The Laryngoscope

Glottic Configuration in Patients With Exercise-Induced Stridor: A New Paradigm

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Objectives/Hypothesis: Paradoxical vocal fold motion and exercise-induced paradoxical vocal fold motion (EIPVFM) are two related conditions that do not have definitive diagnostic criteria. Much of the EIPVFM literature describes patients with characteristic physiologic findings of severe upper airway obstruction or obvious airflow limitation in the clinical context of exertional dyspnea with audible stridor. The objective of this study was to highlight a group of patients who demonstrate important clinical findings of EIPVFM (exertional dyspnea with audible stridor) without simultaneously definitive physiologic findings (mild glottic adduction and normal flow volume loops).

Study Design: Retrospective medical record review.

Methods: We reviewed the records of 150 patients who performed continuous laryngoscopy during exercise for inclusion in a case series. We excluded patients for technical (incomplete records) and physiologic (extremes of disease severity) reasons. Three blinded physicians (practicing in laryngology, pulmonology, and allergy/immunology) independently evaluated isolated audio tracks, video tracks, and flow volume loops of the remaining patients for the presence or absence of stridor, the glottic configuration, and the presence or absence of inspiratory limitation on exercise flow volume loops at peak work capacity.

Results: Exercise laryngoscopy and flow volume loops were fully evaluated for 23 patients. Five patients with exertional dyspnea were unanimously described as having audible stridor, open glottic configuration, and normal flow volume loops.

Conclusions: EIPVFM can occur in the absence of widely recognized confirmatory physiologic measures. Improved quantitative metrics are needed to better characterize patients with EIPVFM.

Key Words: Exercise-induced paradoxical vocal fold motion, continuous laryngoscopy in exercise, vocal cord dysfunction, paradoxical vocal fold motion.

Level of Evidence: 4.

***Laryngoscope*, 00:000–000, 2014**

INTRODUCTION

Vocal cord dysfunction, or paradoxical vocal fold motion (PVFM), is a heterogeneous, pathologic respiratory process that is classically described as inappropriate vocal fold adduction during respiration causing intermittent airway obstruction, stridor, and dyspnea.[1–3] Its etiology, presence, and severity are thought to be related to coexisting gastroesophageal reflux, allergic rhinitis, irritant exposures, maladaptive psychological profiles, and other sources.[4]

Exercise-induced paradoxical vocal fold motion (EIPVFM) was first described in 1984.[5] This form of laryngeal dyspnea occurs exclusively during exertion.[6] Although there is a lack of agreement regarding the diagnostic criteria of EIPFVM, it is based on a combination of history, flexible laryngoscopy, and exercise flow volume loops.[7] Laryngoscopy is traditionally performed immediately after the cessation of the exertional trigger, with at least 50% glottic closure recommended to confirm diagnosis.[8,9] Flow volume loops are more easily obtained during exercise, and variable inspiratory blunting strongly suggests laryngeal obstruction.

In the past decade, several groups have advocated for the use of continuous laryngoscopy during exercise to differentially document glottic and supraglottic behavior during, rather than after, a period of exercise.[10–12] This approach eliminates the need for endoscopists to infer upper airway behavior during exertion from observations made under a different set of conditions (i.e., during recovery).

Our institution is a referral center for respiratory disease and possesses expertise in upper airway dysfunction as well as in continuous laryngoscopy during exercise. In the recent past, our clinical observations suggested that some patients with a history highly suggestive of EIPVFM do not demonstrate physiologic

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Editor's Note: This Manuscript was accepted for publication June 5, 2014.

Presented at the American Laryngology Association Meeting, Las Vegas, Nevada, U.S.A., May 15, 2014.

This work was performed at National Jewish Health, Denver, Colorado, U.S.A.

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DOI: 10.1002/lary.24812

findings that satisfy traditional diagnostic criteria, even during symptomatic periods.

The purpose of this article was to examine glottic configurations in patients with exercise-induced stridor, which has classically been ascribed to inappropriate glottic closure, and to specifically describe a series of observed patients who challenge diagnostic findings believed to exist in EIPVFM. We describe a series of five patients with simultaneously documented audible stridor, normal flow volume loops, and an open glottic configuration.

MATERIALS AND METHODS

This study is a retrospective case series review approved by the Institutional review board of National Jewish Health.

Patient Selection

Sequential clinical patients who underwent continuous laryngoscopy during exercise between March 2012 and February 2014 at National Jewish Health were included in this series. The first author (J.T.O.) performed 150 procedures over this period of time. All of these patients were referred for the procedure due to a high pretest probability for exertional upper airway obstruction (defined as either a subjective description of stridor or characteristic dyspnea refractory to conventional asthma therapy). Patients were excluded for a variety of technical reasons, including poor quality endoscopic video and audio recordings, unclear time synchronization between video and ventilatory recordings, and incomplete recording of flow volume loops during exercise. Patients were also excluded for several physiologic reasons at the extremes of disease severity specific to this proof of concept series. This group, selected because their findings do not strongly challenge current diagnostic criteria, included patients with no notably audible breathing as well as patients with severe glottic adduction.

After the above exclusions were performed, three fellowship-trained reviewers (a laryngologist, an allergist, and a pulmonologist) individually evaluated the exercise laryngoscopy findings and exercise flow volume loops during the 15-second window corresponding to peak work capacity of the remaining 23 patients. The exams were evaluated for the presence of stridor, the glottic configuration, and the presence of inspiratory limitation on the exercise flow volume loops. To maximize simplicity, glottic configuration was rated as yes or no in response to the question: Does the glottis demonstrate total closure or near-total closure in the 15-second window corresponding to 100% peak work capacity? This is in contrast to a semiquantitative scale previously described.[13] During the evaluation of these three parameters, reviewers were blinded to the other two parameters. We present only patients for whom there was unanimous agreement regarding the presence of stridor, an open glottic configuration, and normal inspiratory flow volume loops during this time window.

Nasolaryngoscopy Protocol

Flexible nasolaryngoscopy was performed in all cases using techniques conceptually similar to those previously described in the literature.[10] Patients' nasal cavities were initially topically treated with oxymetazoline hydrochloride 0.05% and lidocaine gel 2%. The flexible fiberoptic nasolaryngoscope (Olympus ENF-P4; Olympus, Tokyo, Japan) was placed and then suspended from the ceiling by a custom apparatus. To minimize changes in the distance between the laryngoscope and anatomic structures of interest, the laryngoscope was secured to the patient with a clamp mounted to a bicycle helmet as well as to the mouthpiece of the metabolic cart (MCG Diagnostics, St. Paul, MN). Images were recorded continuously across rest and exercise.

Exercise Protocol

All patients performed incremental ramp protocols on a cycle ergometer (Lode Corival; Lode B.V., Groningen, the Netherlands) after 3 minutes of rest and 3 minutes of unloaded cycling. Work rate increments were selected (rounded to the nearest 5 W/min) based on clinical experience, guided by predicted equations, with the intention of achieving patient exhaustion or symptoms within 8 to 12 minutes of loaded cycling.[14] All patients received strong verbal encouragement to continue to exhaustion. Test termination was defined as voluntary cessation of pedaling or the point at which the pedal cadence dropped below 50 rpm.

The metabolic cart continuously recorded electrocardiograph tracing, air flow, and end-tidal gas concentrations to calculate ventilation, oxygen uptake, and other derived parameters. Specific 15-second time windows within the exercise portion of the examination, corresponding to 75%, 90%, and 100% of peak work capacity, were selected for analysis.

Quantitative Image Analysis

Laryngoscopy images were digitally processed to precisely quantify the anterior glottic angle. Because this is a proof of concept descriptive series, no attempt was made to correct for image distortion or quantify the impact of the supraglottic structures.[15,16] Image processing modules from the Open Computer Vision (http://opencv.org/) library were developed to construct a custom image-processing pipeline for detecting vocal cords and anterior glottic angle measures in image frames.[17] The pipeline deploys a shape-based template-matching algorithm and normalized cross-correlation scoring to isolate the region of interest of each image.[18] The maximum template score of the region is used within a color-based flood fill algorithm to isolate precise segments of the vocal cords.[19] The anterior glottic angle was determined by detecting maximum boundary points of the anterior portion of the vocal cords and performing a dot product calculation.

Data Presentation and Analysis

Demographic and basic physiologic data are presented with descriptive statistics. Agreement between reviewers is quantified as an overall percentage with confidence quantified via Light's kappa (R version 3.0.2; R Foundation for Statistical Computing, Vienna, Austria).[20] Anterior glottic angle at peak work capacity, time-averaged during the entire 15-second window without differentiation with respect to the respiratory cycle, is presented as a percentage of the angle achieved at 75% peak capacity. This is a time presumed to be relatively free of both vocalizations and changes characteristically seen at high levels of exertion.

RESULTS

Screening and Reviewer Evaluation

A total of 150 clinical exertional dyspnea patients who underwent continuous laryngoscopy during exercise were screened for inclusion (Fig. 1). Twenty-four patients were excluded for technical reasons including poor video signals (obstructed endoscopic view of the

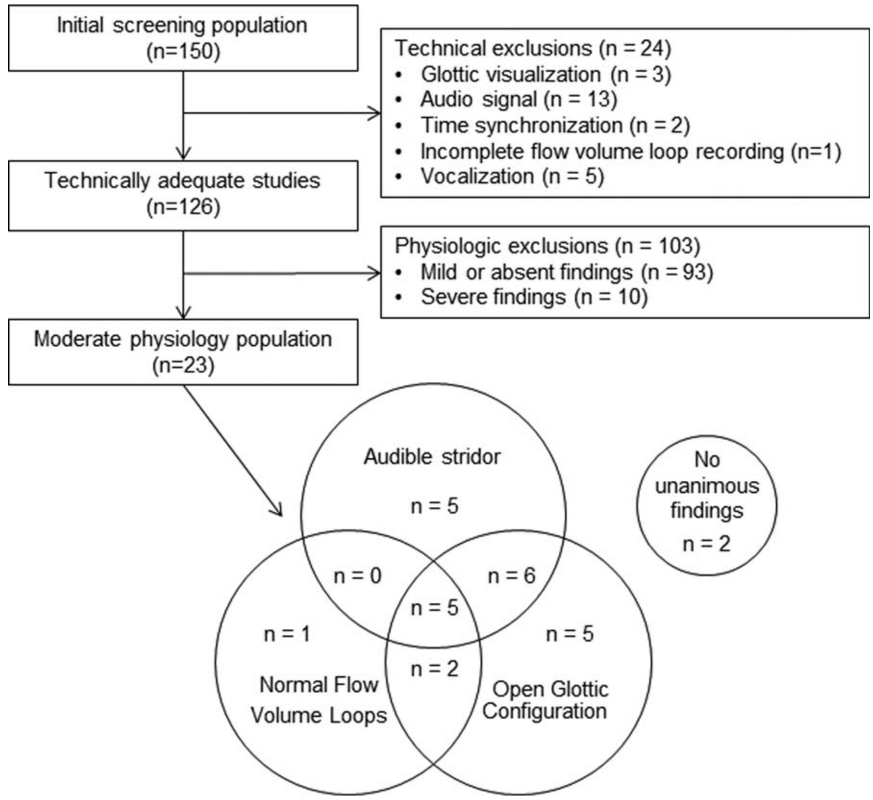

Fig. 1. Patient screening and characterization. Patients were excluded from the descriptive study if data could not be analyzed for technical reasons or if disease severity was extremely mild or extremely severe.

anterior glottic angle during a critical time window) (n = 3), poor audio signals (n = 13), unclear time synchronization between video recording and the metabolic recording (n = 2), incomplete recording of flow volume loops during exercise (n = 1), and vocalizations during critical time windows (n = 5). Ninety-three patients were excluded for absent or mild findings, including subjectively normal breathing volume and pitch at peak work capacity. Ten patients were excluded for grossly positive findings of total or near-total glottic adduction at peak work capacity because, as stated above, their findings do not challenge current diagnostic criteria for EIPVFM.

After the exclusions above, 23 patients remained. All 23 patients described characteristic dyspnea during their exercise test. Eighteen of the 23 patients were unanimously identified as having an open glottic configuration. Inter-rater agreement regarding the glottic configuration was high (83%, Light's kappa = 0.48). Thirteen of the 23 patients were unanimously identified as having audible stridor. Inter-rater agreement regarding the presence of stridor was also high (78%, Light's kappa = 0.69). Eight of the 23 patients were unanimously identified as having no evidence of inspiratory limitation by flow volume loop analysis. There was low inter-rater agreement regarding flow volume loop analysis (52%, Light's kappa 0.33). Eleven patients were unanimously identified as having both an open glottic configuration and audible stridor. Of these, five patients did not have evidence of inspiratory limitation by flow volume loop analysis. Data from these five patients follow.

Baseline Characteristics

The five subjects included in this report were athletic and fit, but as a group possessed body mass indices and oxygen consumption rates that are fairly representative of the general adolescent and young adult population (Table I). One subject was a varsity level collegiate runner. The others participated in recreational and high school-level sports.

Exercise Findings

All five of the patients increased their peak inspiratory flow between 90% and 100% of peak work capacity (Table II). There was no plateau in peak inspiratory flow with incremental work increases for any patient at any point in the testing. The degree of glottic closure was generally mild in these patients, ranging from 70% to 86% open when referenced against the average opening at 75% peak work capacity.

Between 90% and 100% peak work capacity, tidal volume decreased 8% (2.02 ± 0.25 to 1.87 ± 0.34 L, $P = .02$), respiratory rate increased 43% (47 ± 5 to 67 ± 4 bpm, $P = .002$) and total ventilation increased 30% (95 ± 18 to 123 ± 21 L/m, $P < .001$).

TABLE I.
Clinical Characteristics of Patients.

Age, yr	16.8 (±2.8)
Sex (M:F)	1:4
Race	Caucasian (all 5)
BMI (kg/m^{-2})	22.3 (±2.4)
FEV1 (% predicted)	106.8 (±11.9)
VO_2 peak ($mL/kg^{-1}/min^{-1}$)	39.2 (±5.5)
V_E peak (L/min^{-1})	123.4 (±20.7)

BMI = body mass index; F = female; M = male.

DISCUSSION

We present data from patients who simultaneously demonstrated exertional dyspnea, an open glottic configuration, audible stridor, and apparently normal airflow during exercise.

This group of four simultaneous findings is important for multiple reasons. First, it demonstrates that stridor during exercise, presumably a surrogate for important physiologic abnormalities, can occur in the context of an open glottic configuration. Second, it demonstrates that inspiratory flow volume loops during exercise may not be a sensitive marker of upper airway airflow resistance in patients with partial glottic adduction. Third, it demonstrates that current diagnostic criteria for EIPVFM may exclude a group of patients with physiologic findings often considered nondiagnostic. Finally, it supports the concept that EIPVFM is characterized by a spectrum of upper airway findings rather than binary (open vs. closed) findings at the glottic or supraglottic level.

Exertional Stridor and Glottic Configuration

The exertional stridor is likely caused by a combination of high airflow rates in conjunction with partial upper airway obstruction. Although either parameter may not be sufficient in isolation to generate audible stridor, in some cases the combination is sufficient. These findings are in agreement with observations groups performing continuous laryngoscopy during exercise. Roksund et al. described 113 patients with moderate to severe supraglottic or glottic adduction during exercise, 77 of whom developed audible stridor. The correlation between stridor and severity of adduction did not appear in the article.[21] Tervonen et al. described nine patients with exertional stridor, only five of whom demonstrated closure of the glottis of more than 90%.[11]

We do not feel that these findings represent patients with subglottic or trachea lesions for several reasons. The immediate subglottis was visible in all procedures and did not demonstrate obstruction. All five have demonstrated clinical improvement with behavioral interventions including the ability to exercise at or above previous levels without stridor. None of the five patients have ever demonstrated spirometric findings suggestive of fixed subglottic or trachea lesions. Three of the five were presumably intubated for procedures in the remote past (one tonsillectomy, one renal surgery, and one genital surgery). None of these patients underwent flexible or rigid bronchoscopies. From a diagnostic perspective, this assessment is important because we do not feel that formal visualization of the trachea is required after demonstrating mild to moderate glottic adduction during stridor unless other clinical findings implicating the trachea exist.

Flow-Volume Loops

To our knowledge, this is the first description of normal flow volume loops during exercise-induced stridor with dyspnea. In nearly half of our small subset of patients with stridor and an open glottic configuration (5/11), flow volume loops were interpreted as normal. There is not a large body of data in pediatrics comparing flow volume loops to continuous laryngoscopy during exercise findings, but rather several cases in the literature demonstrating extreme findings.[5] Many of these cases illustrate findings with recovery maximal flow volume loops rather than exercise tidal flow volume loops.[6] Although our case series is small and was not designed to evaluate the sensitivity of exercise flow volume loops for upper airway obstruction, we recommend caution in interpreting negative findings using conventional diagnostic criteria in young patients.[22] Moreover, our analysis suggests that interpretation of inspiratory flow volume loops in exercise is inconsistent across reviewers (52% agreement).

TABLE II.
Upper Airway Exercise Findings.

Subject No.	Audible Stridor (Present/Absent)	Peak Inspiratory Flow at 90% Peak Work Capacity, L/s	Peak Inspiratory Flow at Peak Work Capacity, L/s (% Increase)	Qualitative Glottic Configuration at Peak Work Capacity	Quantitative Glottic Configuration at Peak Work Capacity, % Open vs. 75% Peak Work Capacity
1	Present	5.6	6.6 (18%)	Open	86%
2	Present	4	4.7 (18%)	Open	84%
3	Present	3	4.4 (47%)	Open	81%
4	Present	4.9	6.4 (31%)	Open	70%
5	Present	4.1	5.5 (34%)	Open	83%

Model for Observations

The physiologic mechanism explaining the simultaneous presence of dyspnea, stridor, an open glottic configuration, and normal flow volume loops is somewhat unclear. Presumably (although not directly measured), mild to moderate glottic adduction represents an increase in inspiratory resistance. To maintain normal measured airflow, an increase in the inspiratory pressure is required. We believe that these patients increased their negative intrathoracic pressure sufficiently during inspiration to overcome the increased resistance and preserve the apparently normal airflow. Further study is required to confirm this hypothesis.

Implications

Regardless of mechanism, this series of patients challenges current diagnostic guidelines for EIPVFM. The diagnostic gold standard for this condition is direct visualization, with published guidelines requiring over 50% closure to confirm diagnosis.[8] Currently, the diagnosis of EIPVFM is excluded if there are not definitive visualized findings during a symptomatic period. Our patients, although clearly symptomatic with stridor, did not demonstrate visualized findings conventionally considered consistent with audible stridor, and thus may be considered false negatives as per current diagnostic schema. However, their symptoms were ameliorated by behavioral methods used for respiratory retraining in patients with presumed EIPVFM. Our findings do not refute the previous literature documenting total and near total glottic adduction postexercise.[5,7,23] There are reports of partial glottic adduction (often in conjunction with supraglottic obstruction) in patients with dyspnea.[13,21] Our findings add to this literature as it pertains to symptomatic patients with partial vocal cord adduction visualized in exercise.[11,21]

This series also demonstrates the need for improved quantitative metrics in the diagnosis of EIPVFM. Some groups have advocated for a more inclusive definition of PVFM, which includes glottic adduction of more than 50% (rather than complete closure).[8] Although a simple concept to understand, the practical challenges of measuring precise angles in exercise are notable. First, respiration is dynamic, and whereas most clinicians can evaluate and compare single images, evaluating the larynx over time in a quantitative fashion is more of a challenge (although possible).[13] Second, multiple time points are required to assess relative glottic change. However, the realistic problems of repeat laryngoscopy or continuous laryngoscopy in exercise are not insignificant, and include the possibility that introduction of the flexible endoscope during a period of notable dyspnea can induce a degree of glottic adduction. Third, as other groups performing continuous laryngoscopy during exercise have suggested, abnormal findings may rapidly resolve and continuous visualization may be preferable.[10,11] Finally, due to a lack of normative data in large populations (which are not available due to feasibility and ethical concerns in pediatrics), there is not a clear threshold level of upper airway obstruction that defines clinical significance.[24]

Currently, as demonstrated in this study, there is a lack of quantitative physiologic metrics for the diagnosis of EIPVFM. Although improved methods of symptom characterization and quantification are needed, it is possible that diagnostic criteria based solely on physiologic measurements obtained during challenge testing will never be able to capture the affected population with acceptable predictive value. Therefore, better symptom characterization is required and may support the clinician faced with the challenge of quantitating intermittent physiologic phenomenon. Furthermore, symptom scoring is likely the most feasible way to follow symptom frequency, disease severity over time, and patient response to treatment.

Future Directions

Our data support the concept that mild degrees of vocal cord adduction can coexist with important symptomatic evidence of respiratory distress and without objective evidence of airflow obstruction during exercise. This, in itself, is revolutionary to the current understanding of EIPVFM. Yet there is much need of other information: 1) a definition of threshold levels of airway obstruction that are of clinical significance; 2) a better understanding of the pathophysiology of EIPVFM, especially as it relates to the three-dimensional interactions of anatomic structures and airflow across time, the respiratory cycle, and work rate; and 3) a discernment of sound production in the airway relative to number 2. It is paramount that improved quantitative metrics of physiology and symptoms are needed to better characterize the relevance of findings in patients with EIPVFM.

CONCLUSION

This series challenges current diagnostic models of EIPVFM by highlighting patients who demonstrate important clinical findings (audible stridor and dyspnea) without the widely accepted measurable findings of severe glottic adduction and obstructive-appearing flow volume loops. Improved quantitative metrics are needed to better characterize all patients with EIPVFM.

Acknowledgments

The authors thank Jennifer Taylor-Cousar, MD, for evaluation of exercise findings, Anna Faino, MS, for statistical support, and George Zeman, Valerie Keever, Brenda Cox, Becky Kolenbrander, Kathy Brown, Mark Fleming, Lisa Fails, and Dave Gurka, for ongoing support of continuous laryngoscopy during exercise at National Jewish Health.

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