Exercise-Induced Bronchoconstriction / Exercise-Induced Asthma

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Goals :

1. Differentiate between EIA & EIB.
2. Identify those who are most susceptible to EIB.
3. Know the pathophysiology.
4. Know challenge tests that can be performed to determine if airways are responsive to exercise.
5. Know what treatments are available for EIA & EIB.

EIA vs EIB

EIA - Symptoms of asthma occurring after exercise.

Asthmatic subjects without anti-inflammatory treatment are at risk to have an asthma attack induced by exercise, up to 75 - 80 %.

EIB - The reduction in lung function happening after exercise, as observed in an exercise test.

Temporary contraction of respiratory muscles after exercise that happens frequently in subjects without a diagnosis of asthma.

- European Academy of Allergy and Clinical Immunology and European Respiratory Society.

What is Exercise-Induced Bronchoconstriction

- Transient narrowing of lower airways occurring after exercise. Occasionally DURING exercise this can also occur.
- Occurs mostly in patients with recognized asthma but can occur in those without signs of clinical asthma (elite athletes).
- Symptoms : Cough, Wheeze, Chest tightness, Dyspnea, Excess mucus prod.
- Why test for EIB:

  - ~50% elite athletes reporting symptoms during exercise have no airway narrowing

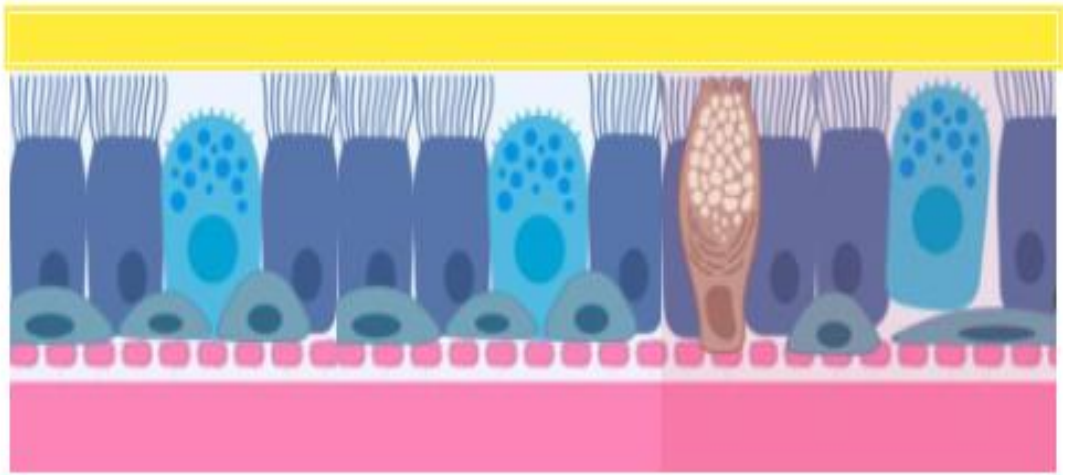
  - ~50% reporting no symptoms will test positive for EIB

    - “Field and laboratory exercise challenges for identifying exercise-induced bronchoconstriction” - Breathe

Who are the most susceptible to EIB?

- Endurance sports
- Cold weather athletes
  - Cross Country Skiers
  - Ice Skaters
  - Hockey players
- Swimmers

Airway Epithelium



What do we know about EIB and EIA?

Longitudinal studies have shown that airway hyperresponsiveness to exercise or cold air at an early age are among the strongest predictors of persistent asthma.

- Patients with EIB :
  - Epithelial disruption
  - Increased cysteinyl leukotrienes
  - Mast cell and eosinophil involvement
  - Increased levels of phospholipase A2 (Pla2) increasing leukotriene development.
  - Increased levels of Transglutaminase 2 (TGM2) which enhances Pla2.
    - “New Insights into the Pathogenesis of Exercise-induced Bronchoconstriction”

During Exercise

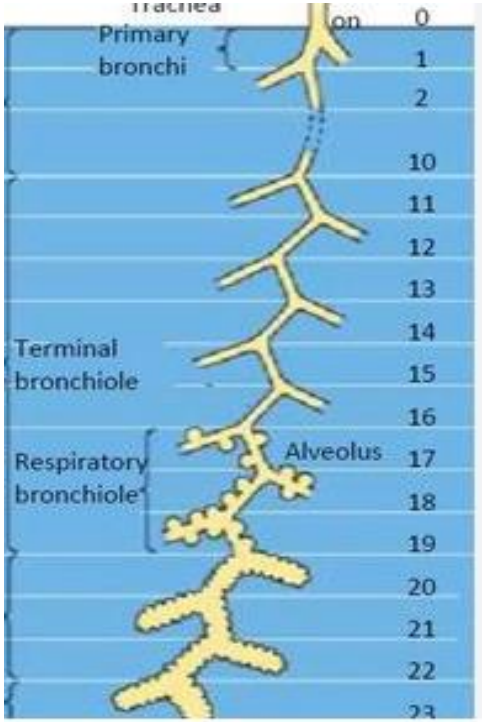
- The ventilatory rate increases to meet the oxygen requirements of the muscles.
- This challenges the airways ability to condition the air to correct moisture and heat.
- Inhalation of cold, dry air causes :
    - Osmotic changes
    - Thermal changes
    - Epithelial injury
    - Airway inflammation
    - Neuronal activation

Challenge of Airway to condition heat / H2O

Air needs to be heated and humidified to body conditions before entering the aveoli.

- Resting ventilation - 6 Liters/min
  - Nasal mucosa provides conditioning
- Moderate hyperpnoea up to 30 Liters/min
  - Sol layer of airway surface liquid
  - Air still not conditioned by 5th generation of airways
- Vigorous exercise >40 Liters/min
  - Smaller airways ~ 12 generations
  - H20 moves Bronchial circlualtion -> Epithelium -> Sol layer

- “Stimulus and mechanisms of exercise-induced bronchoconstriction”



Cause: Osmotic vs Thermal changes

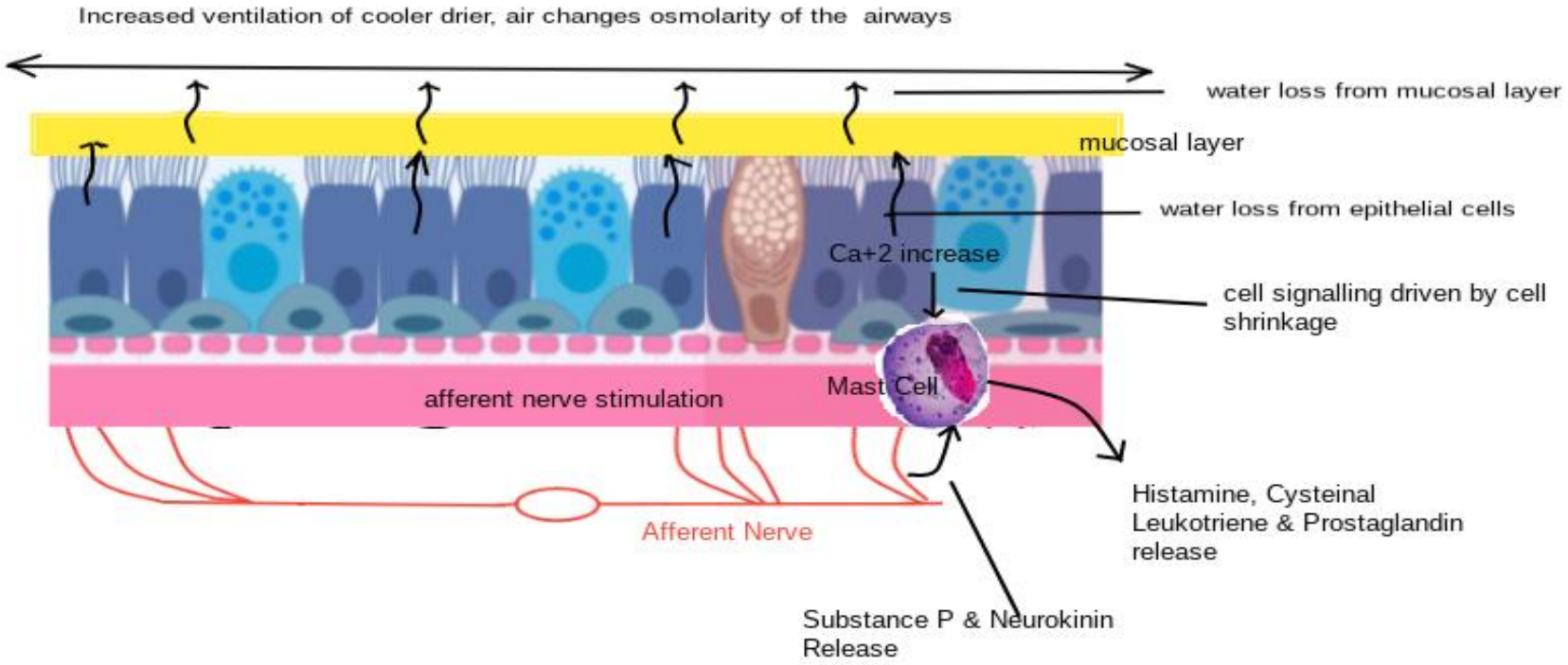
Colder air is Drier Air - Hello!

Results of hyperpnea / osmosis hypothesis

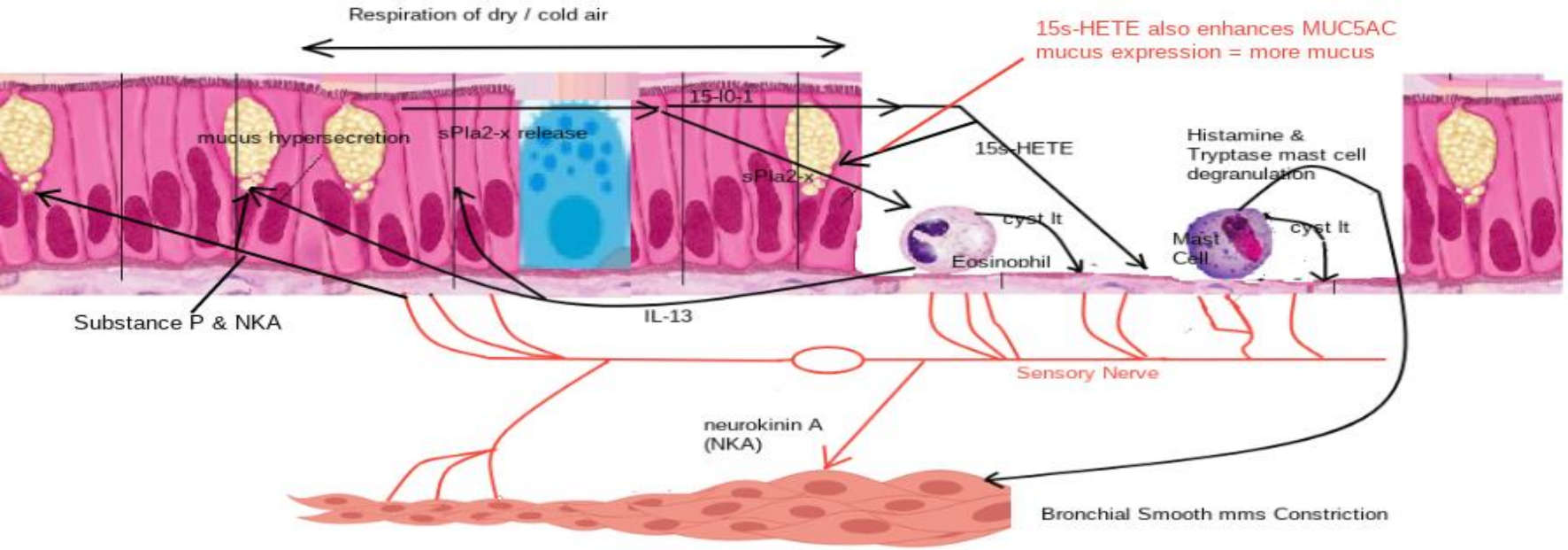
- During exercise the deeper breathing of cool, dry air will trigger :
- IL-13 to increase (in asthmatics and non asthmatics)
- Epithelial cells “shrink” as they release water to the upper mucosal layer.

- Increased intracellular Ca+2 levels in cells
- Other cell signalling events - not fully understood
- Stimulates afferent vagus nerve - substance P and Neurokinin A release
    - Above events cause mast cell degranulation & mucus secretion:
        - Histamine & Heparin release from mast cells
- This trauma to the epithelium causes Phospholipase A2 to be released which stimulates mast cells and eosinophils to manufacture Prostaglandin D2 and Cysteinyl Leukotrienes.
- Mast cells and Eosinophils release IL-13 which blocks Prostaglandin E2 (a suppressor of mast cells)
    - Greater cysteinyl leukotriene / PGE2 ratio = Bronchoconstriction
- The cysteinyl leukotrienes and prostaglandins = bronchoconstriction and increase mucus production in goblet cells.
        - “New Insights into the Pathogenesis of Exercise-induced Bronchoconstriction”

Mast cell activation by cell shrinkage



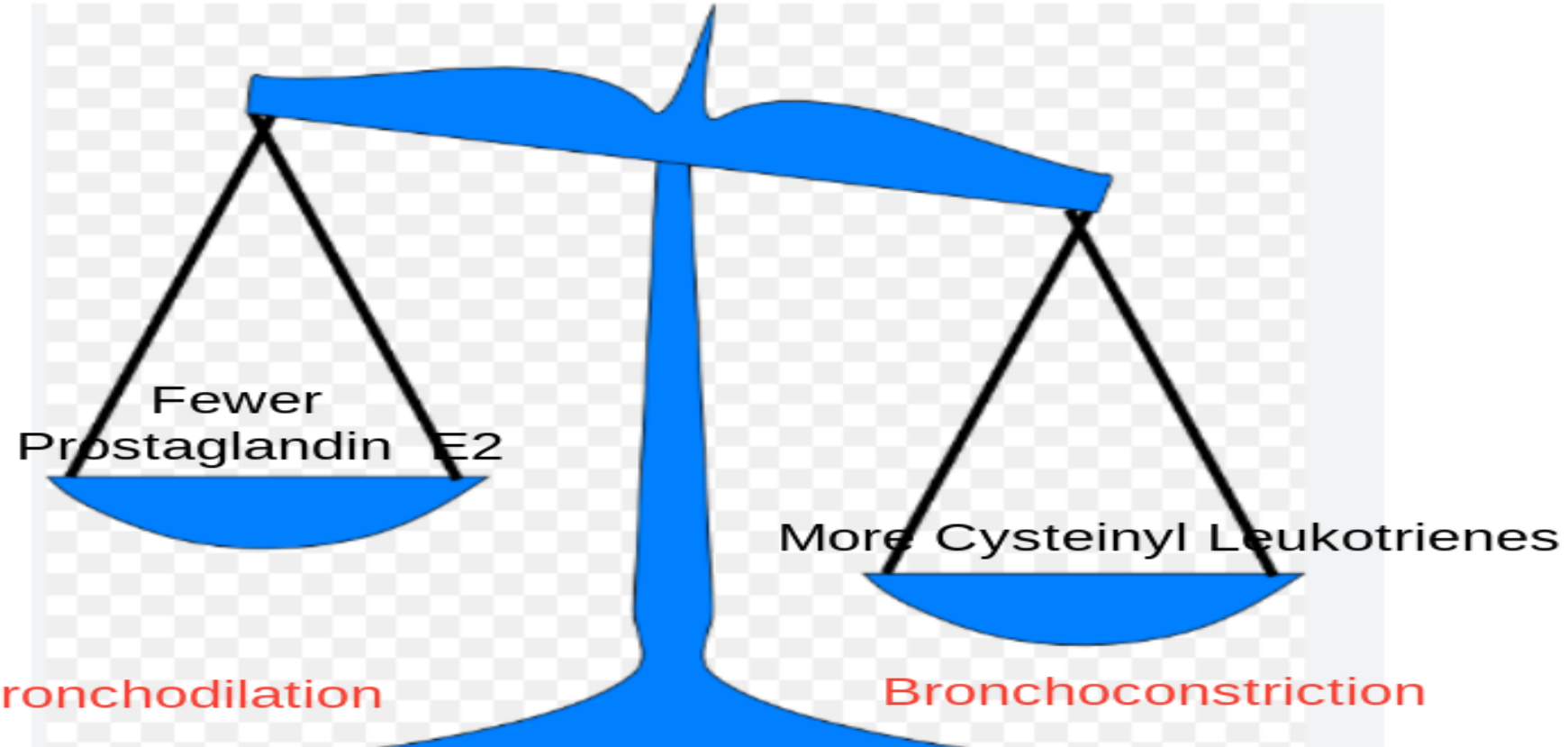
Pathophysiology of EIB



Leukotrienes stimulate sensory nerves causing the release of Sub P and NKA which stimulates mucus release from goblet cells

IL-13 stimulates epithelial release of sPla2-x -> cysteinyl leukotriene formation in eosinophils and in asthmatics with EIB it block the release of PGE2 (a bronchodilator) = Bronchoconstriction

PGE2 / Cysteinyl Leukotriene Imbalance



Pathophysiology of EIB in asthmatics

Patients with asthma susceptible to EIB:

- Higher levels of columnar epithelium in airway sputum than asthmatics without EIB

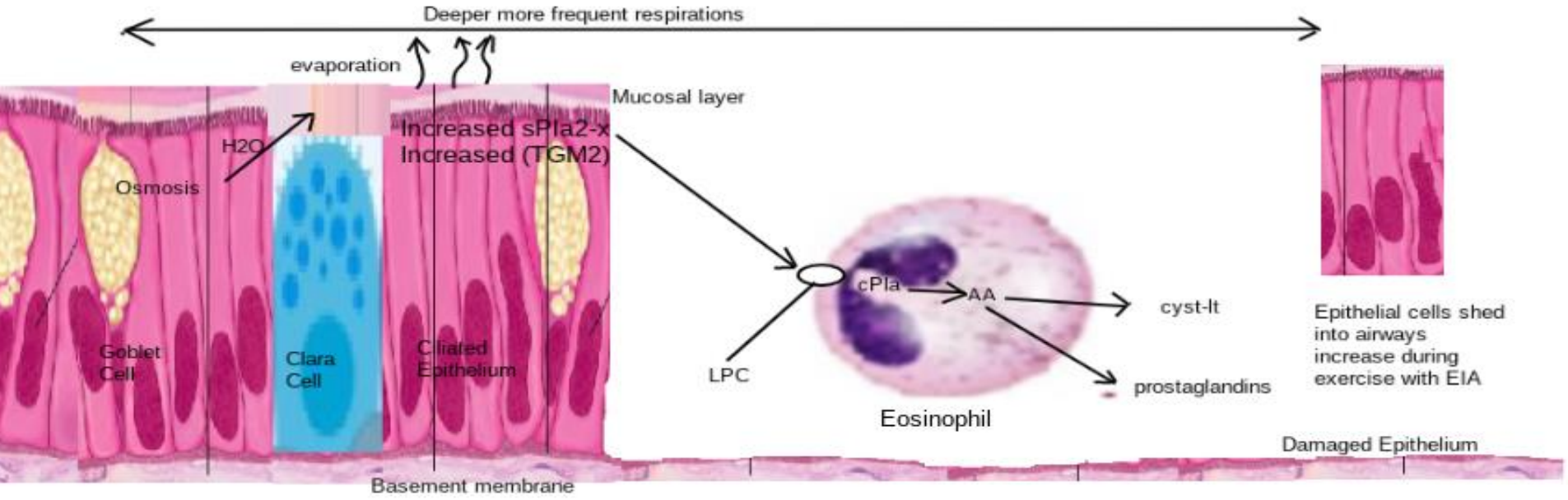
- Higher levels of mucin MUC5AC gene expression, and MUC5AC release into airways along with higher levels of Cysteinal Leukotrienes and Neurokinin A following an exercise challenge.
  - MUC5AC - mucin secreted by goblet cell

- This implicates a mechanism where mucus release occurs via the leukotriene mediated activation of airway sensory nerves.

  - “Role of MUC5AC in the pathogenesis of exercise-induced bronchoconstriction”

Exercise: Epithelial Cell / Eosinophil crosstalk

Increased frequency and depth of breathing caused cooler, drier air to circulate deeper into the tracheobronchial tree which causes evaporation of water from the mucosal layer of the airways. This water is replaced by the airway epithelium by osmosis. This "trauma" to the cells increase the expression of secreted phospholipase A2-x (sPla2-x) in the cells and also increases Transglutaminase 2 (TGM2) which enhances the sPla2-x activity in the cell. sPla2-x increases cellular phospholipase A (cPla) which creates arachidonic acid (AA) and this creates cysteinal leukotrienes (cyst-lt) and prostaglandins.



LPC- Lysophosphatidylcholine -amplifies cPla activity releasing arachidonic acid.

Thermal Hypothesis - Temp. changes ⇒ EIB

- Degree of bronchial narrowing that follows hyperpnea depends upon:
  - Thermal events within the airways
    (cooler air being warmed to airway temperature = heat loss from airway)
  - Degree of cooling that takes place during the exercise challenge
  - Thermal environment present in the immediate post exercise period

- The magnitude and rate of airway rewarming play an important role in EIA.

- Cooling brought about by hyperpnea is followed by rewarming once hyperpnea ceases.

  - “Post exertional Airway Rewarming and Thermally Induced Asthma”

Mechanisms of the Thermal Hypothesis

- Hyperpnea cools and drys the airways leading to vasoconstriction.
- This leads to stimulation of cholinergic receptors that bring on bronchial constriction and bronchial secretions.
- Shortly after exercise ceases and hyperpnea ceases and the airways rewarm leading to:

  - vascular distension

  - vascular congestion

  - increased vascular permeability

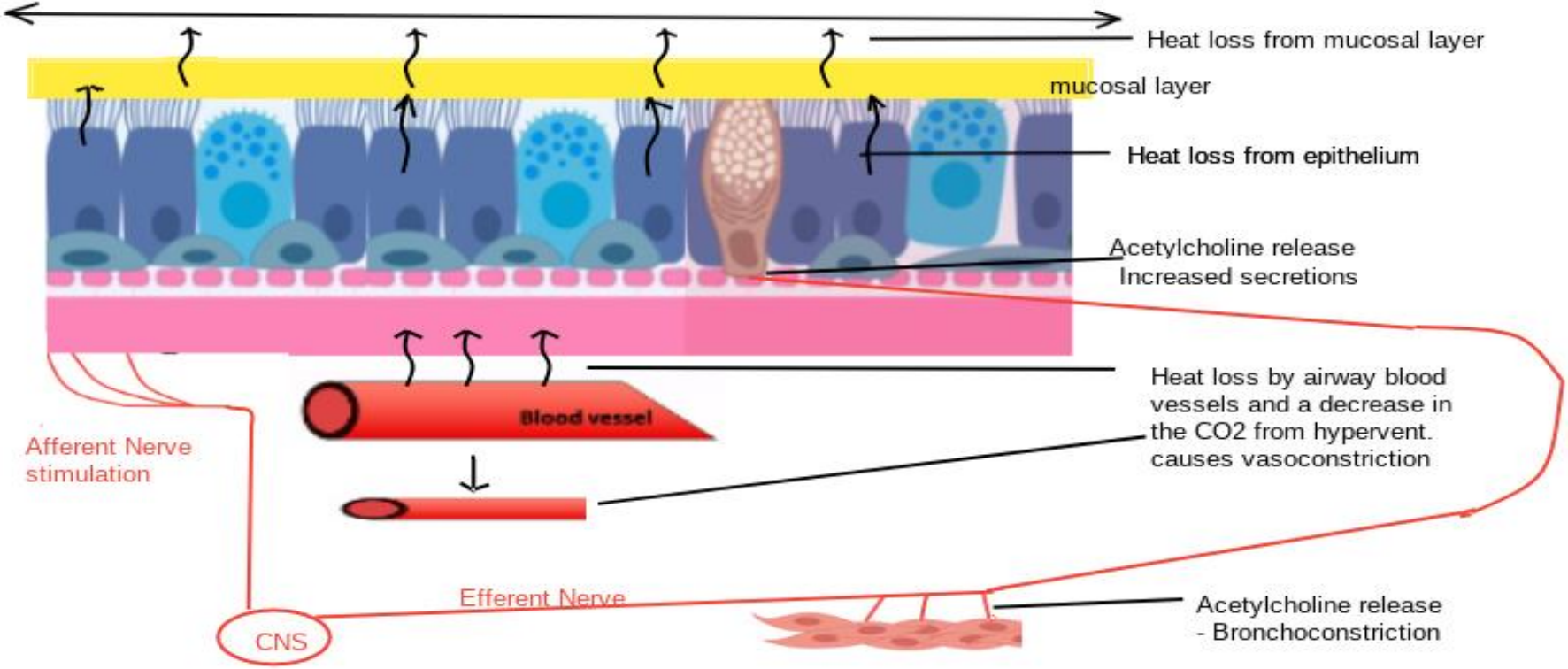
  - bronchial wall edema

- The above 4 events coupled with bronchoconstriction & airway secretions bring about the narrowing of the airway

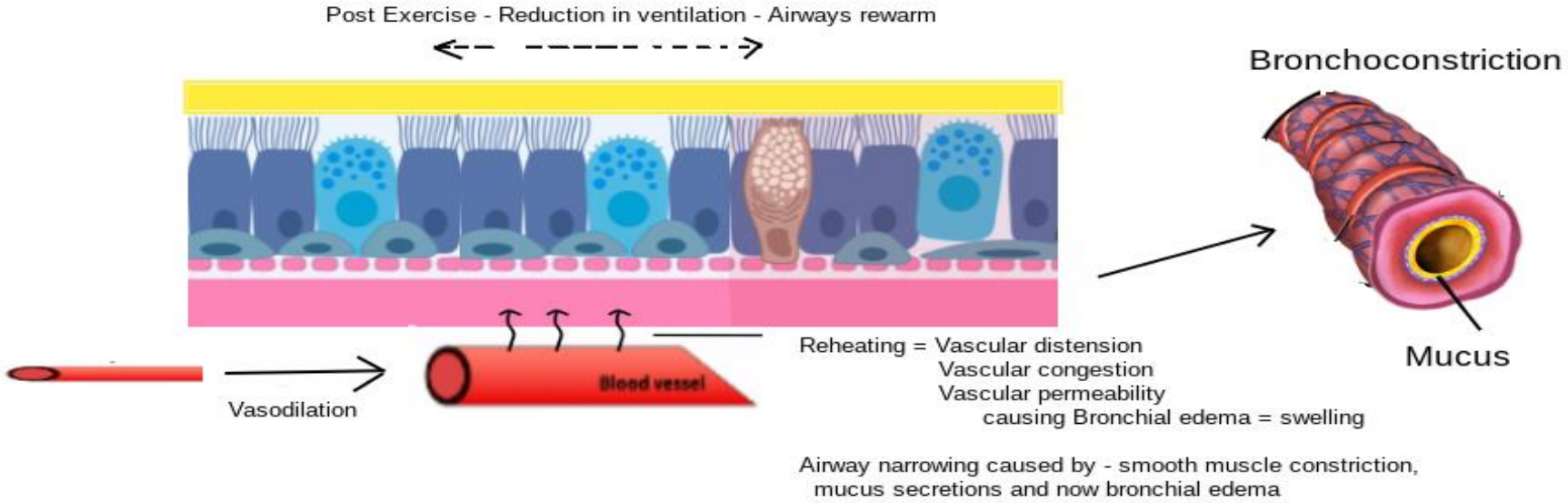
  - "Everything you need to know about Exercise-induced Bronconstriction and Exercise-induced Asthma" - RTmag

Thermal Hypothesis part 1 - airway cooling

Increased ventilation of cooler, drier air decreases the temperature of the airways and blood and their blood vessels



Thermal Hypothesis part 2 - airway rewarming

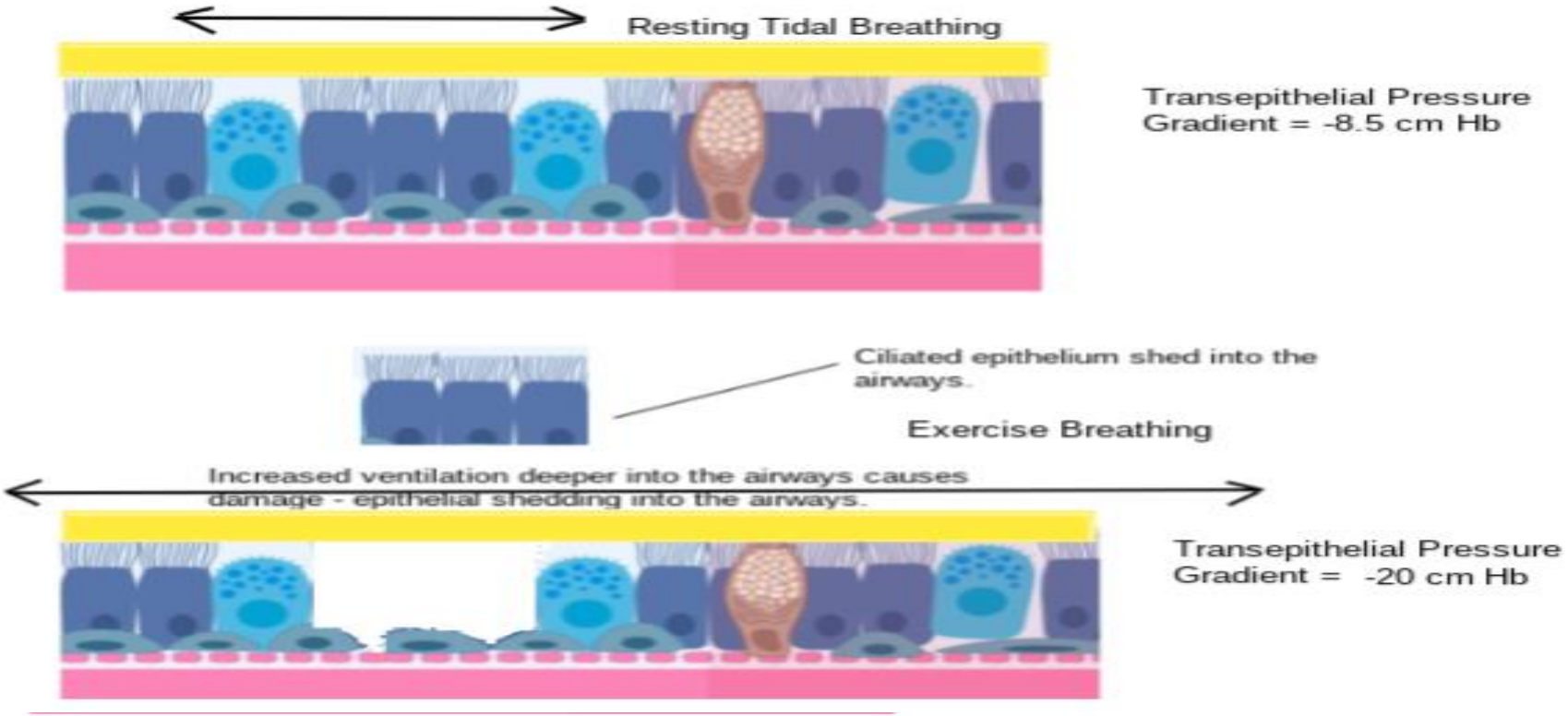


Epithelial Microtrauma Hypothesis

Deeper faster breathing penetrating into smaller airways:

- Dehydration
- Shear stress experienced in smaller airways
  - due to increased air flow
  - due to transepithelial pressure gradient
- Result disruption and injury to epithelial cells
- Repeated damage:
  - Repair
  - Bronchial hyperreactivity
  - Airway remodeling
  - “Everything you need to know about Exercise-induced Bronchoconstriction and Exercise-induced Asthma”

Shear stress cause by increased airflow



Airway remodeling

Repetitive microtrauma leads to airway remodeling hyperreactivity :

- During exercise IL-13 is increased
  - Stimulates airway epithelium to IL-8 (neutrophil recruitment)
  - Induce goblet cells to release more mucus
- Neutrophils
  - Induce clara cell secretory protein to be released from airway epithelium
    - Halts neutrophil recruitment
  - Induce release of mucus from goblet cells and pregoblet cells
  - Induce differentiation of Clara cells into pregoblet cells and goblet cells.
- More goblet cells produce more mucus.

- “IL-13 induced Clara cell secretory protein expression in airway epithelium: role of EGFR signaling pathway”

Airway remodeling

Clara cells differentiate into goblet cells producing more mucus

Diagnosing EIB

- Symptoms alone are not enough to diagnose EIB
- Pre / Post Bronchodilator Spirometry to detect underlying asthma
- Tests specific to EIB diagnosis :
  - Spirometry pre/post exercise challenge test (Gold Standard) (Indirect EIB Test)
    - Treadmill
    - Cycle ergometer (Bike)
    - FEV1 measurement 5, 10, 15, 20 & 30 min post challenge
    - Greater than 10% drop in FEV1 post = positive test.
  - Alternatives to exercise challenge tests:
    - Methacholine challenge (Direct Test)
    - Mannitol challenge (Indirect EIB Test)
    - Eucapnic voluntary hyperventilation (Indirect EIB Test)
    - Hypertonic saline, Dry air, Cold air, and Histamine challenges.

Exercise Challenge Testing

- Prior to testing :
  - Hold breathing medications, caffeine and no cigarette smoking
  - No exercise
- Spirometry performed
- Nose clips on - dictates mouth breathing (some labs use medically dry air)
- Inhaled air should be dry - water content < 10 mg H20 / Liter of air.
- EKG, SPO2 and BP monitored during the test.

Treadmill Exercise Challenge

- Use belt speed and grade to achieve desired ventilatory and heart rate targets
- Within 4 minutes of beginning exercise :
  - Minute Ventilation = predicted FEV1 x (14 to 21) or 40-60% of MVV
  - Heart rate = 80 - 90% of maximum predicted

- The heart rate and minute ventilation should be sustained 4 minutes during exercise.
  (may have to adjust speed / grade to keep a steady state)

- Post spirometry 5, 10, 15, 20 & 30 minutes post exercise spirometry

- Greatest decreases usually observed 10 - 15 minutes post challenge
  - “Field and laboratory exercise challenges for identifying exercise-induced bronchoconstriction”

Treadmill EIB Exercise Challenge

- Within first 4 minutes of exercise
  use belt speed and grade to reach:

  - Minute Ventilation =
    14 - 21 x predicted FEV1
    40-60% MVV
    HR = 85% pred max

- Sustain HR & VE 4 min.

- Spirometry
  5, 10, 15, 20 & 30 min post

Ergometer EIB Exercise Challenge

- No warmup - go directly into exercise:
- Predicted work rate on Bike :

  Predicted Watts = (53.76 X FEV1) - 11.07

  1st min - Watts = predicted Watts X .60

  2nd min - Watts = predicted Watts X .75

  3rd min - Watts = predicted Watts X .90

  4th min - Watts = predicted Watts
- Within 4 minutes of beginning exercise :

  - Minute Ventilation = predicted FEV1 x (14 to 21) or 40-60% of MVV

  - Heart rate = 80 - 90% of maximum predicted

- The heart rate and minute ventilation should be sustained 4 minutes during exercise.

  (may have to adjust watts to keep a steady state)
- Post spirometry 5, 10, 15, 20 & 30 minutes post exercise spirometry

Exercise Ergometer

- Predicted work rate on Bike :

  Predicted Watts = (53.76 X FEV1) - 11.07

  1st min - Watts = predicted Watts X .60

  2nd min - Watts = predicted Watts X .75

  3rd min - Watts = predicted Watts X .90

  4th min - Watts = predicted Watts

- Within 4 minutes of beginning exercise :

  - Minute Ventilation =

    14 - 21 x predicted FEV1

    40-60% MVV

    HR = 85% pred max

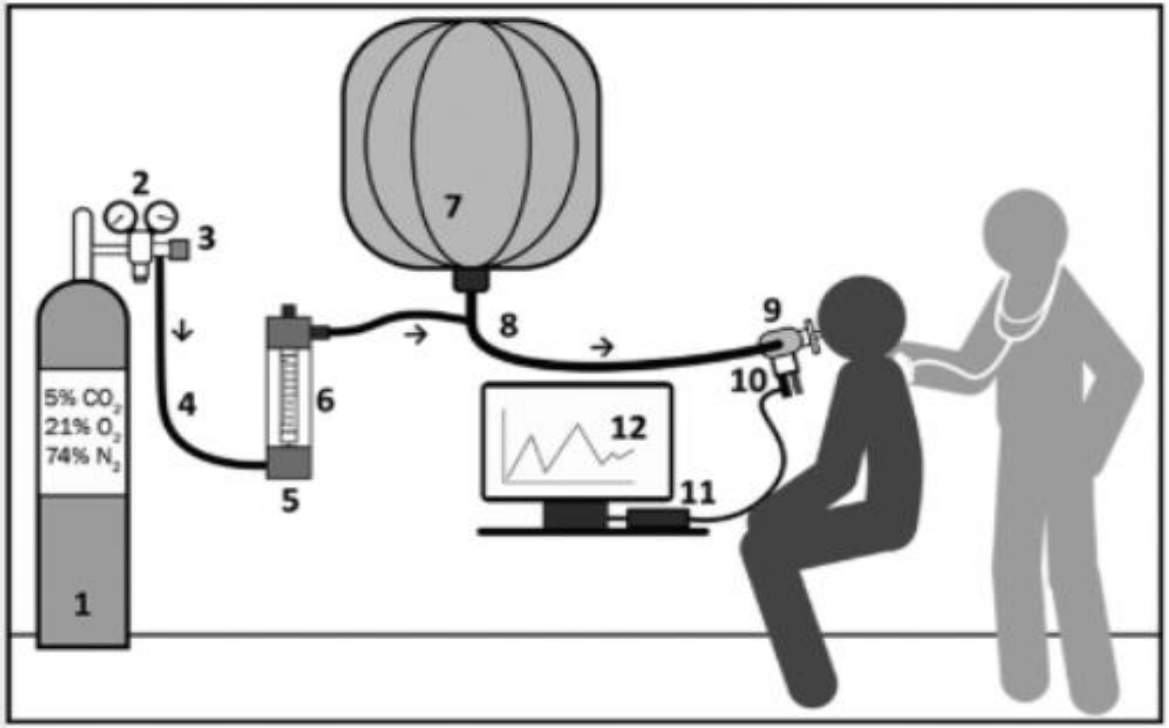
- Sustain HR & VE 4 min.
- Spirometry

  5, 10, 15, 20 & 30 min post exercise

Eucapnic Voluntary Hyperventilation

- Mimics hyperventilation during exercise causing drying & cooling of smaller airways
- Pretest baseline spirometry performed.
- Patient rapidly inhales and exhales special gas mixture for 6 minutes:
  - Gas Mixture = 21% O_2, 5% CO_2 & N_2 balance
  - Higher CO_2 keeps pt from passing out from depressed PCO_2.
- Post Spirometry performed 5, 10, 15, 20 & 30 min post exercise.
- 10% or greater decrease in FEV1 from baseline = positive test.

Eucapnic Voluntary Hyperventilation



1. Compressed gas
2. Pressure relief valve
3. Pressure valve
4. High pressure flexible tubing
5. Regulator for rotameter
6. Rotameter
7. Meteorological balloon
8. Metal connector with tap that simultaneously allows gas to enter and leave the balloon
9. 2-way valve and subject´s mouthpiece with filter
10. Air flow sensor, electronic flow volume measurement
11. Sensor data acquisition interface
12. Computer, flow volume measurement software

Mannitol Challenge

- It is a sugar alcohol
- Drying effect on the airways

- Mannitol is dispensed as a dry powder inhaler at increasing dosages

- Spirometry is performed to obtain a baseline
- Lowest dose of mannitol is given and spirometry is repeated
- Concentrations of mannitol are increased and spirometry is repeated
- Positive test :

  - 15% reduction in the FEV1 from baseline or

  - 10% reduction in the FEV1 between consecutive doses.

Managing EIB/EIA

Physical activities have been proven to improve an asthmatics:

- Forced Expiratory Volume in 1 sec (FEV1) & Forced Vital Capacity (FVC)
- Peak flow
- Reduce symptoms
- Improve quality of life

Non Pharmacologic intervention :

- Exercise modification
- Diet
- Special modifications tailored to the activity

Pharmacologic intervention

Exercise Modifications

- Get to the activity area (gym, playing field, pool…) early and warm up:
  - Example : take a few slow laps lasting 5 minutes prior to getting in the game.

- “Come down from your activity slowly” - cool down
  - Instead of stopping immediately from your activity continue your activity at a much slower intensity for a few minutes more minutes.

Diet

Gut microbiota plays a key role in immune response to diet in asthma

- Sugar or Fats = Inflammation
- Fruit

  Studies support a higher fruit diet helps to reduce inflammation.
- Low salt diet (2 weeks)

  Increased DLCO, Decreased capillary blood volume - less engorgement post exercise.
- Fish oil

  May have anti-inflammatory effect
- Caffeine - bronchodilator effect

Special Modifications Tailored to Activity

- Face Masks :
  Colder or dryer environments:
  - Face mask serves as heat / moisture exchanger

  Reduce amount of inhaled allergens

- Choosing a better environment for the activity:
  Exercise in areas where there is lower levels of air pollution, avoid busy highways or industrial areas.

Pharmacologic Interventions

GINA (Global Initiative for Asthma) recommends:

- Reliever medications and an inhaled cortiocosteroid (ICS)

- When breakthrough symptoms are a problem:
  - Warming up prior to exercise
  - Taking a Short Acting Beta Agonist (SABA) or a low dose ICS-formoterol before exercise.

- Some patients will get relief with an ICS combined with a Long-Acting Beta Agonist (LABA).

- Patients that can not take beta agonists may use short or long-acting muscarinic antagonists.

- Leukotriene receptor antagonists may also be used - Montelucast.

References

1) “Everything you need to know about Exercise-Induced Bronchoconstriction and Exercise-Induced Asthma” - RT Magazine Vol 35 No 5,
2) “Type 2 inflammatory biomarker response after exercise challenge testing” - Ellen Tufvesson, Henning Stenberg ...
3) “Exercise-Induced Bronchospasm in Elite Athletes” - Pigakis, Konstantinos M., Stavrou,Vasileios T. ...
4) “Cellular and Functional heterogeneity of airway epithelium” - Davis, Jordan D. & Wypych, Tomasz P.
5) ”Anti-muscarinic drugs as preventive treatment of exercise-induced bronchoconstriction (EIB) in children and adults” - Bonini, Matteo, Cilluffo, Giovanna...
6) ”Global strategy for Asthma management and prevention” - GINA

Questions?????

Back to our "hypothesis tug of war::

Osmosis

Thermal