Short of Breath: A Primary Care Approach to Evaluating Dyspnea

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Objectives

- Review the definition and mechanisms of dyspnea
- Review different approaches to assessing dyspnea
- Review tools/tests used for dyspnea evaluation

Disclosures

- Astra Zeneca speaker bureau

Patient case…

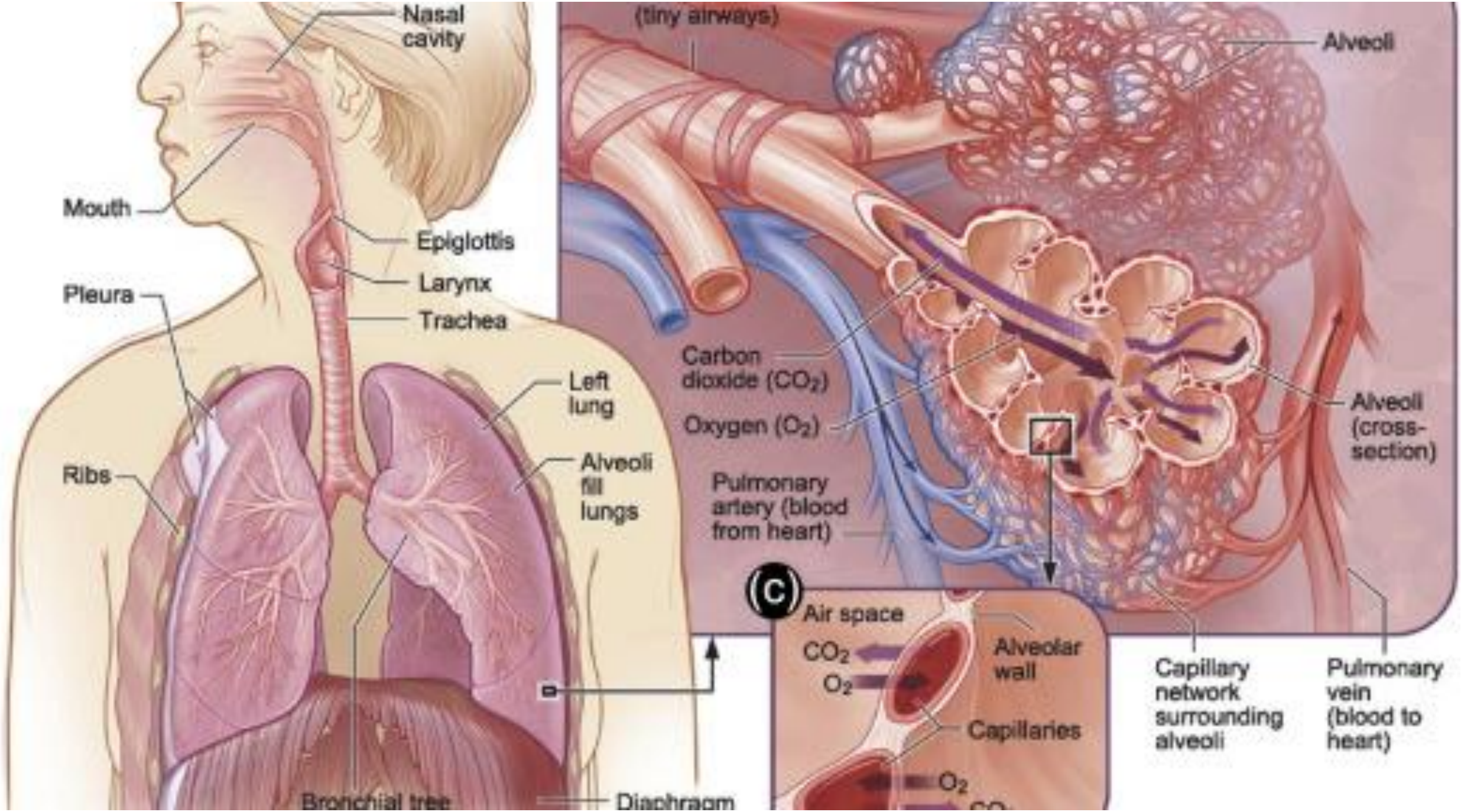
- 76 yo WM
- Chronic, worsening dyspnea over months, esp with exertion (walking < 100 ft). Started after getting a URI on a cruise. Dyspnea fluctuates over days at times. “Feels like he cannot get a big enough breath” “Wheezing at times”
- Cough with thick mucus; some postnasal drip
- 25 pack year smoker, quit 2012. Retired from IT. No pets or hobbies. Fam Hx of COPD in father
- O2 sats 98% on RA. No pertinent findings on exam.

Dyspnea: Definition

- ATS definition: A subjective experience of breathing discomfort that consists of **qualitatively distinct sensations** that vary in intensity
- ”Chronic” dyspnea – over one month duration
- A physiologic impairment that leads to stimulation of pulmonary and extrapulmonary afferent receptors and the transmission of afferent information to the cerebral cortex, where the sensation is perceived as uncomfortable or unpleasant
- It is generally accepted that dyspnea involves central, peripheral (chest wall and lung receptors), and chemoreceptor mechanisms

Dyspnea: Prevalence

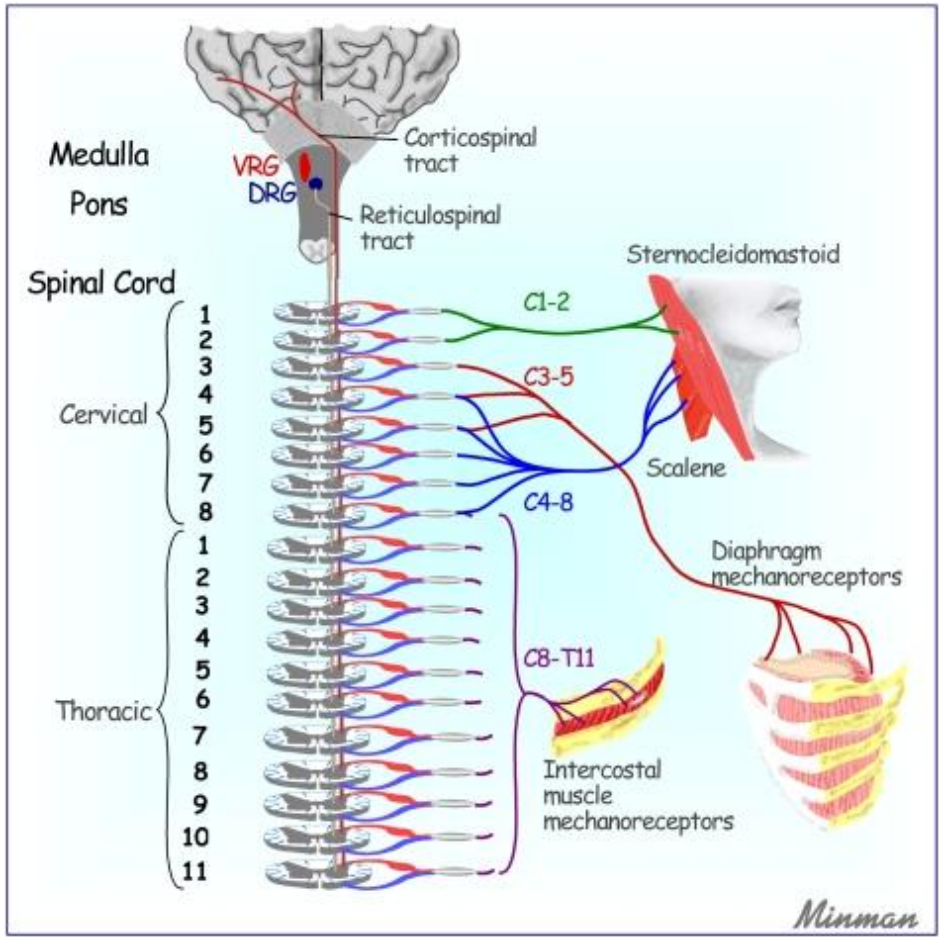
- “Shortness of breath” or “Labored/difficult breathing” accounts for 3-4M ED visits annually in the US
- Probably most common accompaniment of lung disease
- Prevalance of 9-13% mild to mod dyspnea in gen population, 15-18% in >40yo and 25-37% in >70yo
- Predictor of hospitalization and mortality in patient with chronic lung disease
- Dyspnea is more closely associated with cardiac mortality than angina


Nasal cavity
Mouth
Epiglottis
Larynx
Pleura
Trachea
Left lung
Alveoli fill lungs
Ribs
Bronchial tree
Diaphragm
(tiny airways)
Alveoli
Carbon dioxide (CO_2)
Oxygen (O_2)
Alveoli (cross-section)
Pulmonary artery (blood from heart)
C
Air space
CO_2
O_2
Alveolar wall
Capillaries
O_2
Capillary network surrounding alveoli
Pulmonary vein (blood to heart)

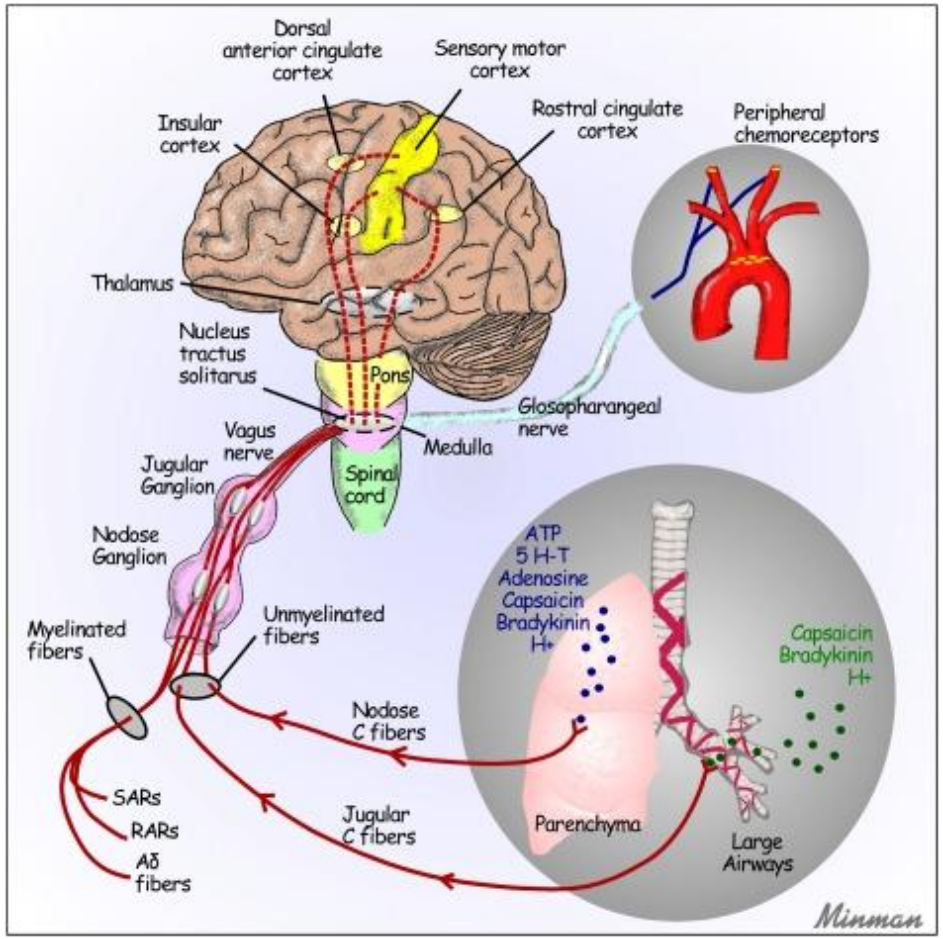
Possible Afferent Sources for Respiratory Sensation

Source of Sensation	Adequate Stimulus
Medullary respiratory corollary discharge	Drives to automatic breathing (hypercapnia, hypoxia, exercise)
Primary motor cortex corollary discharge	Voluntary respiratory drive
Limbic motor corollary discharge	Emotions
Carotid and aortic bodies	Hypercapnia, hypoxemia, acidosis
Medullary chemoreceptors	Hypercapnia
Slowly adapting pulmonary stretch receptors	Lung inflation
Rapidly adapting pulmonary stretch receptors	Airway collapse, irritant substances, large fast (sudden) lung inflations/deflations
Pulmonary C-fibers (J-receptors)	Pulmonary vascular congestion
Airway C-fibers	Irritant substances
Upper airway “flow” receptors	Cooling of airway mucosa
Muscle spindles in respiratory pump muscles	Muscle length change with breathing motion
Tendon organs in respiratory pump muscles	Muscle active force with breathing motion
Metaboreceptors in respiratory pump muscles	Metabolic activity of respiratory pump
Vascular receptors (heart and lung)	Distention of vascular structures
Trigeminal skin receptors	Facial skin cooling
Chest wall joint and skin receptors	Tidal breathing motion

Schematic representation of afferent pathways from respiratory muscle mechanoreceptors to the CNS



Schematic representation of afferent pathways of dyspnea from vagal receptors and peripheral chemoreceptors to the CNS

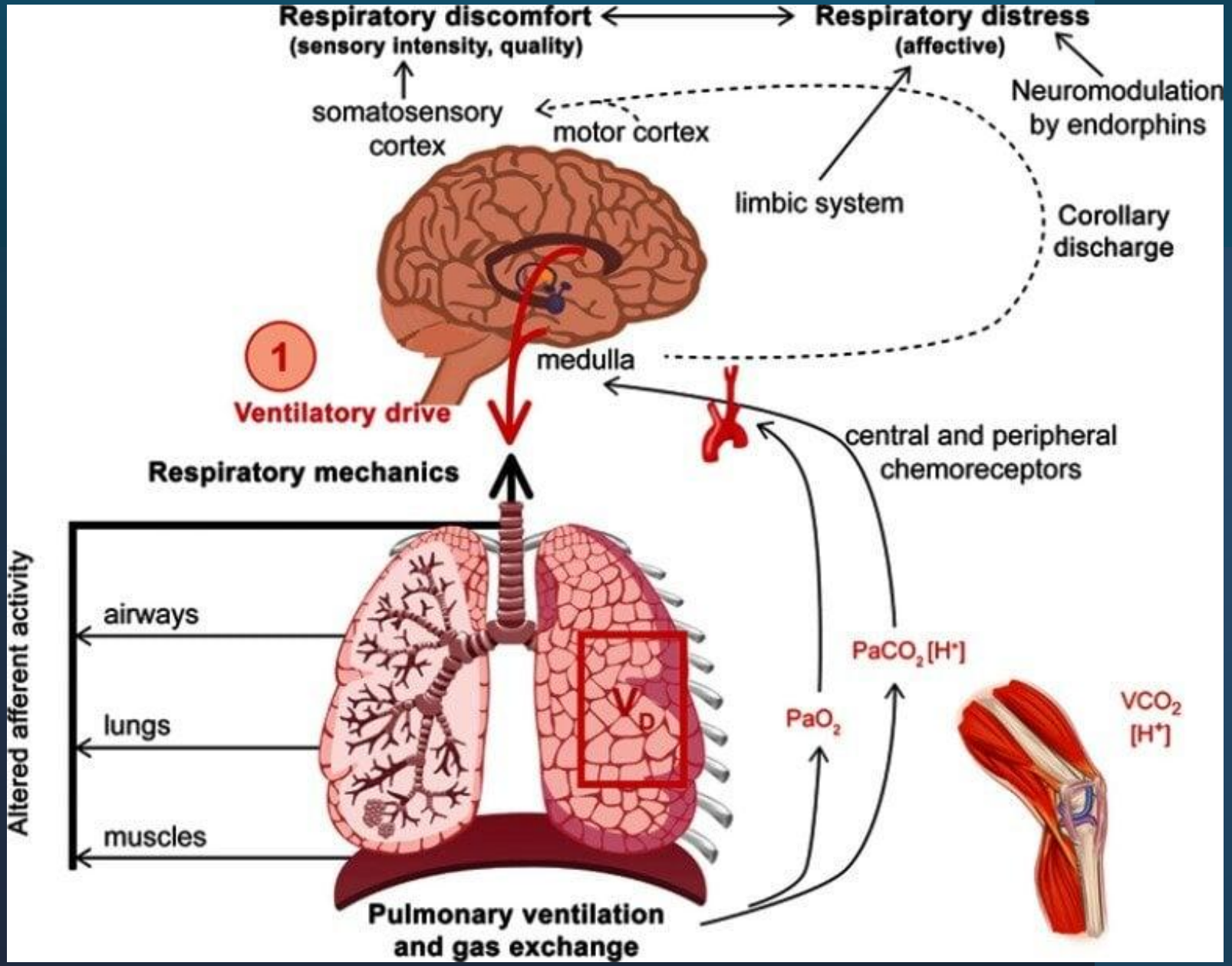


Dyspnea: Different sensations?

- Work/Effort : Resp muscle afferents projecting to cortex
- Tightness: ”Bronchoconstriction” likely related to stimulation of airway receptors
- Air hunger/unsatisfied inspiration: Imbalance between motor drive to breathe and afferent feedback from mechanoreceptors (“corseting the chest during exercise”)
- These separate sensations rarely occur in isolated fashion. Multiple uncomfortable sensations are usually present in the same patient

Dyspnea: Perception

- Dyspnea occurs when there is an increase above usual levels of reflex afferent information from the peripheral sensors (chemoreceptors, vagal C fibers, mechanoreceptors), processed in the insula and cortex
- Afferent feedback provided by stretch and chest wall receptors
- If CNS output does not provide expected output (airflow / ventilation changes) due to abnormal lung mechanics (e.g. COPD), sensation of dyspnea is generated
- Extent of mismatch between afferent/efferent information and preexisting memory determines the intensity of dyspnea


Respiratory discomfort
(sensory intensity, quality)
Respiratory distress
(affective)
somatosensory cortex
motor cortex
Neuromodulation by endorphins
limbic system
Corollary discharge
1
Ventilatory drive
medulla
central and peripheral chemoreceptors
Respiratory mechanics
Altered afferent activity
airways
lungs
muscles
V_D
$PaCO_2$ [H+]
PaO_2
VCO_2 [H+]
Pulmonary ventilation and gas exchange

Examples of Conditions and Causes of Dyspnea Grouped by Physiological Mechanism

Increased respiratory drive—increased afferent input to respiratory centers

Stimulation of pulmonary receptors (irritant, mechanical, vascular)†

- Interstitial lung disease
- Pleural effusion (compressive atelectasis)
- Pulmonary vascular disease (e.g., thromboembolism, idiopathic pulmonary hypertension)
- Congestive heart failure

Simulation of chemoreceptors

Conditions leading to acute hypoxemia, hypercapnia, and/or acidemia

- Impaired gas exchange, e.g., asthma, pulmonary embolism, pneumonia, heart failure‡
- Environmental hypoxia, e.g., altitude, contained space with fire

Conditions leading to increased dead space and/or acute hypercapnia

- Impaired gas exchange, e.g., acute, severe asthma, exacerbations of COPD, severe pulmonary edema
- Impaired ventilatory pump (see below), e.g., muscle weakness, airflow obstruction

Metabolic acidosis

- Renal disease (renal failure, renal tubular acidosis)

Decreased oxygen carrying capacity, e.g., anemia

Decreased release of oxygen to tissues, e.g., hemoglobinopathy Decreased cardiac output

Pregnancy

Behavioral factors

- Hyperventilation syndrome, anxiety disorders, panic attacks

Impaired ventilatory mechanics—reduced afferent feedback for a given efferent output (corollary discharge of motor command)

Airflow obstruction (includes increased resistive load from narrowing of airways and increased elastic load from hyperinflation)

- Asthma, COPD, laryngospasm, aspiration of foreign body, bronchitis

Muscle weakness

- Myasthenia gravis, Guillain-Barre, spinal cord injury, myopathy, post-poliomyelitis syndrome

Decreased compliance of the chest wall

- Severe kyphoscoliosis, obesity, pleural effusion

Adapted from Murray & Nadel Textbook of Respiratory Medicine 2012

Part	Description	Manifestations	Examples
Controller	Malfunction presents as abnormal respiratory rate or depth. Often related to abnormal feedback to brain from other parts of the system	Air hunger, need to breathe	Abnormal feedback to brain from other systems. Metabolic acidosis, anxiety
Ventilatory pump	Composed of muscles, nerves that signal the controller, chest wall, and pleura that create negative thoracic pressure, airways and alveoli allowing flow from atmosphere and gas exchange	Increased work of breathing, low tidal volumes	Neuromuscular problems (eg, Guillain-Barré), decreased chest wall compliance, pneumothorax, pneumonia, bronchospasm (COPD, asthma)
Gas exchanger	Oxygen and carbon dioxide cross the pulmonary capillaries in the alveoli. Membrane destruction or interruption of the interface between the gas and capillaries by fluid or inflammatory cells limit gas exchange	Increased respiratory drive, hypoxemia, chronic hypercapnia	Emphysema, pneumonia, pulmonary edema, pleural effusion, hemothorax

- *Adapted from* Schwartzstein RM, Lewis A. Dyspnea. In: Broaddus V, Mason RC, Ernst JD, et al, editors. Murray & Nadel's textbook of respiratory medicine. Elsevier health sciences. 6th edition. Philadelphia: Saunders/Elsevier; 2015.

Systematic approach to dyspnea by assessing the components of the respiratory process

Domains of Dyspnea Measurement

Domain	Definition	Examples*
Sensory–perceptual experience	Measures of what breathing feels like to the patient or research subject.	Single item ratings of intensity (e.g., Borg scale, VAS) Descriptors of specific sensations/clusters of related sensations
Affective distress	Measures of how distressing breathing feels. Focus can be either immediate (e.g. unpleasantness) or evaluative (e.g., judgments of meaning or consequences).	Single-item ratings of severity of distress or unpleasantness Multi-item scales of emotional responses such as anxiety
Symptom impact or burden	Measures of how dyspnea/breathlessness affects functional ability, employment (disability), quality of life, or health status.	Unidimensional rating of disability or activity limitation (e.g., MRC scale) Unidimensional or multidimensional ratings of functional ability Multidimensional scales of quality of life/health status

The Borg Dyspnea (Breathlessness) Scale

How to Rate your Difficulty of Breathing

Rating	Descriptor
0	No breathlessness at all
0.5	Very, very slight breathlessness
1	Very slight breathlessness
2	Slight breathlessness
3	Moderate breathlessness
4	Somewhat severe breathlessness
5	Severe breathlessness
6	
7	Very severe breathlessness
8	
9	Very, very severe breathlessness
10	Maximal

MODIFIED MRC DYSPNEA SCALE[a]

PLEASE TICK IN THE BOX THAT APPLIES TO YOU | ONE BOX ONLY | Grades 0 - 4

mMRC Grade 0.	I only get breathless with strenuous exercise.	☐
mMRC Grade 1.	I get short of breath when hurrying on the level or walking up a slight hill.	☐
mMRC Grade 2.	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.	☐
mMRC Grade 3.	I stop for breath after walking about 100 meters or after a few minutes on the level.	☐
mMRC Grade 4.	I am too breathless to leave the house or I am breathless when dressing or undressing.	☐

[a] Fletcher CM. BMJ 1960; 2: 1662.

TABLE 2.5

PY OR DISTRIBUTE

Dyspnea: Approaches to evaluation

- Step by Step Assessment: Stage 1 (H&P; Spiro; ECG; CXR; Labs) Stage 2 (ECHO; Stress testing) Stage 3 (Cardiac cath; Bronch). Stage1? 35% diagnosed. Stage 1&2? 65% Stage 1/2/3? 90%
- Package of tests followed by clinical assessment: Pratter et al. 85 pts with H&P and CXR followed by PFT, Bronchoprov, Stress test, ph monitor, CPET. Final diagnosis by 2 experts. Initial evaluation diagnostic in 65% pts (COPD/Asthma/ILD/Cardiomyopathy). Almost 50% of final diagnosis were NOT respiratory. Bronchoprov 95% PPV & 100% NPV. No never smoker had COPD. Absence of crackles had 98% NPV for ILD.

Dyspnea: Approaches to evaluation

- DePaso et al. 72 pts with unexplained dyspnea. Targeted H&P, CXR, Spiro followed by 2nd more focused eval with labs/ABG and PFT, VQ, ECHO, Treadmill, Holter, Bronchoprov, CT, UGIS, ph monitor and CPET, as needed. Diagnosis: Resp 36%, Card 14%, Hyperventilation 19%, GERD 4%, Thyroid dz 3%, Poor conditioning 3%. No diagnosis in 19% of pts.
- Ocal et al. 250 pts with unexplained dyspnea after H&P. Both Spiro and ECHO diagnosed 83% of pts with heart and/or lung dz
- CPET. 554 pts with unexplained dyspnea after initial eval. CPET determined cause of dyspnea in 100%.

Dyspnea: History

- **Get a COMPLETE history and physical examination…**
- New onset? Or known cardiovascular/respiratory/neuromuscular disease?
- Ask the patient, in their own words, to describe what they are feeling!
- Is it acute or chronic?
- Descriptors: Slow and progressive? Waxes and wanes?
- Factors that are Relievers? Aggravators?
- Associated symptoms with their dyspnea? E.g. Chest pain? Cough? Fever?
- Pertinent past medical or surgical history? Ask about mental health history?
- Pertinent social history? E.g. Tobacco? Drugs? Occupational risk?
- Medications? E.g. Bblockers in asthma; Checkpoint inhibitors in CA

Favors Asthma	Favors COPD
Onset in childhood	Onset in adulthood
Symptoms vary over time Symptoms worse at night Symptoms may be triggered by allergens or exercise	Symptoms persist even with treatment Daily symptoms, some days better than others Chronic cough and sputum unrelated to triggers
Variable airflow obstruction	Persistent airflow obstruction
Normal lung function when asymptomatic	Abnormal lung function when asymptomatic
Atopy in self or family	Smoker
No progression over time	Progression over time

Dyspnea: Physical Examination

- Are they tachypneic at rest? Exertion? Do they look dyspneic?
- Hemodynamic stability?
- Are they Hypoxic? Hypercapneic?
- Pulsus pardoxus (10 mmg Hg drop in SBP w inspiration) – COPD, PE, Large effusions, cardiac tamponade, etc
- Neck exam – Tracheal shift? Thyroid size? JVD?
- Cyanosis? Wheezing? Diminished breath sounds? Distant heart sounds? Crackles? Ascites? Kyphoscoliosis? Percussion of lung?
- Digital clubbing? Lung CA, COPD, ILD, etc

Symptom	Differential Diagnosis
Wheeze	COPD/emphysema, asthma, allergic reaction, CHF (cardiac wheeze)
Cough	Pneumonia, asthma, COPD/emphysema
Pleuritic chest pain	Pneumonia, pulmonary embolism, pneumothorax, COPD, asthma
Orthopnea	Acute heart failure
Fever	Pneumonia, bronchitis, TB, malignancy
Hemoptysis	Pneumonia, TB, pulmonary embolism, malignancy
Edema	Acute heart failure, pulmonary embolism (unilateral)
pulmonary edema	Acute and chronic heart failure, end stage renal and liver diseases, ARDS (sepsis)
Tachypnea alone	pulmonary embolism, acidosis (including aspirin toxicity), anxiety

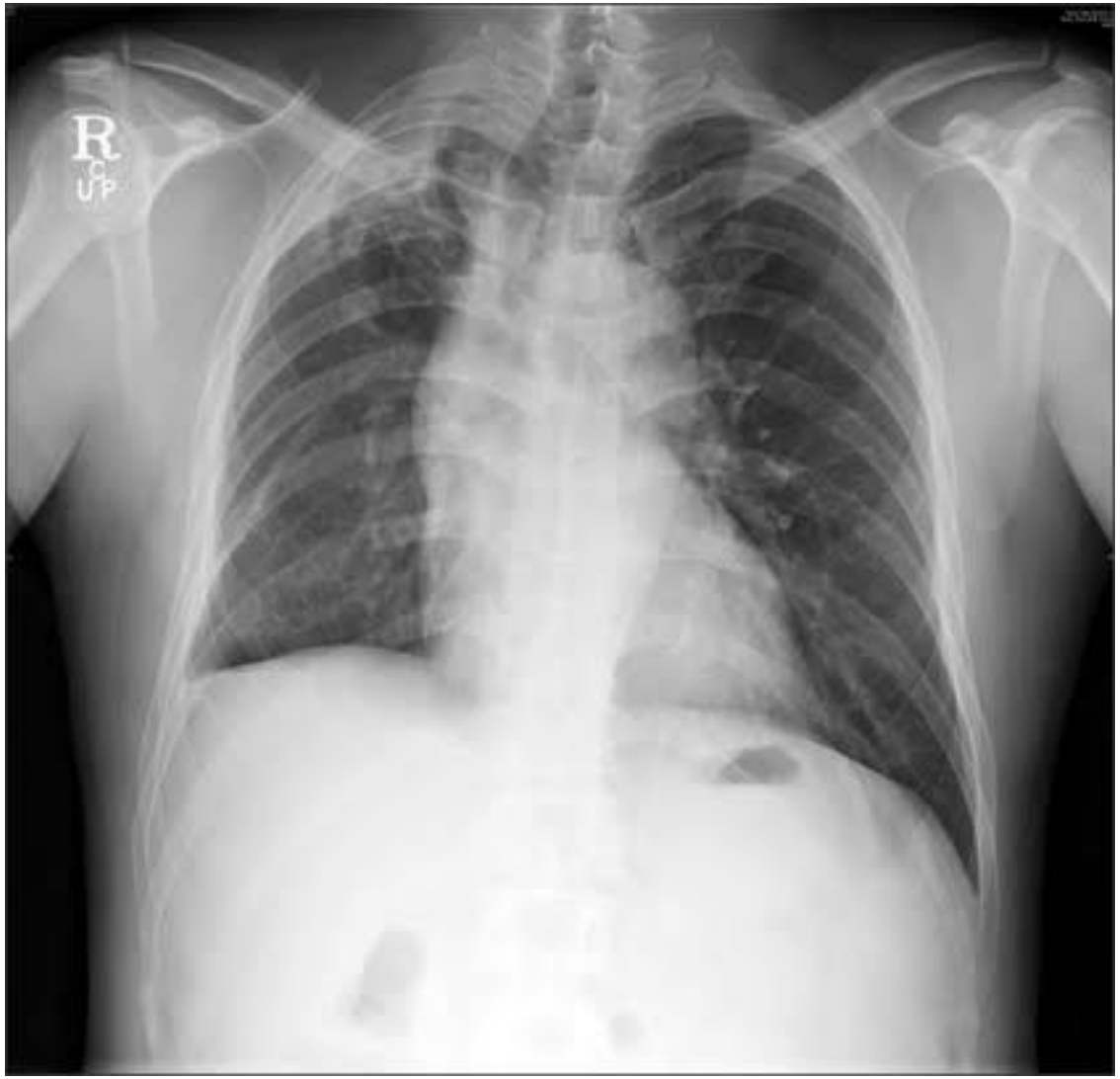
Physical examination findings and correlating diagnoses

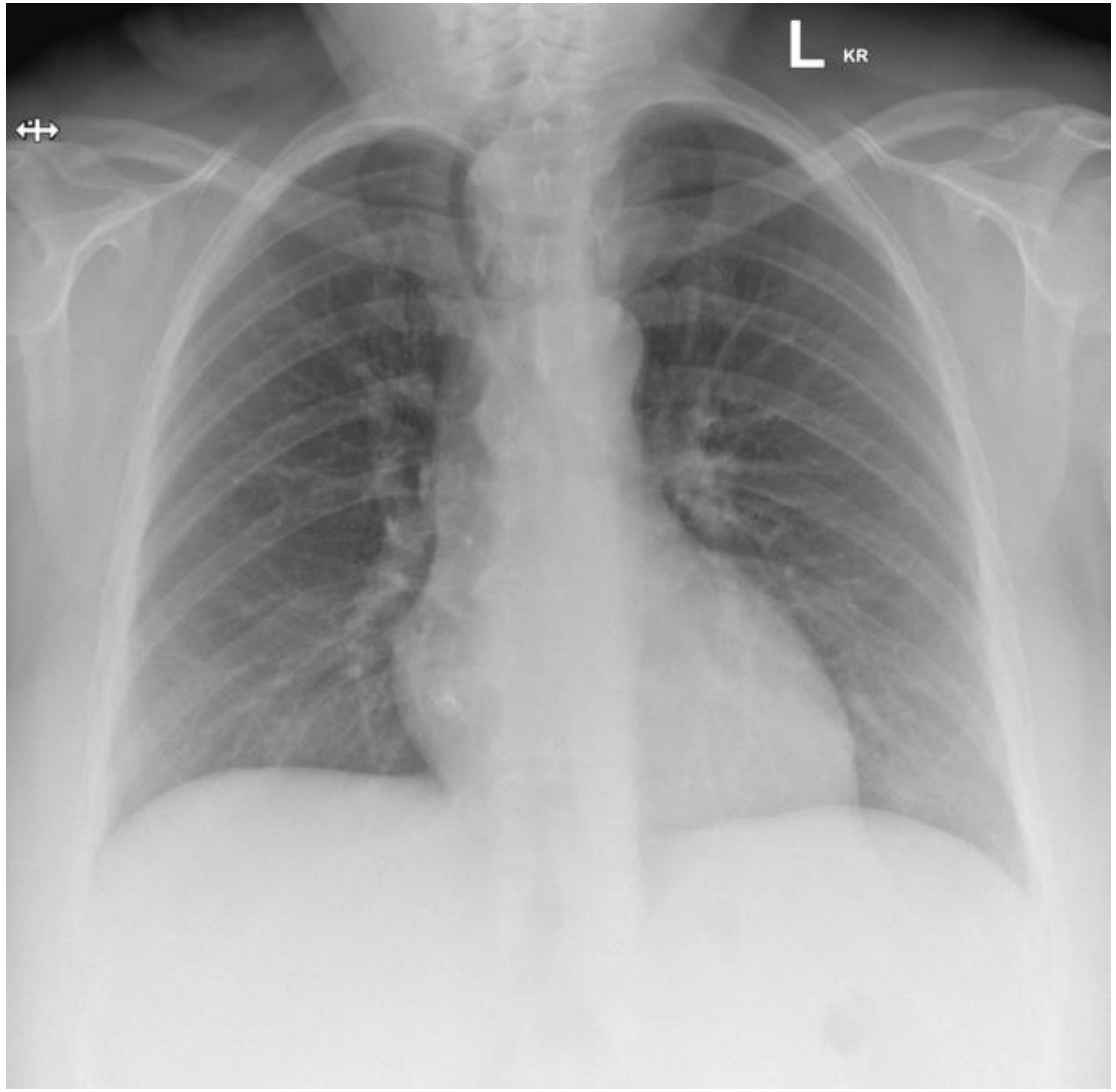
Diagnostic Testing for the Dyspneic Patient

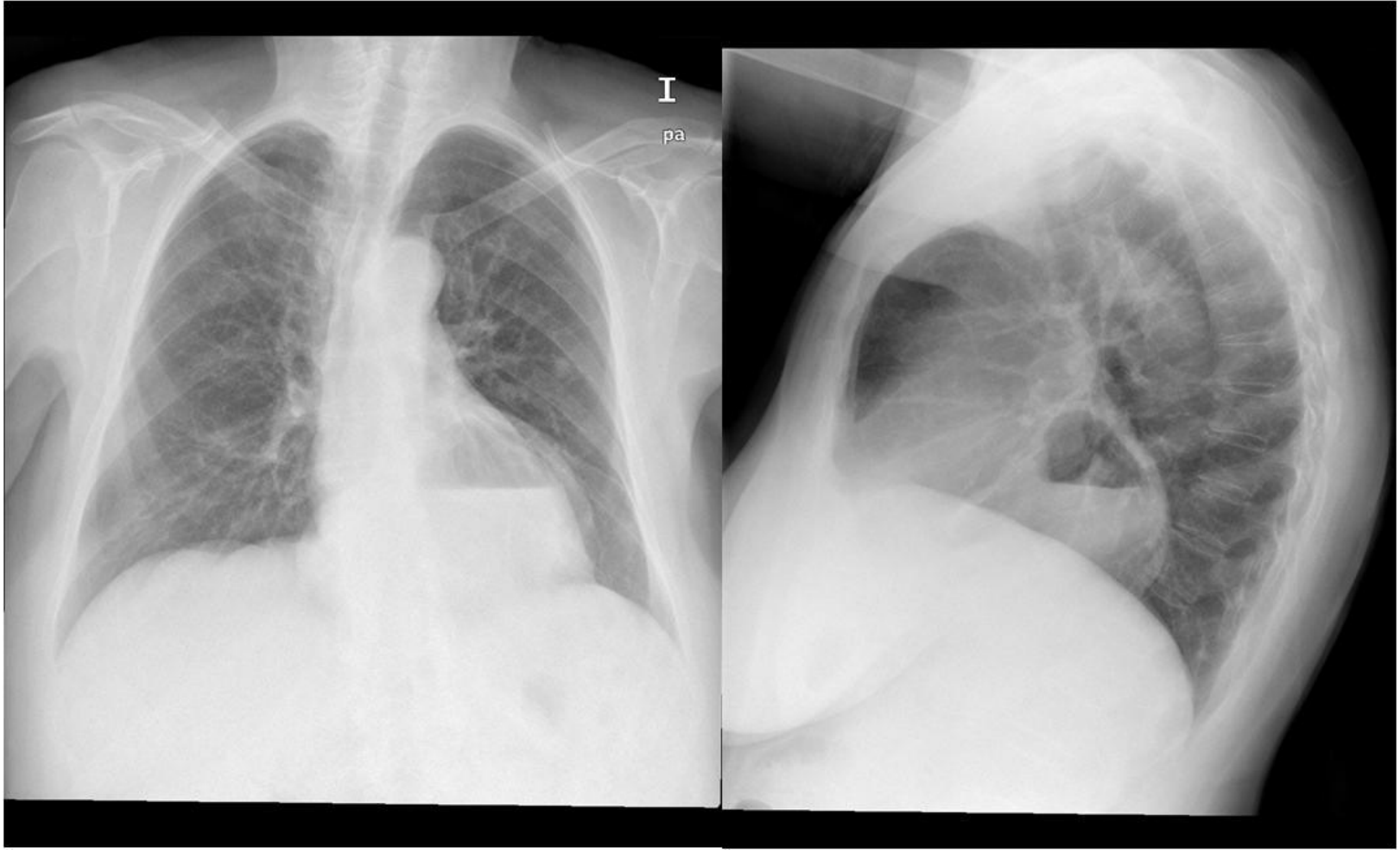
Test	General Information	Pros	Cons
Chest radiograph	Often primary imaging	Low radiation, can assess consolidation, pleural fluid, hyperinflation, pneumothorax, and subcutaneous air. Heart size is apparent	Low sensitivity in acute dyspnea. In one series only 8 of 26 pneumonias diagnosed on CT met CXR criteria[37]
Ultrasonography	Multiple protocols to assess acute dyspnea	No radiation, fast, reproducible bedside test, can be done on unstable patients in department and in semirecumbent position	Requires some skill to acquire and interpret bedside images. Patient factors such as subcutaneous air, body habitus, and so forth may limit images
D-dimer	Marker of fibrinolytic activity. When measured by ELISA or second-generation latex agglutination can be used to rule out PE in selected patients	Serum test readily available	Requires risk assessment and clear clinical question. Also increased in consumptive coagulopathy, infection, malignancy, trauma, dissection, preeclampsia, and other cardiovascular disorders
Arterial blood gas	Provides additional information about ventilation ($Paco_2$) to patients with reliable pulse oximetry and bicarbonate level available on BMP	May be faster than general laboratory tests. Useful in assessing anxiety-induced hyperventilation[36]	Limited evidence for routine use in undifferentiated dyspnea
Electrocardiogram	Initial cardiac assessment for assessing dyspnea	Fast and inexpensive. Easy to compare with prior examinations. Specific for dysrhythmias or ACS limiting perfusion	May be nonspecific in findings such as right heart strain and P pulmonale
Troponin	Serum indicator of myocardial damage	Serum test readily available	Can narrow differential to cardiac causes. PE with right heart strain may have increased troponin levels; this finding predicts worse outcomes
BNP and proBNP	Useful in assessing for acute heart failure	Serum test readily available	Limited in obesity, mitral regurgitation, flash pulmonary edema, and renal insufficiency. Context is essential
Complete blood count	Provides information about oxygen carrying capacity based on hemoglobin and hematocrit. White blood cell count may indicate infection	Serum test readily available	Nonspecific
CT scan	Provides detailed imaging of cardiorespiratory system. Use is increasing, but practitioners should maintain clinical context and consider whether other modalities can answer the clinical question	Offers sensitive and specific results	Significant radiation exposure, contrast nephropathy, intravenous contrast dye reactions
Ventilation/perfusion scan	Radiolabeled aerosol and albumin aggregates are used to study ventilation and perfusion. Read as negative or low, medium or high probability for pulmonary embolism	Low in radiation	Limited by underlying pulmonary disease and availability of isotopes

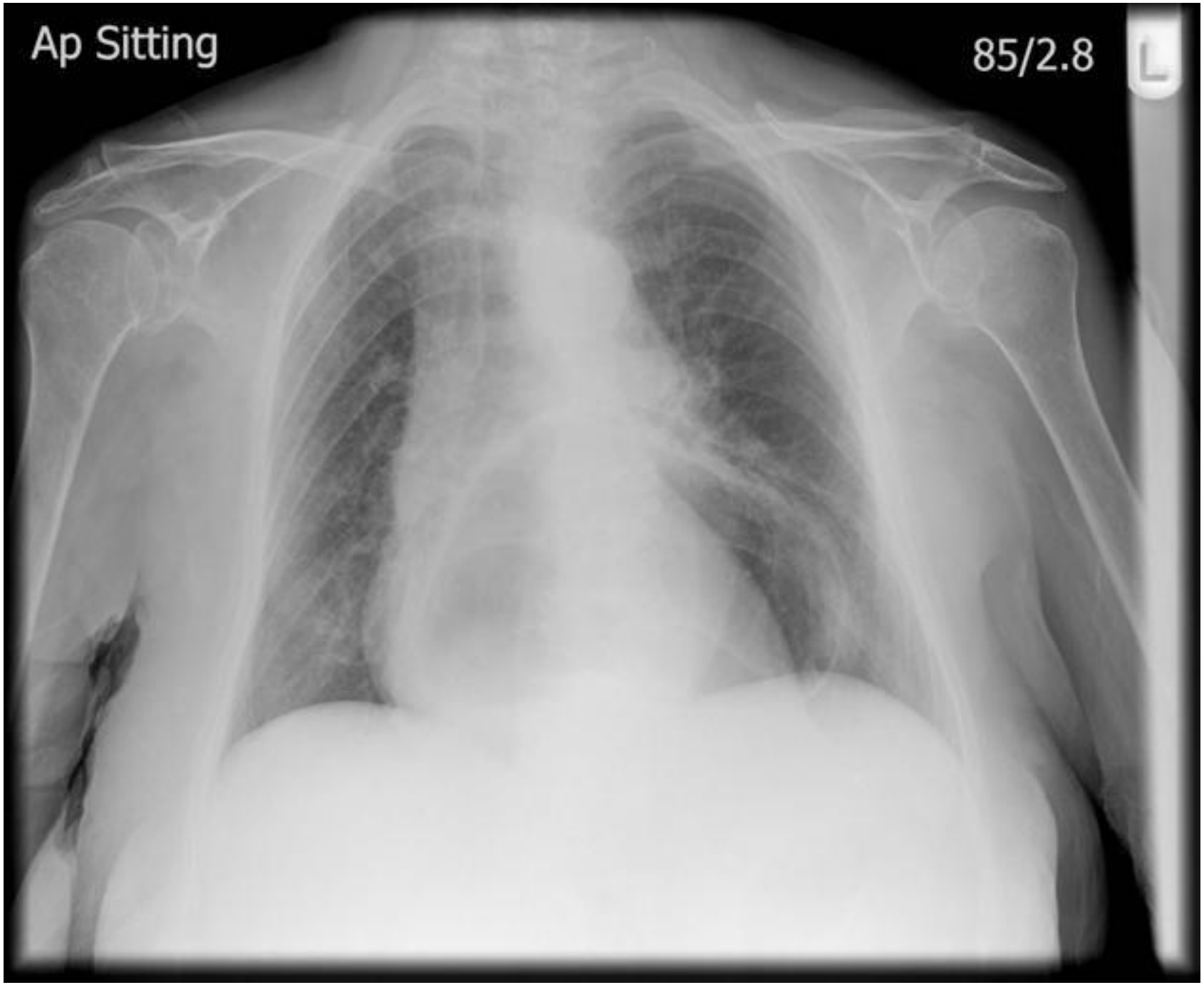



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Ap Sitting
85/2.8
L

Dyspnea: Diagnostic Testing: Labs & ECG

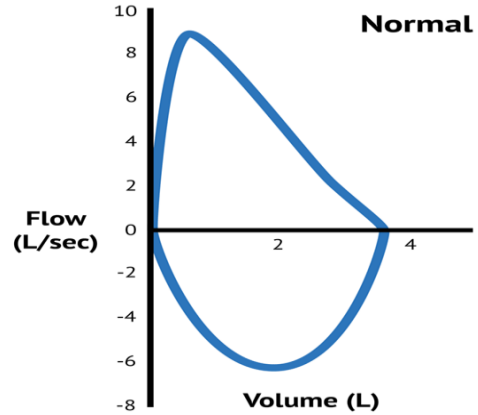
- BNP / NT-pro BNP. Useful in ruling OUT heart failure in dyspnea (high sensitivity and NPV 94-98%). Age, renal function, etc can raise levels. 30% of pts have intermediate/equivocal values.
- D-dimer. Useful ONLY as a rule out test for PE/VTE and only after pretest probability has been estimated. High sensitivity (negative result excludes PE in low or intermed clinical probability. Low specificity (high level does NOT confirm PE/VTE). False + in older pts, CA, infection/inflammation. NO ROLE IN NON-PE DYSPNEA
- CBC – Anemia? Leucocytosis? Secondary erythrocytosis?
- TSH / Thyroid function tests
- ECG – Afib? Normal ECG has low likelihood of HF (89% sensitivity)

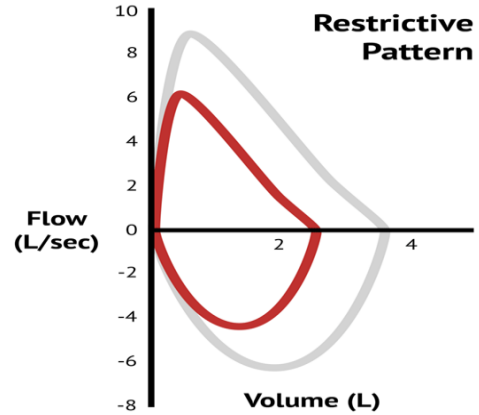
Dyspnea: Diagnostic Testing; Spirometry

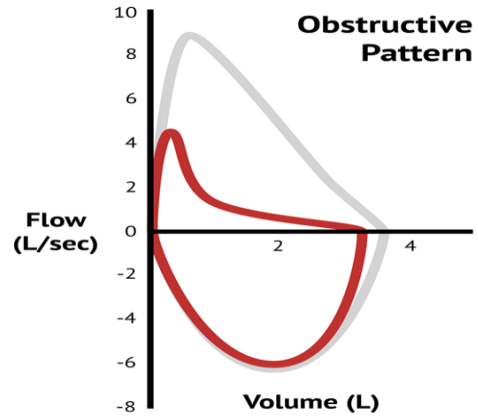
- FEV1/FVC below LLN (used to be 70%) indicates obstructive lung disease (E.g. COPD, Asthma)

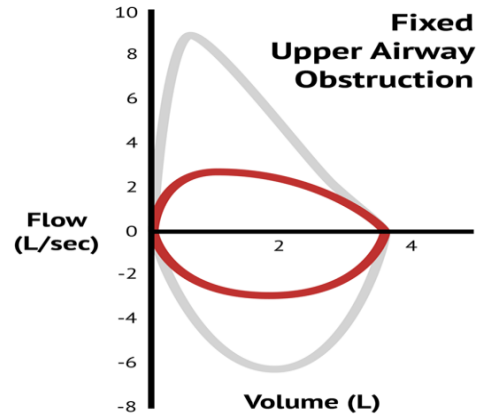
- FVC reduction with normal FEV1/FVC? Restrictive lung disease (E.g. Obesity, Interstitial lung disease/fibrosis, thoracic cage dz)

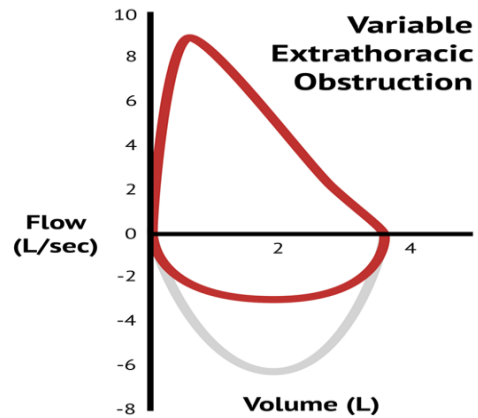
- Flow volume loop?

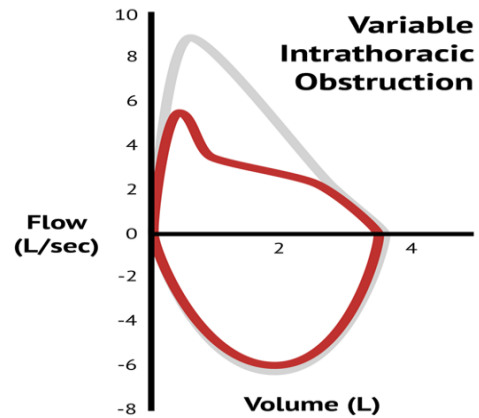

Normal
Flow (L/sec)
Volume (L)
10
8
6
4
2
0
-2
-4
-6
-8
2
4


Restrictive Pattern
Flow (L/sec)
Volume (L)
10
8
6
4
2
0
-2
-4
-6
-8
2
4


Obstructive Pattern
Flow (L/sec)
Volume (L)
10
8
6
4
2
0
-2
-4
-6
-8
2
4


Fixed Upper Airway Obstruction
Flow (L/sec)
Volume (L)
10
8
6
4
2
0
-2
-4
-6
-8
2
4


Variable Extrathoracic Obstruction
Flow (L/sec)
Volume (L)
10
8
6
4
2
0
-2
-4
-6
-8
2
4


Variable Intrathoracic Obstruction
Flow (L/sec)
Volume (L)
10
8
6
4
2
0
-2
-4
-6
-8
2
4

Height(in): 73 Weight(lb): 277 Age: 60 Gender: Male
Date: 05/19/99 Race: Caucasian Physician: GMC

SPIROMETRY

		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
FVC	Liters	5.04	2.19	43	2.55	51	16
FEV1	Liters	4.04	1.01	25	1.18	29	17
FEV1/FVC	%	79	46		46		
FEF25-75%	L/sec	4.02	0.49	12	0.56	14	13
FEF50%	L/sec	4.92	(0.41)	(8)	(0.52)	(10)	25
FEF75%	L/sec	1.87	(0.27)	(14)	(0.25)	(13)	-7
PEF	L/sec	9.33	4.09	44	3.92	42	-4
MVV	L/min	150	(42)	(28)			
MVV Length			12				

PLETHYSMOGRAPH LUNG VOLUMES

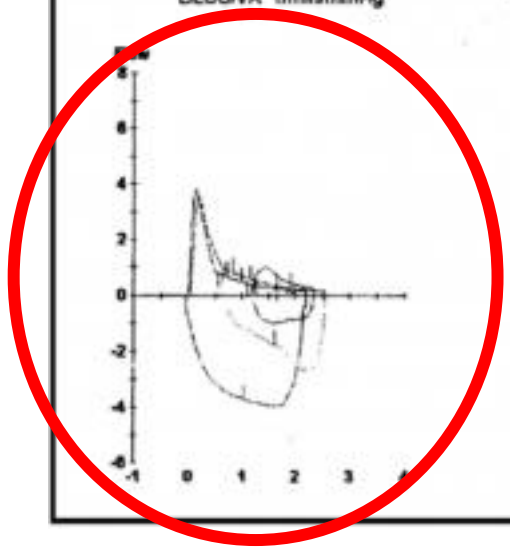
		Pre Meas	Ref	Pre % Ref
TLC	Liters	(8.82)	7.38	(120)
Vtg	Liters	6.85		
RV	Liters	(5.36)	2.58	(208)
FRC PL	Liters	(6.09)	3.51	(174)
VC	Liters	3.47	5.04	69
IC	Liters	2.74		
ERV	Liters	0.73		
Raw	cmH2O/L/sec	3.65	1.29	284
RV/TLC	%	(61)	37	

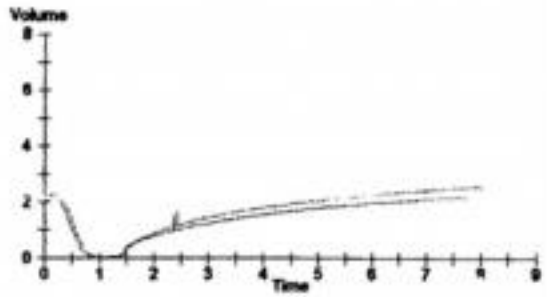
ARTERIAL BLOOD GAS

FIO2
pH
PCO2
PO2
HCO3
SaO2

DIFFUSING CAPACITY

		Pre Meas	Ref	Pre % Ref
DLCO	mL/min/mmHg	(12.5)	30.8	(41)
VA	Liters	6.19		
DLCO/VA	1/min/mmHg	2.03	3.83	53





Dyspnea: Diagnostic Testing: CT scans

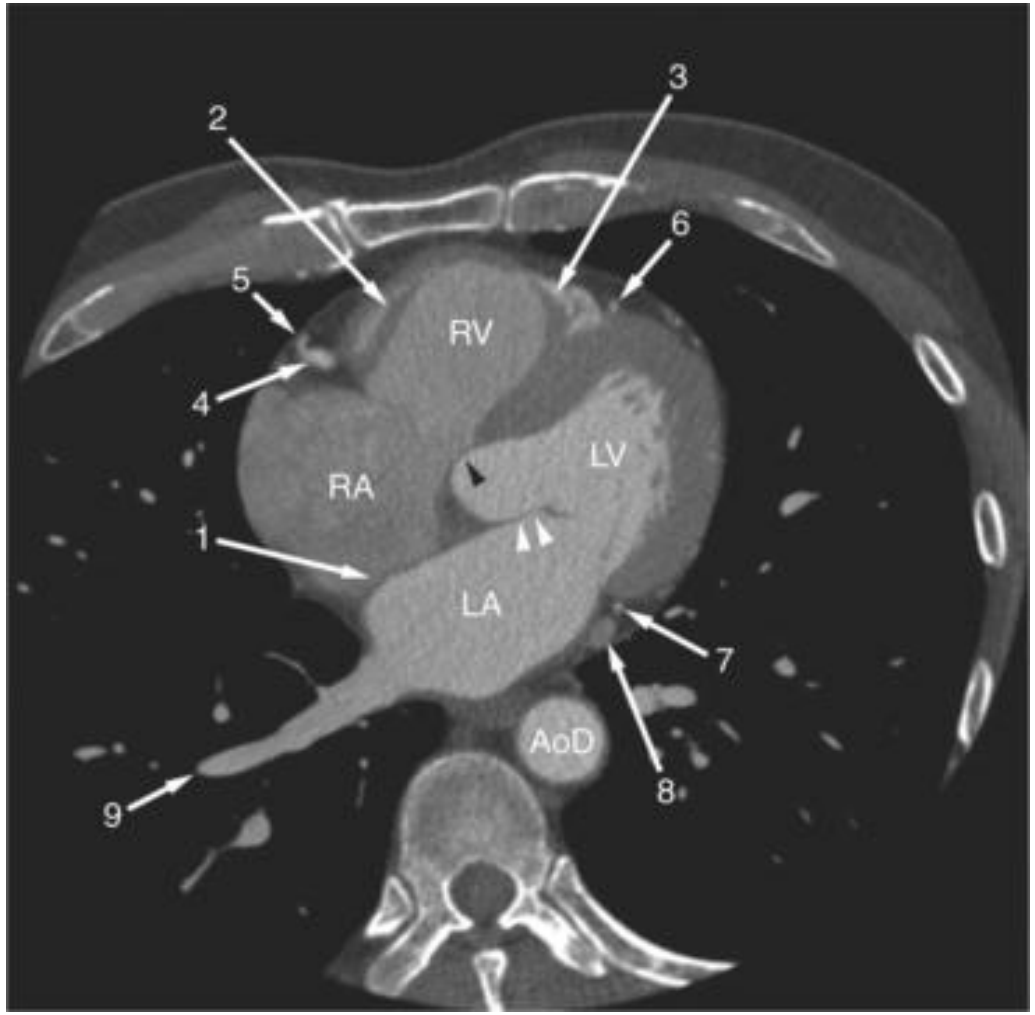
Standard CT chest

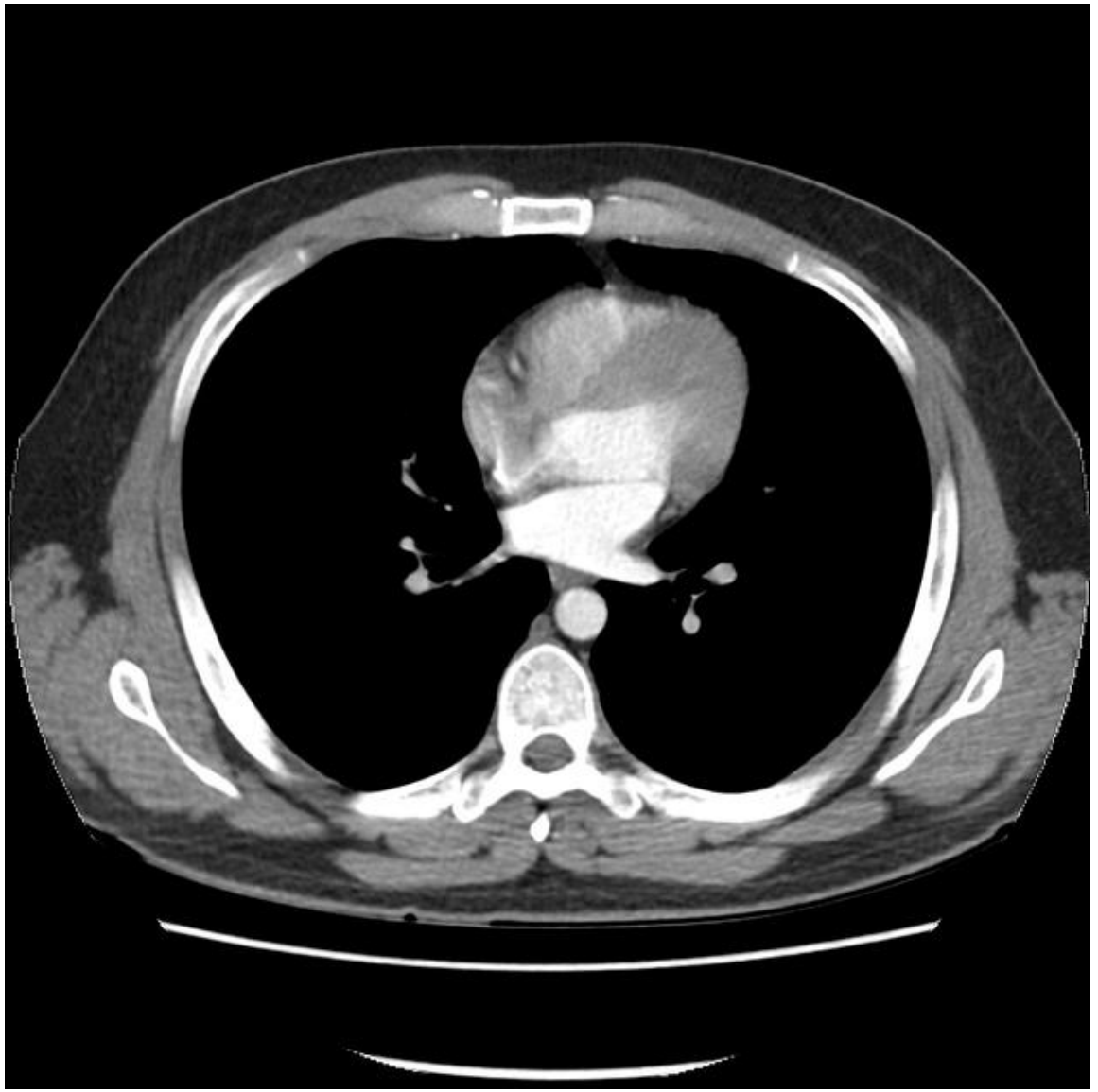
- 5-10 mm sections
- Volume averaging
- General localization of masses, fluid collections, mediastinal structures; screening studies
- With / without contrast

High-resolution CT chest (HRCT)

- Thin 1-2 mm sections
- High spatial frequency
- Fine architectural lung detail to assess ILD, small airways disease, emphysema, bronchiectasis,etc
- Non contrast

Cardiac CT is NOT a Chest CT





CT Abdomen is NOT a Chest CT

Dyspnea: Diagnostic Testing: 6MW test

- Does NOT identify the cause of dyspnea
- Objectively quantifies functional exercise limitation from dyspnea, to unmask exertional desaturation, estimate prognosis and to track response to interventions.
- Reflects extrapulmonary contributors (frailty, deconditioning) therefore correlates more with peak work capacity/physical activity than with lung function
- 6MWD < 350 m is associated with higher mortality in COPD, HF and PAH

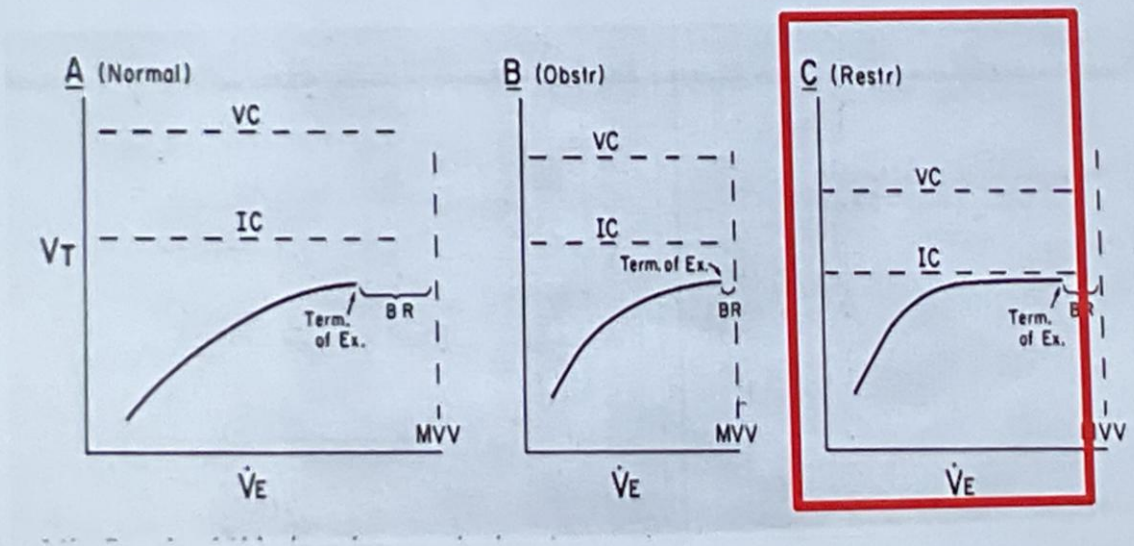
Dyspnea: Diagnostic Testing: CPET

- Most comprehensive noninvasive test for unexplained dyspnea
- Measures exercise capacity objectively and points to mechanism of limitation (cardiac, pulmonary vascular/ventilatory/gas exchange, peripheral/deconditioning or poor effort)
- A normal study makes significant cardiopulmonary disease unlikely
- Cycle ergometer or treadmill
- Testing protocol with resting phase, 3 min unloaded phase, 1-12 min incremental phase with work rate increased every min followed by recovery phase of 2-3 min



CHEST
AMERICAN COLLEGE of CHEST PHYSICIANS

Breathing Patterns During CPET Exercise (Normal, Obstructive, Restrictive)



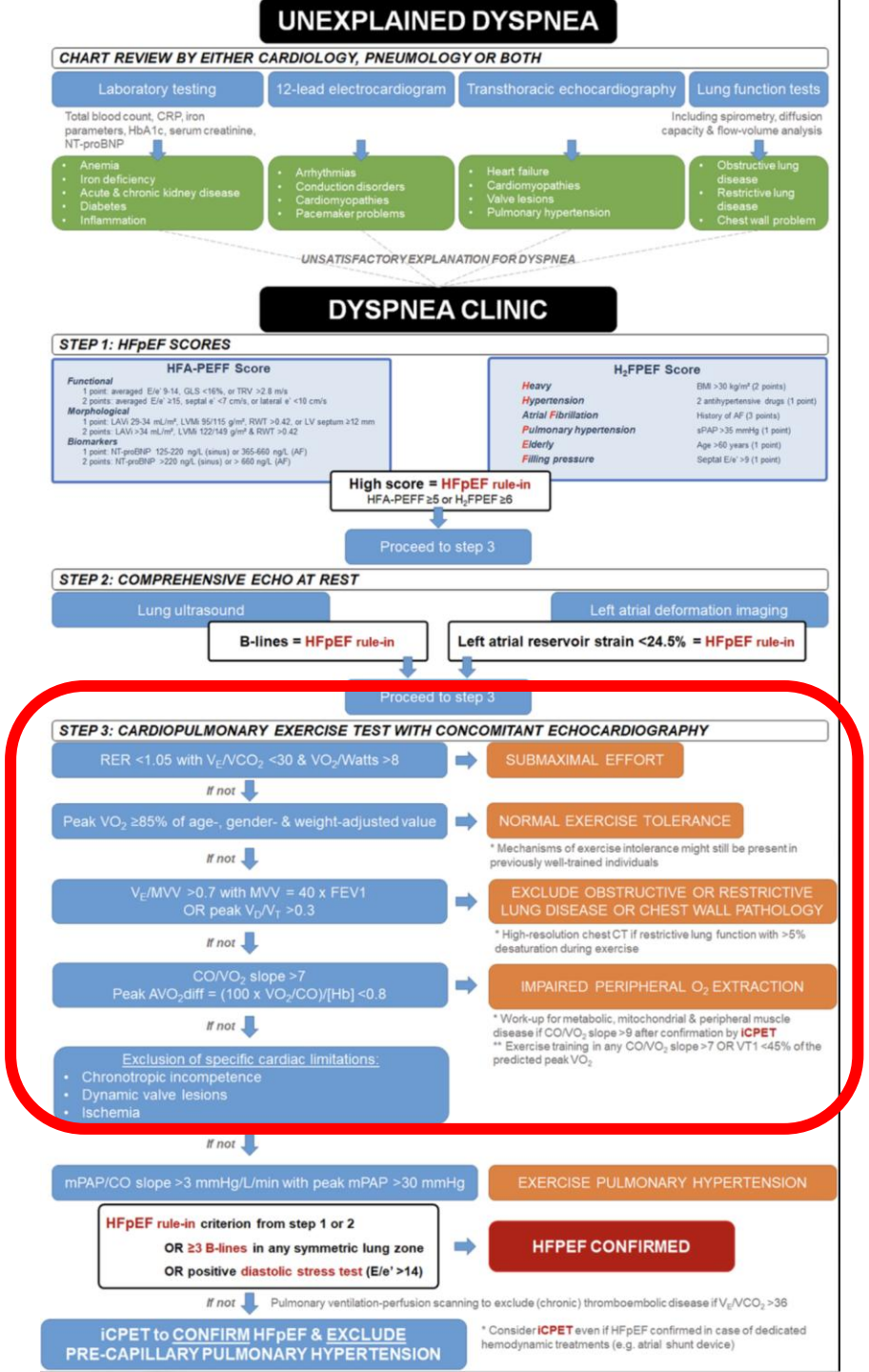
Dyspnea: Diagnostic Testing: CPET

Limitation

- Cardiovascular
- Ventilatory
- Deconditioning/Normal

Key CPET findings

- Low or flattening ΔVO2/ΔWR slope; flattened O2 pulse; low anaerobic threshold; ECG/BP abnormalities
- Peak VE approaching MVV (low breathing reserve); expiratory flow limitation (>40–50% of VT); fall in inspiratory capacity
- Reduced peak VO2 with no circulatory or gas exchange abnormality



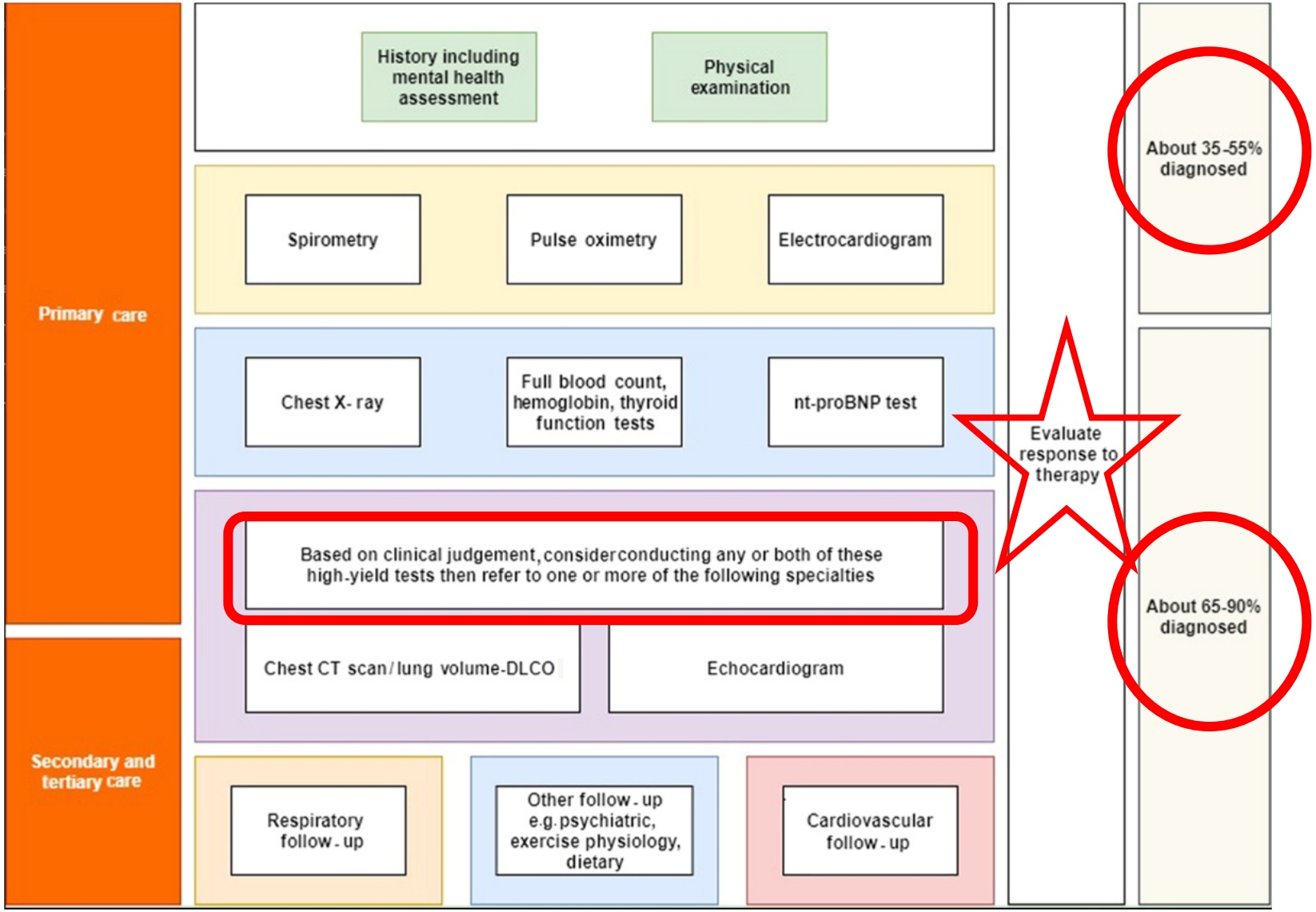
Proposed diagnostic algorithm for a dedicated Dyspnea clinic. JAHCC Heart Fail. Feb 1, 2023

Patient case…

- 76 yo WM
- Chronic, worsening dyspnea over months, esp with exertion (walking < 100 ft). Started after getting a URI on a cruise. Dyspnea fluctuates over days at times. "Feels like he cannot get a big enough breath" "Wheezing at times"
- Cough with thick mucus; some postnasal drip
- 25 pack year smoker, quit 2012. Retired from IT. No pets or hobbies. Fam Hx of COPD in father
- O2 sats 98% on RA. No pertinent findings on exam.

Patient case…

- Spirometry is normal; Flow volume loop is normal.
- CTA chest (ER): No PE;   Air trapping; Bronchial wall thickening
- BNP normal
- CBC normal.   Abs Eos 0.4 K/mcl (elevated since 2022)
- Trial of ICS-LABA with some improvement in symptoms
- Diagnosis? Eosinophilic asthma
- CT sinuses: B/l frontal/eth/sphenoid mucosal thickening; possible nasal polyps
- Maximal inhaled Rx with Anti IL5 biologic Rx added later on



A summary of the stepwise approach for dyspnea assessment and the probability of elucidating the causal diagnosis based on the included studies.

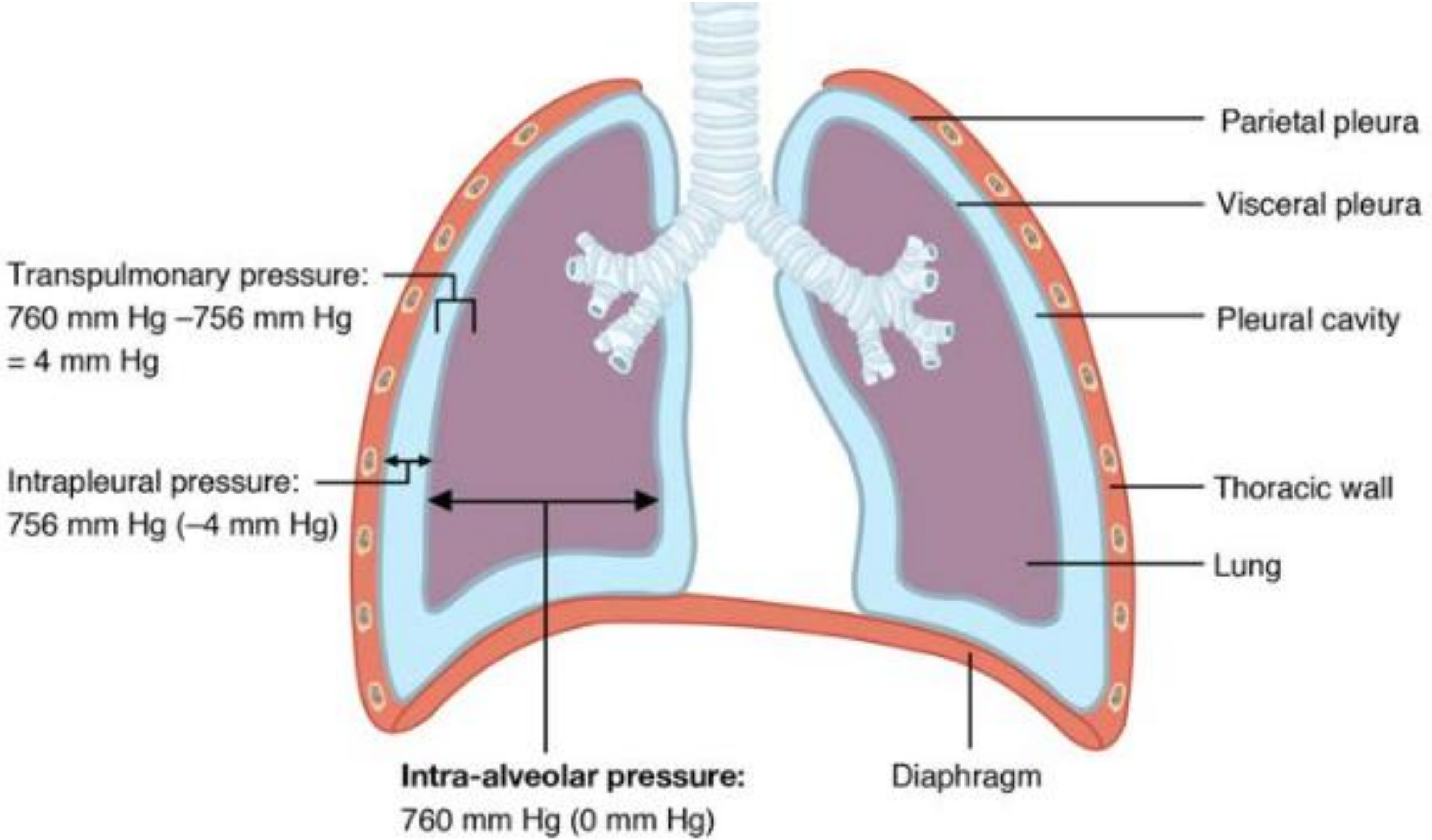
Adapted from Assessment and diagnosis of chronic dyspnoea: a literature review
NPJ Prim Car Resp Med. 2022.

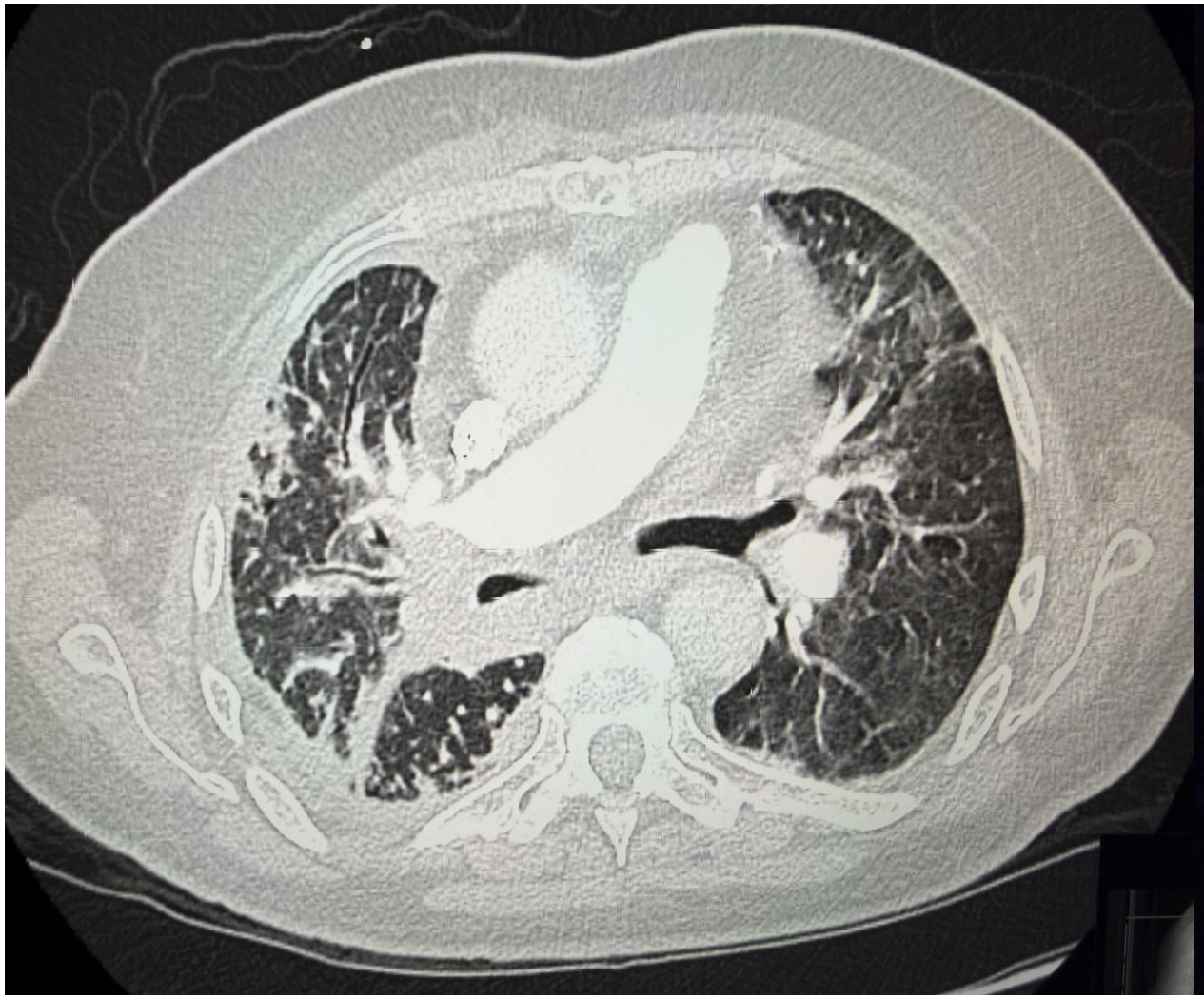
Thank you

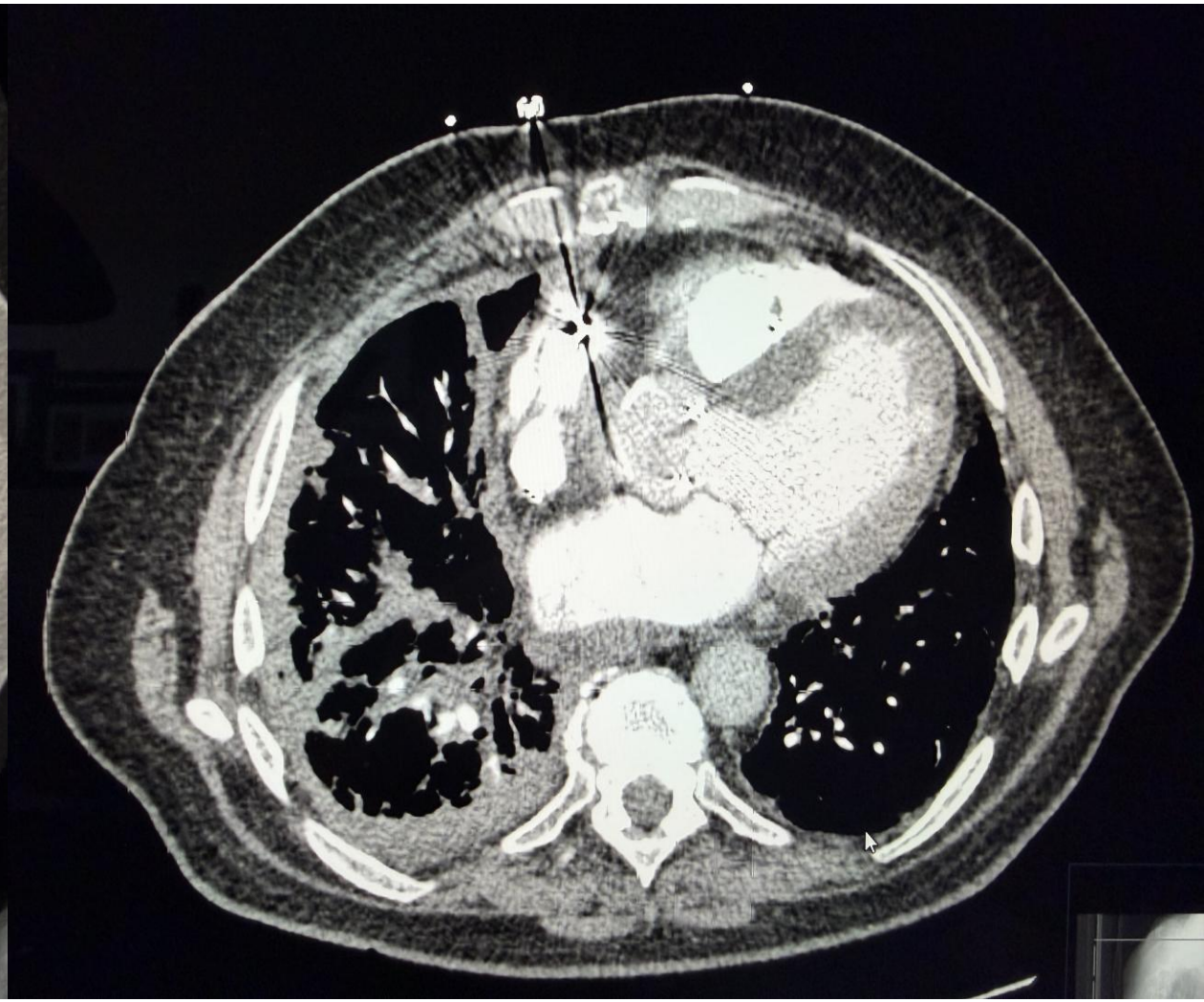
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Parietal pleura
Visceral pleura
Transpulmonary pressure:
760 mm Hg –756 mm Hg
= 4 mm Hg
Pleural cavity
Intrapleural pressure:
756 mm Hg (–4 mm Hg)
Thoracic wall
Lung
Intra-alveolar pressure:
760 mm Hg (0 mm Hg)
Diaphragm





Condition	Commonly Encountered Pathogens
Alcoholism	*Streptococcus pneumoniae*, oral anaerobes, *Klebsiella pneumoniae*, *Acinetobacter* species, *Mycobacterium tuberculosis*
COPD and/or smoking	*Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Legionella*species, *S pneumonia*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae*
Aspiration	Gram-negative enteric pathogens, oral anaerobes
Lung abscess	CA-MRSA, oral anaerobes, endemic fungal pneumonia, *M tuberculosis*, atypical mycobacteria
Exposure to bat or bird droppings	*Histoplasma capsulatum*
Exposure to birds	*Chlamydophila psittaci* (if poultry: avian influenza)
Exposure to rabbits	*Francisella tularensis*
Exposure to farm animals or parturient cats	*Coxiella burnetii* (Q fever)
HIV infection (early)	*S pneumoniae*, *H influenzae*, *M tuberculosis*
HIV infection (late)	The pathogens listed for early infection plus *Pneumocystis jirovecii*, *Cryptococcus*, *Histoplasma*, *Aspergillus*, atypical mycobacteria (especially *Mycobacterium kansasii*), *P aeruginosa*, *H influenzae*
Hotel or cruise ship stay in previous 2 wk	*Legionella* species
Travel to or residence in southwestern United States	*Coccidioides* species, Hantavirus
Travel to or residence in southeast and east Asia	*Burkholderia pseudomallei*, avian influenza, SARS
Influenza active in community	Influenza, *S pneumoniae*, *Staphylococcus aureus*, *H influenzae*
Cough>2 wk with whoop or post-tussive vomiting	*Bordetella pertussis*
Structural lung disease (eg, bronchiectasis)	*P aeruginosa*, *Burkholderia cepacia*, *S aureus*
Injection drug use	*S aureus,* anaerobes, *M tuberculosis*, *S pneumoniae*
Endobronchial obstruction	Anaerobes, *S pneumonia*, *H influenzae*, *S aureus*
In context of bioterrorism	*Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), *Francisella tularensis* (tularemia)

Chest wall mechanoreceptors

- Muscle spindles and tendon organs in the respiratory muscles act as mechanoreceptors
- Sense muscle tension/contraction and project to somatosensory cortex
- Spinal cord block/transection does not prevent the ability to detect lung volume change or alter the sensations induced by an increase in PCO_2, breath holding or added respiratory loads
- Chest wall receptors have a modifying effect on dyspnea but respiratory muscle activity does not appear to be essential to the perception of dyspnea

Chemoreceptors

- In normal subjects, induction of hypercapnia or severe hypoxemia causes breathlessness
- CO_2 induced dyspnea may be due to stimulation of peripheral or central chemoreceptors
- In high altitude hypoxia, the intensity of exercise-induced breathlessness is more related to level of reflexly stimulated ventilation rather than level of hypoxia.
- Weight of evidence suggests that hypercapnia is dyspnogenic in normal subjects and is dependent on the level of reflex stimulation of the respiratory centers; Source of signal (Peripheral? Vagal? Central?) is unclear
- Hypoxia? Unclear if this is dyspnogenic.

Lung receptors

- Sensory information from lungs is transmitted via the vagus nerve to the brainstem
- Rapidly and slowly adapting receptors are involved in pulmonary stretch and cough reflexes, modulating airway caliber and ventilatory pattern – afferent information on lung volume changes to the respiratory centers permits “awareness” of the level of stretch occurring in the lungs
- Vagal C fibers in the airway can be stimulated by substances (e.g. adenosine) causing dyspnea and attenuated by others (e.g. lidocaine, theophylline)

Central mechanisms

- Vagal C fibers carry afferent information from the periphery to the NTS (nucleus tractus solitarius) in the medulla – a key relay site for all respiratory afferent signals to the higher centers
- NTS information ascends via the thalamus to the viscerosensory insular cortex
- Divergent areas of the cortex are stimulated by different respiratory stimuli (e.g. hypercapnia activates middle frontal gyri)
- Functional MRI confirm that induced dyspnea is associated with activations in the right anterior insula and right amygdala and perception of dyspnea was blunted by lesions in this area

Dyspnea perception?

- Dyspnea activates cortico-limbic structures that also subserve interoceptive awareness and nociceptive sensations such as pain. Opioids (endo/exogenous) may relieve dyspnea by altering central processing of efferent and afferent sensory information

Dyspnea perception?

- Sensory-perceptual mechanisms underlying sensations of work or effort in breathing are similar to those underlying similar sensations in exercising muscle
- Tightness is relatively specific to stimulation of airway receptors in conjunction with bronchoconstriction
- Intensity of air hunger/unsatisfied inspiration is magnified by imbalances among inspiratory drive, efferent activation (outgoing motor command from the brain), and feedback from afferent receptors throughout the respiratory system.

Physiology of respiration

- **Boyle's Law** : Amount of gas is inversely proportional to its volume
- Inhalation: Diaphragm/IC muscles contract, enlarging thoracic cavity and lung volume. Intrapulmonary pressure drops below atmospheric pressure. Air rushes down this pressure gradient.
- Exhalation: Resp muscles relax, decreasing thoracic/lung volume. Intrapulmonary pressure rises and air is forced out.
- **Dalton's Law** : Total pressure of gas mixture is equal to sum of partial pressures of each individual gas in the mixture; Individual gases diffuse indendently down their own partial pressure gradients
- O_2 moves from alveoli (pO_2 104 mm Hg) into deoxygenated blood (pO_2 40 mm Hg)
- CO_2 moves in reverse from blood (pCO_2 45) into alveoli (pCO_2 40)