EXERCISE-INDUCED

BRONCHOCONSTRICTION

IN ATHLETES

Pathophysiology · Diagnosis · Management
for the Competitive and Recreational Athlete

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LEARNING OBJECTIVES

1. Nomenclature & Epidemiology
2. Pathophysiology & Mediators
3. Clinical Phenotypes
4. Diagnostic Criteria & Challenge Testing
5. Pharmacologic Management
6. Non-pharmacologic Strategies
7. WADA / Anti-doping Regulations
8. Special Populations
9. Biomarkers & Precision Management
10. Emerging Evidence

Mass General Brigham
for Children

Nomenclature & Operational Definitions

ATS Clinical Practice Guideline — Parsons et al., Am J Respir Crit Care Med 2013

EIB — Exercise-Induced Bronchoconstriction

≥10% fall in FEV_1 from pre-exercise baseline on standardized challenge. May occur with or without asthma.

Preferred term per ATS 2013 & GINA 2024; replaces "exercise-induced asthma."

EIB with Underlying Asthma (EIB+A)

EIB in patient with persistent asthma. ~90% of asthmatic patients have EIB.

Dual management: controller ICS + pre-exercise bronchodilator.

EIB without Asthma (Isolated EIB)

Objective EIB confirmed; normal resting spirometry, no BHR. Osmotic mechanism — not always eosinophilic.

ICS often unnecessary. Avoid over-labeling.

EILO — Exercise-Induced Laryngeal Obstruction

Extrathoracic obstruction at peak effort: inspiratory stridor, throat tightness. Diagnosed by CLE-test. Does NOT respond to bronchodilators.

Misdiagnosed as EIB in 30–40% of athletes. Coexists with EIB in ~30%.

Parsons JP et al. Am J Respir Crit Care Med. 2013;187(9):1016–1027
GINA 2024. https://ginasthma.org

Epidemiology of EIB in Athletes

Objective Testing Reveals Higher Prevalence than Symptom-Based Estimates

5–8%

General population prevalence (US)

[Weiler et al. 2016]

~50%

Winter Olympic athletes (EVH+)

[Sue-Chu 2012]

35–45%

Elite endurance athletes (objective)

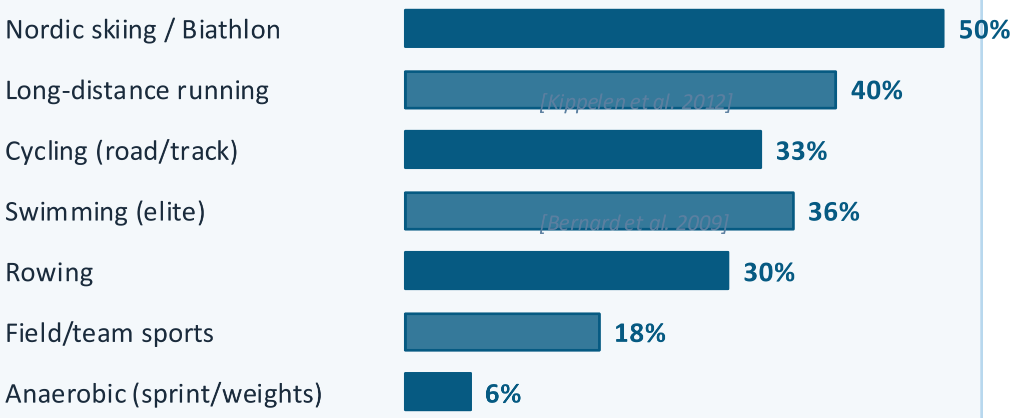
[Carlsen et al. 2008]

11–55%

Competitive swimmers (varies by pool type)

[Bernard et al. 2009]

Objective EIB Prevalence by Sport (EVH or Exercise Challenge)



Prevalence Determinants

- Diagnostic : objective testing yields 2–3× higher prevalence than symptom questionnaire [Rundell 2008]
- Training vol: dose-response relationship between lifetime pool hours and EIB in swimmers [Bernard 2009]
- Cold air exposure: EVH prevalence correlates inversely with mean training temp [Sue-Chu 2012]
- Atopic status: atopy doubles EIB risk independent of sport [Boulet 2015]
- Time of testing: prevalence higher in competitive season than off-season

Sue-Chu M. Respirology. 2012;17(3):474–490

Pathophysiology I — The Osmotic Hypothesis

Anderson SD, Daviskas E. J Allergy Clin Immunol. 2000;106(3):420–428

TRIGGER

Eucapnic hyperpnea
Large VE (up to 200 L/min) with unconditioned air

Evaporative water loss
Periciliary fluid becomes hyperosmolar (>320 mOsm/kg H_2O)

Thermal cooling
Cold air → vascular rebound post-exercise

→

MAST CELL ACTIVATION

Hyperosmolarity activates mast cells via osmosensitive channels

Degranulation products:

- Histamine
- Prostaglandin D_2 (PGD_2)
- Cysteinyl leukotrienes (LTC_4, LTD_4)
- Bradykinin
- Tryptase (biomarker)

Confirmed by urinary LTE_4 and $9\alpha,11\beta$-PGF_2 rise post-challenge

→

AIRWAY RESPONSE

Smooth muscle contraction
$CysLT_1R$ activation → rapid bronchoconstriction

Mucosal edema
Vascular engorgement → airway wall thickening

Mucus hypersecretion
Goblet cell response, MUC5AC upregulation

Net effect: ≥10% FEV_1 fall peaking 5–15 min post-exercise
Spontaneous resolution ~60 min

Anderson SD, Daviskas E. J Allergy Clin Immunol. 2000;106(3):420–428
Hallstrand TS et al. J Allergy Clin Immunol. 2005;116(6):1332–1339
McFadden ER Jr, Gilbert IA. N Engl J Med. 1994;330(19):1362–1367

Pathophysiology II — Refractory Period & Airway Remodeling

Mechanistic Basis for Warm-Up Protocols & Long-Term Structural Changes

THE REFRACTORY PERIOD — Mechanistic Basis

Mechanism: Depletion of performed mast cell mediator stores (histamine, PGD_2, LTs) after initial degranulation. Mast cell resynthesis requires 40–120 min. Prostaglandin E_2 (PGE_2) may additionally provide protective bronchodilatory feedback [O'Sullivan 1998].

Clinical exploitation: High-intensity warm-up (8–10 × 30-s sprints at >80% $\dot{V}O_2max$, 30 min pre-competition) exploits mast cell depletion to perform in the refractory window [Stickland et al., 2012, J Appl Physiol]

[Manning 1990; Stickland 2012]

AIRWAY REMODELING IN ELITE ATHLETES

Histologic evidence (Price 2014, AJRCCM): Endobronchial biopsies from elite athletes without asthma show:

- RBM thickening, subepithelial fibrosis
- Smooth muscle hypertrophy
- Goblet cell hyperplasia, ↑ intraepithelial mast cells

Functional consequence: Some remodeling may be irreversible → persistent small-airways obstruction post-career [Karjalainen 2000, Thorax]

[Price OJ et al. Am J Respir Crit Care Med. 2014;189(12):1522–1524]

PHENOTYPIC HETEROGENEITY — Two EIB Subgroups with Different Biology

Eosinophilic EIB: FeNO >25 ppb, blood eos >300/µL, BAL eosinophilia. Associated with atopy and asthma. ICS-responsive. More persistent. **Non-eosinophilic EIB:** Normal FeNO and eos. Prevalent in elite non-atopic athletes. Mast cell-mediated. ICS response limited. May be reversible with training modification.

Manning PJ et al. J Appl Physiol. 1990;69(3):1096–1100 · Stickland MK et al. J Appl Physiol. 2012;112(8):1407–1415

Clinical Features & Differential Diagnosis

Symptom History Has Limited Sensitivity in Athletes — Objective Testing Is Mandatory

Classic EIB — Clinical Presentation

- Symptoms during or immediately after vigorous exercise
- Peak obstruction: 5–15 min post-exercise
- Spontaneous resolution: 30–90 min
- Wheeze, dyspnea, chest tightness, cough
- Worse with: cold air, low humidity, pollutants, pollen, post-viral

⚠ Symptom Sensitivity Gap

Symptoms have only 50–65% sensitivity. Up to 50% with objective EIB deny symptoms. Objective testing is mandatory before pharmacotherapy.

Differential Diagnosis — Key Features

EILO (supraglottic/glottic)
Inspiratory stridor during peak effort; no SABA response. CLE-test diagnostic.

Cardiac (SVT, HCM, AVNRT)
Palpitations, near-syncope. Exclude with ECG, echo, Holter.

Vocal Cord Dysfunction
Psychogenic trigger, variable, inspiratory component.

Deconditioning / Poor aerobic fitness
Normal spirometry + challenge testing excludes diagnosis.

Anaphylaxis (exercise-induced)
Urticaria, angioedema, hypotension. Often food-dependent (FDEIA).

Rundell KW, Jenkinson DM. Med Sci Sports Exerc. 2002;34(10):1662–1668.

Diagnostic Criteria & Challenge Testing

ATS Guidelines: Objective Testing Required Before Pharmacotherapy in Athletes

ATS Diagnostic Criterion: ≥10% fall in FEV_1 from pre-exercise/pre-challenge baseline on standardized testing [Parsons et al., AJRCCM 2013]

Exercise Challenge Test (ECT)

Protocol:

Treadmill/cycle at 80–90% max HR for 6–8 min; FEV_1 q5 min × 30 min post

Threshold: ≥10% fall in FEV_1

Sensitivity ~55% in athletes

ATS standard; most accessible. May under-diagnose in elite athletes.

[Parsons 2013 AJRCCM] [Anderson 2001 Eur Resp J]

EVH — Eucapnic Voluntary Hyperventilation

Protocol:

Hyperventilates cold dry air at 30× FEV_1 for 6 min with 5% CO_2; FEV_1 q2 min × 20 min post

Threshold: ≥10% fall in FEV_1

Sensitivity 60–70%; gold standard for elite athletes

Required for WADA TUE. Specialized equipment; refer to expert lab.

[Anderson 2001 Eur Resp J] [Holzer 2002 J Allergy Clin Immunol]

Indirect Pharmacologic Challenge (Mannitol / AMP / Hypertonic Saline)

Protocol:

Mannitol 5–635 mg; AMP 0.39–400 mg/mL; Hypertonic saline 4.5%

Threshold: Mannitol: ≥15% FEV_1 fall; AMP: ≥20%; Hypertonic saline: ≥15%

Sensitivity ~60%; specific for eosinophilic inflammation; predicts ICS response

Mannitol (Aridol) is FDA/EMA-approved, portable. Use when EVH unavailable.

[Anderson SD et al. Eur Resp J. 2009] [Leuppi et al. Am J Respir Crit Care Med 2001]

Note: Methacholine PC20 lacks specificity for EIB — not primary tool for athletes. Negative result helps exclude AHR.

Interpreting Spirometry in the Athletic Patient

Supranormal Values, Inspiratory Loops & Post-Challenge Assessment

Spirometry Pearls for Athletic Patients

- **Supranormal volumes**
  FVC 110–135% predicted is common in elite athletes. 'Normal' values may represent a relative decrement.
- **Percent-change calculation**
  Always calculate as % of pre-challenge baseline — NOT % predicted. Example: 5.2→4.4 L (−15%) = positive EIB.
- **FEV_1/FVC ratio**
  Ratio <LLN warrants evaluation; does not exclude EIB.
- **$FEF_{25–75}$%**
  <65% predicted suggests small-airway involvement. Sensitive, not specific.
- **Inspiratory limb of F-V loop**
  Flat inspiratory plateau = extrathoracic obstruction → EILO/VCD. Always obtain both loops.
- **Reversibility testing**
  ≥12% + ≥200 mL reversibility at baseline → EIB+A (underlying asthma).

Diagnostic Thresholds

Exercise challenge	**≥10% FEV_1 drop**
EVH (6 min, cold/dry)	**≥10% FEV_1 drop**
Mannitol (Aridol)	**≥15% FEV_1 drop**
AMP	**≥20% FEV_1 drop**
Hypertonic saline 4.5%	**≥15% FEV_1 drop**
Methacholine PC_{20}	<4 mg/mL (severe) 4–16 mg/mL (mild-mod)
FeNO (adults)	**>25 ppb: eosinophilic** **>50 ppb: high probability**

Stanojevic S et al. Am J Respir Crit Care Med. 2022 [GLI reference equations]

Pharmacologic Management — Evidence Review

Stepwise, Phenotype-Guided Approach

Agent	Timing	Efficacy*	Level†	Notes / References
SABA — Albuterol 180–360 mcg MDI	15–30 min pre-exercise	80–95% FEV_1 protection	***1A***	First-line; 80–95% FEV_1 protection. Tachyphylaxis with daily use. WADA: permitted ≤1600 mcg/24h.
LABA — Formoterol 12–24 mcg DPI	15 min pre-exercise	85–90% FEV_1 protection	***1A***	Similar to SABA; rapid onset (~3 min), 12h duration. Tachyphylaxis. Never without ICS in asthma. WADA: ≤54 mcg/24h.
ICS — Budesonide/Fluticasone (low-medium dose)	Daily maintenance	35–70% attenuation	***1B (EIB+A)***	For EIB+A. In isolated EIB, ICS alone provides only partial attenuati analysis). Predicts response in eosinophilic phenotype (FeNO>25, e WADA: inhaled ICS permitted; oral/IV prohibited in-competition.
LTRA — Montelukast 10 mg oral	2 h pre-exercise or daily	40–55% attenuation	***1A***	Attenuates FEV_1 drop; additive to ICS. No tachyphylaxis. FDA black-box: neuropsychiatric effects — counsel adolescents. No WADA concern.
Mast Cell Stabilizer — Cromolyn/Nedocromil	15 min pre-exercise	30–50% attenuation	***2B***	Mast cell stabilizer. Inferior to SABA. Use if SABA not tolerated. No anti-doping issues.
Omega-3 FA (EPA 3.2g + DHA 2g/d)	Daily × 3 weeks	~50% attenuation	***2B***	RCT evidence in athletes. COX-2 inhibition → reduced PGD_2/LTC_4. 3-week onset. arachidonic acid competition, No WADA concern. Good adjunct.

**Efficacy = % EIB attenuation vs. placebo in challenge-test RCTs. †Evidence levels: 1A = strong RCT support; 1B = RCT, smaller/indirect; 2B = small RCT/observational.*

Non-Pharmacologic Strategies — Evidence Summary

Particularly Valuable for Anti-Doping Athletes and Those Seeking Medication Minimization

High-Intensity Warm-Up Protocol

Level B — RCT

8–10 × 30-s sprint intervals at >80% V̇O_2max, 30 min pre-competition. Exploits mast cell mediator depletion (refractory period). Stickland 2012 (J Appl Physiol): reduces post-exercise FEV_1 drop by 40–60% in cyclists. McKenzie 1994 (Med Sci Sports Exerc): confirmed in multiple endurance athletes.

[Stickland 2012 J Appl Physiol; McKenzie 1994 MSSE]

Cold Air Face Masks / RHEX Masks

Level B — RCT

RHEX masks warm/humidify inspired air, reducing osmotic stimulus. RCT-confirmed EIB reduction. Compliance may be challenging.

[Anderson SD, Kippelen P. Curr Allergy Asthma Rep 2005]

Omega-3 Fatty Acids

Level B — RCT

EPA 3.2g + DHA 2.0g daily × 3 weeks. RCT: 46% reduction in FEV_1 drop. Competes with arachidonic acid → less PGD_2/LTC_4. 3-week onset.

[Mickleborough TD et al. Chest. 2003;123(6):1921–1929]

Nasal Breathing / Nasal CPAP

Level C — Observational

Nasal breathing conditions air more effectively. Reduces osmotic stress at ≤50% V̇O_2max. Not feasible at maximal effort.

[Bonsignore MR et al. Respir Physiol Neurobiol 2015]

Environmental Optimization

Level C — Expert Consensus

Train indoors during high pollen/pollution days (AQI >100). Pool athletes: prefer outdoor or well-ventilated (<10 trichloramine) indoor pools. Avoid exercise in extreme cold (<−20°C). Air quality monitoring apps integrated into training planning. IOC 2021 recommendations for elite athletes.

[IOC Consensus. Br J Sports Med 2021;55:304–307]

Breathing Retraining (Buteyko/Speech Therapy)

Level C — Small RCT

Treatment of choice for EILO. Limited EIB evidence. May reduce hyperventilation component.

[McHugh P et al. Thorax. 2003;58(8):674–679]

WADA Anti-Doping Regulations — Beta-2 Agonists

2025 Prohibited List: Current as of January 1, 2025

⚠ **Beta-2 agonists are Category S3 (Beta-2 Agonists) on the WADA Prohibited List. All beta-2 agonists are prohibited EXCEPT specific inhaled forms at declared doses. Updated annually — verify at wada-ama.org**

Agent	Route	WADA Status (2025)	Urine Threshold	Clinical / TUE Notes
Salbutamol (albuterol)	Inhaled MDI	**PERMITTED**	≤1000 ng/mL	≤1600 mcg/24h. Counsel athletes — urinary threshold can be approached at max dose.
Formoterol	Inhaled DPI	**PERMITTED**	≤40 ng/mL	≤54 mcg/24h. Rapid onset (~3 min); can be used pre-exercise and as maintenance.
Salmeterol	Inhaled	**PERMITTED**	≤200 ng/mL	≤200 mcg/24h. ICS/LABA combinations count toward limit.
Indacaterol	Inhaled	**PERMITTED**	≤150 ng/mL	≤150 mcg/24h. Limited EIB data.
Terbutaline	Any	**TUE REQUIRED**	N/A — prohibited	TUE required in advance. Common prescribing error — not freely permitted.
Vilanterol	Any	**TUE REQUIRED**	N/A — prohibited	In Breo Ellipta — TUE required for competitive athletes.
Any oral beta-2 agonist	Oral/IV/IM/SC	**PROHIBITED**	Any detectable	Prohibited in and out of competition. Includes oral salbutamol.

WADA Prohibited List 2025. https://www.wada-ama.org/en/prohibited-list (updated Jan 1, 2025)

Integrated Management Algorithm

Phenotype-Guided, Evidence-Based Stepwise Approach

STEP 1 — Objective challenge testing. EVH for competitive athletes; exercise challenge for recreational/children.

STEP 2 — Biomarker phenotyping: FeNO + blood eosinophils. FeNO >25 ppb or eos >300/µL = eosinophilic phenotype → ICS-responsive. Low FeNO + normal eos = non-eosinophilic → SABA/LTRA-focused approach.

STEP 3 — Non-pharmacologic: warm-up, environmental modification, omega-3 FA. No WADA concerns.

STEP 4 — Pre-exercise SABA: salbutamol 200–400 mcg MDI, 15–30 min pre-exercise. Monitor for tachyphylaxis (use >3×/wk → reassess). WADA-permitted ≤1600 mcg/24h.

STEP 5 — Add montelukast 10 mg if SABA insufficient. Counsel re: FDA neuropsychiatric box warning.

IF EOSINOPHILIC EIB (+A)

- Start ICS (budesonide 200–400 mcg BID)
- Add LABA only with ICS (never monotherapy)
- Repeat EVH at 6–8 weeks to document response
- FeNO-guided dose adjustment: target FeNO <25 ppb

REFRACTORY EIB — ESCALATION

- Confirm adherence and inhaler technique
- Review aggravating factors: atopy, GERD, rhinitis, environment
- Biologics for severe eosinophilic asthma + EIB (all WADA-permitted)

Parsons JP et al. Am J Respir Crit Care Med. 2013;187(9):1016–1027 [ATS Algorithm]

Biomarkers for Phenotyping & Treatment Guidance

Moving Beyond Empiric Therapy — Precision Approach

Biomarker	Interpretation
FeNO (Fractional Exhaled NO) *Normal: Adults: <25 ppb | Children 5–17: <20 ppb* **↑ >50 ppb: high probability eosinophilic inflammation**	Predicts ICS response (AUC ~0.78). False-low: smoking, recent exercise. False-high: untreated rhinitis.
Blood Eosinophil Count *Normal: <300 cells/µL (some centers use <150)* **↑ ≥300/µL: eosinophilic phenotype; ≥500: predicts biologic response**	Inexpensive, widely available. Draw AM (circadian nadir PM, peak ~4-6AM). Serial monitoring: useful for tracking controller therapy response. Very high (>1000): rule out ABPA, EGPA, HES.
Urinary LTE_4 & 9α,11β-PGF_2 *Normal: Post-exercise: elevation correlates with EIB severity* **↑ Elevated post-EVH challenge confirms mast cell mediator release**	Research tool; rise post-challenge correlates with FEV_1 drop. Useful for omega-3/LTRA response monitoring.
Induced Sputum Eosinophils *Normal: <3% sputum eosinophils* **↑ ≥3%: eosinophilic airway inflammation**	Gold standard for airway phenotyping. More invasive/labor-intensive than blood eos or FeNO. Eosinophilic sputum: ICS-responsive. Neutrophilic sputum (>64%): often non-eosinophilic EIB, ICS response limited, azithromycin has been studied. Paucigranulocytic: most isolated EIB in athletes.

Dweik RA et al (ATS FeNO guidelines). Am J Respir Crit Care Med. 2011;184(5):602–615
Hallstrand TS et al. J Allergy Clin Immunol. 2005;116(6):1232–1239 — Price DB et al. Lancet Respir Med. 2015;3(11):849–858

Special Populations: Swimmers & Winter Sport Athletes

Distinct Pathomechanisms, Distinct Management Priorities

SWIMMERS — Trichloramine-Mediated Airway Injury

Chloramines in Pool Environments

Cl_2 + urea → trichloramines (NCl_3). Accumulates above water surface (0.1–1.5 mg/m^3 indoors).

Mechanisms of Injury (Bernard 2009)

Oxidative epithelial damage → neurogenic inflammation. CC16 falls with pool exposure → reduced protection.

Epidemiology

2.3× risk per 1000 pool-hours/year (Bernard 2009). EIB: 36% competitive vs. 8% recreational.

Management: Outdoor pools preferred; ≥6 ACH ventilation; shower pre-entry; ICS if FeNO elevated.

[Bernard A et al. Occup Environ Med 2009;66:276–279]

WINTER SPORT ATHLETES — Cold Air + Extreme Hyperpnea

Biophysical Parameters

VO_2max 80–90 mL/kg/min; VE 160–200 L/min. At −15°C, inspired air is severely dry. Maximal osmotic + thermal load.

Histopathology

RBM thickening, SM hypertrophy, mast cell excess in asymptomatic skiers (Price 2014). Post-career: higher obstruction rates (Karjalainen 2000).

Prevalence

Sue-Chu 2012 (Respirology): ~50% of winter Olympic athletes have EVH-confirmed EIB. Nordic skiing > biathlon > speed skating > alpine.

Management: RHEX masks; annual EVH screen; SABA ± ICS; yearly spirometry.

[Price OJ 2014 AJRCCM; Sue-Chu M 2012 Respirology; Karjalainen 2000 Thorax]

EIB in Pediatric & Adolescent Athletes

Developmental Considerations, Diagnostic Adaptation, Age-Specific Management

Diagnostic Approach in Children

Free-Running Test vs EVH

EVH often not feasible in children <10. Free-running test (6 min, 80–85% max HR) recommended for ages 5+.

FeNO Reference Ranges for Pediatrics

Ages 5–17: normal <20 ppb (lower than adults). Use GLI reference equations. Atopic children have higher baselines.

Symptom Recognition in Children

Young children often do NOT describe wheeze or dyspnea in classical terms. Key presentations: stopping activity abruptly, coughing post-exertion (often during cool-down), 'chest pain,' reduced participation vs. peers. Clinician must actively ask and observe — parents/coaches may normalize symptoms.

EILO in Adolescents

Adolescent females disproportionately affected. May present during competition. CLE-test essential; speech therapy for retraining.

Pediatric Treatment Notes

Albuterol MDI + spacer
Spacer mandatory <8 yr. DPI from ~8+ yr. 180–360 mcg pre-exercise.

Montelukast
5 mg (6–14 yr), 10 mg (≥15 yr). FDA black-box: monitor mood/behavior. Discuss with families.

ICS — growth monitoring
~0.5 cm/yr growth impact (dose-dependent). Minimal effect on final height.

LABA in children
Never as monotherapy. ICS/LABA fixed combination only (approved ≥5 yr).

Anti-doping — junior
Anti-doping programs begin at U16–U18 elite. Counsel athletes and parents early.

School action plan
Written action plan: symptoms, PRN albuterol at PE, emergency criteria.

GINA Pediatric Asthma Report 2024 · Stanojevic S et al. Am J Respir Crit Care Med. 2022 [GLI reference equations]

Clinical Case Discussion

Applying Diagnostic & Management Framework

CASE 1	28M elite Nordic skier. Asymptomatic. FEV_1 5.8L (128%), FeNO 18 ppb, eos 180/μL. 600+ hr/yr at −10 to −15°C. ***Q: What testing? What management?***	EVH challenge. If EVH+: low FeNO + normal eos → non-eosinophilic EIB → salbutamol + warm-up + RHEX mask. No ICS unless progression or FeNO rises.
CASE 2	17F competitive swimmer. Chronic post-practice cough, occasional tight chest indoors. FeNO 42 ppb, eos 380/μL. Exercise challenge: −14% FEV_1 at 10 min. ***Q: Phenotype and treatment plan?***	Eosinophilic EIB (NCl_3-driven). Plan: ICS (budesonide 200 mcg BID) + salbutamol + montelukast 5 mg. Repeat EVH post-ICS. Improve pool ventilation. Monitor growth.
CASE 3	22M collegiate soccer. Dyspnea mid-sprint, inspiratory throat tightness. NOT post-exercise. No SABA response. Normal spirometry; EVH negative (−3%). ***Q: Diagnosis? Next step?***	EILO (supraglottic/glottic). Refer for CLE-test. If confirmed: speech therapy retraining. Stop escalating bronchodilators.

15-year-old female soccer player

History	SOB + audible wheeze Albuterol no help ED - admitted
Time course	Few mins into a game
Physical Exam	Insp / exp wheeze Sats briefly 80’s
PMH	Asthma – well controlled x 10 years

Meds

continuous albuterol, solumedrol, magnesium

NO O2 needed

Work up

D/C in AM

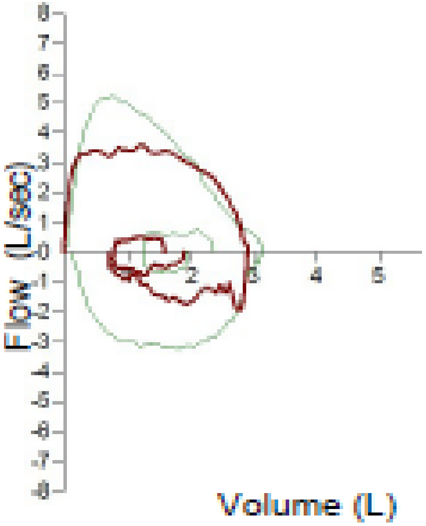
Pulm referral

Pulmonary Clinic

At rest

Normal exam

Normal PFTs



With exercise

Central inspiratory wheeze

Abnormal PFTs

Diagnosis

- **Clinical hx consistent and other etiologies ruled out**

OR

- **Vocal cord adduction on laryngoscopy**

Vocal Cord Dysfunction (VCD) / Inducible Laryngeal Obstruction

A Functionally Distinct Mimic of Asthma That Demands Separate Recognition

Defining Features

- **Definition:** Paradoxical adduction of the vocal cords during inspiration (and sometimes expiration), generating functional extrathoracic airway obstruction
- **Preferred Term:** EILO — Exercise-Induced Laryngeal Obstruction — per the European position paper (Christensen et al., 2019); VCD remains the term in North American literature
- **Prevalence:** Estimated 5–10% of patients referred for "refractory asthma"; 2–5% of adolescent athletes; female predominance (~75%)
- **Trigger Spectrum:** Exercise (commonest in athletes), strong odors, airway irritants, emotional stress, GERD, post-nasal drip

Pathophysiology

- **Mechanism:** Loss of neural inhibition of laryngeal adductor muscles during high ventilatory demand; paradoxical inspiratory glottic closure
- **Laryngeal anatomy:** Posterior glottic chink spared in classic VCD vs. supraglottic obstruction in arytenoid-predominant EILO — two distinct sub-phenotypes (Maat et al., 2011)
- **Physiologic consequence:** Variable extrathoracic obstruction: flattening of inspiratory loop on flow-volume curve; no measurable lower-airway obstruction on spirometry
- **Gold standard diagnosis:** Continuous laryngoscopy during exercise (CLE-test) — observing dynamic glottic closure at peak ventilation

Christensen PM et al. Eur Respir J. 2019;53(4):1801545   Maat RC et al. Eur Arch Otorhinolaryngol. 2011;268(10):1533–1538

VCD vs. Asthma: Overlapping Symptoms, Divergent Mechanisms

Clinical Features That Distinguish the Two Conditions — and When They Coexist

Features Mimicking Asthma

- **Dyspnea on exertion:** Both present with exertional breathlessness, often misattributed to bronchospasm
- **Chest tightness:** Reported in both; VCD tightness localizes to the throat/neck in up to 70% — an important discriminator
- **Wheeze:** Both can wheeze; VCD wheeze is predominantly inspiratory and suprasternal; asthma wheeze is expiratory and diffuse
- **Exercise limitation:** Both cause abrupt exercise limitation; VCD onset is often more sudden at peak intensity
- **Response to bronchodilators:** VCD shows NO objective spirometric response to albuterol — a key distinguishing feature at challenge testing

Distinguishing Clinical Clues

- **Timing:** VCD: symptoms peak during exercise, resolve within 5 min of stopping. EIB: peak symptoms 5–10 min AFTER exercise
- **Stridor:** Audible inspiratory stridor is VCD until proven otherwise; absent in pure EIB
- **History of anxiety/stress:** VCD has strong psychosocial co-morbidity; screen all adolescent athletes with atypical exercise symptoms
- **Throat-clearing, dysphonia:** Both suggest laryngeal involvement; uncommon in pure EIB
- **Coexistence rate:** VCD and EIB co-occur in 20–40% of athletes — both diagnoses must be actively excluded

Weinberger M, Abu-Hasan M. Pediatrics. 2007;119(5):e1388–e1394   Christensen PM et al. Br J Sports Med. 2017;51(23):1679–1685

Diagnostic Approach to VCD / EILO

From Clinical Suspicion to Laryngoscopic Confirmation

Diagnostic Algorithm

- **Step 1: Clinical screen:** Throat-centered symptoms, inspiratory stridor, symptoms during peak exercise, no post-exercise peak, failure of bronchodilators
- **Step 2: Resting spirometry:** Typically normal; may show variable extrathoracic pattern (inspiratory loop flattening, FIF50/FEF50 ratio >1.0)
- **Step 3: Bronchial challenge:** EVH or methacholine challenge — if NEGATIVE, EIB excluded; VCD more likely; do NOT stop here
- **Step 4: CLE-test:** Continuous laryngoscopy during incremental cycle or treadmill exercise to symptom-limited maximum. Gold standard per ERS 2019 position paper
- **Step 5: FULL characterization:** Classify as glottic vs. supraglottic vs. combined EILO to guide targeted therapy (Olin et al. classification)

CLE-Test Interpretation

- **Normal:** Stable glottis; minimal vocal cord movement during inspiration; full exercise capacity maintained
- **Glottic EILO (VCD):** Paradoxical inspiratory vocal fold adduction with posterior chink preservation; grade 1–3 on Maat/Olin scale
- **Supraglottic EILO:** Arytenoid prolapse and aryepiglottic fold collapse over glottis during inspiration; often more severe
- **Mixed:** Combination of glottic and supraglottic obstruction; worst exercise limitation; may require combined therapy
- **Treatment implications:** Glottic: speech therapy, inspiratory muscle training. Supraglottic: supraglottoplasty may be indicated in refractory cases

Olin JT et al. Clin J Sport Med. 2015;25(5):437–443   Halvorsen T et al. Eur Respir J. 2017;50(5):1602221

Management of VCD / EILO in Athletes

Behavioral, Pharmacologic, and Procedural Strategies

First-Line: Behavioral & Rehabilitative

- **Respiratory retraining:** Speech-language pathology-directed breathing retraining: diaphragmatic breathing, pursed-lip expiration, laryngeal control exercises — 70–80% response rate
- **Biofeedback:** Real-time laryngoscopic biofeedback during exercise training; accelerates neuromuscular re-patterning
- **Psychological support:** CBT for anxiety comorbidity; important especially in adolescent athletes; addresses psychosomatic triggers
- **Education:** Athletes taught to recognize prodromal symptoms and apply abort maneuvers (panting, throat-open posture) during exercise
- **Heliox acutely:** 70:30 helium-oxygen reduces laryngeal turbulence during acute severe episodes while awaiting definitive therapy

Refractory & Surgical Options

- **CPAP/NIV:** Continuous positive airway pressure pneumatically stents the glottis; useful in severe exercise-triggered cases; impractical for competition
- **Botulinum toxin:** Intralaryngeal BoNT-A injection into thyroarytenoid muscle reduces adductor force; 3–6 month duration; evidence from case series
- **Supraglottoplasty:** Surgical division of aryepiglottic folds for supraglottic EILO subtype; 80% improvement rate (Chandra et al.); not appropriate for glottic subtype
- **WADA considerations:** VCD treatments (speech therapy, BoNT) require NO therapeutic use exemptions — important advantage over ICS/LABA escalation
- **Follow-up:** CLE-test at 3–6 months post-treatment to confirm laryngoscopic improvement correlates with symptom resolution

Chandra RK et al. Laryngoscope. 2015;125(4):1003–1009 Hicks M et al. J Allergy Clin Immunol Pract. 2021;9(2):722–731

Outcome

- **59 children ages 8-18 yrs**
- **Average of 3-4 sessions**
- **Tx failures**
  - **Resolve spontaneously**
    - **2 yrs after diagnosis**

TABLE 1 Treatment Results

	n (%)
Overall treatment success	45 (76)
Speech therapy for patients with symptoms during exercise	23 (68)
Speech therapy for patients with symptoms at rest	5 (56)
Psychiatric therapy for patients with symptoms at rest	8 (100)

Pediatrics 2011;128:e1443-e1449

Pulmonary Function Testing in the Evaluation of EIB

Spirometry, Bronchodilator Reversibility, and Flow-Volume Loop Interpretation

Resting Spirometry: Role & Limits

- **Baseline FEV1:** Normal in isolated EIB (by definition) — this is NOT a reliable screening tool; sensitivity <50% for EIB in athletes
- **Obstruction pattern:** Reduced FEV1/FVC ratio (<0.70) with post-bronchodilator reversibility >=12%/200mL establishes asthma, not isolated EIB
- **Flow-volume loop:** Concave expiratory limb: lower airway obstruction. Variable inspiratory loop flattening: extrathoracic (VCD) obstruction. Variable expiratory loop flattening: intrathoracic variable obstruction
- **FIF50/FEF50 ratio:** Ratio >1.0 raises suspicion for extrathoracic obstruction; best interpreted with clinical context and serial testing
- **DLCO:** Normal in EIB/VCD; low DLCO suggests alternative diagnoses (ILD, pulmonary vascular disease, emphysema) — screen when clinically indicated

Pre- vs. Post-Bronchodilator Strategy

- **Bronchodilator reversibility:** >=12% and >=200mL FEV1 improvement = significant reversibility; supports asthma, mandates ICS therapy
- **In EIB without asthma:** Bronchodilator response often absent at rest — this is EXPECTED; do not use absence of resting reversibility to exclude EIB
- **Post-exercise spirometry:** Serial FEV1 at 5, 10, 15, 30 min post-exercise challenge; >=10% fall = positive EIB (ATS 2013 criterion)
- **Methacholine PC20:** Direct bronchial hyper-responsiveness; PC20 <4 mg/mL = asthma; 4–16 mg/mL = borderline; used when EVH unavailable
- **ATS evidence grade:** For formal EIB diagnosis: EVH preferred; exercise challenge acceptable; methacholine supplementary. Spirometry alone insufficient

Parsons JP et al. Am J Respir Crit Care Med. 2013;187(9):1016–1027   Miller MR et al. Eur Respir J. 2005;26(2):319–338

Bronchoprovocation Challenge Testing: EVH, Exercise, and Comparative Utility

Selecting the Right Test for the Right Athlete

Eucapnic Voluntary Hyperpnea (EVH)

- **Protocol:** Patient hyperventilates dry air (5% CO_2, 21% O_2) at 85% of predicted maximal ventilation for 6 minutes; FEV1 measured at 0, 5, 10, 15, 30 min post-challenge
- **Positive criterion:** >=10% fall in FEV1 from pre-challenge baseline (ATS 2013); some use >=15% for elite athlete screening
- **Sensitivity/specificity:** Gold-standard surrogate for field exercise: sensitivity 90–95%, specificity 93% for EIB diagnosis in athletes [Anderson 2001]
- **ATS/IOC preferred:** Preferred challenge method for WADA therapeutic use exemption documentation in elite athletes since 2000
- **Advantages vs. exercise:** Standardized stimulus; achieves higher ventilatory loads than treadmill exercise; not affected by fitness level; reproducible

Exercise Challenge Testing

- **Protocol:** 8-min continuous treadmill or cycle ergometer at 80–90% predicted max heart rate; breathing cold/dry air when possible; serial FEV1 post-exercise
- **Sensitivity vs EVH:** Lower sensitivity (50–70%) in athletes due to inability to achieve sufficiently high ventilatory provocation on ergometer
- **Ecological validity:** More directly simulates the athlete's sport; useful when sport-specific mechanism is suspected (e.g., swimmer in chlorinated pool)
- **Pediatric use:** Preferred first-line challenge in children <8 years when EVH compliance is problematic; lower target HR: 85% predicted
- **Combined approach:** For maximal sensitivity in competitive athletes: EVH first; if negative but high clinical suspicion, repeat with sport-specific exercise

Anderson SD et al. Chest. 2001;120(4):1514–1521   Weiler JM et al. J Allergy Clin Immunol. 2016;138(5):1292–1295

Cardiopulmonary Exercise Testing (CPET) in EIB and VCD Evaluation

Beyond Spirometry: Integrative Physiologic Assessment of Exertional Dyspnea

Why CPET in EIB/VCD Workup?

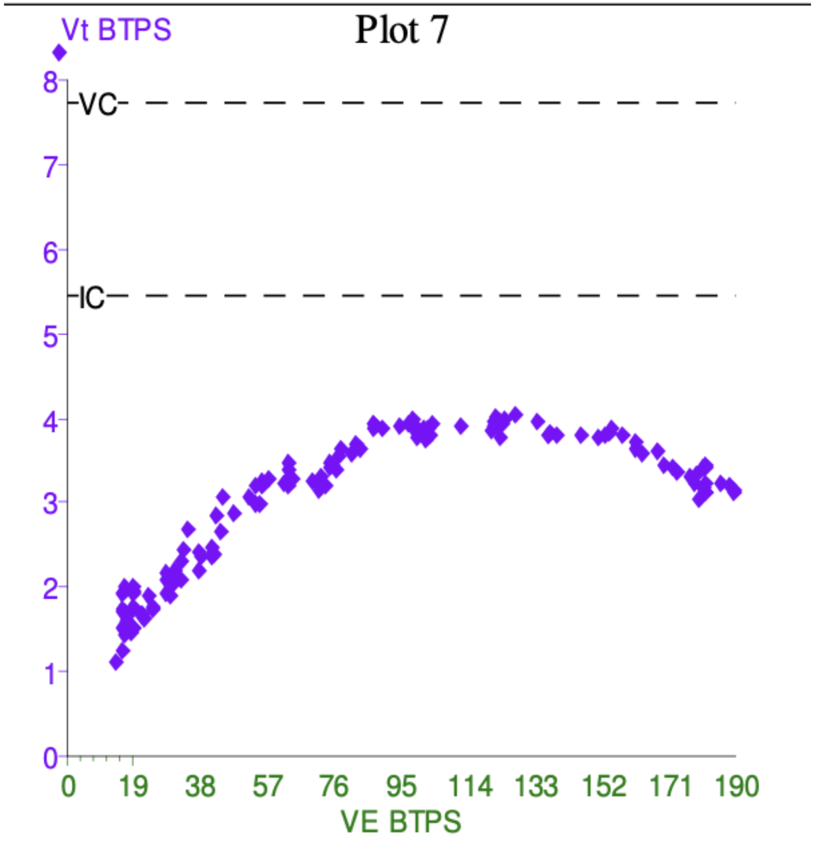
- **Unexplained dyspnea:** When spirometry, PFTs, and bronchial challenge are inconclusive, CPET identifies the limiting physiologic system: cardiac, pulmonary, muscular, or dysfunctional breathing
- **VCD/EILO differentiation:** During incremental CPET: abrupt drop in VE/PETCO2 with stridorous breathing suggests upper airway limitation; different from smooth ventilatory response in pure EIB
- **VO2 peak characterization:** Objectively quantifies exercise capacity; <80% predicted suggests true impairment vs. effort limitation; critical in disability evaluation
- **Ventilatory pattern:** Breathing pattern irregularity index (BPRI), tidal flow-volume loops at multiple exercise stages, and inspiratory-to-expiratory ratio inform VCD vs. EIB
- **Dysfunctional breathing:** Irregular breathing, excessive VE relative to VCO2, low PETCO2 at peak exercise = hyperventilation/dysfunctional breathing pattern — common

CPET Patterns Distinguishing EIB vs. VCD

- **EIB pattern:** Normal exercise VE, normal flow-volume loops DURING exercise; FEV1 falls >=10% in POST-exercise spirometry; O2 pulse and cardiac response normal
- **VCD/EILO pattern:** Normal FEV1 post-exercise; inspiratory flow limitation on intra-exercise tidal loops; abrupt exercise termination without cardiac or ventilatory limit; rapid recovery
- **Cardiac limitation:** O2 pulse plateau, abnormal BP response, premature heart rate reserve exhaustion — excluded by CPET before attributing dyspnea to airways
- **Deconditioning:** Low VO2 peak with normal ventilatory, cardiac, and airway parameters — important to distinguish from true airway disease in sedentary patients
- **MGH CPET Lab interpretation:** Integrated tidal flow-volume loops, breathing pattern analysis, and concurrent laryngoscopic data can be combined for definitive phenotyping of complex cases

Johnson BD et al. Chest. 2014;145(6):1322–1334 Kenn K, Balkissoon R. J Asthma. 2011;48(8):760–764

CPET



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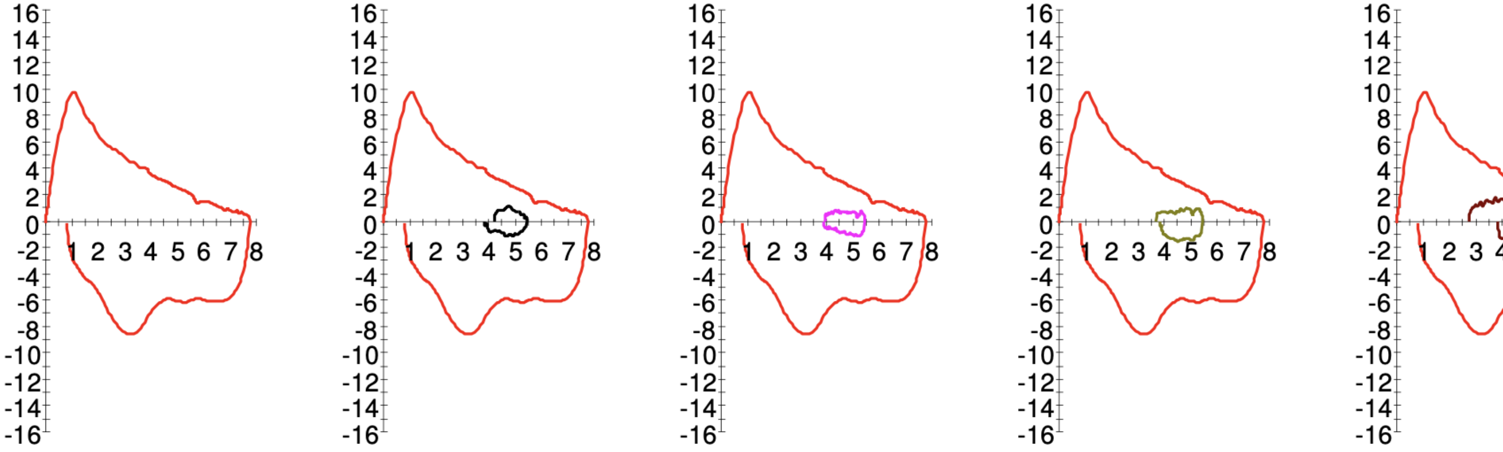

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Emerging Evidence & Research Frontiers

What the Literature Is Telling Us Now

Biologics in EIB with Severe Eosinophilic Asthma

Dupilumab (−46% exacerbations) and mepolizumab (−47%) for EIB+A uncontrolled on ICS/LABA with eos ≥300. All approved biologics are WADA-permitted.

[Castro M et al. NEJM 2018; Ortega HG et al. NEJM 2014]

EILO Classification & CLE-Test Standardization

Standardized EILO grading (0–3 scale, glottic and supraglottic). Treatment research: CPAP, laryngoscopic biofeedback (Phase 2 underway).

[Christensen PM et al. Br J Sports Med 2017;51:1679–1685]

Post-COVID Airway Dysfunction in Athletes

Post-COVID AHR in athletes without prior history. Mechanism: neurogenic inflammation, mast cell sensitization. Evaluate with EVH or mannitol before attributing to fatigue.

[Singh I et al. Lancet Respir Med 2022; Lim EJ et al. Lancet 2023]

Airway Microbiome & EIB Susceptibility

Asthmatic airways: Proteobacteria enriched, Firmicutes depleted. Oral breathing may alter microbiota in athletes. Probiotic RCTs ongoing — no clinical recommendations yet.

[Huang YJ et al. Am J Respir Crit Care Med. 2011;184(8):842–849]

Smart Inhalers & Digital Adherence Monitoring

Digital sensors track actuation timing and GPS location. Integration with training apps identifies tachyphylaxis and environmental patterns. RCTs show improved adherence.

[Merchant RK et al. J Am Med Inform Assoc. 2016;23(3):485–490]

Primary Prevention in Young Athletes

Reducing NCl_3 pool exposure may prevent EIB in swimmers. Omega-3 FA early in career: plausible prevention. Nasal breathing training: pilot data promising. Prevention RCTs needed.

[Bernard A. Occup Environ Med 2009; Mickleborough TD. Chest 2003]

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Key Take-Away Messages for the Pulmonary Physician

01 Isolated EIB is mechanistically distinct from asthma — osmotic mast cell activation, not eosinophilic inflammation. Avoid over-labeling.

02 Symptom sensitivity only ~55%. EVH is gold standard for elite athletes. Requires ≥10% FEV_1 drop.

03 FeNO + eosinophils guide ICS decisions. Low FeNO/eos → SABA + LTRA + non-pharm strategies.

04 EILO in 35% with exertional dyspnea. Inspiratory, during peak effort, no SABA response. CLE-test → speech therapy.

05 Daily SABA → tachyphylaxis within 1–2 weeks. Reassess: phenotype, ICS, non-pharm strategies.

06 Salbutamol ≤1600 mcg/day, formoterol ≤54 mcg/day — permitted. Terbutaline = TUE required. Oral beta-2 agonists = prohibited.

07 Evidence-based: warm-up protocol (Level B), fish oil (Level B), RHEX masks for cold-air athletes.