Detection of Upper Airway Obstruction With Spirometry Results and the Flow-Volume Loop: A Comparison of Quantitative and Visual Inspection Criteria

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BACKGROUND: There are important gaps in our understanding of the epidemiology and diagnosis of upper-airway obstruction. METHODS: We examined the diagnostic value of several criteria for predicting upper-airway obstruction, and we measured the frequency of detecting upper-airway obstruction via quantitative and visual assessment of flow-volume loops. We studied 4 quantitative and 3 visual criteria for their ability to detect upper-airway obstruction. The quantitative criteria were: ratio of forced expiratory volume in the first second (FEV_1) to maximum expiratory flow (MEF) > 10 mL/L/min; ratio of the flow at the mid-point of the forced expiratory maneuver ($MEF_{50\%}$) to the flow at the mid-point of the forced inspiratory maneuver ($MIF_{50\%}$) < 0.3 or > 1; $MIF_{50\%}$ < 100 L/min; and $FEV_1/FEV_{0.5}$ > 1.5. The visual criteria were: presence of a plateau; biphasic shape; and oscillations. The accepted standard tests for diagnosing upper-airway obstruction were bronchoscopy, laryngoscopy, and chest or neck computed tomogram. We considered 979 consecutive flow-volume loops from the Cleveland Clinic's pulmonary function laboratory. We calculated the sensitivity, specificity, and positive and negative predictive values of the individual criteria and an aggregate criterion for predicting upper-airway obstruction. RESULTS: We excluded 504 flow-volume loops because the workups for those patients did not include any of the accepted standard tests for diagnosing upper-airway obstruction, so there were 475 eligible flow-volume loops (48.6% of the 979 loops considered). Thirty-six (7.5%) of the 475 workups that included an accepted standard test reported a cause of upper-airway obstruction. The aggregate sensitivity for detecting upper-airway obstruction was 69.4%. Receiver-operating-curve analysis found that the individual criteria had poor diagnostic performance (area under the curve < 0.522) but that a newly proposed aggregate criterion performed better (area under the curve 0.605). CONCLUSIONS: The prevalence of reported upper-airway obstruction was 7.5%. The quantitative criteria showed low sensitivity for detecting upper-airway obstruction but exceeded that of visual criteria. The aggregate criterion increased the sensitivity to 69.4%, which suggests the need for additional criteria to help predict upper-airway obstruction. *Key words: upper-airway obstruction, flow-volume curve, pulmonary function test, spirometry.* [Respir Care 2009;54(4):474–479. © 2009 Daedalus Enterprises]

Introduction

Upper-airway (ie, tracheal) obstruction has been the subject of growing attention since the early 1970s, when Miller and Hyatt[1] and Yernault et al[2] first proposed diagnostic criteria. Since then, various criteria, based on visual inspection of the flow-volume loop without quantitative metrics ("visual criteria") and/or measurement of various flows ("quantitative criteria"), have been proposed for detecting structural and functional upper-airway abnormalities. Indeed, the value of flow-volume loops for diagnosing up-

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per-airway obstruction, and various characteristics of the loop for identifying specific upper-airway abnormalities have been examined in various settings, including in children,[3] following single lung transplantation (to diagnose focal bronchial obstruction),[4] and with fixed and variable tracheal lesions.[5,6] Despite this broad attention to the diagnostic value of the flow-volume loop and studies to correlate flow-volume-loop features with various other diagnostic techniques (eg, tantalum tracheography,[5] tracheal fluoroscopy,[6] and bronchoscopy[6]), important gaps remain in our understanding of the epidemiology and diagnosis of upper-airway obstruction.[7] Specifically, what is the prevalence of upper-airway obstruction? How do the available visual and quantitative criteria compare in their ability to detect upper-airway obstruction? The present study addresses these questions based on a consecutive series of pulmonary function tests performed in the pulmonary function laboratory of the Cleveland Clinic.

Methods

This study was approved by the investigational review board of the Cleveland Clinic. The data set consisted of 995 consecutive spirometries performed at the Cleveland Clinic's pulmonary function laboratory during January 2006. We chose that data set based on convenience; the data were available in our recently implemented database (Viasys Healthcare, Yorba Linda, California). Spirometry was performed with 2 spirometry systems (MasterScreen Body and MasterScope, Jaeger, Würzburg, Germany). If a patient underwent multiple spirometry sessions in January 2006 ($n = 16$), only the first session was included in the sample, so there were 979 evaluable spirometries.

The goal of each spirometry session was to obtain 3 acceptable forced expiratory efforts, with repeatability (2 forced vital capacity and 2 forced expiratory volume in the first second [FEV_1] measurements within 0.15 L of the largest value). At the end of each exhalation, the patient was coached to inspire to total lung capacity as rapidly as possible. Three inspiratory efforts were routinely performed, and the one with the highest mid-inspiratory flow ($MIF_{50\%}$) and maximum inspiratory flow (MIF) was considered the best inspiratory curve and selected for analysis. From the expiratory maneuvers, the highest forced vital capacity and FEV_1 were reported, even if they were from different efforts. All other variables were reported from the best expiratory curve, which was the effort that had the highest combined sum of forced vital capacity and FEV_1. The expiratory and inspiratory flow-volume curves were reported from the best expiratory and inspiratory curves, respectively, which were those selected for visual analysis.

Based on the different criteria proposed by Miller and Hyatt,[1,8] Yernault et al,[2] Empey,[9] and Rotman et al,[10] we used 4 quantitative criteria to detect upper-airway obstruction:

- Ratio of FEV_1 to maximum expiratory flow (MEF) > 10 mL/L/min (based on the criteria of Empey[9])
- Ratio of $MEF_{50\%}$ to the flow at the mid-point of the forced inspiratory maneuver ($MIF_{50\%}$). An abnormal $MEF_{50\%}/MIF_{50\%}$ was defined as < 0.30 or > 1 (based on the criteria of Miller and Hyatt[8])
- $MIF_{50\%} < 100$ L/min (based on the criteria of Rotman et al[10])
- Ratio of FEV_1 to forced expiratory volume in the first 0.5 s ($FEV_{0.5}$) > 1.5 (based on the criteria of Rotman et al[10])

As described by Miller and Hyatt,[1] Anzueto et al,[11] Sanders et al,[12] and Vincken et al,[13] the visual criteria for upper-airway obstruction were the presence of a plateau, biphasic shape, or oscillations in the inspiratory or expiratory curves. All loops were independently examined and scored according to the aforementioned criteria, by 2 reviewers (AMM and RG), who were blinded to the results of the accepted standard tests for diagnosing upper-airway obstruction (bronchoscopy, laryngoscopy, neck computed tomogram [CT], and chest CT). Discordant ratings were resolved with a Delphi technique, in which the 2 reviewers discussed the loop in question and reached agreement.

To determine whether the patient had undergone one of the accepted standard tests for diagnosing upper-airway obstruction, we reviewed the Cleveland Clinic hospital records of all 979 evaluable patients for the presence of a chest or neck CT, bronchoscopy, and/or laryngoscopy performed at the Cleveland Clinic. The imaging and endoscopy reports were reviewed for any statements regarding upper-airway abnormality. To assure relatedness of the flow-volume loop to the clinical findings, eligible test reports were restricted to those within 6 months of the spirometry. A patient record was included only if the patient had both an evaluable spirometry and one of the aforementioned imaging or endoscopic upper-airway examinations.

Statistical Methods

Continuous variables are reported as mean ± SD, and percentiles. Categorical variables are reported as frequencies and percentages. Receiver operating characteristic (ROC) curves under logistic regression were performed to

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Table 1. Demographics and Pulmonary and Otolaryngologic Diagnoses

	Patients (n = 475)	Percentage*
Female	270	57
Age (mean y)	58	NA
Diagnosis		
COPD	52	11
Asthma	22	5
Lung transplantation	80	17
Sarcoidosis	26	5
Lymphoma	8	2
Malignancy	5	1
Goiter	2	< 1
Not reported	280	59

* Because of rounding the percentages do not sum to 100.
NA = not applicable
COPD = chronic obstructive pulmonary disease

Table 2. Sensitivity, Specificity, and Positive and Negative Predictive Values for Single and Aggregate Criteria

Criterion	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
$FEV_1/FEV_{0.5} > 1.5$	30.5	60.5	5.9	91.4
$FEV_1/MEF > 10$	8.3	96.8	17.6	92.7
MIF < 100 L/min	8.3	91.1	7.1	92.3
$MEF_{50\%}/MIF_{50\%} < 0.3$ or > 1.0	47.2	55.2	7.9	92.7
Visual	5.5	93.8	6.8	92.3
Aggregate quantitative criteria (≥ 1 quantitative criterion)	69.4	30.2	7.5	92.3
Aggregate criteria (≥ 1 quantitative or visual criterion)	69.4	29.1	7.4	92.0

FEV_1 = forced expiratory volume in the first second
FEV_1 = forced expiratory volume in the first 0.5 second
MEF = maximum expiratory flow
MIF = maximum inspiratory flow

assess the prediction ability of identifying positive upper-airway obstruction with $MIF_{50\%}$, $FEV_1/FEV_{0.5}$, FEV_1/MEF, and $MEF_{50\%}/MIF_{50\%}$, alone, and with linear combination of all 4 of those criteria. We checked the linearity assumption for logistic regression. We used a cutoff value on the scale of the predicted probabilities from the logistic regression to classify patients into 2 groups: upper-airway obstruction, and no upper-airway obstruction. The objective was to select a cutoff with sufficiently high sensitivity and specificity for distinguishing patients with and without upper-airway obstruction. The relationship between the sensitivity and the specificity of various cutoff points can be plotted as an ROC curve. We compared various logistic models with the areas under their ROC curves (the C statistic). The model with the highest C statistic was considered to have the best ability to properly classify patients with and without upper-airway obstruction. We used statistics software (SAS 9.1.3, SAS Institute, Cary, North Carolina) for all analyses.

Results

Of the 979 evaluable patients, 475 (48.6%) were eligible (ie, had both an acceptable spirometry and one or more of the accepted standard tests for diagnosis of upper-airway obstruction) (Table 1). The accepted-standard tests included bronchoscopy (n = 93 patients, 19.5%), laryngoscopy (n = 4, 0.8%), neck CT (n = 17, 3.5%), and chest CT (n = 447, 94%). Eighty-four patients had more than one accepted standard test.

The mean ± SD interval between performance of the accepted standard test and the flow-volume loop was 12.0 ± 22.3 d. Thirty-six patients (7.5% of the eligible patients) had a cause of upper-airway obstruction given in their medical record: tracheal granulation in 10 patients, vocal cord paralysis in 3 patients, dynamic tracheal collapse in 8 patients, goiter with tracheal compression in 4 patients, laryngeal edema in 2 patients, hypopharyngeal edema 2 patients, and subglottic stenosis due to Wegener granulomatosis in 2 patients. Those diagnoses were made via bronchoscopy. The remaining 5 patients had evidence of focal tracheal narrowing on chest CT, though no specific diagnosis was cited in the those medical records.

Of the 184 patients who had an $FEV_1/FEV_{0.5} > 1.5$, only 11 (6%) had upper-airway obstruction.

Of the 17 patients who had an $FEV_1/MEF > 10$ mL/L/min, 3 (17.6%) had upper-airway obstruction.

Of the 40 patients who had a MIF < 100 L/min, 3 (7.5%) had upper-airway obstruction.

Of the 207 patients who had a $MEF_{50\%}/MIF_{50\%} < 0.3$ or > 1.0, 17 (8.2%) had upper-airway obstruction.

With "aggregate quantitative criteria" defined as the presence of at least 1 quantitative criterion, 345 patients had abnormal flow-volume loops. Of those 345 patients, 25 had evidence of upper-airway obstruction. We defined "aggregate criteria" as the presence of at least 1 quantitative or visual criterion. The prevalence of flow-volume loop abnormalities among those with aggregate criteria was not different from that based on aggregate quantitative criteria.

Table 2 presents the diagnostic performance of the quantitative and visual criteria, and the aggregate performance of all the criteria (ie, aggregate criteria) in assessing the presence of upper-airway obstruction. The sensitivity of individual criteria ranged from 5.5% to 47.2%; the latter

value was for $MEF_{50\%}/MIF_{50\%} < 0.30$ or > 1.[8] On the other hand, that criterion was the least specific (55.2%); the specificity range of the other criteria was 60.5–96.8%. In the context that the prevalence of upper-airway obstruction was low (7.5%) in the study population, the positive predictive values were uniformly low (all < 18%) and the negative predictive values were high (91.4–92.7%).

Regarding the 29 patients who had abnormal flow-volume loops as judged by the visual criteria, 6 had evidence of variable extrathoracic obstruction, and 23 had evidence of variable intrathoracic upper-airway obstruction. None showed fixed upper-airway obstruction. Five flow-volume loops showed a biphasic obstruction pattern,[11] and 4 showed oscillations.

In no instance was the inspiratory curve missing. Of the 29 patients with abnormal flow-volume loops as judged by visual criteria, only 2 were considered true positives; one patient had subglottic stenosis due to Wegener granulomatosis, and the other had a stenosis at the right main bronchial anastomosis following single lung transplantation. Regarding the aggregate performance of the criteria, the number of false positive tests exceeded the number obtained with any single quantitative criterion. On the other hand, the sensitivity of the aggregate criterion exceeded that of any single criterion (see Table 2).

We generated the ROC curves from logistic regression for each of the 4 quantitative criteria. The area under the ROC curve (the C statistic) for each of the 4 individual criteria was low ($FEV_1/FEV_{0.5}$ 0.449, FEV_1/MEF 0.439, $MIF_{50\%}$ 0.522, and $MEF_{50\%}/MIF_{50\%}$ 0.408), which suggests that none of the individual criteria can significantly improve the detection of upper-airway obstruction over chance. With the aggregate criterion (a linear combination of the 4 quantitative criteria) the area under the curve is 0.605, which exceeds that of any of the individual criteria.

Table 3 shows the probabilistic values from the regression model for various sensitivity and specificity values depicted by the ROC curve. An appropriate cutoff value to differentiate patients with and without upper-airway obstruction can be selected based on the clinical importance of the sensitivity and specificity. The formula that relates the cutoff value and the quantitative criteria is:

$$\text{Natural log}\,[C/(1-C)] = -1.5468 - 0.0006 \times MIF_{50\%} - 0.0899 \times (FEV_1/FEV_{0.5}) - 0.0416 \times (FEV_1/MEF) - 0.7320 \times (MEF_{50\%}/MIF_{50\%})$$

in which C is the cutoff value.

As an example, if we select a sensitivity of 0.6944 and a specificity of 0.5297 (row 160 in Table 3), the cutoff value is 0.0778, which corresponds to a natural log [C/(1 − C)] value of −2.47. Based on the above equation, if

Table 3. Cutoff Values in the Equation to Differentiate Upper-Airway Obstruction From Non-Upper-Airway Obstruction*

Observation	Cutoff Value	Sensitivity	Specificity
1	0.1354	0	0.9977
2	0.1348	0	0.9954
…	…	…	…
7	0.1280	0	0.9840
8	0.1278	0.0278	0.9840
…	…	…	…
13	0.1222	0.0556	0.9703
14	0.1212	0.0833	0.9703
…	…	…	…
30	0.1146	0.0833	0.9292
52	0.1077	0.1667	0.8744
53	0.1072	0.1944	0.8744
…	…	…	…
152	0.0798	0.5833	0.5571
153	0.0795	0.6111	0.5571
…	…	…	…
159	0.0781	0.6667	0.5365
160	0.0778	0.6944	0.5297
161	0.0775	0.6944	0.5251
…	…	…	…
169	0.0747	0.7222	0.5000
170	0.0745	0.7222	0.4954
…	…	…	…
185	0.0714	0.7500	0.4429

* Each pair of sensitivity/specificity values corresponds to a cutoff value. For example, if a sensitivity of 0.6944 and a specificity of 0.5297 is selected (row 160 in Table 3), the cut-off value is 0.0778. This corresponds to a natural log value of −2.47. Based on the equation, if the result is > −2.47, then the patient is classified as having upper-airway obstruction.

$$-1.5468 - 0.0006 \times MIF_{50\%} - 0.0899 \times (FEV_1/FEV_{0.5}) - 0.0416 \times (FEV_1/MEF) - 0.7320 \times (MEF_{50\%}/MIF_{50\%}) > -2.47$$

then the patient will be classified as having upper-airway obstruction. Figure 1 shows the ROC curve for the aggregate criterion. Because the area under the curve is well below 1.0, the aggregate criterion is an imperfect criterion for detecting upper-airway obstruction.

Discussion

The main findings of this study are:

1. The prevalence of upper-airway obstruction in this consecutive series of patients who underwent spirometry in the pulmonary function laboratory of an academic medical center was 7.5%.

2. All the tested diagnostic criteria for detecting upper-airway obstruction from the flow-volume loop had low sensitivity, which could cause upper-airway obstruction to

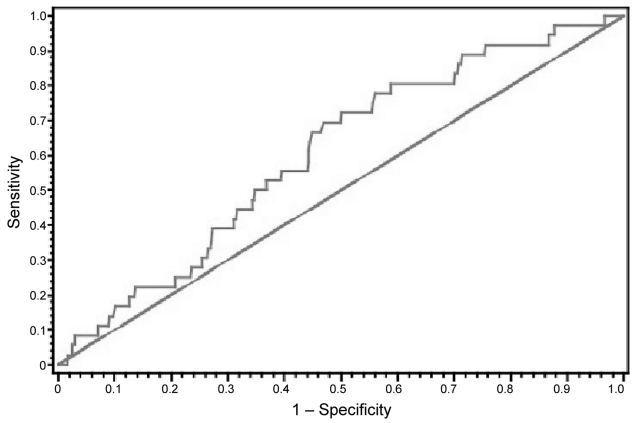

Fig. 1. Receiver-operating-characteristic curve for the aggregate quantitative criterion.

go undetected if the clinician relied on analysis of the flow-volume loop. The ROC analysis indicated that the overall diagnostic performance of the tested criteria is low. The poor sensitivity of these flow-volume-loop criteria in detecting upper-airway obstruction invites further research on other criteria, and should prompt clinicians to pursue imaging and/or endoscopy when clinical suspicion of upper-airway obstruction is unsupported by the flow-volume loop.

3. The diagnostic accuracy of the aggregate criterion exceeded that of the individual criteria, though the aggregate criterion's performance clearly requires validation in an independent series.

Our findings also extend the literature by providing an estimate of the prevalence of confirmed upper-airway obstruction in a population undergoing pulmonary function tests, and by directly comparing the diagnostic performance of various proposed criteria for upper-airway obstruction. To our knowledge, only 2 prior studies have compared the diagnostic performance of criteria for upper-airway obstruction. Specifically, Neukirch et al[7] compared the FEV_1/MEF and $MEF_{50\%}/MIF_{50\%}$ to visual evidence of a sawtooth pattern and found a significant relationship between the sawtooth pattern and both of the quantitative criteria, but there was no significant correlation between the individual quantitative criteria. Rotman et al[10] reported that 4 criteria distinguished patients with confirmed upper-airway obstruction: $MIF_{50\%} < 100$ L/min; $MEF_{50\%}/MIF_{50\%} > 1$; $FEV_1/MEF > 10$ mL/L/min; and $FEV_1/FEV_{0.5} > 1.5$. Limitations of applying those studies to the current series include that Neukirch et al analyzed a group of normals, and the study by Rotman et al lacked an independent, hypothesis-testing sample.

Empey[9] compared the FEV_1/MEF between 10 normal subjects and 18 patients with upper-airway obstruction. In all the patients with upper-airway obstruction, the diagnosis was confirmed with direct or indirect endoscopy. The $FEV_1/MEF > 10$ in the patients with upper-airway obstruction, whereas none of the normals had such a high FEV_1/MEF. However, 16 of those 18 patients presented with stridor, which reflects the severity of the upper-airway obstruction in that sample.

Flow-volume loops have been used widely for assessing the severity, progression, and resolution of many causes of upper-airway obstruction, including post-surgical changes. For example, Mohsenifar et al[14] reviewed flow-volume loops from patients before and after laser resection of airway tumors. Farmer et al[15] reported 5 patients who had flow-volume loop improvement after correction of tracheal stenosis. Vincken et al[16] described the association of flow-volume loop abnormalities with neuromuscular diseases. In patients with Parkinson disease, they described 2 abnormal flow-volume-loops patterns: oscillations and irregularities. In another study,[17] they reported that flow-volume loops had 90% sensitivity and 85% specificity for determining bulbar muscle involvement in patients with Parkinson disease. Similarly, quantitative aspects of the flow-volume loop have also been evaluated and used to assess upper-airway obstruction. In addition to the aforementioned series,[8-10] studies of patients with vocal-cord paralysis found abnormally high $MEF_{50\%}/MIF_{50\%}$,[18,19] and FEV_1/MEF.[9]

To our knowledge, estimates of the prevalence of upper-airway obstruction are only available from series whose populations differed markedly from that of the present study. In the series by Das et al,[20] the prevalence of $MEF_{50\%}/MIF_{50\%} > 1$ was 86.5% in Persian Gulf war veterans, versus 29% in control subjects, but none of the patients in that study had evidence of upper-airway obstruction, only laryngotracheitis. In another study, Miller et al[21] reported an upper-airway-obstruction prevalence of 31% in 144 patients with goiter.

Several potential sources of bias could have caused our estimate of the prevalence of upper-airway obstruction to be low. First, in the context that the presence of severe airflow obstruction (eg, chronic obstructive pulmonary disease, asthma) can mask upper-airway obstruction on the flow-volume loop,[22] and that 15.5% of eligible patients in the present series had chronic obstructive pulmonary disease or asthma, upper-airway obstruction could have escaped diagnosis if the clinician relied on the flow-volume loop.

Another potential bias that could have caused us to underestimate the frequency of upper-airway obstruction is that we depended on only the imaging and endoscopies done at our institution to ascertain the presence of upper-airway obstruction. In a referral population such as that at our hospital, it is conceivable that some evaluable patients had CT or endoscopy at the referring institution and thus would have escaped detection because we reviewed only the Cleveland Clinic medical records.

Third, our estimate of the prevalence of upper-airway obstruction may have been biased because 504 of 979 flow-volume loops were excluded from the analysis because those patients' workups did not include any of the accepted standard tests for diagnosing upper-airway obstruction.

Another shortcoming of this analysis is that the presence of upper-airway obstruction was ascertained retrospectively from the available reports from diagnostic studies, rather than from prospective imaging or endoscopy, so our diagnosis of upper-airway obstruction rested on the diagnostic impression of the clinician who initially analyzed those reports, and we could not assess the severity or clinical importance of the reported upper-airway obstruction. Future studies will review all imaging and use prospective endoscopy criteria for upper-airway obstruction, so that bronchoscopies and laryngoscopies can be prospectively graded, which will provide better assessment of the clinical importance of the upper-airway obstruction.

Conclusions

The available quantitative and visual diagnostic criteria for detecting upper-airway obstruction performed poorly in detecting or ruling out upper-airway obstruction. Because flow-volume-loop assessment has low sensitivity for detecting upper-airway obstruction, clinicians should pursue imaging and endoscopy if they suspect upper-airway obstruction. Further study, including validation of our proposed aggregate criterion, is warranted.

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