Exercise-Induced Bronchospasm

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EIB

- Episodic bronchoconstriction with exercise
  - May be an exacerbation of chronic asthma
  - May be an independent syndrome with no chronic symptoms
  - Can occur at any age
  - Increases with intensity and duration of aerobic exercise
  - Correlates poorly with baseline spirometry findings
  - Often difficult to distinguish from vocal cord dysfunction and many other causes of dyspnea

EIB Epidemiology

- 7-20% of the general population
- Occurs in 80-100% of chronic asthmatics
- Correlates strongly with airway eosinophilia
- Occurs in up to 50% of endurance athletes
- Is poorly correlated with childhood wheezing or general atopy

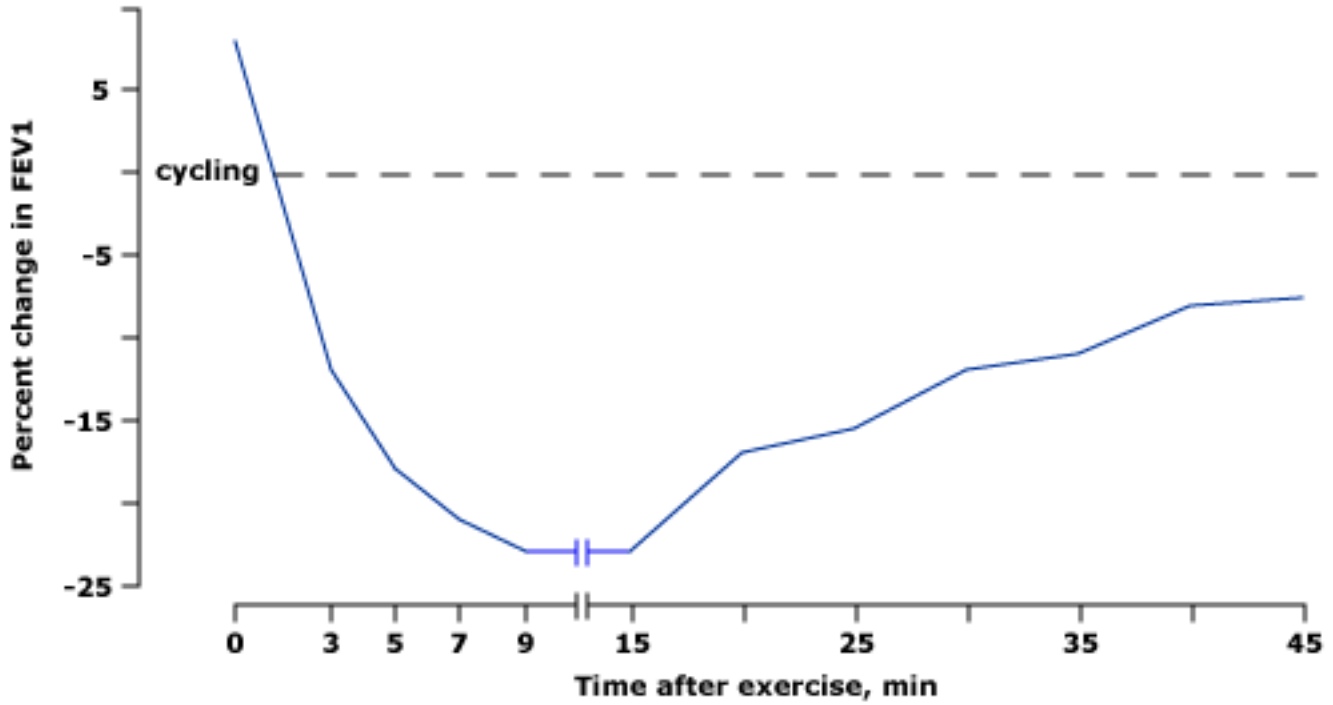
EIB Pathogenesis

- Triggered by drying and cooling of the airway
- Primarily depends on minute ventilation and environmental conditions
- Mediated by:
  - leukotriene proteins & interleukins
  - T-cells
  - Eosinophils
  - IgE
  - **Not** by NO

EIB Clinical Presentation

- Begins 3-6 minutes after onset of exercise
- Peaks at 10-15 minutes into exercise or after stopping
- Resolves within 60 minutes
- SOB, chest tightness and cough
- Improves with repeated exercise (refractory)
- Relieved with B-agonist therapy

Exercise-induced bronchoconstriction



The time course of exercise-induced bronchoconstriction in an asthmatic patient in whom the FEV1 fell by more than 20 percent after cycling.
FEV1: forced expiratory volume in one second.

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Differential Dx

- Vocal cord dysfunction/Laryngeal disease
- Anxiety
- Deconditioning
- Fixed airway obstruction/foreign body
- GERD/Aspiration
- Parenchymal lung disease
- CHF/CAD/Angina
- Congenital heart disease

Diagnosis

- No need for challenge testing in a chronic asthmatic
- Follow Asthma Guideline directed therapy for controllers
- Pre-treat with SABA agent and monitor peak flows and symptoms
- Primarily an issue in new-onset symptoms, athletes and children, atypical symptoms, normal baseline spirometry
- Requires challenge testing to verify, along with symptoms, response to inhaled SABA

Rationale for Challenge Testing

- Negative testing argues against asthma or EIB
- Airway reactivity can be variable and transient
- Airway responsiveness is predictive of disease and risks of future life-threatening EIB or asthma
- Measures asthma control
- Useful in asymptomatic, stoic asthmatics
- Predicts future asthma risks
- Safe and easily performed

Challenge Testing

- Exercise testing & serial spirometry
- Methacholine inhalational challenge
- Mannitol inhaled testing
- Cold air challenge
- Eucapnic Voluntary Hyperpnea

Dyspnea on Exertion Workup

1st

- History, PE and Symptoms
- Spirometry, CXR, labs, EKG

2nd

- Response to albuterol
- 6-Minute Walk Testing, Echo

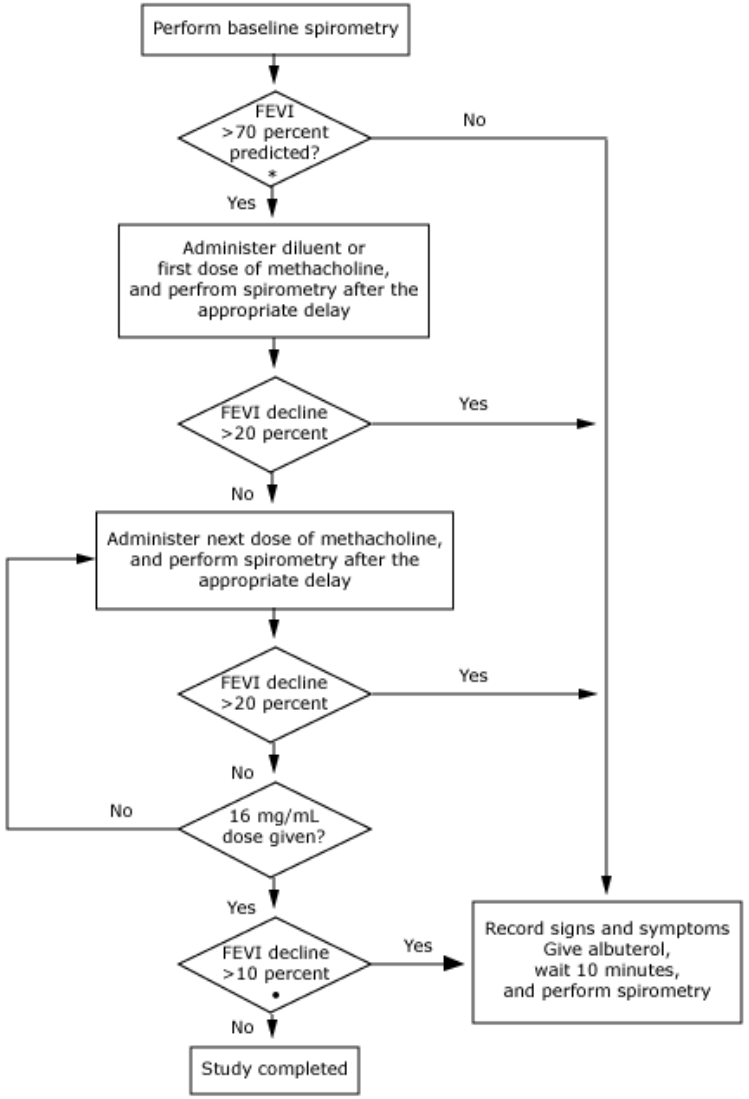
3rd

- Methacholine Challenge
- Exercise-induced challenge or $V0_2$ max

Methacholine Challenge

- Baseline spirometry off all meds
- Nebulized saline, then spiro
- Nebulized Methacholine in logarithmic increased doses, then repeat spiro
- >20% drop in FEV1 considered the primary endpoint
- Reversed with albuterol neb
- Extrapolate to concentration at which FEV1 dropped 20%
- PC_{20}<8 mg/ml considered positive, >16 mg/ml negative

Methacholine challenge testing sequence



* The choice of the FEV1 value considered a contraindication may vary from 60 to 70 percent of predicted.
• The final dose may vary depending on the dosing schedule used. Final doses discussed in this statement are 16, 25 and 32 mg/mL.

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Contraindications to bronchoprovocation challenge testing

Absolute
Severe airflow limitation (FEV1 <50 percent predicted or <1 L)
Myocardial infarction or stroke in last three months
Uncontrolled hypertension (systolic BP >200 or diastolic BP >100)
Known aortic aneurysm
Relative
Moderate airflow limitation (FEV1 <60 percent predicted or <1.5 L)
Inability to perform acceptable-quality spirometry
Pregnancy
Nursing mothers

FEV1: forced expiratory volume in one second.

Reproduced with permission from: Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. American Journal of Respiratory and Critical Care Med 2000; 161:309. Official journal of the American Thoracic Society. Copyright © 2000 American Thoracic Society.

Mannitol Challenge

- Similar to Methacholine but dried powder inhalation
- 15% drop considered positive
- Frequent cough as a side-effect
- 15% drop at less than 635mg inhaled total considered positive

Medications that may affect bronchoprovocation challenge test

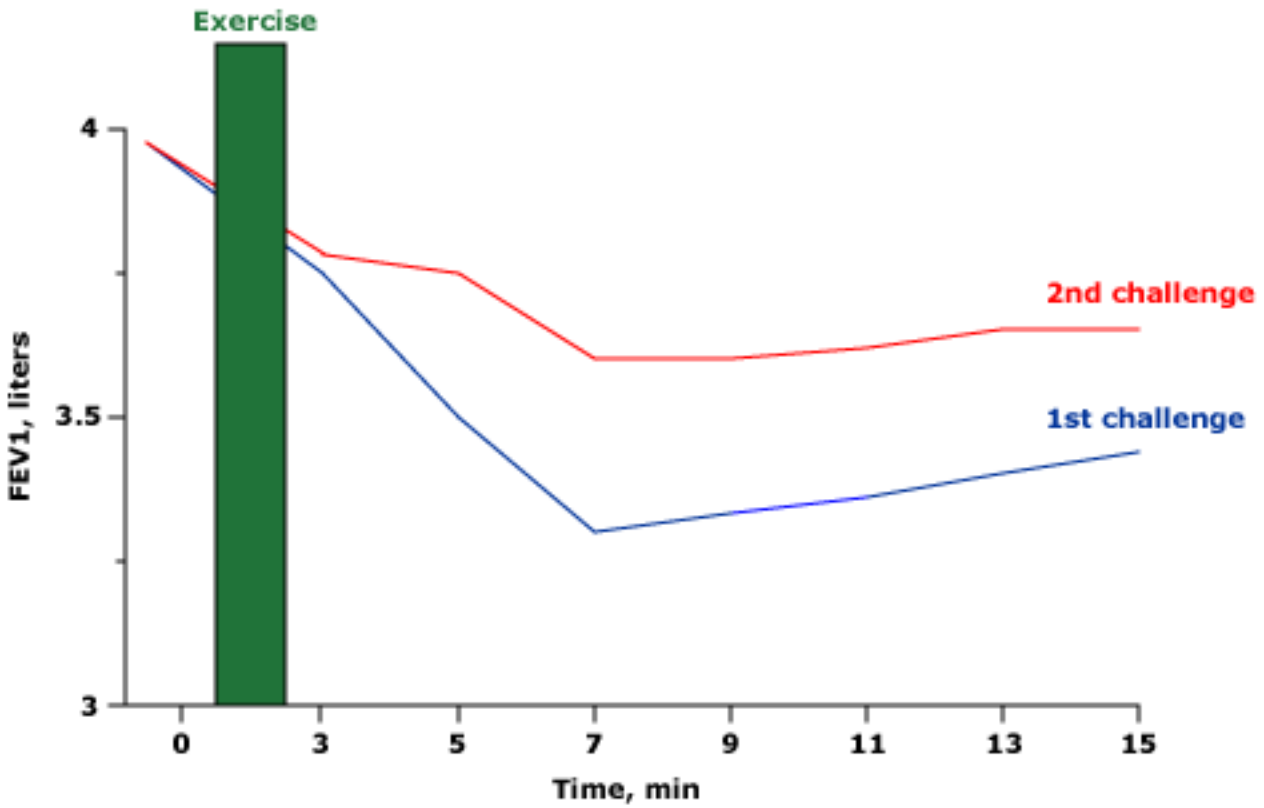
Medication	Minimum time to omit medication before challenge tests
Inhaled bronchodilators	
Albuterol	8 hours
Metaproterenol	8 hours
Terbutaline	8 hours
Ipratropium	24 hours
Salmeterol	48 hours
Formoterol	48 hours
Tiotropium	1 week
Oral bronchodilators	
Liquid theophylline	12 hours
Intermediate-acting theophylline	24 hours
Long-acting theophylline	48 hours
Albuterol tablet	12 hours
Long-acting albuterol tablet	24 hours
Inhaled glucocorticoid*	2-3 weeks
Oral glucocorticoid*	2-3 weeks
Mast cell stabilizers	
Cromolyn sodium	8 hours
Antihistamines•	
Diphenhydramine	72 hours
Chlorpheniramine	72 hours
Hydroxyzine	72 hours
Cetirizine	72 hours
Leukotriene modifiers	
Montelukast	24 hours
Zafirlukast	24 hours

* The authors do not recommend routinely withholding inhaled or oral glucocorticoids, but their antiinflammatory effect may decrease bronchial responsiveness. A negative test while the patient is using glucocorticoids implies that the patient's current symptoms are not due to asthma.
• Antihistamines are discontinued because of their anticholinergic effect.

Exercise Challenge

- Baseline spirometry
- EKG, pulse ox, BP, HR and minute ventilation monitored
- Treadmill or bike
- Inhale dry air via facemask
- Achieve 80-90% max HR for 15-20 minutes
- Repeat spirometry @ 1, 5 10, 15, 20, 25 and 30 minutes post-exercise
- 10% drop in FEV1 considered +

Refractoriness to repeated exercise-induced bronchoconstriction



Exercise-induced bronchoconstriction (as measured by a fall in FEV1) is attenuated when a second exercise challenge is performed one hour after an initial challenge.
FEV1: forced expiratory volume in one second.

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Eucapnic Voluntary Hyperventilation

- Baseline spirometry
- Breathes 5% CO2 21% 02 mix
- Breathes 60-85% of MVV (FEV1 x 40)
- Post maneuver spirometry @ 5, 10 & 15 minutes
- 10% drop in FEV1 considered +

Treatment of EIB

- Pre-exercise albuterol
- Regular exercise
- Improve chronic asthma control therapy
- Eliminate triggers
- Measures to decrease cooling, drying of airway
- Diet rich in Omega 3 fatty acids

Classifying asthma severity and initiating treatment in youths greater than or equal to to 12 years of age and adults

Components of severity		Classification of asthma severity (≥12 years of age)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8 to 19 years 85 percent 20 to 39 years 80 percent 40 to 59 years 75 percent 60 to 80 years 70 percent	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3 to 4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80 percent predicted • FEV_1/FVC normal	• FEV_1 ≥80 percent predicted • FEV_1/FVC normal	• FEV_1 >60 but <80 percent predicted • FEV_1/FVC reduced 5 percent	• FEV_1 <60 percent predicted • FEV_1/FVC reduced >5 percent
Risk	**Exacerbations requiring oral systemic glucocorticoids**	**0 to 1/year (see footnote)**	**≥2/year (see footnote)**		
		Consider severity and interval since last exacerbation			
		Frequency and severity may fluctuate over time for patients in any severity category			
		Relative annual risk of exacerbations may be related to FEV_1			
Recommended step for initiating treatment		Step 1	Step 2	Step 3 And consider short course of oral systemic glucocorticoids	Step 4 or 5
		In two to six weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

Assessing severity and initiating treatment for patients who are not currently taking long-term control medications. The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs. Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous two to four weeks and spirometry. Assign severity to the most severe category in which any feature occurs. At present, data are inadequate to correlate frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (eg, requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic glucocorticoids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; ICU: intensive care unit.

Reproduced from: National Heart, Blood, and Lung Institute Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma. NIH Publication no. 08-4051, 2007.

Treatment of EIB

- Leukotriene modifiers
- Inhaled corticosteroids
- LABA's- formoterol, salmeterol, terbutaline
- Cromolyn's
- **No role** for oral B-agonist, theophylline

Usual doses of antileukotriene agents in the management of persistent asthma

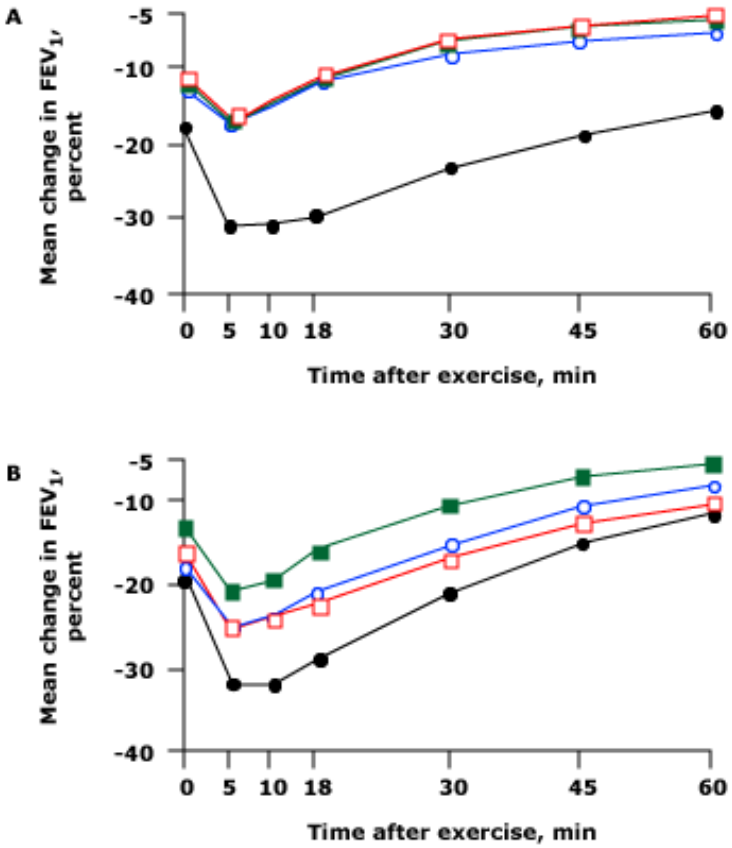
Medication	Preparations	Infant and small child	Pediatric	Adolescent and adult
Montelukast	Granules: 4 mg per packet Chewable tablets: 4 mg, 5 mg Tablet: 10 mg	12 months* to 5 years: 4 mg granules or chewable tablet once daily in evening	6 to 14 years: 5 mg chewable tablet once daily in evening	≥15 years and adult: 10 mg tablet once daily in evening
Zafirlukast•	Tablets: 10 mg, 20 mg	(Not studied)	5 to 11 years: 10 mg twice per day	≥12 years and adult: 20 mg twice per day
Zileuton•	Immediate-release tablet: 600 mg Extended-release tablet: 600 mg	(Not studied)	(Not studied)	≥12 years and adult: ▪ Immediate release: 600 mg four times per day ▪ Extended release: 1200 mg twice per day
Pranlukast[Δ]	Capsules: 112.5 mg, 225 mg Granules: 50 mg, 70 mg, 100 mg per packet	24 months to 5 years: 7 to 10 mg/kg granules per day in two divided doses	6 to 11 years: 7 to 10 mg/kg per day granules in two divided doses (maximum 225 mg twice per day)	≥12 years and adult: 225 mg twice per day

* Approved for use in infants ≥6 months in some countries other than United States.
• Elevated transaminases and severe hepatoxicity have been reported.
Δ Not available in United States. Available in Japan and some countries of Central and South America.

Data from:

1. *US Food & Drug Administration approved prescribing information. Available at http://dailymed.nlm.nih.gov/dailymed/about.cfm (Accessed April 15, 2014).*
2. *Bisgaard H, et al. Pediatric Pulmonol 2009; 44:568.*
3. *Keam SJ, et al. Drugs 2003; 63:991.*

The FEV1 after exercise in patients who received montelukast (A) and salmeterol (B)



The mean response curves are shown for percentage change in FEV_1 from prechallenge FEV_1 at baseline (closed circles), days 1 to 3 (closed squares), week 4 (open squares), and week 8 (open circles) after study treatment.

FEV_1: forced expiratory volume in one second.

Data from Edelman, et al. Ann Intern Med, 2000; 132:100.

Summary

- Nearly **all patients** with chronic asthma have EIB symptoms
- All patients **with** chronic asthma will respond to challenge testing (Methacholine, Mannitol, etc)
- EIB **without** chronic asthma can be diagnosed only if challenge testing is completed
- EIB can be confused with many other diagnoses and is often over or under-treated

Summary (cont)

- In patients with chronic asthma and EIB symptoms, increased controller therapy and elimination of triggers is the primary therapy
- All patients with chronic asthma or EIB only should have a SABA available, and use pre-exercise
- If EIB only patients do not tolerate SABA's then cromolyns are a good 2nd choice
- Improved cardiovascular fitness and regular exercise decrease EIB episodes

Summary (cont)

- If EIB is not controlled with SABA therapy, add either leukotriene daily or inhaled steroids
- Avoid LABA monotherapy in EIB (and in all chronic asthma) due to increased risk of refractory EIB over time
- Avoid combination agents of LABA/ICS for EIB as most patients will not require multiple controllers
- Never use oral B-agonist for any adult asthma or EIB