Making the Diagnosis of Asthma

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What is Asthma?

Asthma is a chronic inflammatory disease of the airway with

- Airway obstruction that may or may not be reversible, either spontaneously or with medication
- Airway inflammation caused by many cellular components
- Increased airway hyperresponsiveness

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History
Symptoms

- Has the patient had an attack or recurrent attacks of wheezing?
- Does the patient have troublesome cough at night?
- Does the patient have a cough or wheeze after exercise?
- Does the patient have a cough, wheeze, or chest tightness after exposure to airborne allergens or pollutants?
- Do the patient's colds "go to the chest" or take more than 10 days to clear up?

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History
Pattern of Symptoms

* Perennial
* Continuos
* Nocturnal
* Diurnal variation

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History
Precipitating Factors

* Viral infections
* Allergies
* Exercise
* Occupational exposure
* Drugs

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History
Development of Disease

* Age of Onset
* Number of hospitalizations
* Need for oral corticosteroids
* ER visits
* H/O intubation

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History
Social History

* Tobacco & Cannibus use
* Environmental
* Day care
* Pets

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Diagnosis
Physical Exam

- Physical exam may be normal in asymptomatic patient
- Clinical signs of dyspnea, airflow limitation (wheeze), and hyperinflation
- Wheezing may be absent in severe asthma exacerbations, but usually patients have other physical signs reflecting severity: cyanosis, drowsiness, difficulty speaking, tachycardia, hyperinflated chest, use of accessory muscles, pulsus paradoxus

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Differential Diagnosis
Infant & Children

- Upper Airway
  - Allergic Rhinitis/Sinusitis
- Obstruction/Large Airway
  - Foreign body, VCD, Vascular ring, laryngeal web, tracheomalacia, tracheal stenosis, bronchostenosis
- Obstruction/Small airways
  - Viral bronchitis, bronchiolitis obliterans, cystic fibrosis, BPD, heart disease, aspiration secondary to GERD

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Differential Diagnosis
Adults

* VCD
* COPD
* CHF
* PE
* Tumor
* PIE syndromes
* Drugs (ACEI)

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Case 1

- 64-year-old Caucasian female with PMH asthma (diagnosed 2 years ago), allergic rhinitis, endometrial carcinoma presenting with 10 years of progressively worsening cough and intermittent wheeze/dyspnea.
- Symptoms never significantly responded to ICS/LABA or SABA.

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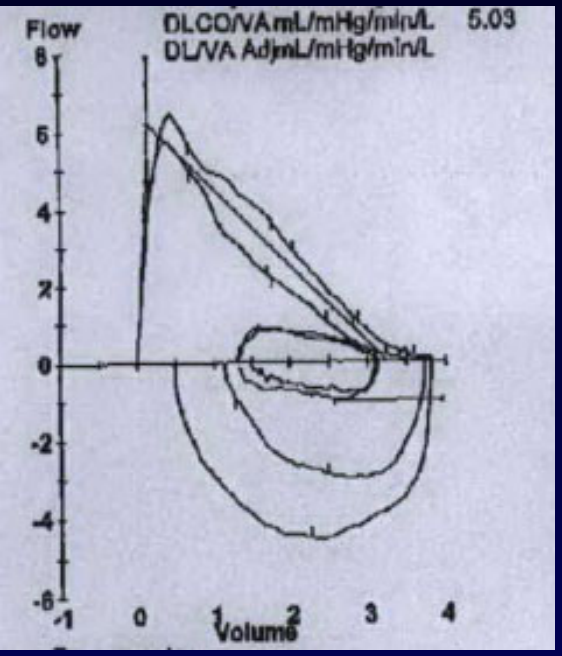

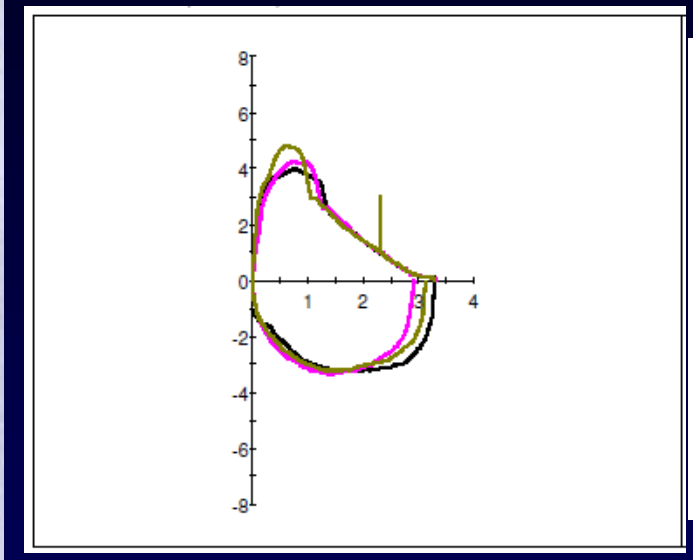

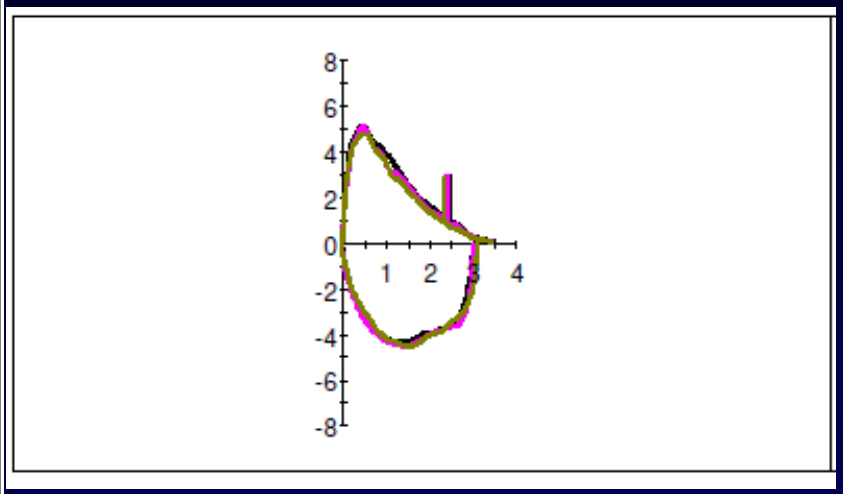

1/2015 (pre-dilation)

11/2016 (pre-dilation

3/2017 (post-dilation)

- Diagnosed with CT imaging and bronchoscopy. Bronchoscopy with balloon dilation and steroid injection (3/2017).

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Case 2

- 45-year-old Caucasian female with PMH allergic rhinitis with 4 years of progressively worsening dyspnea, inspiratory wheeze, and cough.
- Symptoms did not improve with ICS or SABA.
- Similarly, non-contrast neck CT imaging and bronchoscopy showed subglottic narrowing and was treated with balloon dilation and steroid injection

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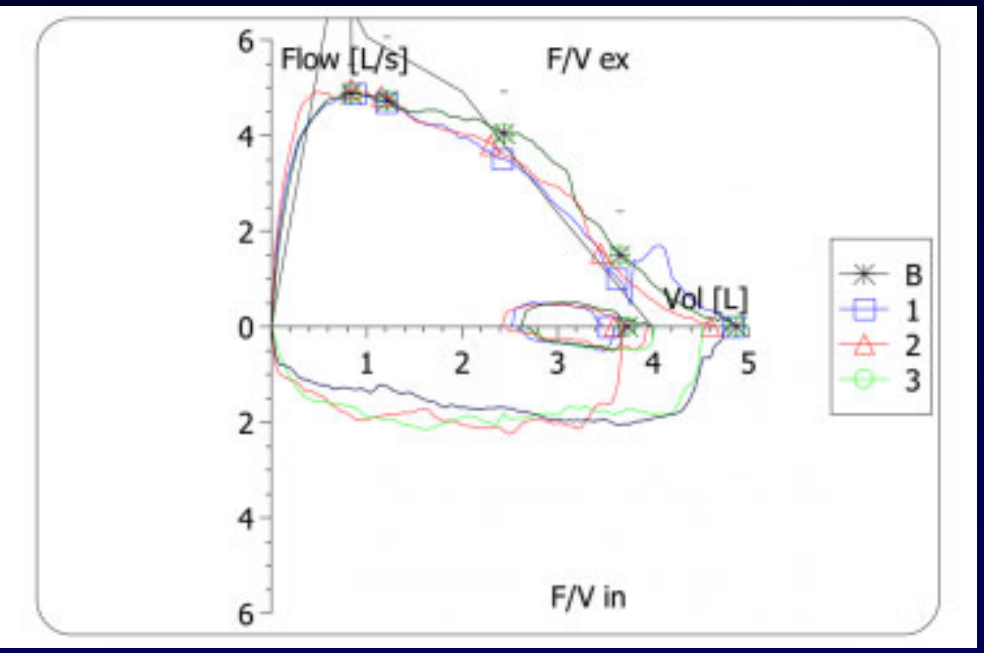
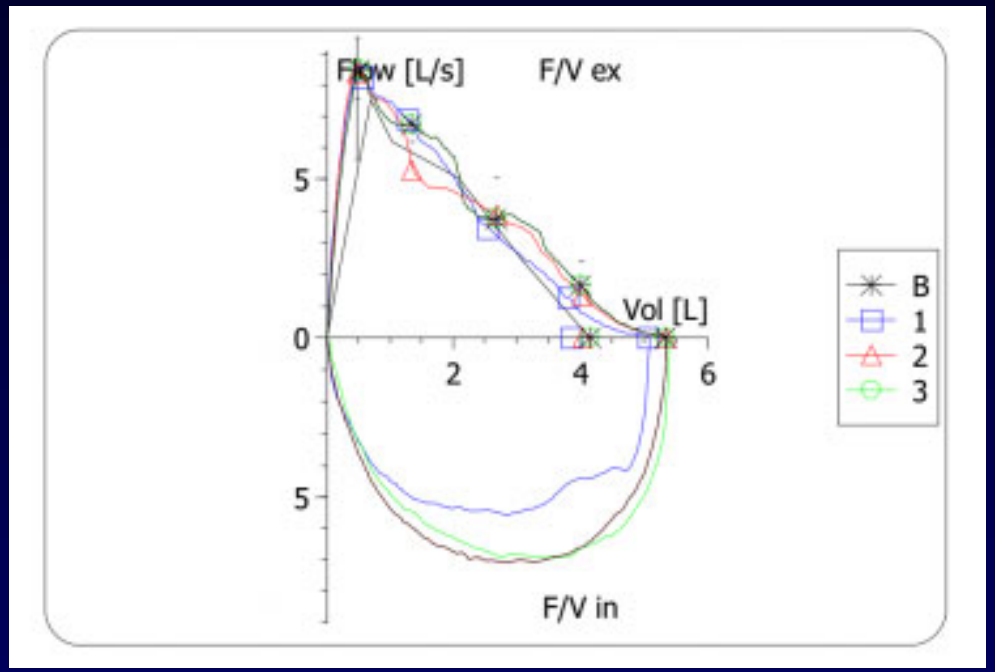


5/2012 (pre-dilation)



9/2012 (post-dilation)

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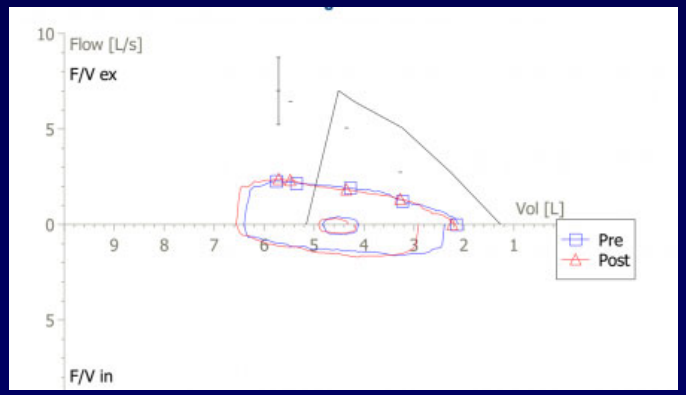
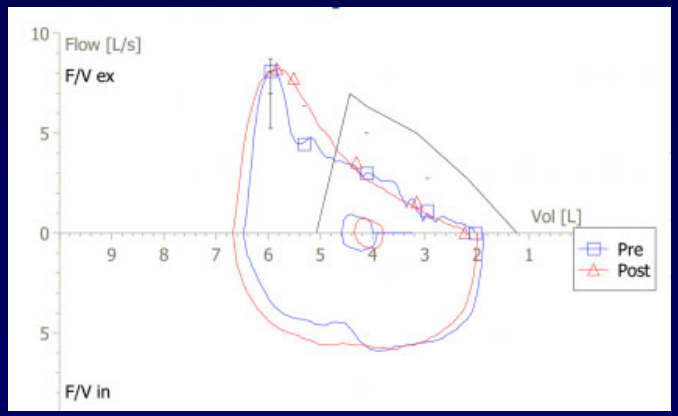
- 21-year-old Caucasian female with PMH asthma (diagnosed 15 years ago), VCD presenting with several months of cough, wheeze, and exertional dyspnea.
- Symptoms previously improved with ICS and SABA but no longer. Recent oral steroid burst had no effect.
- Bronchoscopy and non-contrast neck CT imaging revealed subglottic narrowing and was treated with laser cautery and balloon dilation (7/2009).



7/2009 (pre-dilation)



1/2012 (post-dilation)

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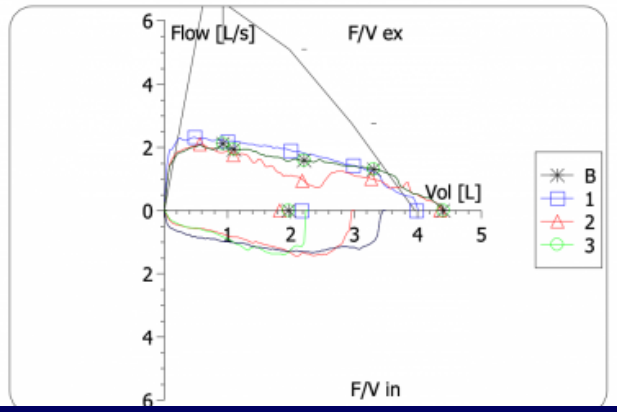
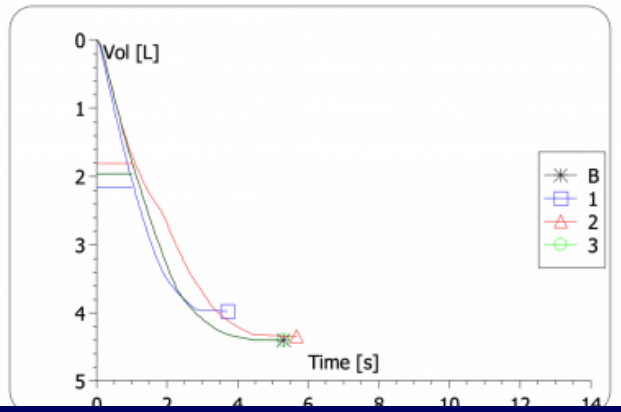
Spiro

	LLN	Pred	Best	%Pred	Act1	Act2	Act3	Act4	Act5	Act6	Act7	Act8	Act9	Act10
FVC	3.23	3.95	4.40	111.5	3.97	4.35	4.40							
FEV 1	2.83	3.44	1.96	57.1	2.16	1.82	1.96							
FEV1/F	77	86	45		54	42	45							
PEF	5.27	7.06	2.10	29.7	2.31	2.09	2.10							
F25/75	2.51	3.80	1.62	42.6	1.86	1.17	1.62							
PIF		4.30	1.34	31.1	1.34	1.45	1.41							
FE/FIF		124	130	104.7	157	90	149							
FET			5.21		3.66	5.60	5.21							
VBe/FV			1.63		0.87	1.28	1.63							





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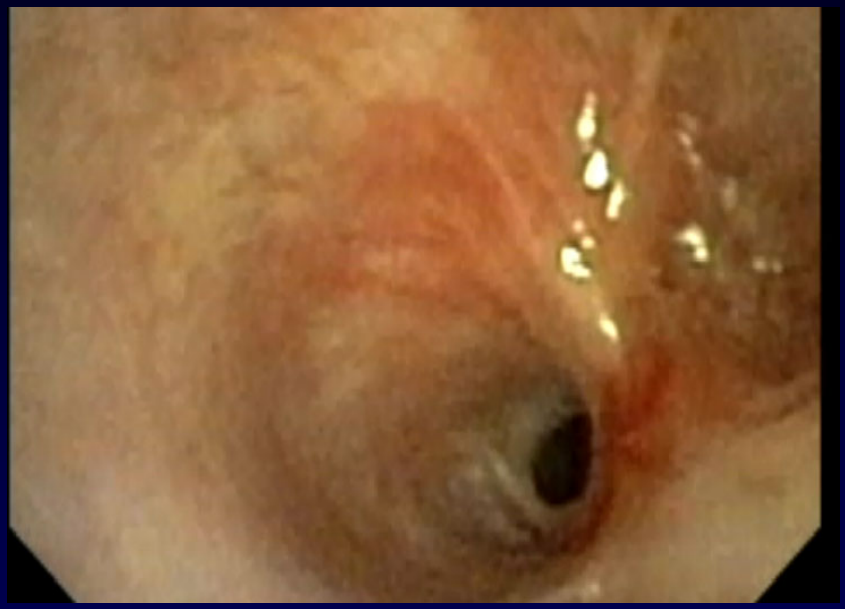

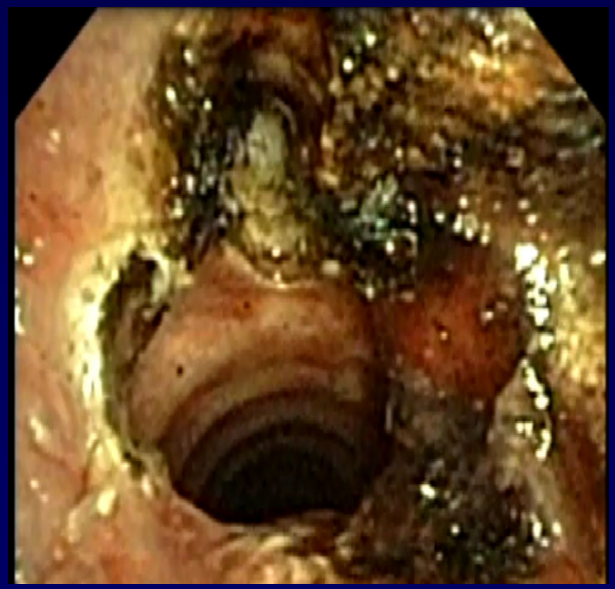

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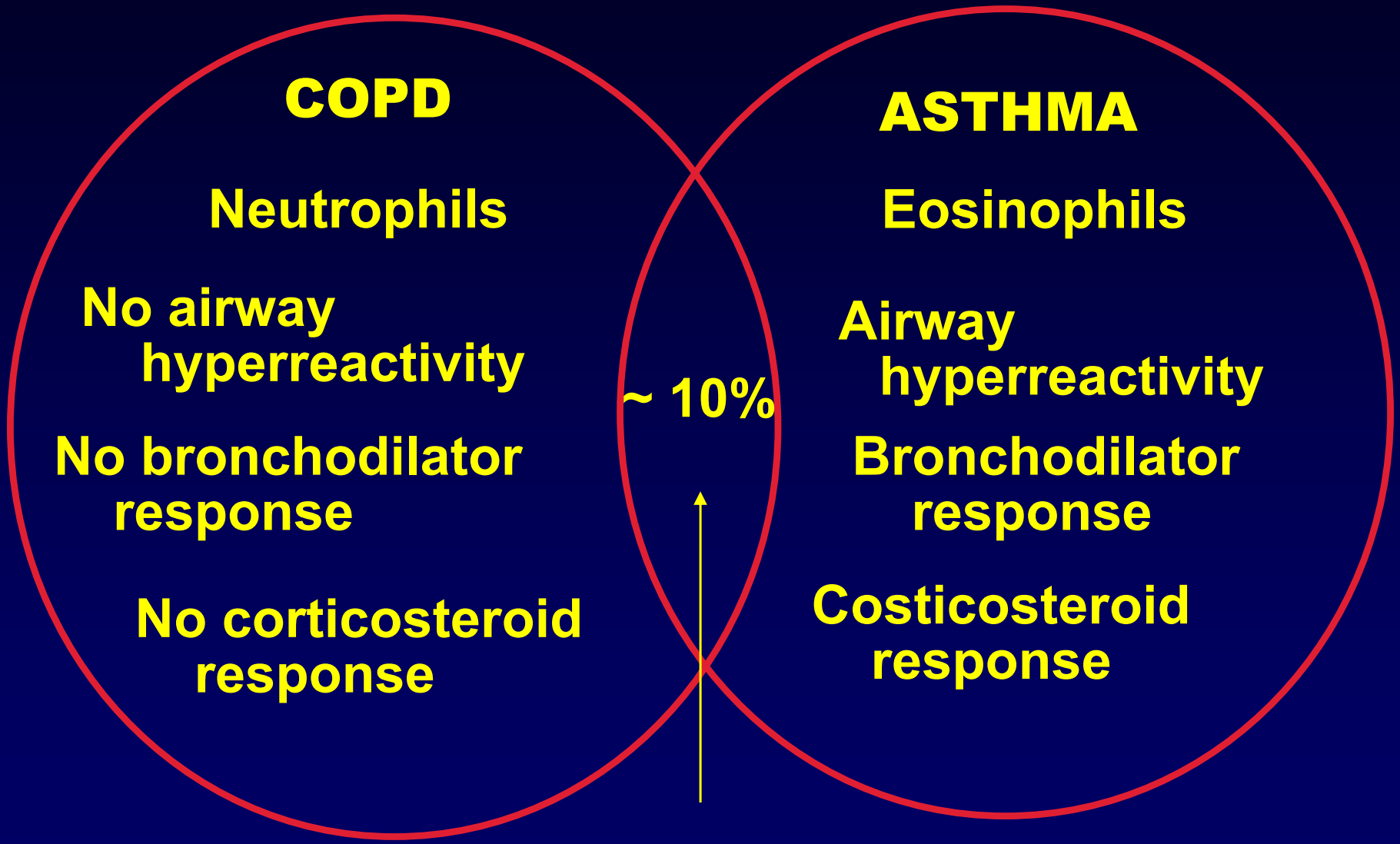
OVERLAP BETWEEN COPD AND ASTHMA



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Key Differences Between COPD and Asthma

- **COPD**
- Onset in midlife
- Symptoms slowly progressive
- Long smoking history
- Dyspnea during exercise
- Partially reversible airflow limitation

- **Asthma**
- Onset early in life (often childhood)
- Symptoms vary from day to day
- Symptoms at night/early morning
- Allergy rhinitis, and/or eczema also present
- Family history of asthma
- Largely reversible airflow limitation

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease Updated 2003. Available at: www.goldcopd.com/revised.pdf.

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Diagnosing COPD and Asthma

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Assessment of Airway Physiology

- **Airflow:**
  - PEF
  - **Spirometry**
  - Body plethysmography
  - **Rhino-laryngoscopy**
  - Direct & Indirect Challenges
- Inflammation
  - Bronchoscopy/BAL
  - Endobronchial/transbronchial biopsy
  - Exhaled gases; Nitric Oxide, carbon Monoxide, Ethane, Pentane
  - EBC; ph and volatile and non-volatile organic acids
  - Induced sputum; cells, LTs, cytokines, antibodies,

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Why Do PFTs?

- Assessment of dyspnea
- Pre-operative evaluation
- Functional assessment to correlate with clinical & radiographic assessment
- Asthma diagnosis and management

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Spirometry

“Measuring Breath”

Simple measurements of volume exhaled and inhaled and the time it takes to do this

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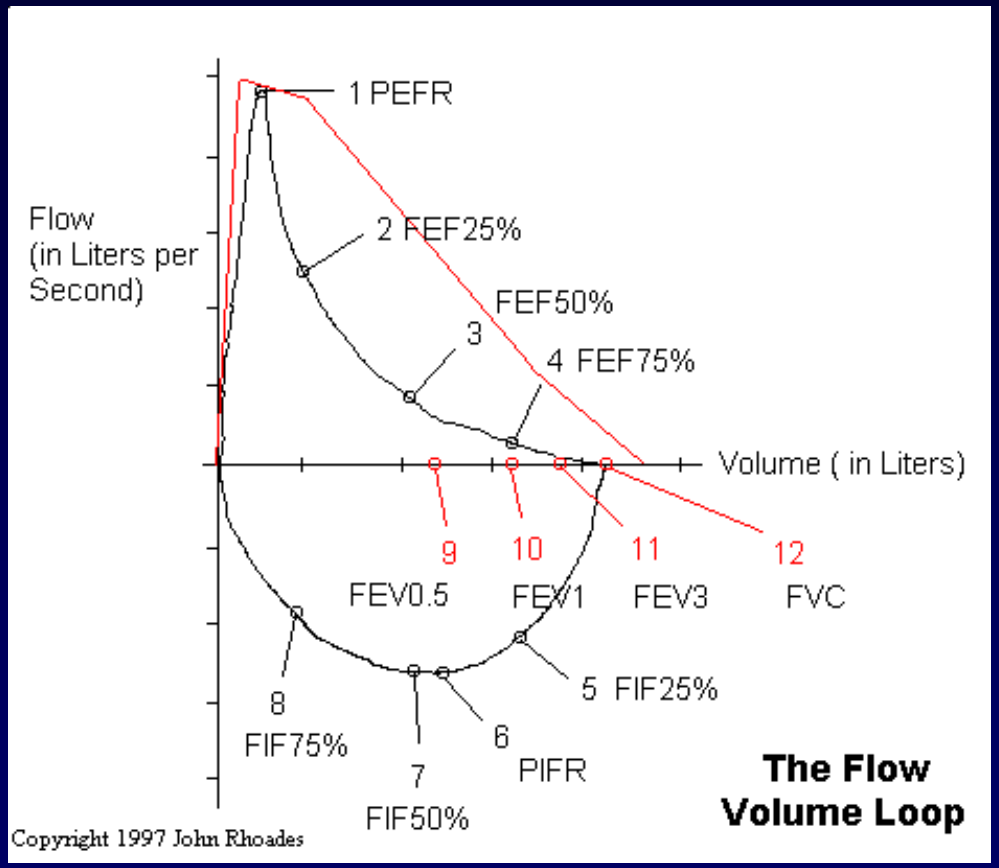
Flow-Volume Loop



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Test Quality

Volume / time curve

- Must be smooth
- Must plateau
- 6 Second Effort is Mandatory
- If the patient does not perform this maneuver correctly or the technician does not ensure a 6 second effort, the study cannot be interpreted accurately (would likely indicate falsely low lung volumes)
- Spirometry is only worth doing if it is done properly

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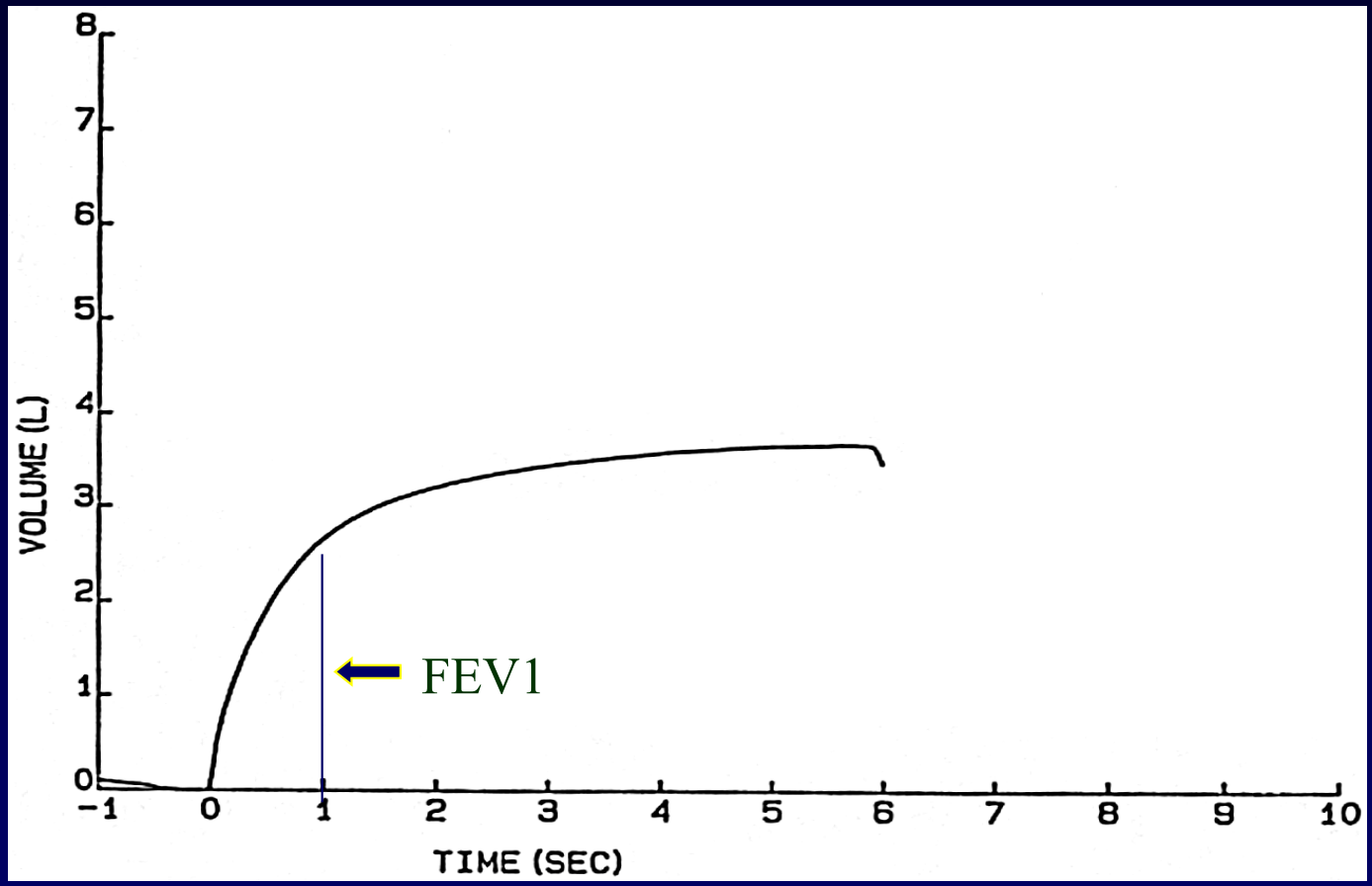
Time-Volume Graph



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Abbreviations

PEF	Peak Expiratory Flow
FVC	Forced Vital Capacity
FEV_1	Forced Exhaled Volume in 1 sec
FEV_1/FVC	Index of Airway Obstruction

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Terminology

- FEV1 = the amount of air maximally exhaled in the first second of exhalation
- FVC = the total volume of air that can be exhaled with maximum force, from maximal inhalation to maximal exhalation
- PEF = the maximal flow rate that is attained with a forced maneuver

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Terminology

- FVC & FEV1 expressed as volumes (liters)
- Also expressed as % of predicted values
- Predicted values dependent on age, height, and gender.
- Ratio FEV1/FVC expressed as a percentage

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Factors that Influence Normal Values

- Height - tall people have larger lungs
- Age - respiratory function declines with age
- Gender - lung volumes smaller in women
- Race - studies show Blacks and Asians as a whole have smaller lung volumes (-12%) No studies for Maoris and Pacific People
- Posture - little difference between sitting and standing. Reduced in supine position.

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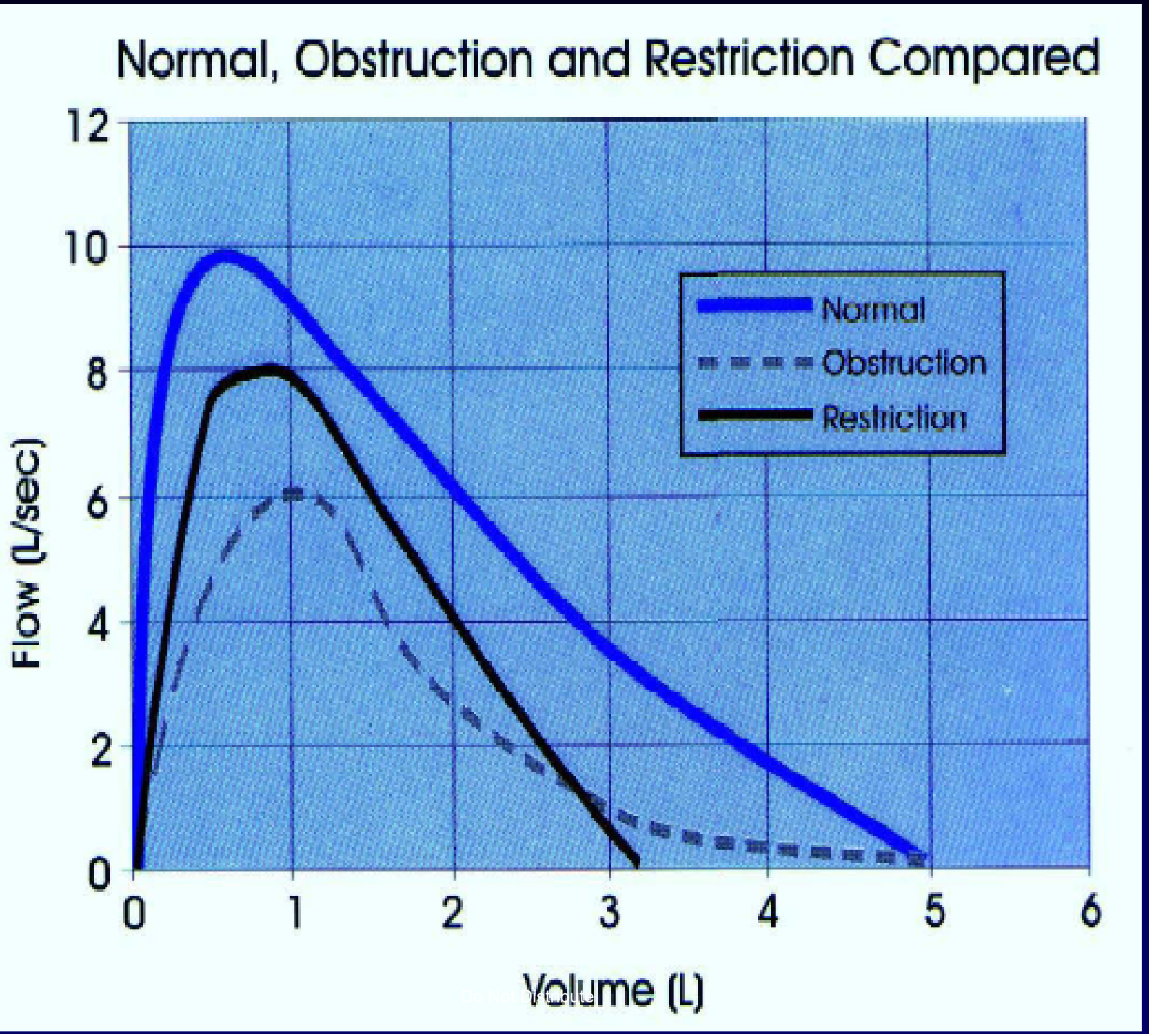
Normal, Obstruction and Restriction Compared
12
10
8
6
4
2
0
Flow (L/sec)
0
1
2
3
4
5
6
Volume (L)
Normal
Obstruction
Restriction

Defining a Bronchodilator Response

- Must have a 12% improvement in FEV1
- If FEV1 < 1 liter, need at least a 200 cc increase to be considered a response
- Can be blunted by recent use of short or long-acting beta-agonists

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BD Response

Table 2 – Definitions used to assess bronchodilator reversibility

Guideline	Definition[a]
ACCP[23]	Improvement in FEV_1 of ≥ 15%
ATS[25]	Improvement in FEV_1 or FVC of ≥ 12% and ≥ 200 mL
ERS[24]	Improvement in % predicted FEV_1 of ≥ 10%
ATS/ERS[22]	Improvement in FEV_1 and/or FVC of > 12% and > 200 mL
GOLD[1]	Improvement in FEV_1 of > 12% and > 200 mL

[a]For all definitions, improvement is referenced to the prebronchodilator value of FEV_1 or FVC.

ACCP, American College of Chest Physicians; ATS, American Thoracic Society; ERS, European Respiratory Society; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Int J Chron Obstruct Pulmon Dis2022; 17: 2623–2633.

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Complete Pulmonary Function Tests

Lung Volumes

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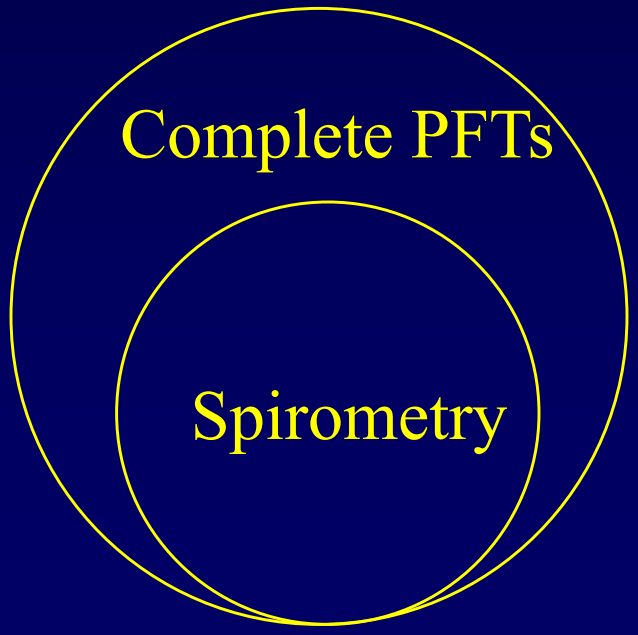
What Comprises “PFTs”

- Spirometry: FEV1, FVC, FEV1/FVC, PEFR
- Lung volumes
- Diffusing Capacity



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Definitions

TLC	Total Lung capacity
RV	Residual Volume
VC	Exhaled Volume from TLC to RV
FVC	Forced Vital Capacity
FEV_1	Forced Exhaled Volume in 1 sec
FEV_1/FVC	Index of Airway Obstruction

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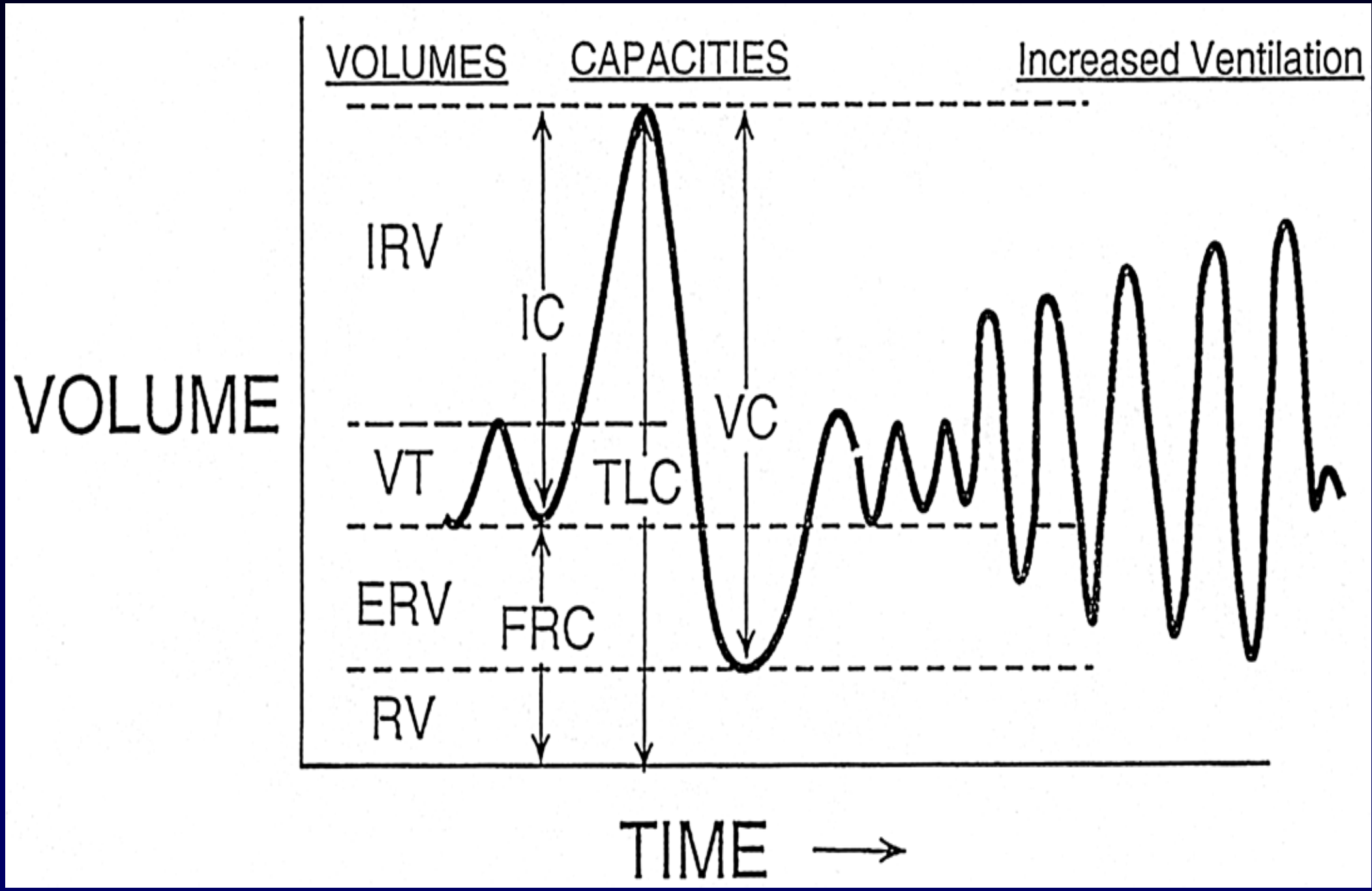

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PEF Monitoring

- A tool for ongoing monitoring, not diagnosis
- Very effort dependent
- Instruction and demonstration
- Frequent review of technique

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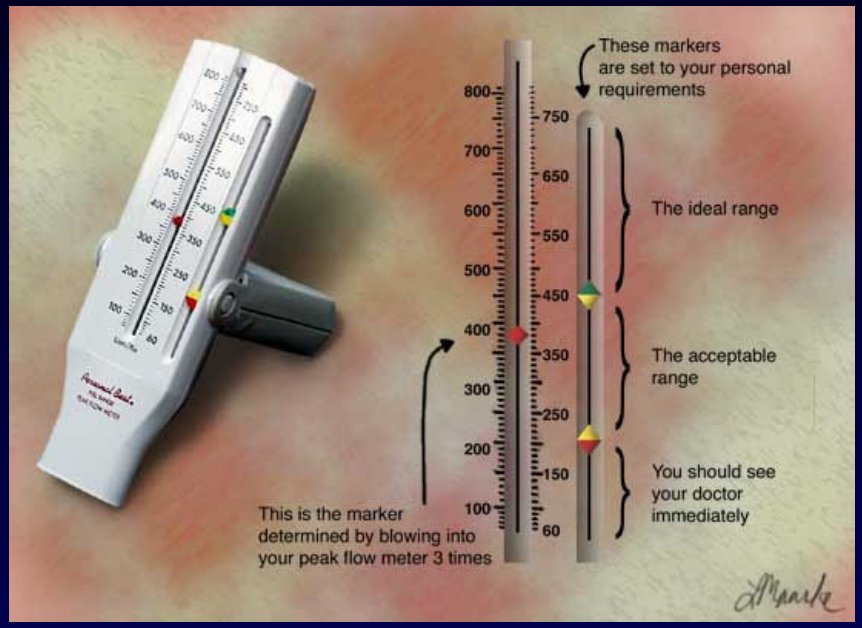
DATE																			
TIME	M	N	E	M	N	E	M	N	E	M	N	E	M	N	E	M	N	E	
850																			
800																			
750																			
700																			
650																			
600																			
550																			
500																			
450																			
400																			
350																			
300																			
250																			
200																			
150																			
100																			



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PEF Monitoring - Uses

* Evaluate responses to changes in tx
* Identify causes of symptoms
* Establish personal best PEF
* Determine severity of exacerbations
* Guide therapeutic decisions

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Establishing Personal Best PEF Value

- Monitor daily for 2 - 3 weeks when asthma is under good control
  - Measure PEF daily between noon and 2PM
  - Measure PEF after prn use of inhaled BD
- Use personal best value as basis of action plan
- Know that published norms are not helpful

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Daily Monitoring of PEF

- Measure PEF just after awakening in the AM -- BEFORE BRONCHODILATOR
- Record the best of at least 3 efforts
- Post bronchodilator measurement gives indication of severity of flare

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Tips on Using PEF

- Have pt use same PFM for all measurements--bring own PFM to office
- Have patient graph data
- Reestablish personal best episodically
  - After steroid treatment
  - With new PFM
  - With growth
- Use PEF as guide in action plan

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Disturbances of Ventilatory Function in Obstructive and Restrictive Disease

Test	Obstructive Disease	Restrictive Disease
VC	↔	↓
$FEV_{1.0}$	↓	↓
$FEV_{1.0}$ / FVC	↓	↔
FRC	↑	↓
RV	↑	↓
TLC	↑	↓

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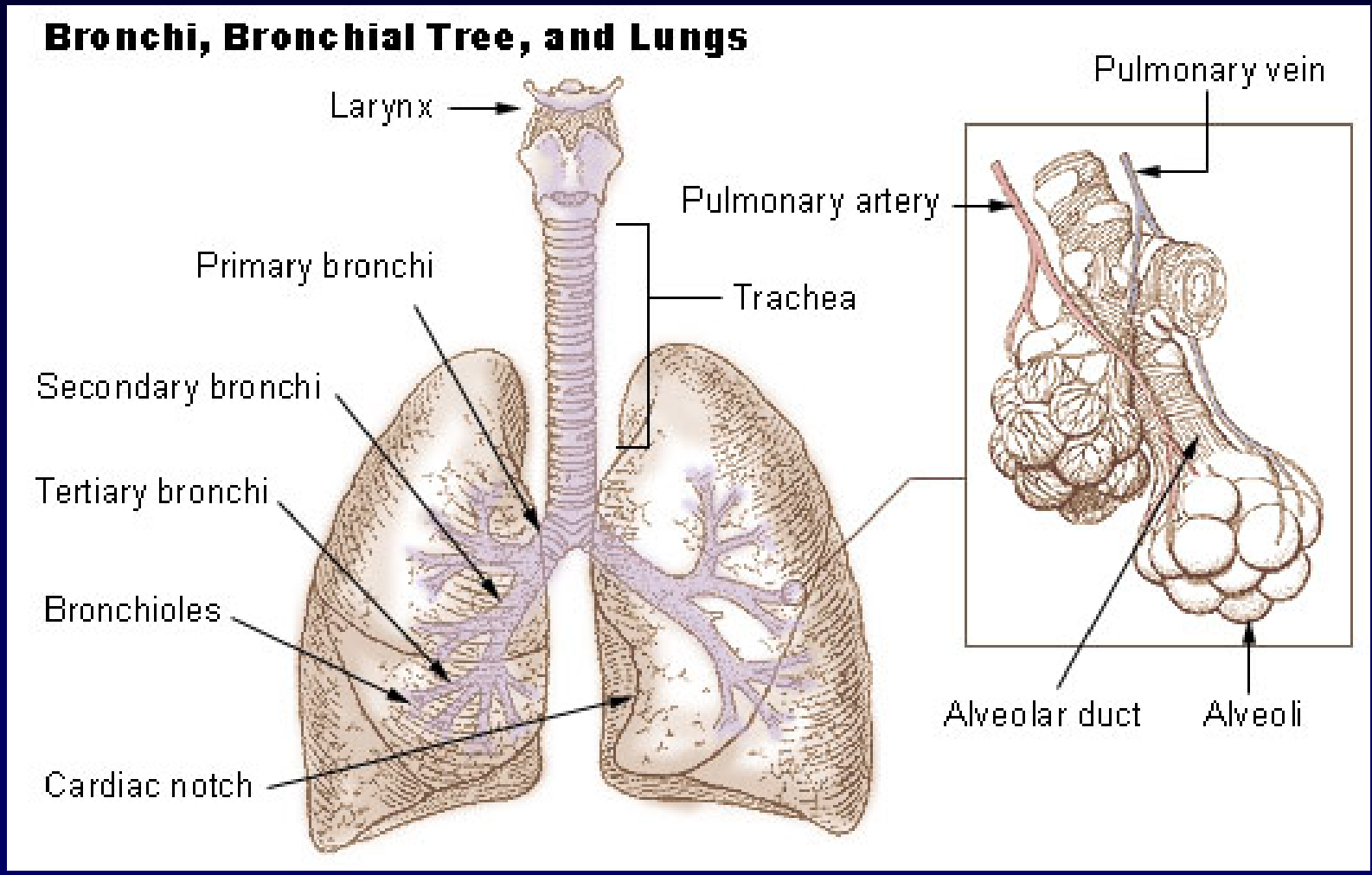
Diffusing Capacity



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Why is this important?

* COPD: normal or LOW (emphysema)
* Asthma: normal or HIGH
* Intersitial Lung Disease: Low

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Gas Exchange - Diffusing Capacity

- Can measure the amount of gas diffusing across the blood-gas barrier in one minute
- Mean differences between alveolus and pulmonary capillary

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Single Breath DLCO

- Subjects expires to RV and then inspires to TLC from a bag or spirometer containing a mix of CO and He in air
- Hold breath for 10 seconds
- Expires into a new bag where gas is collected

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Functional Differences Between COPD and Asthma

COPD

* Obstructive physiology that is not fully reversible
* Normal or reduced diffusing capacity

Asthma

* Reversible obstructive pulmonary physiology
* Normal or elevated diffusing capacity

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Clinical Indications for Bronchial Provocation Testing (BPT)

- History consistent with asthma but with non-diagnostic pulmonary function testing
- Asthma with atypical presentation such as cough-variant asthma
- Occupational asthma
- Prior to beginning an occupation or sporting activity that may exacerbate or cause an attack of asthma

Brannan JD and Lougheed MD. Front Physiol. 2012 Dec 10;3:460.

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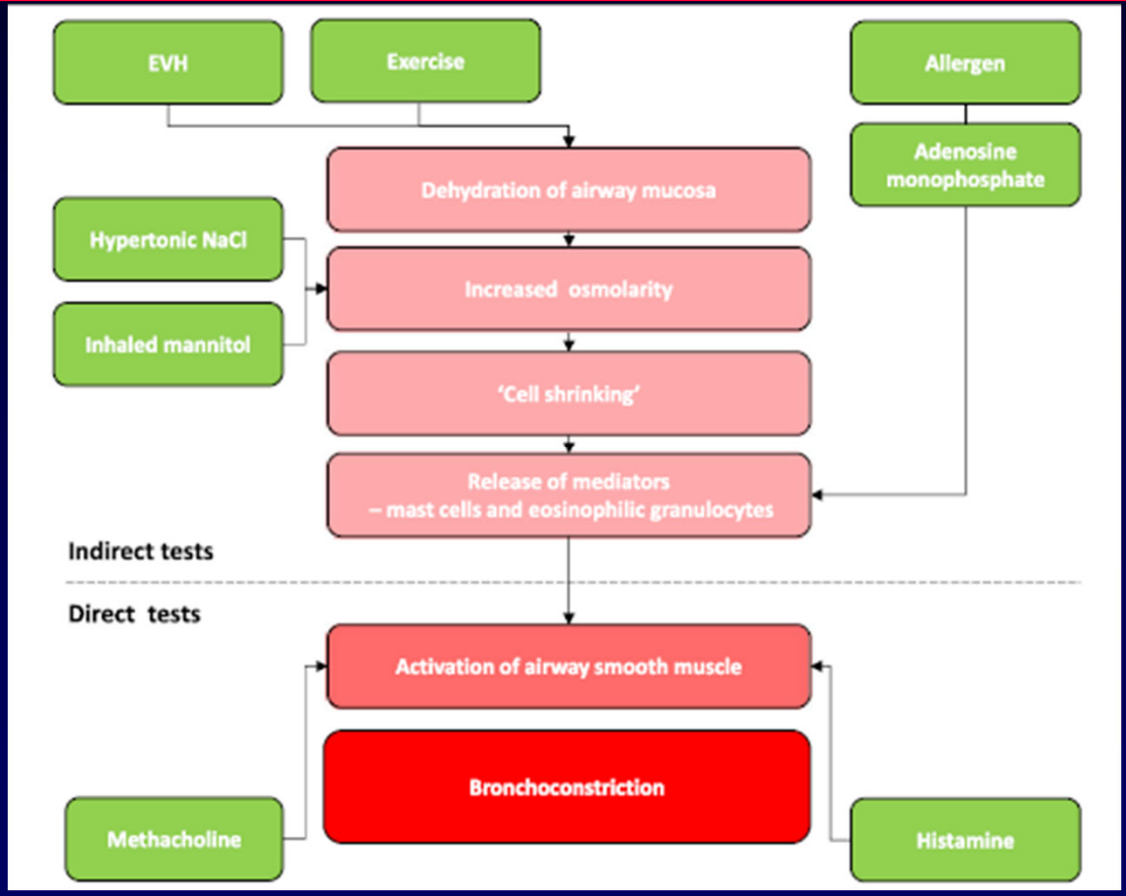

Sverrild A et al. Respir Rsch 2021; 22: https://doi.org/10.1186/s12931-021-01876-9

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Direct vs Indirect BPTs

- Direct BPTs refer to the use of an agonist that act directly on receptors on the airway smooth muscle (ASM) causing contraction:
  - Methacholine - most widely used; acts on muscarinic (M3) receptors
  - Histamine - acts on histamine (H1) receptors
  - More sensitive less specific
  - Less association with airway inflammation than indirect
  - ICS have relative small effect on BHR to direct

- Indirect BPTs refer to stimuli that cause inflammatory cells to release a variety of mediators that lead to bronchoconstriction:
  - Exercise induced bronchoconstriction (EIB)
  - Eucapnic voluntary hyperventilation (EVH)
  - Allergens
  - Osmotic agents (e.g., mannitol or hypertonic saline)
  - Adenosine monophosphate (AMP)
  - Less sensitive especially for pts with mild sx or on ICS More specific

Brannan JD and Lougheed MD. Front Physiol. 2012 Dec 10;3:460.

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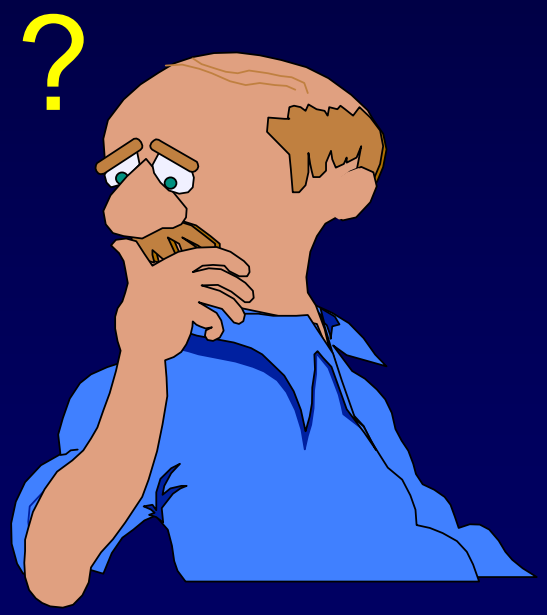
What do most people use to evaluate airway hyperreactivity?



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Direct BPTs

- Method of testing
  - Standardized protocol with incremental dosing, measuring FEV1 change with each dose
  - Tidal breathing using a nebulizer (more sensitive method), or deep inhalations using a dosimeter method
  - Positive test - FEV1 decrease of 20%
  - Provocative concentration (PC20) or dose (PD20) calculated from dose-response curve
- False positives: other lung diseases, atopy, allergic rhinitis, and smoking
- Higher sensitivity in patients with atopy; Low sensitivity in patients with EIB

Brannan JD and Lougheed MD. Front Physiol. 2012 Dec 10;3:460.

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Technical Factors and Aerosols

- Nebulizer output
- Aerosol particle size
- Tubing
- Lung volume
- Inspiratory flow rate
- Breath hold time

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* Put in here TLC vs tidal from Cockcroft paper and comparing to mannitol and MC and feno

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Contraindications

Absolute

- Severe airflow limitation (FEV_1 <50% pred., or < 1.0 L)
- Heart attack or stroke in last 3 months
- Uncontrolled hypertension
- Known aortic aneurysm

Relative

- Moderate airflow limitation (FEV_1 <60% pred., or < 1.5 L)
- Hypoxemia (PaO2 < 60 mmHg)
- Inability to perform acceptable spirometry
- Pregnancy
- Nursing mothers
- Vigorous exercise on day of test

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Safety of a Low Starting FEV_1

- 88 patients with FEV_1 <60% predicted (22% - 59%)
- Mean baseline FEV_1 1.39 $\pm$ 0.28 L (0.64 – 2.4 L)
- Testing was safe and successful
- 84 patient's FEV_1 returned to 90% of baseline, and 4 required a 2nd treatment

Martin, Wanger, Irvin, et al. Chest 1997;112:53-56

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Medication Withholding Schedule

- Short-acting inhaled bronchodilators 6 hrs
- Med.-acting bronchodilators (e.g., ipratropium) 12 hrs
- Long-acting bronchodilators 36 hrs
- Fixed combo ICS/LABA 48 hrs
- Long Acting LAMA 72 hrs
- Leukotriene modifiers 24 hrs

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Representative Methacholine Challenge

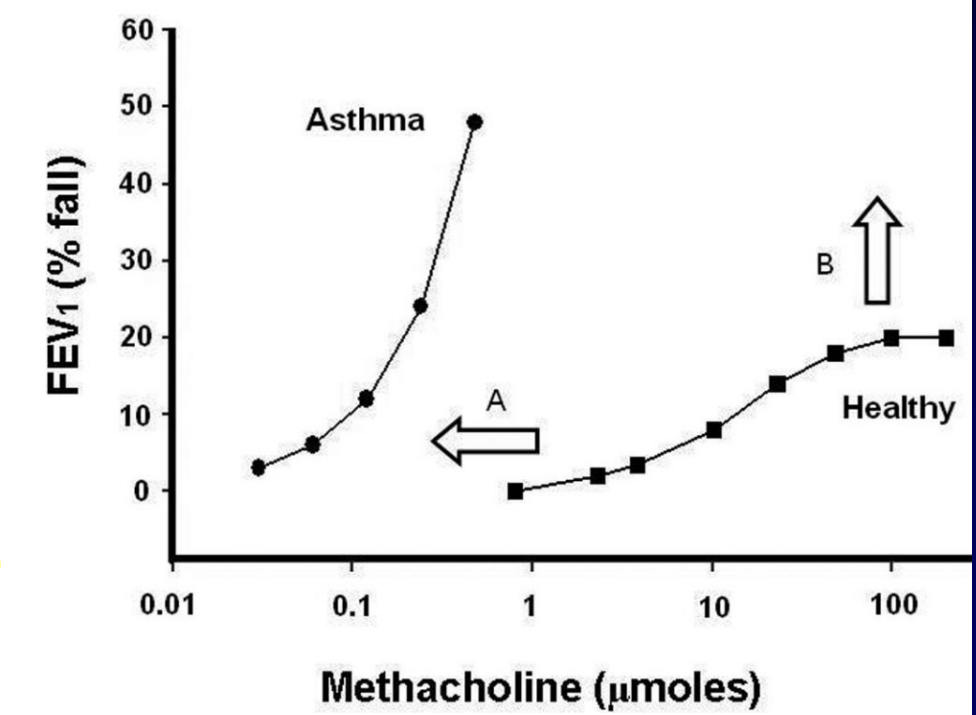

Figure 1. Representative dose response curves (DRC) to methacholine in a healthy and a severely asthmatic subject

Airway hyperresponsiveness is characterised by both an increased sensitivity, seen as the leftward shift in the DRC of the asthmatic patient (A), and excessive bronchoconstriction, resulting in the loss/increase in the maximal response plateau (B).

Chapman DG and Irvin CG. Clin Exp Allergy. 2015; 45(4): 706–719.

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Indirect BPTs

- Method of testing
  - EIB and EVH – FEV1 measured at baseline and following stimulus at various increments up to 20 min; Drop of 10-15% and severity of symptoms measured
  - Hypertonic saline, mannitol, and AMP have standardized protocol with incremental dosing
  - Allergen challenge – mostly research or occupational (late response can occur)

Chapman DG and Irvin CG. Clin Exp Allergy. 2015; 45(4): 706–719.

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Bronchial Challenge Testing

Induce Bronchoconstriction with:

- Nonspecific substances

  Histamine
  Methacholine

- Specific Allergen

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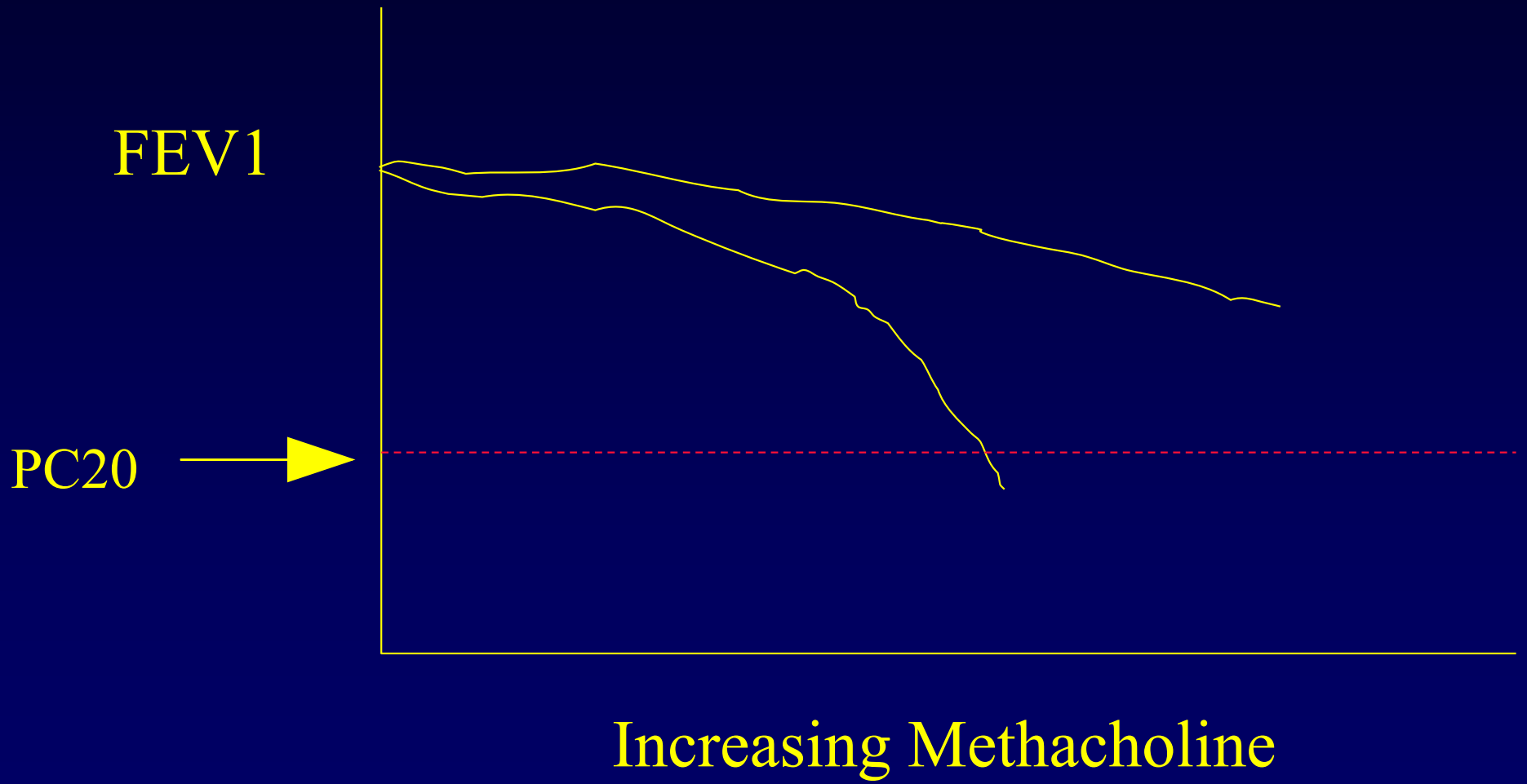
Methacholine Challenge



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Key Points for Methacholine Challenge

- Doses range from 0.31mg/ml up to 25 mg/ml
- FEV1 must fall by 20% from baseline to be diagnostic
- Drop ideally induced by doses of 8mg/ml or less of methacholine

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Exercise Testing and Implications in Obstructive Pulmonary Disease

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Exercise-induced Bronchoconstriction (EIB)

Exercise-induced Asthma (EIA)

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EIB Factors

* Exercise needs to be continuous
* Type of exercise matters
* Duration
* Air temperature and humidity

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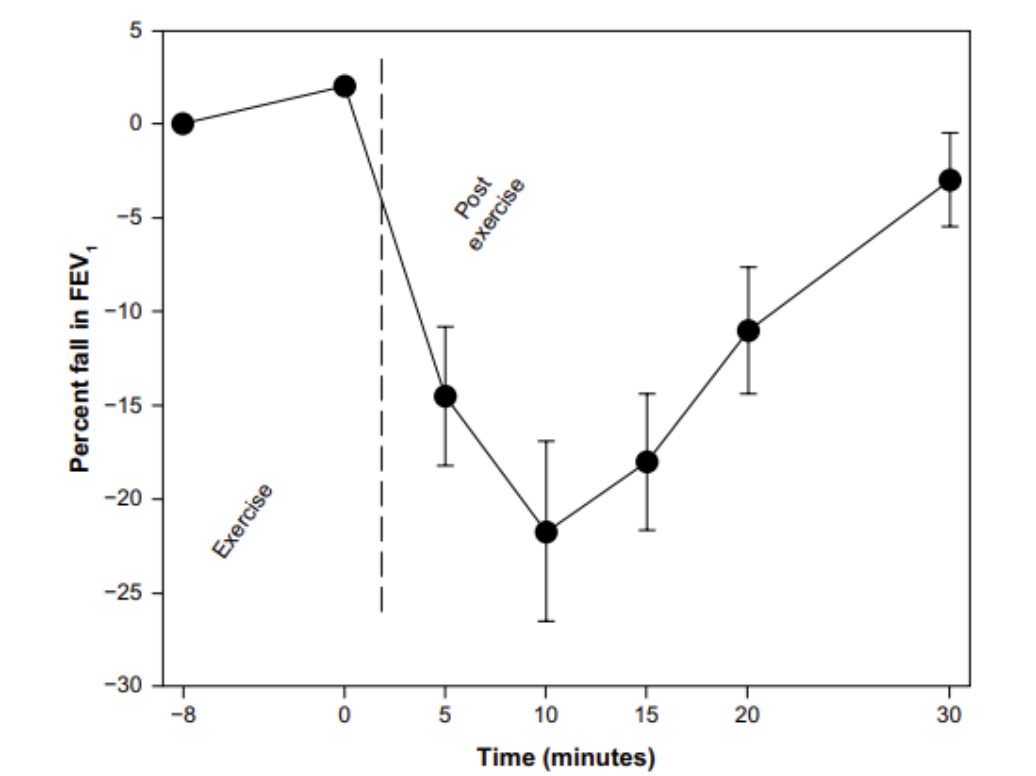
FEV1 during Exercise Challenge



Bussotti M et al. J of Sports Med 2014: 5: 47-63

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Exercise Challenge

- Related to exercise limitation
- Obstruction possibly related to changes in airway osmolarity or temperature
- FEV1 drop of 15% usually after 8-10 minutes of exercise is a positive test

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FDA approves new test to monitor asthma

Thursday, May 1, 2003 Posted: 2:06 PM EDT (1806 GMT)

WASHINGTON (AP) -- A new device that allows doctors to monitor changes in a patient's asthma was approved by the Food and Drug Administration Thursday.

The product, called NIOX, can be used in a physician's office to monitor changes in the levels of nitric oxide in a patient's breath. These levels change in response to anti-inflammatory treatment, the agency said.

An estimated 15 million Americans

Story Tools

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History of Exhaled NO and Asthma

Discovery of NO in biology	Late 1980s
Discovery that NO is present in breath	1991
Discovery that eNO levels are increased in patients with asthma	1993
Discovery that eNO levels decrease after steroid therapy in asthmatics	1994-1995
Expiratory flow dependence of eNO	1997
Approval of NIOX in Europe	April 2000
Relationship of eNO to reactivity and airway inflammation	2001
Modeling of the secretion of NO in the airway with flow-independent parameters	2001
eNO found to be useful in predicting asthma exacerbations	2001
Clearance of NIOX by the FDA	May, 2003

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NIOX

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Exhaled NO measurement

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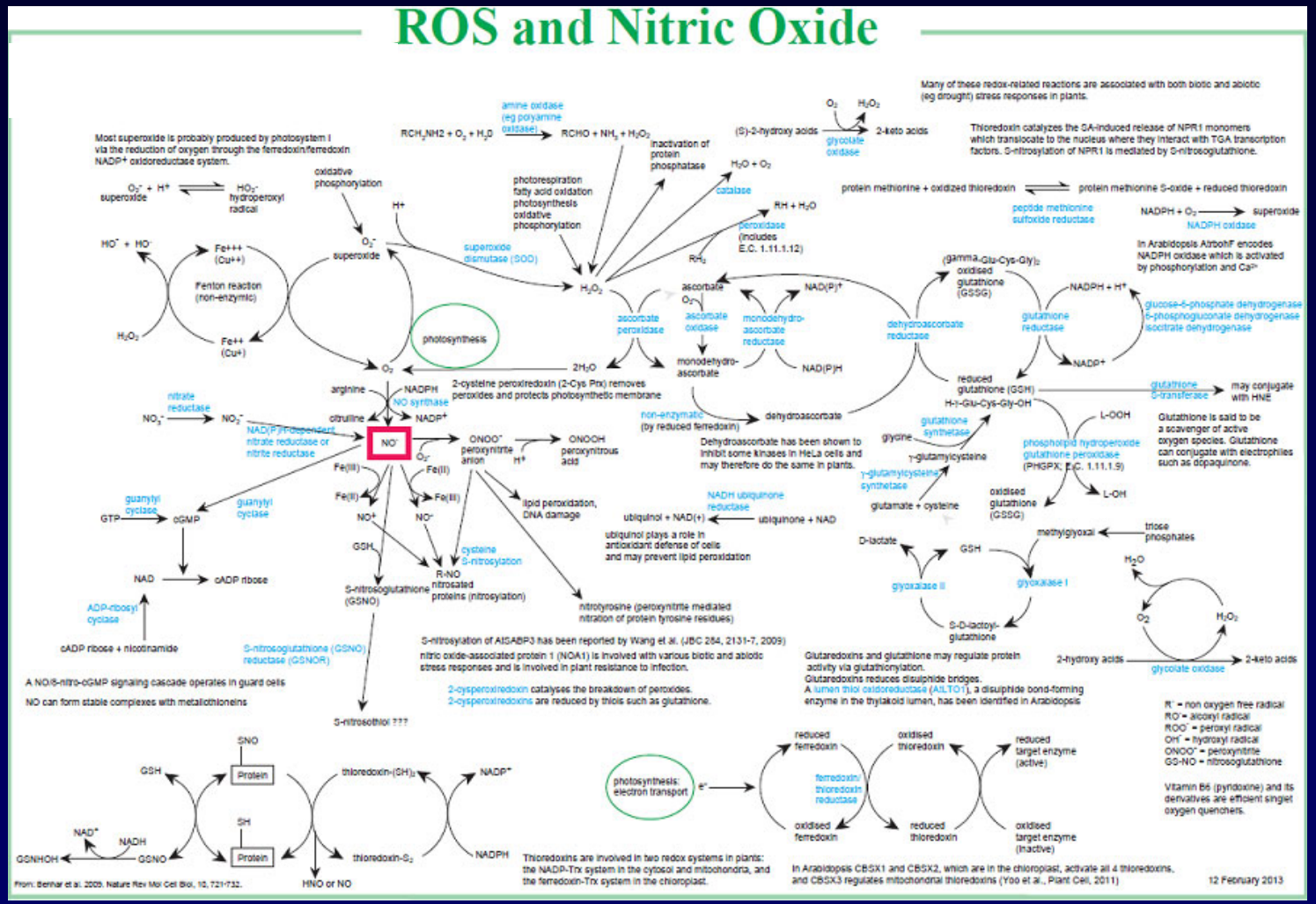
Biology



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NITRIC OXIDE SYNTHASES

Constitutive NOS		Inducible NOS
NOS 1 Neuronal	NOS 3 Endothelial	NOS 2 Inflammatory
Chrom. 12	Chrom. 7	Chrom. 17
Cytosol	Membrane	Cytosol
Ca^{++} dep.	Ca^{++} dep.	Ca^{++} indep.
Small packets (pmols NO)	Small packets (pmols NO)	Continuous (nmols NO)
Neurotransmitter	Smooth muscle relaxation	Immune functions
Steroid resistant		Steroid sensitive

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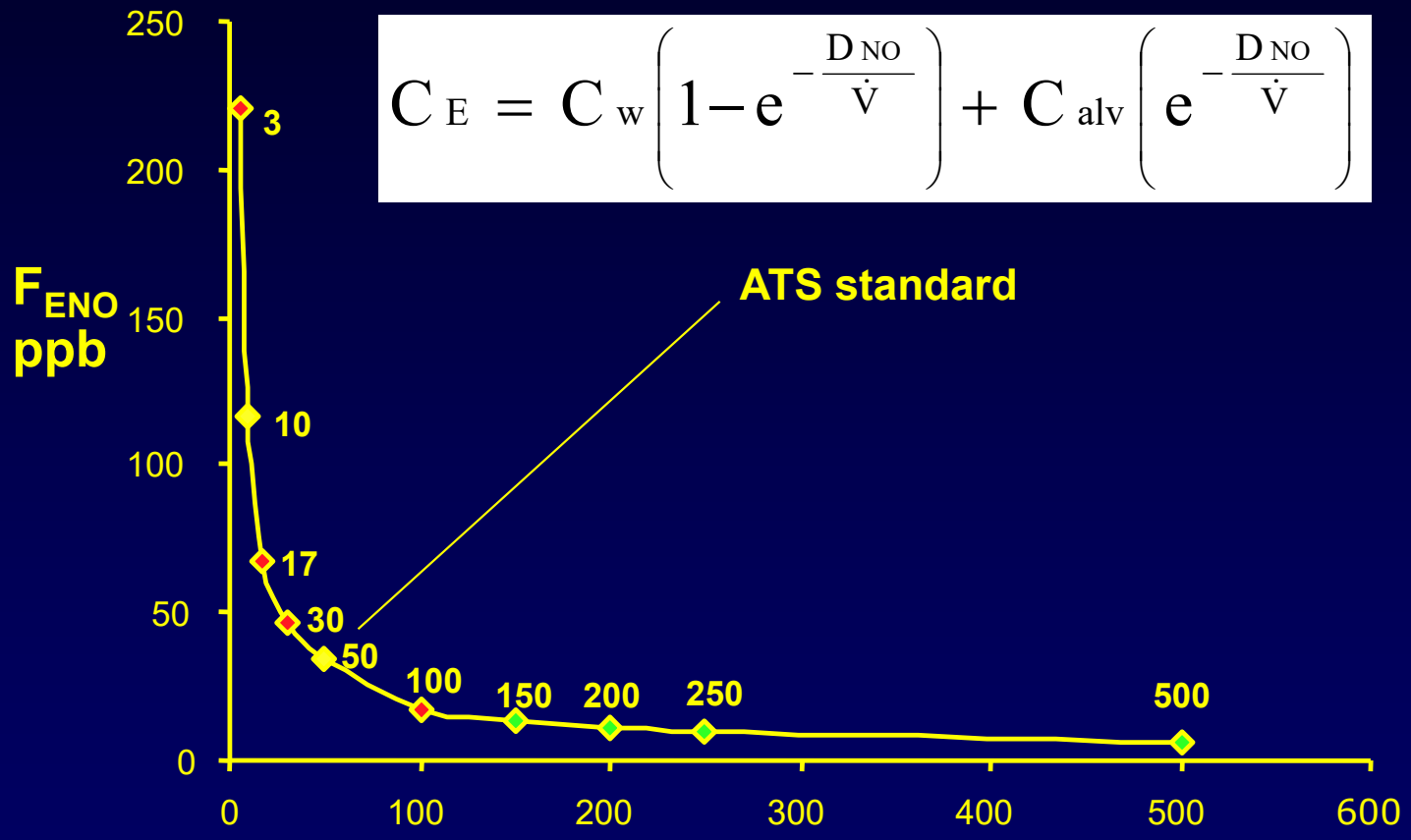
Multiple flows

$$C_E = C_w\left(1 - e^{-\frac{D_{NO}}{\dot{V}}}\right) + C_{alv}\left(e^{-\frac{D_{NO}}{\dot{V}}}\right)$$



Silkoff, Pietrapaoli, Tsoukias, Hogman et al

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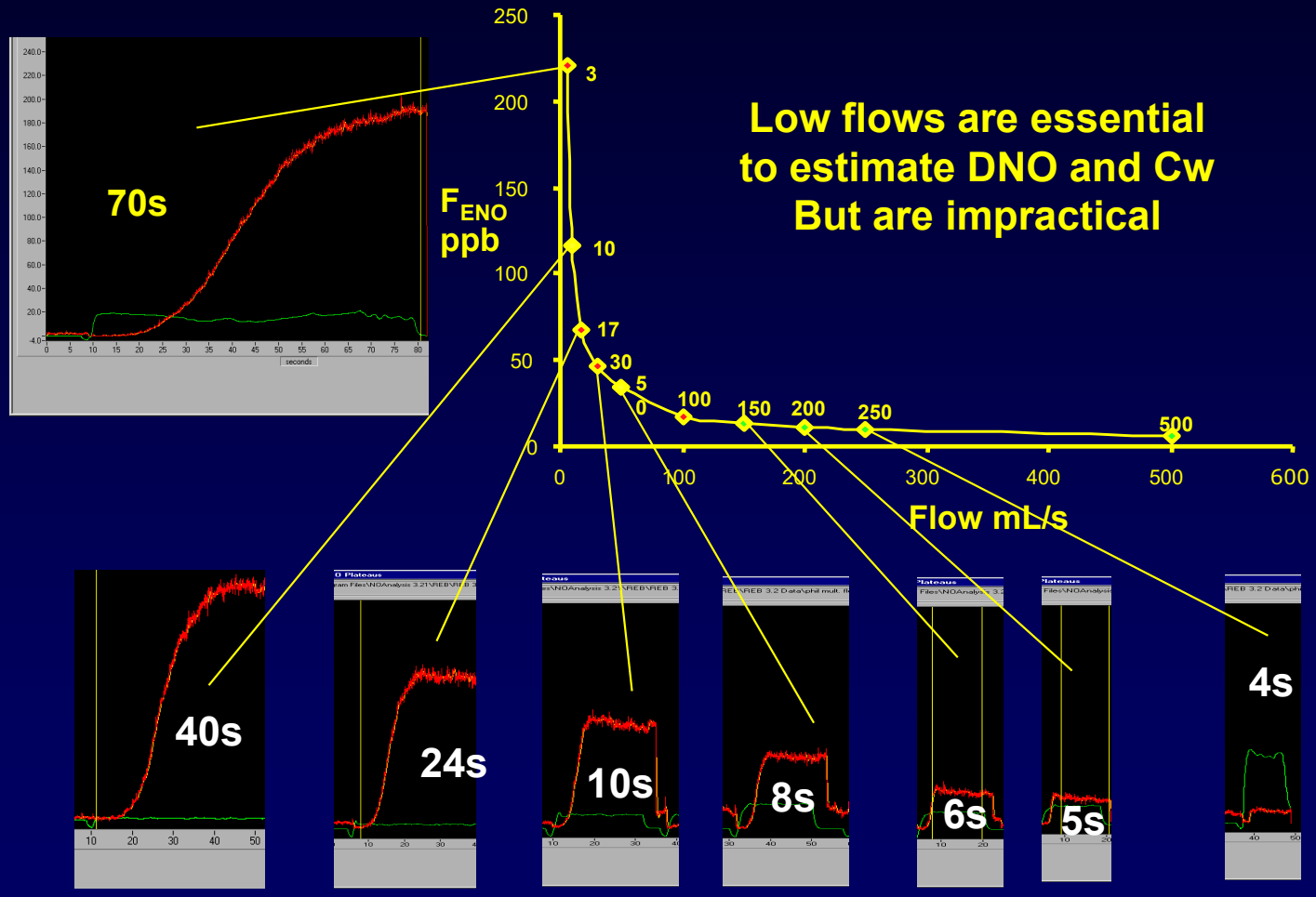
Seconds to NO plateau



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Online Measurement

Inhalation to TLC preferably from NO-free gas

Exhalation at constant flow of 50 mL/s

Nasal NO exclusion e.g by exhalation against resistance

Exhalations continue until steady plateau of at least 3 seconds

Repeated exhalations until 3 plateau values agree at the 10% level

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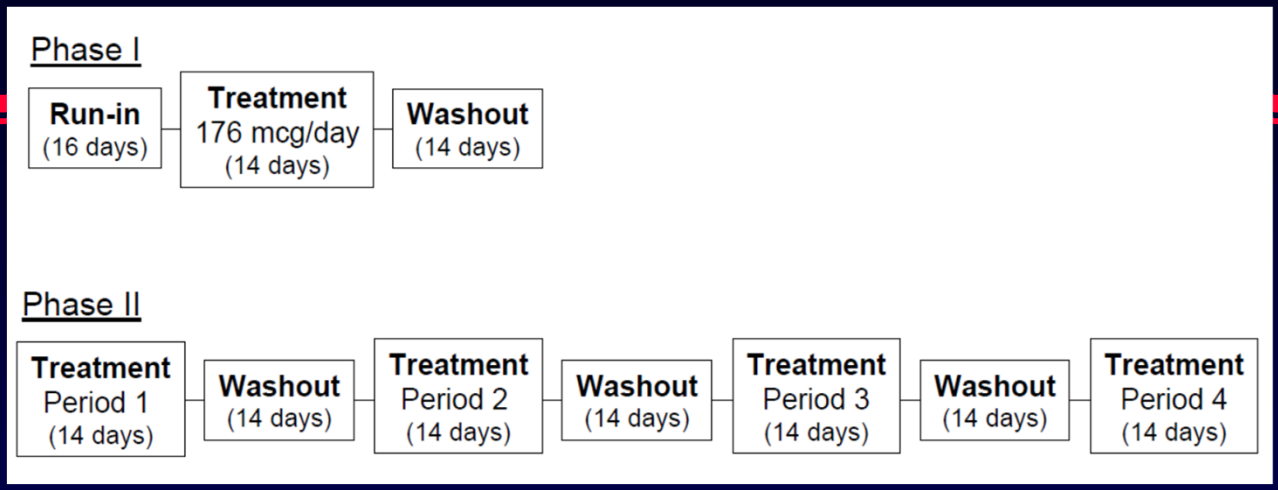
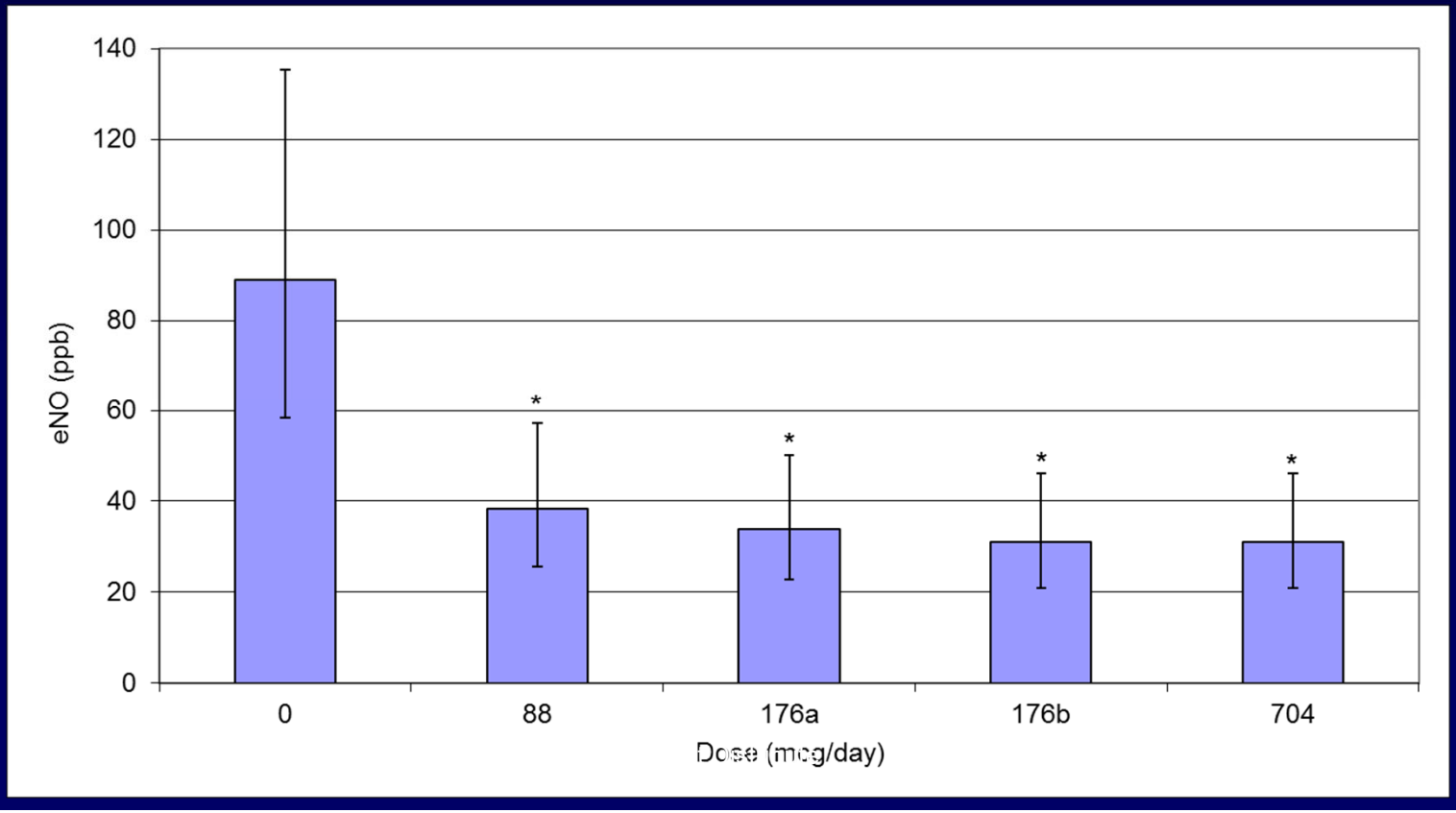
FeNO Steroid Dose Response





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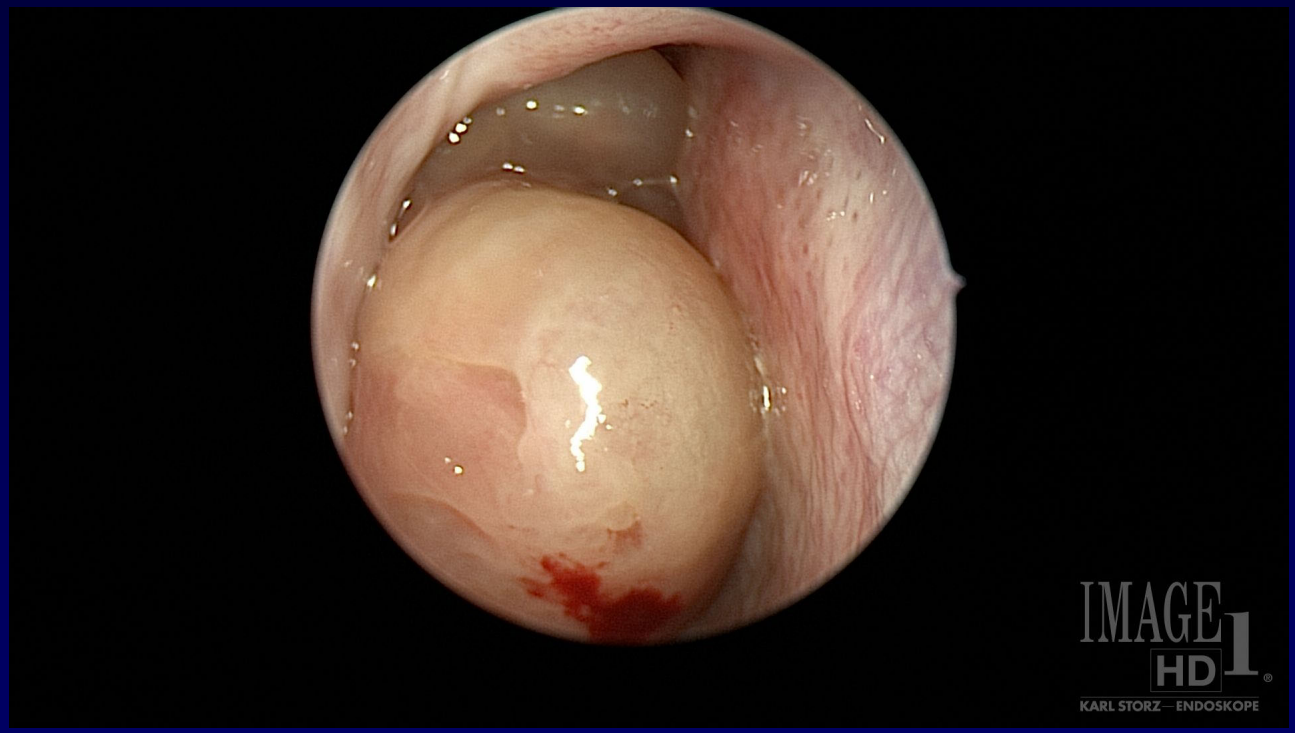

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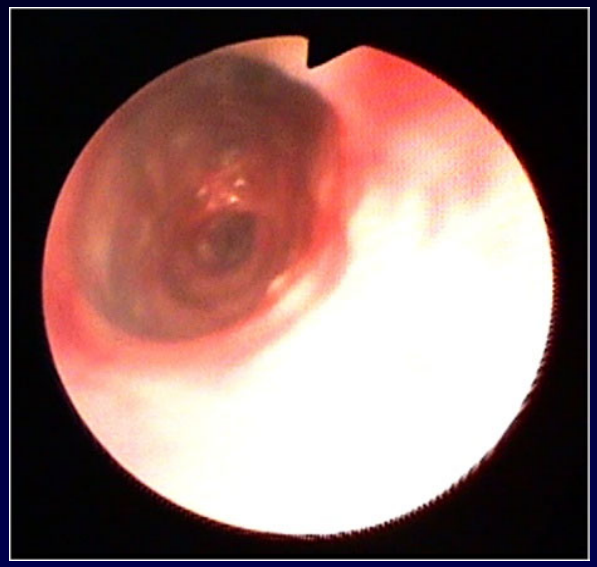

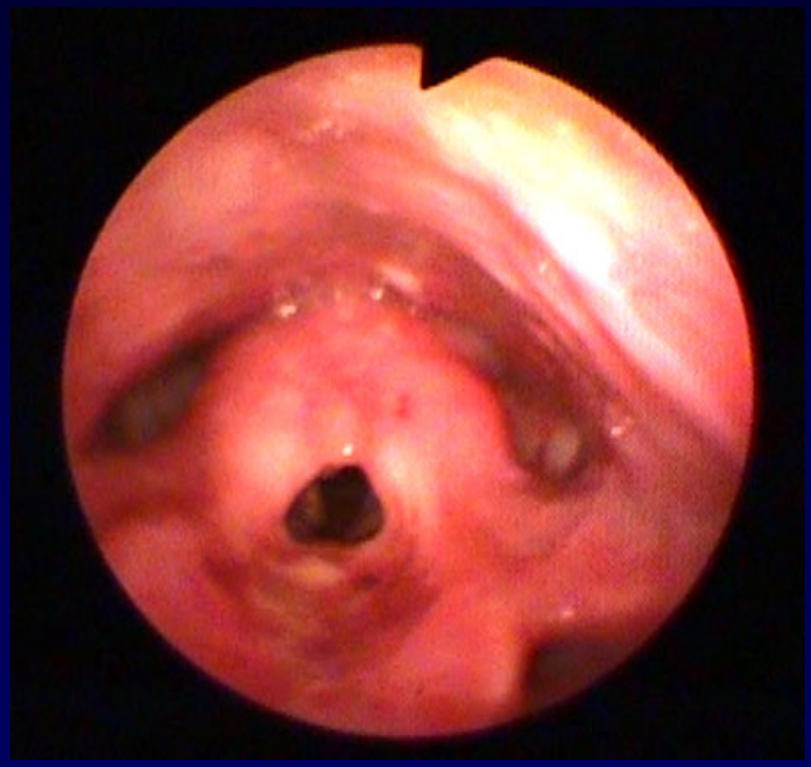

Cicatricial Pemphigoid

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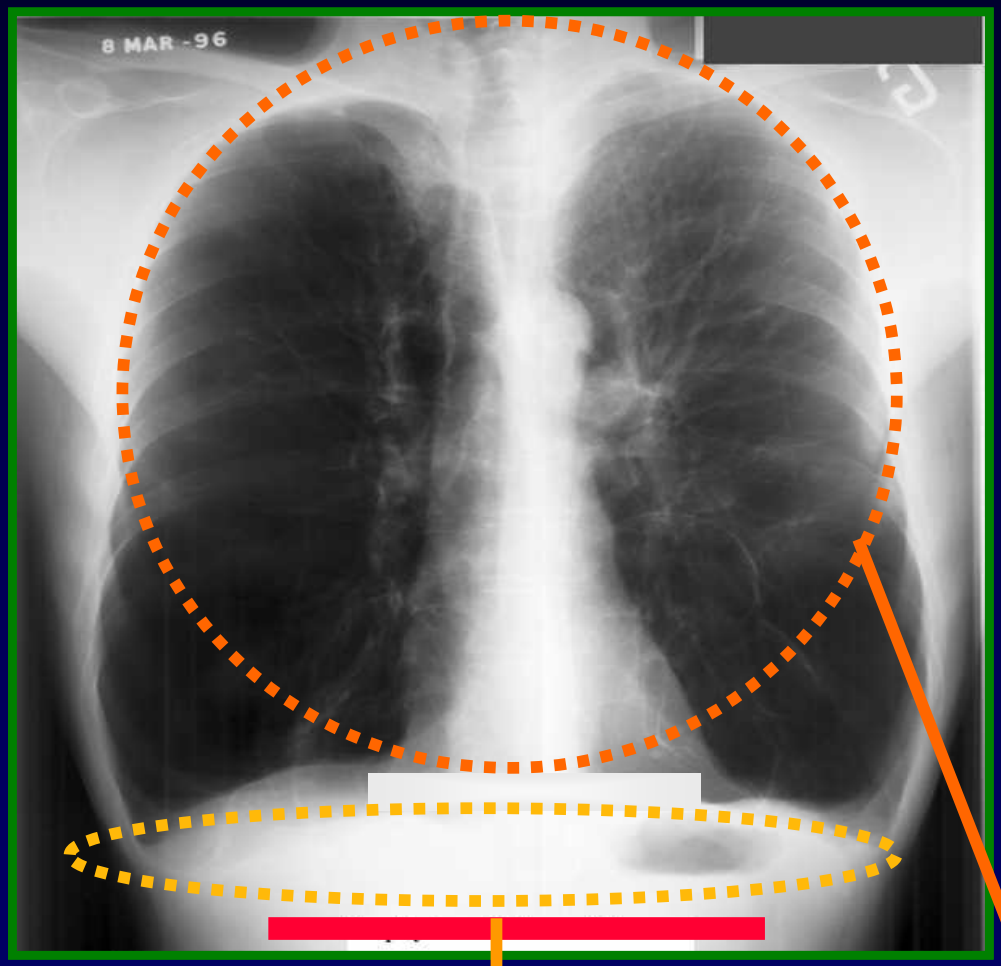
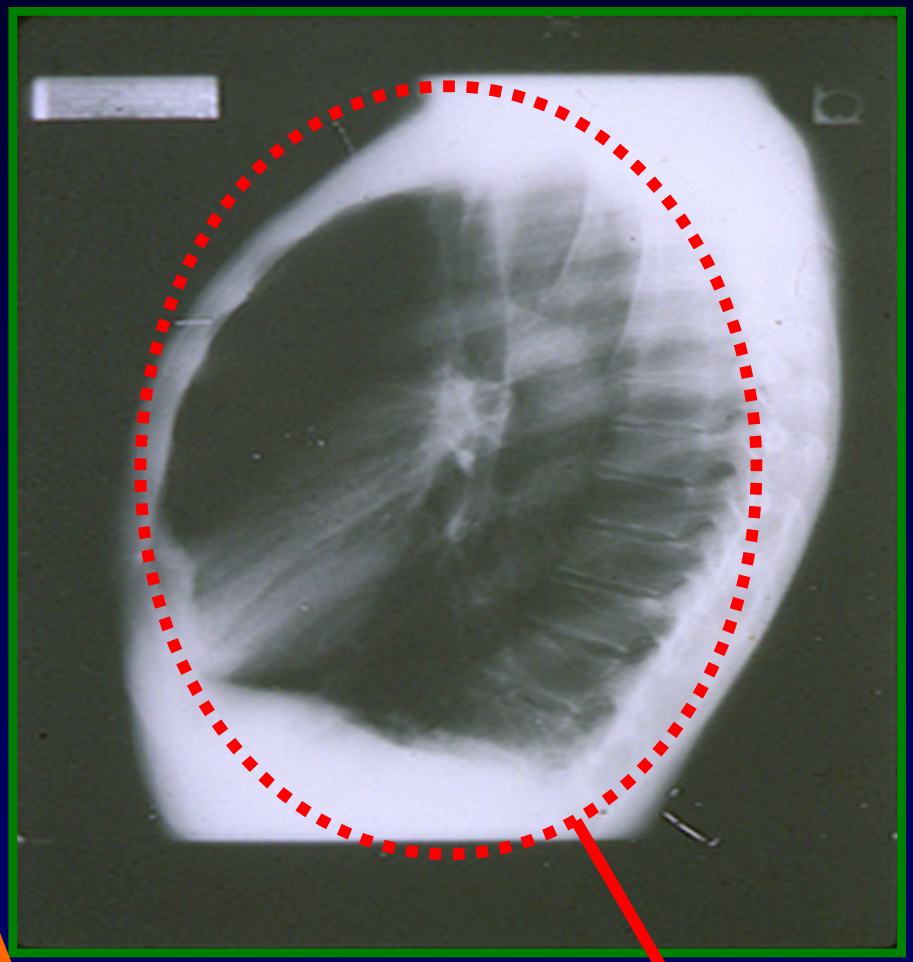
Hyperinflation





Low, Flattened Diaphragm

Air Trapping

Increased A-P Diameter

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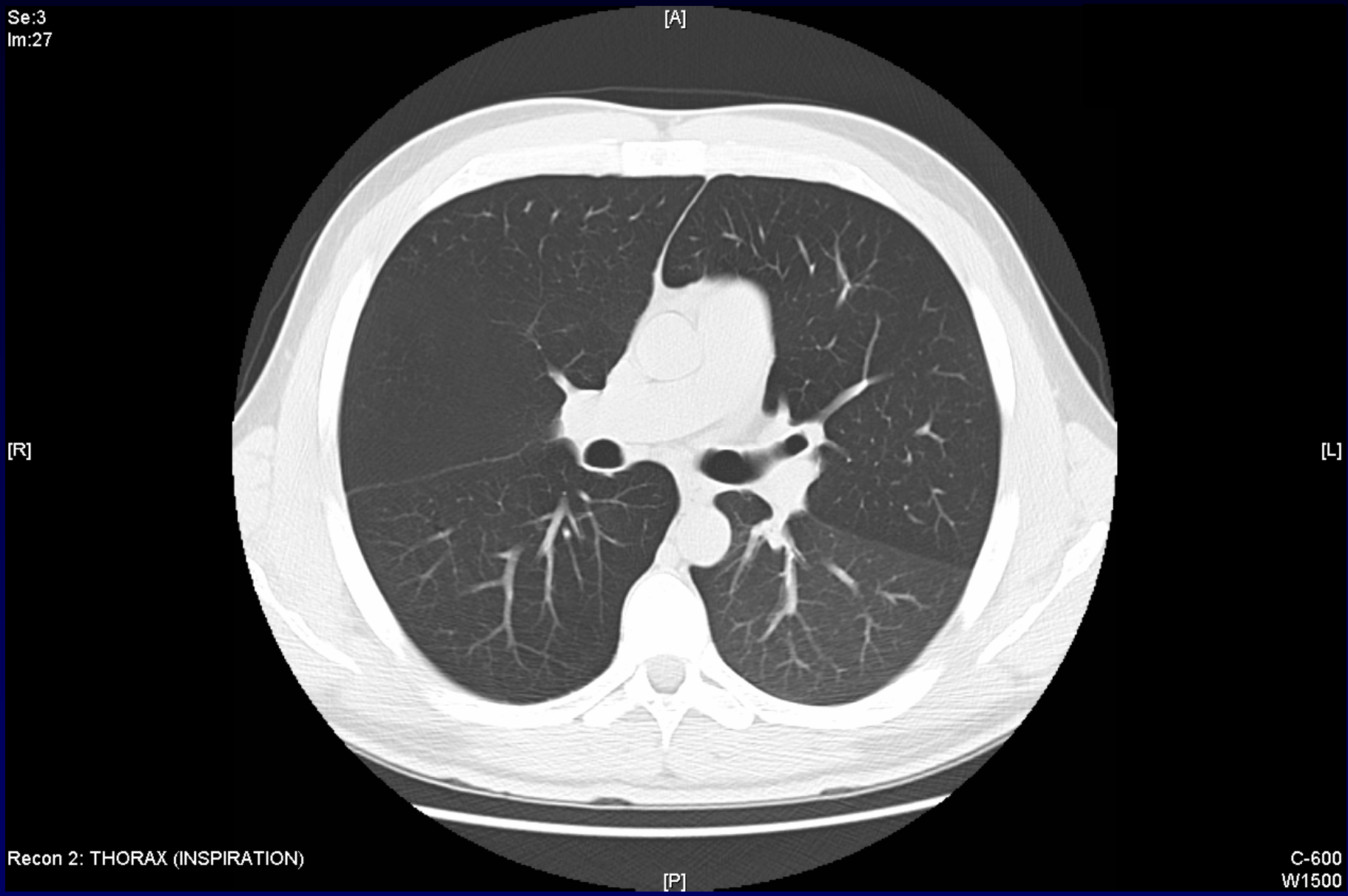

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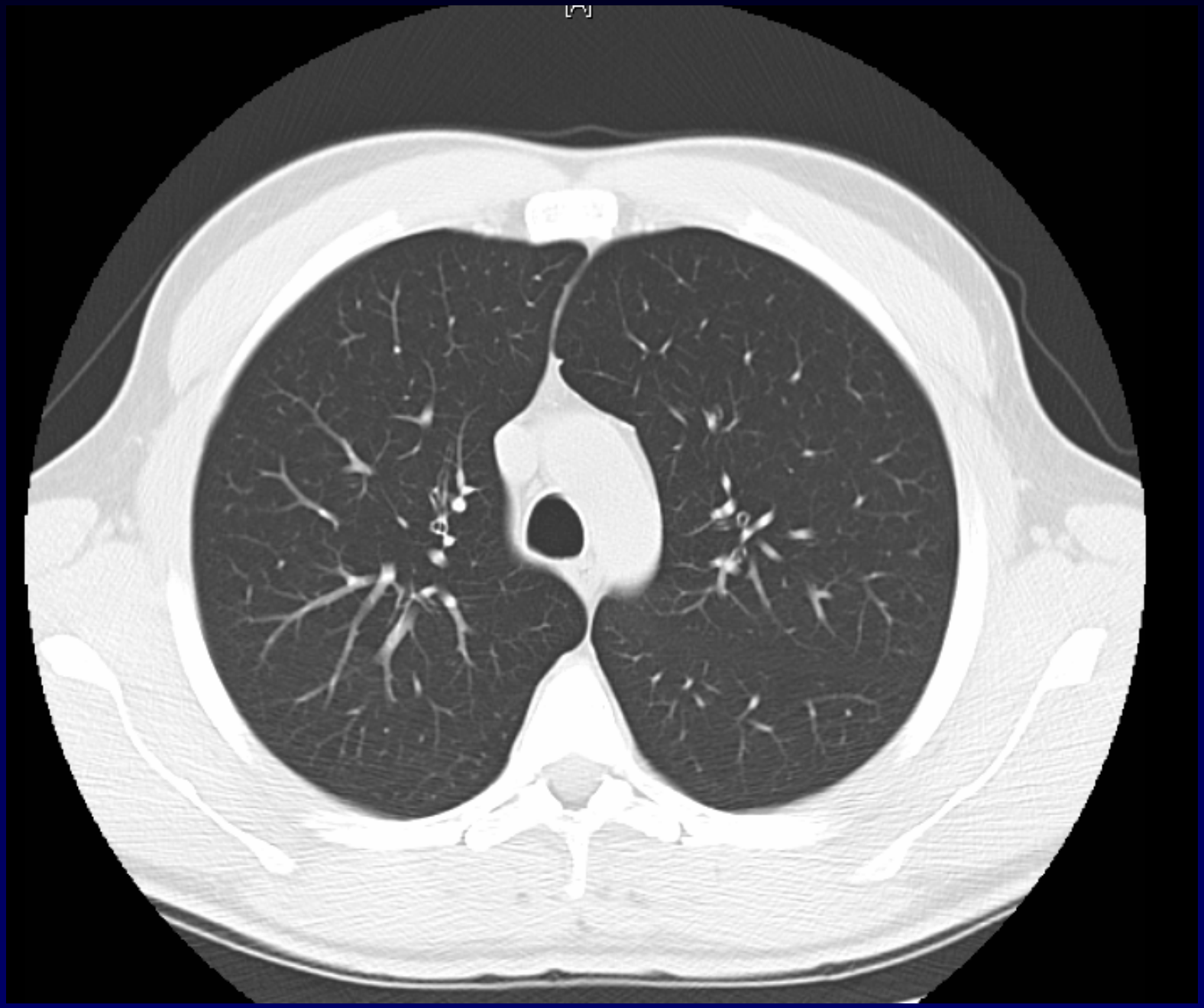

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Summary

- Pulmonary physiology is an integral part of the evaluation of chronic respiratory symptoms
- Spirometry is simple to perform in any office and provides useful information regarding the underlying diagnosis
- Sentinel to asthma diagnosis and management

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