Pulmonary Function and Flow Volume Loop Patterns in Patients with Tracheobronchomalacia.

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Dr. Majid has no conflicts of interest to disclose; Dr. Sosa has no conflicts of interest to disclose; Dr. Ernst has no conflicts of interest to disclose; Dr. Feller-Kopman has no conflicts of interest to disclose; Dr. Folch has no conflicts of interest to disclose; Dr. Anup Singh has no conflicts of interest to disclose; Dr. Gangadharan has no conflicts of interest to disclose.
*Both authors contributed equally to planning, data collection, data analysis and writing of the manuscript.

**Abbreviations:**

PFTs= Pulmonary function tests

FVLs= Flow volume loops

TBM= tracheobronchomalacia

FEFmax= maximal forced expiratory flow

CT= Computed Tomography

GOLD= Global Obstructive Lung Disease initiative

TLC= Total Lung Capacity

ATS= American Thoracic Society

BMI= Body Mass Index

FEV1= Forced expiratory volume in first second

FVC= Forced Volume capacity
Abstract

**BACKGROUND:** Patterns of pulmonary function tests (PFTs) and flow-volume loops (FVLs) among patients with clinically significant tracheobronchomalacia (TBM) are not well described. Small studies suggest four main FVL morphologies: low maximal forced expiratory flow (FEFmax), biphasic expiratory curve, flow oscillations and notching. **OBJECTIVE:** To describe common pulmonary function test (PFT) and FVL patterns among the largest prospective series of patients to date undergoing clinical evaluation for symptomatic moderate to severe TBM. **METHODS:** We conducted a retrospective analysis of prospectively collected data from patients who were referred to the Chest Disease Center from January 2002 to December 2008 with respiratory symptoms that were attributed primarily to TBM. PFT results of 90 patients with symptomatic moderate to severe TBM were evaluated. **RESULTS:** By PFTs, 40 (44.4%) patients had an obstructive ventilatory defect, 16 (17.8%) had a definite or highly likely restrictive ventilatory defect, 15 (16.7%) had a mixed defect, and 19 (21.1%) were within normal limits. Among 76 patients with available FVLs, the most frequent finding was low FEFmax in 62 (81.6%) cases, followed by biphasic morphology 15 (19.7%), notched expiratory loop 7 (9.2%) and expiratory oscillations 2 (2.6%). The balance of 13 patients (17.1%) had no distinctive FVL abnormality. **CONCLUSION:** PFTs and FVLs are normal in a significant number of patients with moderate to severe TBM and should not be used to decide whether tracheobronchomalacia is present or clinically significant.
Introduction

Tracheobronchomalacia (TBM) is an increasingly recognized condition associated with hypercompliant central airways.\(^1,2,3\) While the pathogenesis of diffuse TBM is often not known, it frequently occurs in patients with chronic airway inflammation.\(^1,2\) TBM has been identified in 1 to 4.5% of all patients undergoing bronchoscopy, 23% of patients with chronic bronchitis undergoing bronchoscopy, and 14.1% of patients with chronic cough.\(^4-7\) The most frequent presenting signs and symptoms include dyspnea on exertion, intractable cough, orthopnea, mucostasis and recurrent infections.\(^2,4,8,9\)

The diagnosis of TBM may be challenging, as patients often have other chronic pulmonary conditions such as asthma or COPD that may explain their symptoms. Formal diagnosis can be made with dynamic flexible bronchoscopy (Image 1) and dynamic airway computed tomography (CT) (Image 2).\(^2,3\) However, most patients will have pulmonary function tests (PFTs) as part of the initial work up for their presenting symptoms. While some characteristic PFT and FVL patterns have been described in patients with TBM, the prevalence and diagnostic utility of these patterns have not been determined in a large, well defined, cohort of patients.\(^2,4\)

With increased awareness of TBM as an independent cause of clinical symptoms and functional impairment, the need for a standard diagnostic workup becomes more important. This is especially true in light of effective available therapies, such as airway stenting, tracheoplastastic
surgery and continuous positive airway pressure. Therefore, the role of PFTs in the initial evaluation of TBM needs to be better defined.

Our objective is to describe the most common PFT and FVL patterns in a large series of patients undergoing evaluation for symptomatic moderate to severe diffuse TBM.

**Materials and Methods**

This protocol was approved by the Institutional Review Board, Committee on Clinical Investigation at Beth Israel Deaconess Medical Center (research protocol #2005P-000112), and all patients undergoing evaluation for symptomatic TBM were asked to provide informed consent to become a part of the TBM database for future publications. We conducted a retrospective analysis of prospectively collected data from patients who were referred to the Chest Disease Center from January 2002 to December 2008 with respiratory symptoms that were attributed primarily to TBM. These patients are referred to our center by primary care physicians, pulmonologists and thoracic surgeons from around the country for further evaluation and treatment of suspected TBM. All patients with baseline PFTs prior to any airway intervention were included. Exclusion criteria included a prior airway intervention and mild or no TBM.

Moderate to severe TBM was defined as more than 75% collapse of the airway lumen anywhere along the trachea, mainstem bronchi and bronchus intermedius on forced expiration during a dynamic flexible bronchoscopy. Age, sex, comorbidities, and respiratory symptoms were also recorded.

Dynamic flexible bronchoscopies were performed under light sedation and topical anesthesia. The bronchoscope was advanced into the proximal trachea and the patient was instructed to
forcefully inhale and exhale. This sequence was repeated at the mid-trachea, distal trachea, proximal to the ostium of both mainstem bronchi and bronchus intermedius. The procedure was video recorded in order to generate airway images for subsequent quantitative analysis.

PFTs were all performed using NSpire™ equipment (NSpire Health- LLC, Louisville, CO). The equipment meets ATS standards and follows daily calibration. All maneuvers were done ensuring proper patient effort and reproducibility. Spirometry, lung volumes, and diffusing capacity for carbon monoxide (DLCO) were performed following the ATS guidelines. All results were interpreted by a board certified pulmonologist.

Statistical Analysis

The study is descriptive and results are expressed as frequencies, proportions, medians, means and standard deviations as appropriate. The program used was Microsoft Office Excel 2007 (Redmond, Washington, USA). Statistical analyses were performed by one of the study authors (AFS).

Results

At the time of data collection, 172 patients were referred for evaluation of symptomatic TBM. Ninety patients had both confirmed moderate to severe TBM, and baseline PFTs performed prior to any airway intervention. FVLs were available in 76 (84.4%) of those patients (Figure 1). Fifty-eight (33.7%) had moderate or severe TBM but were excluded due to prior airway interventions (i.e. T-tubes, tracheotomies, stents). Twenty-one patients (12.2%) who had mild TBM and three (1.7%) patients those did not have TBM were also excluded.

The median age of patients in this sample was 65 years (31-95 years), 40 (44%) patients were men, and mean BMI was 30 (+/-6). Forty-three (47.8%) had been diagnosed with COPD, and 21
(23%) had been diagnosed with asthma (Tables 1-2). The most common presenting symptoms 
(Table 3) were dyspnea on exertion 71 (78.9%), severe chronic cough 63 (70%) and recurrent 
respiratory infections 48 (53.3%).

By PFT, 40 of 90 patients (44.4%) had airflow obstruction (defined as FEV1 <80% and 
FEV1/FVC <70% of predicted), 16 (17.8%) had definite or highly likely restriction defined 
respectively as TLC <80% of predicted or, in the absence of TLC measurement, reduced FVC 
with normal FEV1/FVC ratio. 15 (16.7%) had a mixed defect, and 19 (21.1%) were within 
normal limits. PFT values are shown in table 1.

Among patients with FVL (Table 4), the most frequent finding was a below predicted FEFmax in 
62 (81.6%), followed by biphasic morphology in 15 (19.7%); this pattern showed a rapid peak 
and decline in expiratory flow followed by a prolonged plateau extending throughout most of the 
expiratory maneuver (Figure 1A). Notched expiratory loop was seen in 7 (9.2%) patients who 
showed a rapid mid-expiratory dip and return of flow without other indications of cough and that 
was reproducible in several maneuvers (Figure 1B); expiratory oscillations were documented in 
2 (2.6%) patients and were characterized by reproducible large amplitude high frequency 
oscillations over much of the expiratory loop (Figure 1C). The balance of patients 13 (17.1%) had 
no distinctive abnormal FVL characteristics. These findings were not mutually exclusive, and a 
below normal FEFmax was also present in the other three patterns.

Lung volumes and DLCO were obtained in 63 patients. The mean percent predicted total lung 
capacity (TLC) was 86.8 (+/-17.7), residual volume (RV) was 105 (+/- 35.5), and RV/TLC was 
119 (+/- 32.7). The mean percent predicted DLCO was 70.4 (+/-28.3). The spirometric values 
from the groups with and without lung volumes did not differ significantly.
Discussion

In this large series of patients with symptomatic moderate to severe diffuse TBM, we found that pulmonary function tests demonstrate no characteristic and/or common pattern that would help to screen patients during an initial diagnostic workup. Although a substantial number of patients were unable to achieve predicted FEFmax (81.6%), this index does not seem reliable, especially in light of almost 20% of patients showing normal values.

The biphasic morphology is also characterized by a low FEF max which is followed by a rapid fall in flow resulting in a plateau of very low flow for the remainder of exhalation. This pattern was described in 8 of 11 patients with TBM in an observational study by Campbell and Faulks. 

Gandevia also described in 10 patients with emphysema and TBM an initial phase of rapidly exhaled gas, followed by a linear phase of constant, slow flow.

Nuutinen et al and Wyss have described a notch in the expiratory limb of the FVL as typical of TBM. 

The notch was thought to be due to sudden decrease of flow with airway collapse. Their findings contrast with those of the current study, where only 7 (9.2%) patients showed this particular finding. Campbell and Faulks thought that this finding was likely an artifact caused by the water filled spirometer. 

Reinert and Steurich were unable to correlate this pattern with central bronchial collapse. The finding of reproducible notching in only 7 patients in our study suggests that this does not seem to be a particularly reliable indicator of TBM.

Rapid flow oscillations have been defined by Vincken and Cosio as a “reproducible sequence of alternating accelerations and decelerations of flow, creating a saw-tooth pattern superimposed on the general contour of the flow-volume loop produced by the awake subject”. This pattern can be explained by the fact that rapid changes in either driving pressure or airway resistance, can
occur during inspiration and expiration, and have a characteristic frequency of 4-60Hz. These oscillations have been described in different structural or functional disorders of the upper airways including obstructive sleep apnea and neuromuscular disorders (i.e. essential tremor, Parkinson’s, Shy-Drager). Garcia-Pachon described oscillations in a patient with TBM. However, in the present study, oscillations were noted in the expiratory curve of only 2 (2.6%) patients. Although the observed frequency is roughly almost twice that described in the general population, it is still quite infrequent.

Interestingly, 17.1% of patients in our series had a normal flow volume loop. This suggests that compression of the central airways due to TBM is not necessarily the cause of airflow obstruction and that expiratory flow limitation occurs in more peripheral airways. This finding is supported by Loring et al., who described airway pressure-area characteristics by relating airway narrowing to the pressure differences measured across the central airway wall during graded expiratory efforts. They concluded that central airway collapse did not correlate with the degree of obstruction assessed by FEV1 and could be seen irrespective of the degree of expiratory flow limitation. Samad et al., found no correlation between degree of airflow obstruction and tracheobronchial collapse during cough. Reinert and Steurich also found no strong correlations between central airway collapse and lung function parameters in 30 unselected male patients. Consistent with this observation, previous studies have shown that clinical improvement after central airway stabilization is not always associated with an increase in FEV1.

The low mean DLCO seen in our study is likely explained by the high prevalence of parenchymal lung disease in this patient population. It is possible that patients with emphysema
may also have a greater tendency for expiratory central airway collapse due to loss of elastic recoil with reduced airway tethering. It is conceivable that sequelae from copious airway secretions, mucous plugging and from recurrent infections as seen in TBM may lower the diffusing capacity in the absence of primary parenchymal lung disease. We did not find other studies that explore the relationship between diffusing capacity and TBM.

An important limitation in the present study includes the absence of a control group, the entire population of patients included had moderate to severe TBM. We therefore cannot assess the specificity of various PFT abnormalities that may predict the presence of TBM. However, there were a significant number of patients with normal PFTs. Since this finding alone allows some speculation to suggest poor sensitivity, one could make an argument that PFTs are not a precise screening tool for the presence of moderate to severe TBM.

It is also important to mention that many healthy subjects have a forced expiratory collapse > 75%, so the finding of TBM may not have been pathologic in part of our sample population.

Conclusions

Pulmonary function tests are often used in the evaluation of patients with symptomatic TBM. Although some characteristic patterns in the expiratory limb of the flow volume loop have been described, these seem unreliable for the diagnosis of TBM. Of particular interest, a significant percentage of these patients may have normal PFTs. This suggests that a diagnosis of TBM should not be ruled out in the setting of persistent symptoms with normal PFTs. At the same time, it is important to keep in mind that forced expiratory collapse exceeding what is currently viewed as normal, may not be a pathologic finding. Based on our findings, the workup of
TBM should rely on dynamic airway CTs or bronchoscopy and normal PFTs should not drive one away from pursuing this diagnosis.

Acknowledgements:

Dr. Majid: contributed to the conception, planning, data collection, data analysis and writing of the manuscript and takes responsibility for the integrity of the work as a whole, from inception to published article.

Dr. Sosa: contributed to the planning, data collection, data analysis and writing of the manuscript and takes responsibility for the integrity of the work as a whole, from inception to published article.

Dr. Ernst: contributed to the planning, data collection, and manuscript review.

Dr. Feller-Kopman: contributed to manuscript review.

Dr. Folch: contributed manuscript review.

Dr. Anup Singh: contributed to manuscript review.

Dr. Gangadharan: contributed to manuscript review.

Other contributions:

We thank Dr. Rabih Bechara, Dr. Arthur Sung, Dr. Jed Gorden, Dr. Chakravarty Reddy, Dr. Saleh Alazemi, Dr. David Berkowitz, Dr. Dilip Nataraj, Dr. Samaan Rafeq and Dr. Archan Shah for help in gathering the data.
References


**Table 1.** Patient Demographics and PFTs

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean(SD)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.34(13)</td>
<td>65</td>
</tr>
<tr>
<td>BMI (Kg/meter2)</td>
<td>30.67(5.79)</td>
<td>30</td>
</tr>
<tr>
<td>FEV1 (Liter)</td>
<td>1.55(0.8)</td>
<td>1.37</td>
</tr>
<tr>
<td>% of Predicted values</td>
<td>61.7(27.59)</td>
<td>61.5</td>
</tr>
<tr>
<td>FVC (Liter)</td>
<td>2.42(1.04)</td>
<td>2.26</td>
</tr>
<tr>
<td>% of Predicted values</td>
<td>68.51(21.85)</td>
<td>65.5</td>
</tr>
<tr>
<td>FEV1/FVC%</td>
<td>63.2(16.36)</td>
<td>66</td>
</tr>
<tr>
<td>TLC (liter) (n=63)</td>
<td>4.85(1.38)</td>
<td>4.62</td>
</tr>
<tr>
<td>% of Predicted values</td>
<td>86.84(17.71)</td>
<td>89</td>
</tr>
<tr>
<td>RV(liter) (n=63)</td>
<td>2.1(0.76)</td>
<td>1.97</td>
</tr>
<tr>
<td>% of Predicted values</td>
<td>105(35.46)</td>
<td>99</td>
</tr>
<tr>
<td>IC(Liter)</td>
<td>2.3(0.87)</td>
<td>2.13</td>
</tr>
<tr>
<td>% of Predicted values</td>
<td>94(26.7)</td>
<td>95</td>
</tr>
<tr>
<td>RV/TLC(Liter)(n=63)</td>
<td>44(11.93)</td>
<td>44</td>
</tr>
<tr>
<td>% of Predicted values</td>
<td>119.01(32.72)</td>
<td>113</td>
</tr>
<tr>
<td>DLCO (mL CO/min/mm Hg ) (n=63)</td>
<td>15.72(7.4)</td>
<td>14.44</td>
</tr>
<tr>
<td>% of Predicted values</td>
<td>70.46(28.31)</td>
<td>66</td>
</tr>
</tbody>
</table>

**Table 2.** Accompanying Diagnosis in Patients with Moderate to Severe Diffuse TBM

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>43(47.78)</td>
</tr>
<tr>
<td>Asthma</td>
<td>21(23.33)</td>
</tr>
<tr>
<td>OSA</td>
<td>24(26.66)</td>
</tr>
<tr>
<td>ILD</td>
<td>2(2.22)</td>
</tr>
<tr>
<td>GERD</td>
<td>40(44.44)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>4(4.44)</td>
</tr>
<tr>
<td>Mounier-Kuhn</td>
<td>2(2.22)</td>
</tr>
<tr>
<td>Relapsing polychondritis</td>
<td>3(3.33)</td>
</tr>
<tr>
<td>None</td>
<td>4(4.44)</td>
</tr>
<tr>
<td>Other</td>
<td>12(13.33)</td>
</tr>
</tbody>
</table>
Table 3. Presenting Symptoms and history in Patients with Moderate to Severe Diffuse TBM

<table>
<thead>
<tr>
<th>Presenting and History</th>
<th>Total(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to Clear secretions</td>
<td>9(10)</td>
</tr>
<tr>
<td>Recurrent Infections</td>
<td>48(53.33)</td>
</tr>
<tr>
<td>Severe Cough</td>
<td>63(70)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1(1.11)</td>
</tr>
<tr>
<td>SOB/DOE</td>
<td>71(78.88)</td>
</tr>
<tr>
<td>Choking</td>
<td>4(4.44)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>7(7.77)</td>
</tr>
<tr>
<td>Stridor</td>
<td>1(1.11)</td>
</tr>
<tr>
<td>Respiratory Failure</td>
<td>4(4.44)</td>
</tr>
<tr>
<td>Sputum production</td>
<td>4(4.44)</td>
</tr>
<tr>
<td>OTHER</td>
<td>3(3.33)</td>
</tr>
<tr>
<td>Prior Intubation</td>
<td>1(1.11)</td>
</tr>
</tbody>
</table>

Table 4. FVL Morphology in Patients with Moderate to Severe Diffuse TBM

<table>
<thead>
<tr>
<th>FVL</th>
<th>Total(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Peak (FEFmax)</td>
<td>62(81.6)</td>
</tr>
<tr>
<td>Biphasic</td>
<td>15(19.73)</td>
</tr>
<tr>
<td>Notching</td>
<td>7(9.2)</td>
</tr>
<tr>
<td>Oscillations</td>
<td>2(2.6)</td>
</tr>
<tr>
<td>Normal</td>
<td>13(17.1)</td>
</tr>
</tbody>
</table>
Image 1: Dynamic Flexible Bronchoscopy

(a) Forced Inhalation  
(b) Forced Exhalation
Image 2. Dynamic Airway CT

(a) Forced Inhalation  (b) Forced Exhalation
Figure 1. Flow Volume Loop Morphology

(a) Biphasic morphology  (b) Notched expiratory loop  (c) Oscillations