis (LTS) and other respiratory diagnoses. LTS is an uncommon complication of mechanical ventilation or vasculitis or a manifestation of airway compression or malignancy. It frequently masquerades as asthma and evades timely diagnosis, causing prolonged morbidity and airway-related mortality.

Study Design: Observational study.

Methods: We compared spirometry results of 9,357 healthy subjects and nonstenosis pulmonary patients with 217 cases of LTS. Bootstrap analysis, receiver-operating characteristic (ROC) statistics, and Pearson correlation were used to assess the diagnostic utility of the EDI and its correlation with stenosis severity.

Results: Mean EDI values were 36 ± 7 in nonstenosis cases, 76 ± 17 in benign stenoses, and 69 ± 23 in tracheal cancer (P < .0001). A significant correlation existed between anatomic stenosis severity and EDI (P < .0001; R = 0.61). Area under the ROC curve was 0.98, and at a threshold of >50, EDI had a sensitivity of 95.9% and a specificity of 94.2% in differentiating between stenosis and nonstenosis cases.

Conclusions: EDI can reliably diagnose LTS using routine lung function data. Its simplicity and clinical utility, first recognized by Duncan Empey, are underpinned by a unique physiology whereby PEFR, being determined by total tracheobronchial tree resistance, falls disproportionately compared with FEV1, which is determined within small intrathoracic airways. EDI provides valuable information about the presence and extent of LTS particularly in non-specialist clinical settings and its routine inclusion within standard lung function reports could prevent the prolonged morbidity and mortality that currently result from missed and delayed diagnoses.

Key Words: Laryngotracheal stenosis, pulmonary physiology, screening, early diagnosis.

Level of Evidence: 3b.

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INTRODUCTION

Laryngotracheal stenosis (LTS) refers to a spectrum of diseases that cause ventilatory insufficiency through abnormal narrowing of the central air passageways.1 This condition is notoriously difficult to detect, and as many as four in five LTS patients are initially misdiagnosed2 and then unsuccessfully treated for prolonged periods for presumed “resistant” bronchopulmonary pathologies.1,3 This phenomenon causes significant morbidity and exposes the patient to ongoing and potentially fatal risk of acute-on-chronic respiratory decompensation.4 Moreover, diagnostic delay increases the risk of treatment failure, the need for open cervicomedialisternal surgery in benign diseases5,6 and can lead to the loss of the window of curative intervention in central airway cancers.7

At the heart of this diagnostic shortcoming is the fact that LTS is an uncommon cause8,9 of a very common clinical presentation. Breathlessness occurs in approximately 3% to 5% of young patients and in as many as one in five older patients.10 Most patients with LTS present with a constellation of breathlessness, wheezing, effort intolerance, and reduced peak expiratory flow which, without a high index of clinical suspicion, is very similar to the clinical presentation of lower airway disease.11 Indeed, added airway sounds due to the presence of a known LTS are objectively better characterized as wheeze in a higher proportion of patients than they are as stridor.12

As such, even though LTS can be readily distinguished from bronchopulmonary pathologies with flow-volume loop testing,13,14 because managing the latter diseases does not routinely call for flow-volume loop examination, many patients with LTS are not adequately investigated and remain undiagnosed for prolonged periods with potentially fatal consequences.15–20 In this...
study, we evaluated the utility of the expiratory disproportion index (EDI), a variable that can be calculated from routine lung function data, in diagnosing patients with LTS.

MATERIALS AND METHODS

Study Group

Clinical and lung function data recorded by the Pulmonary Function Laboratory at Charing Cross Hospital were anonymously obtained from a prospectively collected database. Information about patient age, sex, height, weight, forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), peak expiratory flow rate (PEFR) and patient diagnosis were obtained. Predicted values were calculated from a European reference population. The dataset included healthy controls in whom lung function was assessed as part of a historic large-scale population-based study conducted at our institution and patients with different known clinical diagnoses. For patients with non-stenotic diseases, diagnoses were assigned according to the gold standard of diagnosis for the particular condition, and in all cases of LTS this involved direct endoscopic or bronchoscopic examination of the laryngotracheal complex.

The EDI

EDI is the ratio of FEV₁ (expressed in liters) to PEFR (expressed in liters per second) multiplied by 100. The physiologic basis of expiratory disproportion is described in Figure 1.
# TABLE I.

Demographic and Lung Function Variables.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients</th>
<th>No. of Measures</th>
<th>Male Sex, No. (%)</th>
<th>Mean Age, yr (SD)</th>
<th>Mean Height, cm (SD)</th>
<th>FEV₁, L (SD)</th>
<th>FVC, L (SD)</th>
<th>PEFR, L/s (SD)</th>
<th>EDI, s (SD)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>[Range]</td>
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<tr>
<td>Nonstenoses</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>1,600</td>
<td>1,600</td>
<td>857 (54)</td>
<td>44.5 (18.2)</td>
<td>167 (10)</td>
<td>2.29 (0.97)</td>
<td>3.49 (1.19)</td>
<td>6.27 (2.44)</td>
<td>36.7 (7.9)</td>
</tr>
<tr>
<td>COPD</td>
<td>3,403</td>
<td>3,403</td>
<td>1,311 (39)</td>
<td>68.8 (10.2)</td>
<td>166 (9)</td>
<td>1.32 (0.67)</td>
<td>2.49 (0.95)</td>
<td>3.95 (1.87)</td>
<td>34.1 (8.4)</td>
</tr>
<tr>
<td>Healthy individual</td>
<td>3,033</td>
<td>3,033</td>
<td>1,499 (49)</td>
<td>55.7 (17.3)</td>
<td>167 (10)</td>
<td>2.77 (0.92)</td>
<td>3.56 (1.1)</td>
<td>7.26 (2.34)</td>
<td>38.8 (7.7)</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>959</td>
<td>959</td>
<td>512 (53)</td>
<td>21.9</td>
<td>165 (10)</td>
<td>1.87 (0.72)</td>
<td>2.42 (0.91)</td>
<td>5.68 (2.22)</td>
<td>34 (8)</td>
</tr>
<tr>
<td>Pulmonary sarcoidosis</td>
<td>317</td>
<td>317</td>
<td>166 (52)</td>
<td>43.7 (14.5)</td>
<td>168 (10)</td>
<td>2.78 (1.03)</td>
<td>3.56 (1.24)</td>
<td>7.69 (2.58)</td>
<td>36.6 (8.1)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>45</td>
<td>45</td>
<td>24 (53)</td>
<td>64.9 (16.5)</td>
<td>163 (10)</td>
<td>1.81 (0.67)</td>
<td>2.3 (0.84)</td>
<td>5.7 (2.37)</td>
<td>33 (8.4)</td>
</tr>
<tr>
<td>Total for nonstenoses</td>
<td>9,357</td>
<td>9,357</td>
<td>4,369 (47)</td>
<td>59 (17.6)</td>
<td>166 (10)</td>
<td>2.06 (1.04)</td>
<td>3.04 (1.18)</td>
<td>5.73 (2.63)</td>
<td>36.1 (8.7)</td>
</tr>
<tr>
<td>Stenoses</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Glottic and tracheal stenosis</td>
<td>7</td>
<td>10</td>
<td>1 (14)</td>
<td>42.9 (15.3)</td>
<td>164 (9)</td>
<td>1.51 (0.56)</td>
<td>2.53 (0.58)</td>
<td>1.71 (0.85)</td>
<td>94.1 (13.6)</td>
</tr>
<tr>
<td>Bilateral vocal fold immobility</td>
<td>16</td>
<td>18</td>
<td>7 (44)</td>
<td>42 (18.6)</td>
<td>165 (12)</td>
<td>1.84 (0.68)</td>
<td>2.81 (0.87)</td>
<td>2.41 (1.18)</td>
<td>80.7 (17.4)</td>
</tr>
<tr>
<td>Idiopathic subglottic stenosis</td>
<td>20</td>
<td>35</td>
<td>0 (0)</td>
<td>46.4 (7.6)</td>
<td>160 (8)</td>
<td>2.17 (0.6)</td>
<td>3.15 (0.45)</td>
<td>3.1 (0.39)</td>
<td>76.5 (18)</td>
</tr>
<tr>
<td>Intubation related</td>
<td>65</td>
<td>85</td>
<td>30 (46)</td>
<td>46.5 (18.2)</td>
<td>165 (11)</td>
<td>1.97 (0.81)</td>
<td>2.8 (0.91)</td>
<td>2.87 (1.49)</td>
<td>74.1 (16.9)</td>
</tr>
<tr>
<td>Laryngeal pemphigoid</td>
<td>3</td>
<td>4</td>
<td>1 (33)</td>
<td>44.6 (14.6)</td>
<td>163 (15)</td>
<td>2.03 (0.72)</td>
<td>2.61 (0.75)</td>
<td>2.73 (1.35)</td>
<td>75.9 (15.8)</td>
</tr>
<tr>
<td>Laryngeal sarcoidosis</td>
<td>6</td>
<td>9</td>
<td>1 (17)</td>
<td>46.7 (18.6)</td>
<td>160 (10)</td>
<td>2.0 (0.43)</td>
<td>2.85 (0.63)</td>
<td>2.62 (0.68)</td>
<td>77.8 (11.1)</td>
</tr>
<tr>
<td>Radiation related</td>
<td>2</td>
<td>3</td>
<td>2 (100)</td>
<td>60.8 (5.4)</td>
<td>170 (15)</td>
<td>2.42 (0.31)</td>
<td>2.93 (0.53)</td>
<td>3.44 (0.4)</td>
<td>71.5 (16.5)</td>
</tr>
<tr>
<td>Respiratory papillomatosis</td>
<td>1</td>
<td>1</td>
<td>1 (100)</td>
<td>23</td>
<td>180</td>
<td>4.34</td>
<td>5.06</td>
<td>8.52</td>
<td>50.9</td>
</tr>
<tr>
<td>TB tracheal stricture</td>
<td>2</td>
<td>2</td>
<td>0 (0)</td>
<td>37.8 (18.7)</td>
<td>165 (10)</td>
<td>1.79 (0.04)</td>
<td>2.35 (0.23)</td>
<td>3.04 (0.62)</td>
<td>60.2 (13.4)</td>
</tr>
<tr>
<td>Tracheal malignancy</td>
<td>13</td>
<td>13</td>
<td>9 (69)</td>
<td>66.5 (15.5)</td>
<td>169 (7)</td>
<td>1.52 (0.93)</td>
<td>2.71 (1.36)</td>
<td>2.35 (1.33)</td>
<td>69.4 (22.8)</td>
</tr>
<tr>
<td>Wegner's granulomatosis</td>
<td>21</td>
<td>37</td>
<td>10 (48)</td>
<td>45.1 (15.9)</td>
<td>165 (13)</td>
<td>1.97 (0.78)</td>
<td>3.07 (0.96)</td>
<td>2.71 (1.08)</td>
<td>74.9 (14.6)</td>
</tr>
<tr>
<td>Total for stenoses</td>
<td>156</td>
<td>217</td>
<td>62 (40)</td>
<td>47.2 (17.2)</td>
<td>165 (11)</td>
<td>1.96 (0.76)</td>
<td>2.89 (0.87)</td>
<td>2.78 (1.38)</td>
<td>75.8 (17)</td>
</tr>
<tr>
<td>Total</td>
<td>9,513</td>
<td>9,574</td>
<td>4,431 (47)</td>
<td>58.7 (17.6)</td>
<td>166 (10)</td>
<td>2.06 (1.04)</td>
<td>3.03 (1.17)</td>
<td>5.66 (2.64)</td>
<td>37 (10.7)</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease; EDI = expiratory disproportion index; FEV₁ = forced expiratory volume in 1 second; PEFR = peak expiratory flow rate; SD = standard deviation; TB = tuberculosis.
Statistical Analysis

Categoric and continuous variables were expressed as binomial percentages and means with standard deviations. Receiver operating characteristic (ROC) statistics were used to determine the diagnostic utility of lung function variables and EDI in differentiating between LTS and the other diagnoses. Optimal sensitivity, specificity, and positive and negative predictive values associated with different EDI thresholds were determined using bootstrap analysis. Pearson correlation was used to investigate the impact of different degrees of upper airway obstruction on EDI. Data were analyzed with MedCalc software (Mariakerke, Belgium), and in all cases \( P < .05 \) was considered statistically significant.

RESULTS

General

Lung function test results of 9,513 adult patients were anonymously retrieved from the prospectively collected database of the pulmonary function laboratory at Charing Cross Hospital. There were 3,033 normal subjects, 5,003 patients with obstructive airway diseases including 1,600 patients with asthma, and 1,321 patients with pulmonary fibrosis, as well as 217 lung function measurements from 156 patients with LTS. Repeated measures from the same patients were only included in cases of late stenosis recurrence. Table I provides further information about patient demographics, lesion characteristics in patients with LTS, and pulmonary function results.

There was a significant difference in EDI values between stenosis and nonstenosis patients \( (P < .0001; \) analysis of variance). There were significant differences in EDI values within the group of patients with glottic, subglottic, or tracheal stenoses and between patients with different anatomic severities of subglottic/tracheal stenosis (Fig. 2). A significant correlation between anatomic stenosis severity and EDI \( (r = 0.61; P < .0001; \) Pearson \( \rho \) ) was identified.

Diagnostic Utility of the EDI

Area under the ROC curve for EDI in differentiating between stenosis and nonstenosis cases was 0.980 \( (95\% \) confidence interval, 0.968-0.992). The optimal sensitivity and specificity tradeoff was determined at 50.6 by bootstrap analysis and at a threshold of >50; EDI had a sensitivity of 95.9\% and a specificity of 94.2\% for differentiating between stenosis and nonstenosis cases (Fig. 3).

DISCUSSION

Our data suggest that the EDI is a sensitive and specific physiologic test for diagnosing LTS as a cause of pulmonary symptoms. It can be deployed in routine clinical practice without the need to subject most patients with lower airway pathologies to investigations over and
above what is necessary for the routine assessment of their presumptive bronchopulmonary diagnoses.

The high sensitivity and specificity of EDI in differentiating between stenosis and nonstenosis cases can be explained through the impact of the presence of an upper airway obstruction on ventilatory physiology. The presence of an obstructive upper airway lesion increases the total resistance of the tracheobronchial tree, which reduces PEFR. The volume of air that can be forcibly expired in 1 second from total lung capacity is determined, however, to a significant degree, by intrinsic elastic recoil of the lungs and dynamic resistance of the small intrathoracic airways, whose elastic collapsible nature explains the long-recognized phenomenon of expiratory flow limitation (Fig. 1). 23 Disproportionate reduction in PEFR in relation to FEV \(_1\), first recognized by Empey, 25 makes EDI a very useful noninvasive test for LTS.

The present study confirms the sensitivity and specificity of EDI as a diagnostic test in a large population and identifies an optimal diagnostic threshold. This study also provides evidence of the utility of the test in determining the urgency with which treatment should be considered and whether or not office-based interventions are likely to be effective or safe. Patients with grade 3 tracheal or laryngeal obstruction are at the greatest risk of sudden acute-on-chronic respiratory decompensation. This is because of the nonlinear relationship between anatomic severity of the stenosis and impairment to airflow. 26 While there are overlaps between anatomic disease severity and EDI values, patients with EDI values greater than 75 are significantly more likely to have a severe anatomic obstruction, and this should direct the treating clinician to consider emergent, rather than urgent, treatment. This may also provide supporting information to help clinicians decide on whether the office or the operating theater may be the safest environment to undertake airway surgery for a particular patient. LTS is often classified as fixed or variable and intrathoracic or extrathoracic; the study population contained a selection of the different disease subtypes. The stenosis can be classified as fixed or variable depending on whether it impairs inspiration and expiration variably or to the same degree and as intrathoracic or extrathoracic depending on whether this variation predominantly affects inspiration or expiration. 13 EDI is derived from expiratory indices and as such it cannot differentiate between fixed or variable, or intrathoracic or extrathoracic obstructions. It can, however, reliably identify the presence of an upper airway obstruction, which can then be further characterized using a flow-volume loop.

Addition of FEV \(_1/\)PEFR to routine lung function testing can provide useful information about upper airway obstruction in the same way that FEV \(_1/FVC\) currently provides information about lower airway obstruction. EDI can identify and reliably point towards upper airway obstruction as a possible cause of respiratory symptoms in unsuspected cases and therefore significantly reduce the likelihood of diagnostic mislabelling and the potentially fatal consequences of delayed or missed diagnosis in LTS. In addition, it can be used as a screening tool for defined at-risk populations like patients who have been mechanically ventilated or have Wegener's granulomatosis. In this respect it could be an important addition to the otolaryngologist's diagnostic armamentarium, as we are regularly called upon to evaluate and provide follow-up for patients with these conditions. We recommend that patients with EDI values >50 be referred for flow-volume loop examination, and if necessary, bronchoscopy to confirm the diagnosis.

**CONCLUSION**

We have shown in a large population that a simple physiologic measurement which can already be calculated from routine lung function data can be used to differentiate between upper and lower airway disease with highly significant sensitivity and specificity. We propose that FEV \(_1/\)PEFR should be routinely calculated and reported as part of pulmonary function testing to allow this commonly performed investigation to provide an assessment of upper, as well as lower, airway pathology.
BIBLIOGRAPHY


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