

Exertional dyspnea and inspiratory stridor of 2 years' duration: A tale of 2 wheezes

Kaiser Lim, MD,^{a,b} and James T. Li, MD, PhD^a Rochester, Minn

INSTRUCTIONS

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the instructions listed below:

1. Review the target audience, learning objectives and author disclosures.
2. Complete the pre-test online at www.jacionline.org (click on the Online CME heading).
3. Follow the online instructions to read the full version of the article, including the clinical vignette and review components.
4. Complete the post-test. At this time, you will have earned 1.00 AMA PRA Category 1 CME Credit™.
5. Approximately 4 weeks later you will receive an online assessment regarding your application of this article to your practice. Once you have completed this assessment, you will be eligible to receive Part II MOC credit from the American Board of Allergy and Immunology.

Date of Original Release: November 2011. Credit may be obtained for these courses until October 31, 2013.

Copyright Statement: Copyright © 2011-2013. All rights reserved.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is

accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates these educational activities for a maximum of 1 AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Kaiser Lim, MD, (author), James T. Li, MD, PhD (author and series editor)

Activity Objectives

1. To understand the utility of provocative tests in the evaluation of exertional stridor.
2. To review the interpretation of exercise flow volume loops.
3. To review the differential diagnosis of exertional stridor.
4. To review the diagnosis and treatment of vocal cord dysfunction.
5. To review the mechanism by which laryngomalacia can cause exertional stridor.

Recognition of Commercial Support: This CME activity has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial

Companies/Organizations: J. T. Li has consulted for Abbott. K. Lim declares that he has no relevant conflicts of interest.

CLINICAL VIGNETTE

A 21-year-old female college student who had never smoked was referred for refractory persistent exertional dyspnea of 2 years' duration. Her past medical and surgical history is significant for congenital aqueductal stenosis with hydrocephalus, status post ventriculoperitoneal shunt, and a perioperative left basal ganglia hemorrhagic stroke. She has adjusted well in spite of the postinfarct delayed-onset dystonia. She was exercising almost daily. She has excellent social support, excels in academics, and denies anxieties or social stressors in her current life situation.

Two years ago, she began to experience an inordinate degree of dyspnea at peak exercise. She described inspiratory restriction with stridor relieved by vigorous coughing. These episodes occur only with maximal exertion, either Nordic skiing or biking. She can otherwise exercise submaximally without limitation. She denies nocturnal awakenings, syncope, cyanosis, respiratory

arrest, emergency department visits, or hospitalizations. Symptoms do not occur at rest and are more severe and frequent in the cold winter months. These episodes have progressively worsened over time. She is currently unable to exercise maximally.

She has not responded to conventional asthma therapy. Pre-medication with inhaled bronchodilators and regular inhaled corticosteroid use has had minimal effects on her symptoms. Results of allergy tests were negative. A year of acid-suppression therapy for presumed nonerosive reflux disease did not improve her episodes of inspiratory stridor. Currently, she is taking 160/4.5 µg of budesonide/formoterol hydrofluoroalkane twice daily, levalbuterol tartrate hydrofluoroalkane and nebulizer solution as needed, 20 mg of esomeprazole twice daily, and 1 g of sucralfate 4 times a day. Laryngeal examinations by otolaryngologists were unrevealing. A speech pathologist in the community concluded she has vocal cord dysfunction (VCD) but did not provide supporting documentation for review.

She saw a pediatric laryngologist for further evaluation. The pediatric laryngologist described normal vocal cord motion with redundant tissue in the supra-arytenoid area. Although the arytenoids were rotated over the laryngeal vestibule, there was no glottic obstruction induced with hyperventilatory maneuver in the office. There has no evidence of paradoxical vocal fold motion at rest. Pulmonary workup revealed a mild restrictive pattern on spirometry with a forced vital capacity (3.12 L, 76% of predicted value) to FEV₁ (2.82 L, 80% of predicted value) ratio of 90.5%

From the Divisions of ^aAllergic Diseases and ^bPulmonary & Critical Care Medicine, Department of Medicine, Mayo Clinic Rochester.

Received for publication September 9, 2011; revised September 21, 2011; accepted for publication September 22, 2011.

Corresponding author: Kaiser Lim, MD, Pulmonary & Critical Care Medicine, Mayo Clinic Rochester, 200 First St SW, Gonda 18-478, Rochester, MN 55905. E-mail: Lim.kaiser@mayo.edu.

0091-6749/\$36.00

© 2011 American Academy of Allergy, Asthma & Immunology

doi:10.1016/j.jaci.2011.09.021

(lower limit of normal, 75.1%; see Fig E1 in this article's Online Repository at www.jacionline.org). Direct provocation with methacholine decreased FEV₁ by 21%. Bugle pressures were reduced, with maximal inspiratory pressure at 50 cm H₂O (54% of predicted value) and maximal expiratory pressure at 52 cm H₂O (33% of predicted value). Forced expiratory and inspiratory vital capacity curves were normal (see Fig E2 in this article's Online

Repository at www.jacionline.org). Results of chest radiography were noncontributory. Fraction of exhaled nitric oxide was 16 ppb (normal value, <35 ppb). A definitive study was performed.

The full version of this article, including a review of relevant issues to be considered, can be found in this article's Online Repository at www.jacionline.org. If you wish to receive CME or MOC credit for the article, please see the instructions above.

DISCUSSION

We provoked the patient's symptoms with a cardiopulmonary exercise test on a bicycle ergometer with continuous flow-volume loop and videolaryngoscopic monitoring (Fig E3). Indirect provocation with pre-exercise and postexercise spirometry was performed. Her test performance was optimal because the peak heart rate was greater than 85% and was anaerobic, with a respiratory exchange ratio of greater than 1.1 at peak exercise. She confirmed that the symptoms were reproduced at peak exercise. Her exercise capacity was normal, achieving her predicted maximal work capacity and maximal oxygen consumption. Based on traditional parameters, she did not have ventilatory limitation (breathing reserve, 35.6 L). There was no expiratory flow limitation based on continuous flow-volume loops (Fig E4). During exercise, flow loops had normal contour, and tidal volume as a percentage of the maximal expiratory flow loops was less than 25% (Fig E5). There was no dynamic air trapping because the end-expiratory lung volume did not shift to the left. Her exercise breathing pattern was normal, with breath size (tidal volume) progressively increasing as a percentage of forced vital capacity together with increasing respiratory rate. Cardiovascular response to exercise was likewise appropriate. Spirometric results before and after exercise were negative for exercise-induced bronchoconstriction (EIB; Fig E6). This would have been interpreted as a normal study result if not for the continuous videolaryngoscopy. She had progressive arytenoid rotation during inspiration at moderate exertion (see Video E1). The supraglottic vestibule was narrowed, even though the flow-volume loops were normal. At peak exercise, paradoxical vocal cord movements were observed.

This is illustrative of the complexity of exertional dyspnea in an otherwise active and fit person. Exercise-related shortness of breath affecting sports performance is a common presenting problem to the practicing allergist. Table E1 summarizes the causes of exertion-related inspiratory stridor. The lack of response to premedication with bronchodilators and inhaled steroids makes EIB unlikely. A normal office laryngeal evaluation result does not exclude the diagnosis of laryngomalacia or paradoxical VCD because of its occurrence during maximal exercise. The 2 conditions coexisted, which further complicates the evaluation. Which one is the limiting pathology?

Laryngomalacia in young adults

Laryngomalacia is collapse of the posterior aryepiglottic folds over the vocal cord caused by redundant tissue or mucosal edema. The resected redundant arytenoid tissue is usually normal histologically.^{E1} One hypothesis for the increased medial prolapse of the aryepiglottic folds toward the airway lumen has to do with the insufficient anchorage of the aryepiglottic folds to the thyroid perichondrium by the submucosal collagenous fiber layer located in the free dorsal margin of the aryepiglottic folds. Laryngomalacia is the most common congenital laryngeal abnormality in children and the most common cause of stridor in children.^{E1} It can occur in later years and is often associated with a central nervous system insult. Arytenoid prolapse or laryngomalacia becomes more pronounced as inspiratory flow increases during exertion. The Venturi effect simply states that the velocity of the air in a conduit will increase when traversing a narrowed segment of the conduit. This increase in forward flow is accompanied by a corresponding reduction in lateral pressure. This draws in compressible tissues, as in paralyzed vocal cords or redundant

arytenoid. The Venturi effect is a derivation of the Bernoulli principle and the continuity equation.

VCD in young adults

Exercise-induced VCD is the inward motion of the vocal cords during inspiration. It is suspected when the clinical history is atypical for asthma, results of provocative studies are negative, and response to asthma therapy is poor.^{E2} The estimated prevalence of VCD is 4% to 26% of athletes. Prevalence is higher in those who play some sports rather than others (ie, swimmers versus runners).^{E2} The prototypical patient is a young female subject engaged in outdoor sports with an overachieving personality (or with parents with such a personality) who has recently been promoted to perform at a higher level of competitive sport.^{E3} Clinical recognition is critical to avoid misdiagnosis and overtreatment as severe refractory asthma. Secondary morbidities from inappropriately high doses of inhaled corticosteroids or systemic steroids are common.^{E4} Asthma often coexists with VCD. Fifty-six percent of patients with VCD had asthma in a large series.^{E4}

The clinical features suggestive of exercise-induced VCD include throat tightness and choking, the absence of nocturnal symptoms,^{E3} abrupt and rapid onset during exercise, fast resolution (5-10 minutes) after exercise cessation, and inspiratory distress during rather than after exercise. In contrast, heavy-intensity exercise with a high airflow rate is necessary to provoke EIB because the mechanism involves mast cell degranulation from increased osmolarity associated with drying of epithelial lining fluid and rewarming of the airways after exercise.^{E5} EIB involves bronchial narrowing and reduction in inspiratory and expiratory airflow. This can take 5 to 10 minutes of exercise (drying) and peaks between 5 and 20 minutes after exercise stops (rewarming). It is unusual for asthmatic patients to have only a single trigger. Auscultation during an episode might detect stridor (inspiratory) coming from the throat compared with the intrathoracic (expiratory) wheeze of asthma. VCD is typically not associated with dysphonia or voice fatigue. Office-based laryngoscopy is diagnostic in only 60% of symptomatic patients.^{E4}

Typical diagnostic tests, such as spirometry and visual inspection of flow-volume loops, have low sensitivity for detection of VCD. Modern office spirometers have algorithms that present only the "best" flow-volume loop for analysis. If the clinical history is suspicious for VCD, inspect all the flow-volume loops generated. Highly variable, flattened, truncated, or aborted flow-volume loop contours might be an early clue in patients with VCD. Abnormalities in the flow-volume loop ranged from 0 to 23%.^{E2,E4} Provocative tests are often performed in patients with an atypical history and normal baseline spirometric results. Self-reported symptoms are poorly predictive of response to methacholine or exercise. The methacholine challenge test has a sensitivity of 36% to 80%, a specificity of 65% to 100%, a positive predictive value of 100%, and a negative predictive value of 61% in predicting EIB.^{E6,E7} Anderson et al,^{E7} using mannitol challenge, reported a sensitivity of 69% and a specificity of 62% to predict EIB (10% FEV₁ decrease) with a correlation coefficient (*r*) of 0.41. Methacholine challenge and EIB have a correlation coefficient of only 0.256. A negative provocative test result with mannitol or methacholine does not exclude EIB. This is why exercise challenges are important.

Role of exercise study

The exercise challenge provokes the symptoms seen during the specific activity to some extent. It provides information

regarding cardiac, ventilatory and breathing patterns, flow-volume loops, and the exercise capacity of the patient. Laryngoscopy immediately after exercise to detect VCD would have missed the laryngomalacia and the VCD because the latter can be episodic. The diagnostic utility of this method is unknown, variably reproducible, and typically anecdotal. Exercise testing in the laboratory does not reproduce all the conditions of the sport (ie, chlorine in swimming pools). Outdoor athletes have to contend with aeroallergens, humidity, temperature, pollution, barometric pressure, and altitude. These cannot be simulated in the laboratory. Testing with field conditions is often impossible. The intensity of the exercise in some highly trained athletes can be challenging to reproduce with either a treadmill or bicycle ergometer. Protocols for either are available.^{E8,E9} It is important for the patient to exert maximally and reproduce their performance-limiting symptoms.

The addition of continuous flow-volume loop analysis and continuous videolaryngoscopy increases detection of subtle expiratory flow limitations and laryngeal abnormalities. In exercise tidal flow-volume loop analysis, each breath (tidal volume) is lined up within the maximal flow-volume loop, which is the same as the flow-volume loop in spirometry but obtained during exercise at different time points. Expiratory flow limitation is present if the expiratory tidal flow-volume loop overlaps or exceeds the expiratory maximal flow-volume loop by more than 25%.^{E10} This is a continuous graphic presentation of the breathing pattern and volume history of the patient during exercise. The leftward shift of the end-expiratory lung volume during exercise is suggestive of dynamic hyperinflation. Unresolved issues regarding the tidal volume over maximal flow-volume loop method is that it does not take into consideration EIB. Also, in some patients thoracic gas compression might lead to an overestimation of expiratory flow limitation. Normative values from large studies are not available. The test is best performed and interpreted by laboratories that routinely perform them.

Outcome

Continuous videolaryngoscopy had a crucial role in the diagnosis and treatment in this case. The abnormalities were intermittent and can occur after formal exercise has terminated. The interpretation of laryngeal motion and description of abnormalities during exercise have been published.^{E9} The motion of the larynx can be divided into a supraglottic (aryepiglottic folds) and a glottic (vocal cords) component. There is a scoring method with good reproducibility and interobserver variability.^{E9} Based on the findings of the exercise study and the eventual response to behavioral therapy, paradoxical vocal cord motion was the predominant operative mechanism of the patient's exertional dyspnea. In this patient the results of continuous flow-volume loop analysis were normal. The paradoxical vocal cord motion was detected at peak exercise and would have been missed if the scope was inserted only after exercise.

Treatment plan

A team approach including an allergist, laryngologist, pulmonologist, and behavioral therapist (speech therapist) is the cornerstone of management. Management techniques have been reviewed^{E11,E12}:

1. The patient, family, and coach should identify and recognize all the symptoms associated with VCD.
2. Behavioral therapy along with medical therapy, if necessary, should be emphasized.
3. The patient is trained to perform specific maneuvers, including "sniff" or pursed lip breathing, at the first sign of VCD. This reflexively abducts the vocal cords.
4. Breathing pattern self-assessment is taught, and retraining is crucial for a good outcome. Patients with VCD often breathe with their neck tensed and their shoulders elevated. Relaxation techniques with "diaphragmatic" breathing exercises (abdominal expansion during inspiration) at the first sign of breathing difficulty should be taught.
5. Home practice outside of sports should be scheduled with family participation to coach the patient. We have found it helpful to demonstrate these techniques with a laryngoscopy to reinforce these maneuvers during the initial session.
6. Recognition and concurrent treatment of underlying depression, anxiety disorder, obsessive-compulsive disorder, and somatization disorder are important. Because asthma and gastroesophageal reflux disease can be comorbid conditions, appropriate therapy should be started. Panic attacks caused by perceived air hunger could be a complicating secondary condition.
7. Counseling is important because many patients are driven athletes and high achievers. The long-term prognosis is usually excellent, with the majority able to continue participating in their sports.^{E12}

THE CASE REVISITED

A family discussion with the pediatric laryngologist and pulmonologist followed. Although the patient had mild laryngomalacia, it was the paradoxical vocal cord motion that was limiting her exercise capacity. We speculate whether the mild laryngomalacia might have led to the VCD. Arytenoid surgery to reduce the redundant tissue was not recommended in the initial care plan. Instead, she had behavioral intervention with speech pathology. She completed a session using a motivational interview technique emphasizing pursed lip breathing and nasal inspiration during exercise. Three months later, her mother reported a satisfactory outcome. She has improved significantly and is planning a mountain-biking trip in the summer. The final diagnosis was exercise-induced paradoxical vocal cord motion with mild laryngomalacia with redundant arytenoid tissues.

REFERENCES

- E1. Reidenbach M. Aryepiglottic fold: normal topography and clinical implications. *Clin Anatomy* 1998;11:223-35.
- E2. Rundell K, Spiering B. Inspiratory stridor in elite athlete. *Chest* 2003;124:468-74.
- E3. McFadden C, Zawadzki D. Vocal Cord dysfunction masquerading as exercise-induced asthma: a physiological cause for "choking" during athletic activities. *Am J Respir Crit Care Med* 1996;153:942-7.
- E4. Newman K, Mason UI, Schmaling K. Clinical features of vocal cord dysfunction. *Am J Respir Crit Care Med* 1995;152:1382-6.
- E5. Anderson S, Daviskas E. The mechanism of exercise-induced asthma is... *J Allergy Clin Immunol* 2000;106:453-9.
- E6. Holzer K, Anderson SD, Chan H-K, Douglass J. Mannitol as a challenge test to identify exercise-induced bronchoconstriction in elite athletes. *Am J Respir Crit Care Med* 2003;167:534-7.
- E7. Anderson S, Charlton B, Weiler J, Nichols S, Spector S, Pearlman AN, et al. Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. *Respir Res* 2009;10:4.

- E8. Tervonen H, Niskanen MM, Sovijärvi AR, Hakulinen AS, Vilkinen EA, Aaltonen LM. Fiberoptic videolaryngoscopy during bicycle ergometry: a diagnostic tool for exercise-induced vocal cord dysfunction. *Laryngoscope* 2009;119:1776-80.
- E9. Maat R, Røksund O, Halvorsen T, Skadberg B, Olofsson J, Ellingsen T, et al. Audiovisual assessment of exercise-induced laryngeal obstruction: reliability and validity of observations. *Eur Arch Otorhinolaryngol* 2009;266:1929-36.
- E10. Johnson B, Weisman I, Zeballos R. Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow-volume loop. *Chest* 1999;116:488-503.
- E11. Sandage M, Zelazny S. Paradoxical vocal fold motion in children and adolescents. *Land Speech Hear Serv Sch* 2004;35:353-62.
- E12. Sullivan M, Heywood B, Beukelman D. A treatment for vocal cord dysfunction in female athletes: an outcome study. *Laryngoscope* 2001;111:1751-5.

21 y.o. Female Wt: 54.4 KG, BMI: 20.3 Ht:163.7 cm
 Previous test: Desk:

	PREDICTED		CONTROL		POST-CHALLENGE	
	NORMAL	RANGE	FOUND	%PRED.	FOUND	%CHANGE
SPIROMETRY						
FVC	4.09	>3.35	3.12*	76%	2.92	
FEV1	3.53	>2.98	2.82*	80%	2.24	-21%
FEV1/FVC	86.2	>75.1	90.5		76.7	
FEF25-75	3.7	> 1.7	3.5	93%	2.0	
FEFmax	6.8	> 4.1	6.4	95%	4.5	-30%
FIFmax			4.9			
FEF50/FIF50			0.9			
MVV	125	> 92	82*	66%		
MAXIMAL RESPIRATORY PRESSURES						
PImax	-93	< -69	-50*	54%		
PEmax	159	> 118	52*	33%		

FIG E1. Baseline spirometric and methacholine challenge test results and maximal respiratory pressures. *BMI*, Body mass index; *FEFmax*, maximal forced expiratory flow; *FEF25-75*, forced expiratory flow at 25% to 75% of forced vital capacity; *FIFmax*, maximal forced inspiratory flow; *Ht*, height; *MVV*, maximal voluntary ventilation; *PEmax*, maximal expiratory pressure; *PImax*, maximal inspiratory pressure; *Wt*, weight.

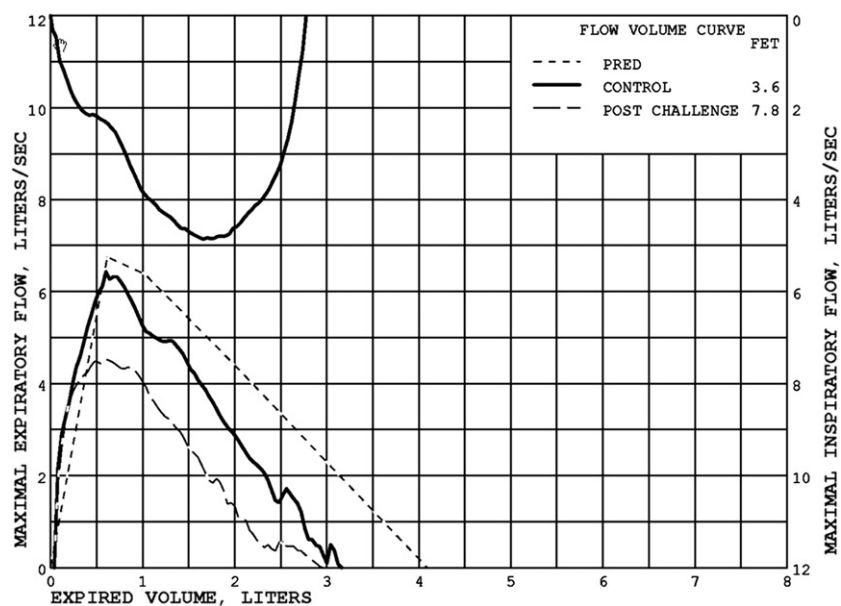


FIG E2. Inspiratory and expiratory flow-volume curves at baseline. The patient had difficulty performing the maneuvers with a forced expiratory time (FET) of less than 6 seconds.

21 y.o. Female	Wt: 54.4 kg	Ht: 163.7 cm	BMI: 20.3	Tested:			
FVC: 3.35	FEV1: 3.18	MVV: 127.2	BSA: 1.58	Physician:			
Indication: Dyspnea		Desk:					
Exercise	UNITS	REST (1)	MID (6)	MAX (10)	PRED MAX	%PRED MAX	
Work	watts	0	100	180	170	106%	
Interval Time	min:sec	9:47	0:59	0:18			
Inspired Oxygen		0.21	0.21	0.21			
Cumulative Exercise Time	min		7.00	10.30			
SpO ₂	%	95.5	96.4	97.0			
Oxygen Consumption ($\dot{V}O_2$)	l/min	0.234	1.478	2.173	2.000	109%	
$\dot{V}O_2$ / kg	ml/kg	4.3	27.2	39.9	36.7	109%	
Respiratory Exchange Ratio		0.86	1.03	1.20			
Cardiac Function							
Heart Rate	bpm	94	150	178	199	89%	
Cuff Blood Pressure	mmHg	106/69	116/66				
Oxygen Pulse	ml/beat	2.5	10.0	12.7	10.0	127%	
Ventilation							
Minute Ventilation	l/min	8.2	47.7	91.6	127.2	72%	
Respiratory Rate	per min	19	44	63			
Tidal Volume	ml, BTPS	457	1110	1453			
Ventilatory Equivalent for O ₂	$\dot{V}_e/\dot{V}O_2$	35.0	32.3	42.2	47.0	90%	
Ti / Ttot	%	34	50	51			
End Tidal PCO ₂	mmHg	36	34	31			
Symptom Scores							
Rate Perceived Exertion	6-20	6	11	19			
Chest Pain	0-4	0	0	3			
Recovery (min)	0	1	2	3	4	5	10
Heart Rate	178	159	133	128			15

FIG E3. Maximal cardiopulmonary exercise test results performed with a bicycle ergometer, with data on the far right expressed as a percentage of the predicted maximal value. Values of greater than 85% are considered within acceptable physiologic limits. *BMI*, Body mass index; *BSA*, body surface area; *Ht*, height; *MVV*, maximal voluntary ventilation; *SpO₂*, pulse oximetry; *Ti/Ttot*, inspiratory time over total respiratory cycle time; *Wt*, weight.

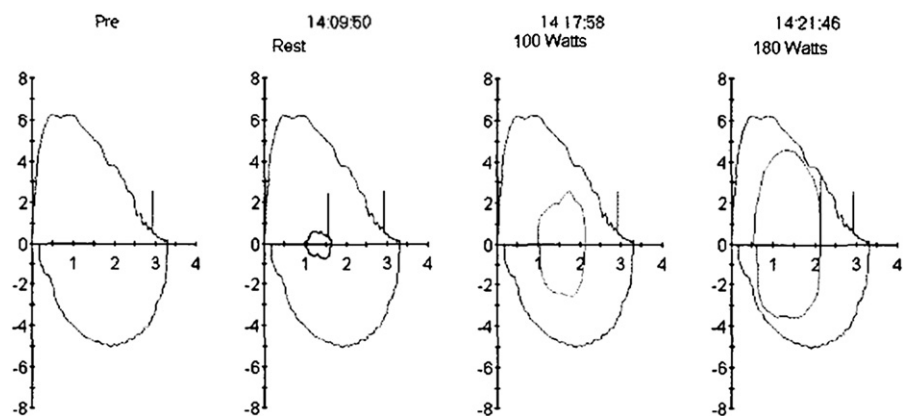


FIG E4. Exercise flow-volume loops at different work intensities: at rest, at 100 W, and at 180 W without interpretations.

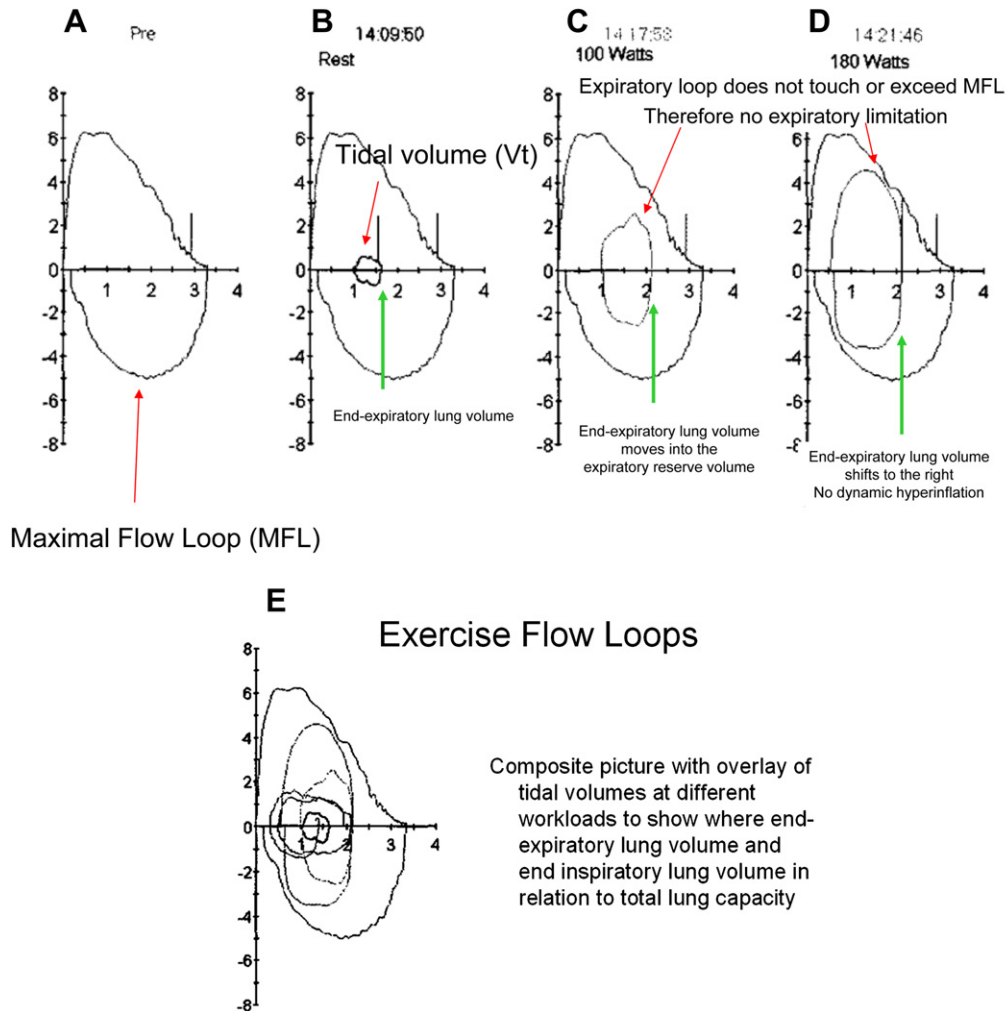


FIG E5. Exercise flow-volume loops at different work intensities: **A**, Maximal Flow Volume Loop; **B**, at rest; **C**, at 100 Watts; **D**, at peak exercise. **E**, Composite overlay of **A**, **B**, **C**, **D** with interpretations.

21 y.o. Female Wt: 54.4 KG, BMI: 20.3 Ht:163.7 cm
Previous test: 3/14/2011 Desk:

	PREDICTED		CONTROL		POST-CHALLENGE**	
	NORMAL	RANGE	FOUND	%PRED.	FOUND	%CHANGE
SPIROMETRY						
FVC	4.09	>3.35	3.35*	82%	3.21	
FEV1	3.53	>2.98	3.18	90%	3.03	-5%
FEV1/FVC	86.2	>75.1	95.1		94.4	
FEF25-75	3.7	> 1.7	4.4	118%	4.3	
FEFmax	6.8	> 4.1	6.7	100%	5.8	-14%

*Outside normal range.

**CHALLENGE: Exercise, room air, cycle ergometer

FIG E6. Pre-exercise and postexercise spirometry. The improvement in baseline spirometric results is due to increased familiarity with the maneuvers with repeated testing. There were no interim medication changes. *BMI*, Body mass index; *FEFmax*, maximal forced expiratory flow; *FEF25-75*, forced expiratory flow at 25% to 75% of forced vital capacity; *Ht*, height; *Wt*, weight.

TABLE E1. Airway causes of exertion-related inspiratory stridor

Laryngomalacia
Vocal cord paralysis/paresis
Obstructing laryngeal tumors
Subglottic stenosis
Postintubation laryngeal granulomas
Postintubation tracheal stenosis
Obstructing goiter
Obstructing vascular ring
Paradoxical vocal cord movement
Severe muscle tension dysphonia (glottic squeeze)
Bronchial obstruction from foreign body or tumors