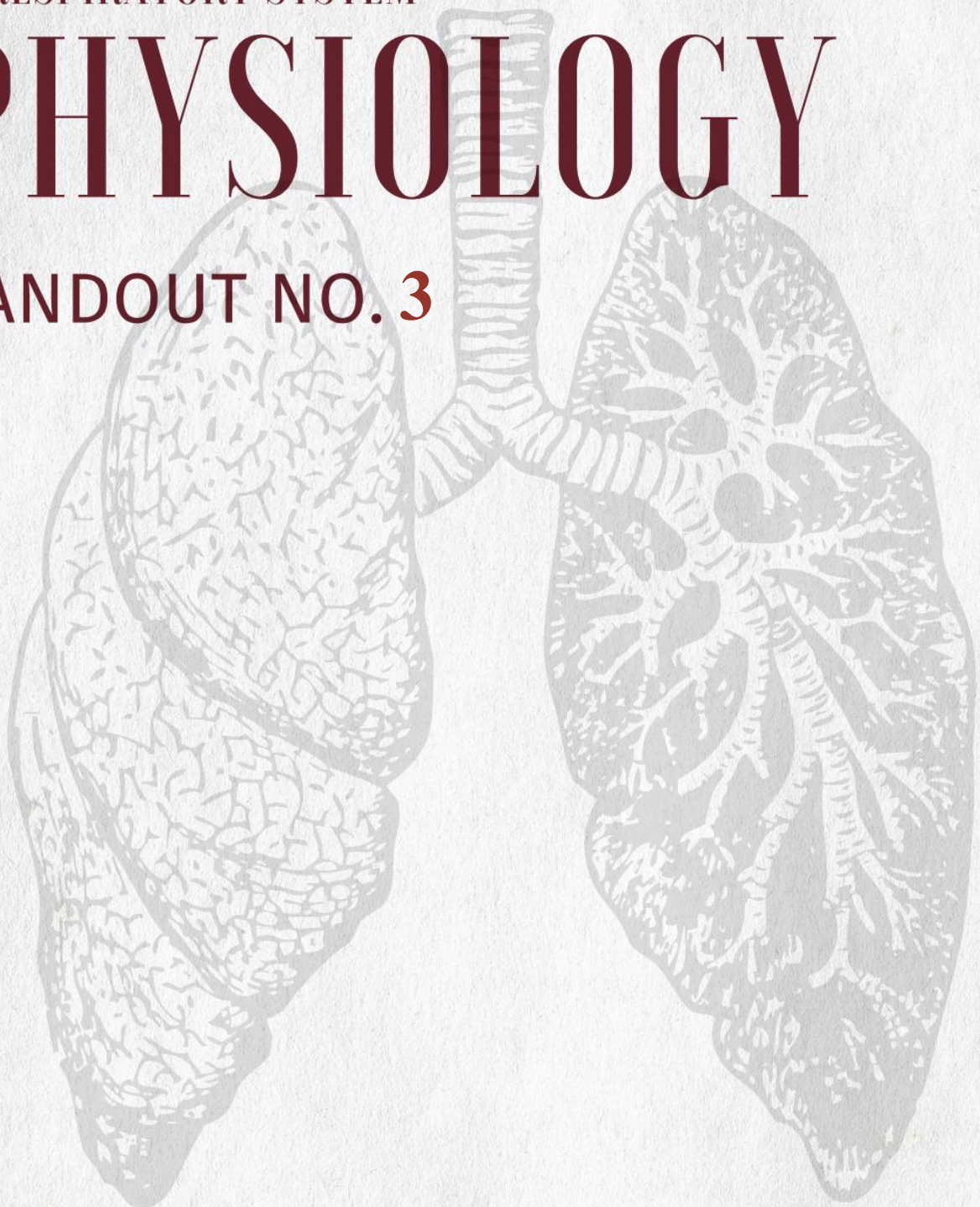
RESPIRATORY SYSTEM

PHYSIOLOGY

HANDOUT NO. 3



Writers : **Zaina AbuDiab , Lama AbuIsmail**

Correctors : **Mais Qashou**

Doctor : **Yanal A. Shafagoj**

Our topic for today is Airway resistance

Color code
slides
doctor
important
Additional

As we mentioned before, lungs diseases are categorised into three groups:

1) obstructive is 70%
2) restrictive is 20-25%
3) vascular is 5-10%

- Obstructive Diseases: Increased resistance to flow, the problem is in the airways
- Restrictive Diseases: Decreased expansion of the lungs, the problem is in the balloon (the lung itself)

Now we will discuss the work of breathing

- Firstly, the **Work** is how much ATP is utilized to support the respiratory system, which equals to => $W = \Delta P \times \Delta V$
- The work of breathing is usually utilized to overcome two types of forces:
  1) **Elastic forces:** represent 70% of total work of breathing. It is **STATIC** force, no flow conditions, which means that it does not involve movement or change over time. For example, when you are lifting weights and stop, that is called static. However, when you are lifting the weights, it is dynamic.
  2) **Non -Elastic forces**: represent 30% of total work of breathing. It is **DYNAMIC** force, which is manifested only when there is air flow (for example during expiration or inspiration, you will face additional force.During inspiration, the airflow encounters resistance from the airways, which requires additional effort to overcome Similarly, during expiration, the airflow faces resistance, contributing to the work of breathing.)
- let's go deeper!

  - **Elastic forces** are subdivided into:

  1) 2/3 is surface tension (A collapsing force, كأنك نافخ أشي وعم يحاول ينفّس ,so we need to overcome this tension by an opposite force, as this is a collapsing force, we need expansion force to overcome it)

  2) 1/3 is elastic fibers (when you stretch them, they have tendency to go back to their resting state, so you have to overcome that and apply force to keep them stretched)

  - Non-Elastic forces are subdivided into:

  1) 80% = **Airways resistance** (our star for today's lecture)

  2) 20% = Tissue viscous resistance 'viscosity', as the play dough, to make it expand you need to put effort, and to return it back you will also need effort! So, it's not elastic.

- **T** Total = **P** Elastic + **P** Nonelastic -> the total pressure is to over the elastic and non elastic
- If there is no air flow = static => Then total pressure will equal **P** Elastic (**P** Nonelastic will be zero)

Let's talk about Ohm's Law

- Remember that the **Flow = ΔP / R.**
- **ΔP** is (Patm -P alveolar) or (P alveolar – Patm), **R** = The resistance
- As we mentioned before, the resistance is small, ΔP of 1 mmHg is enough to overcome it, but if we increase the R, ΔP will increase to keep the flow constant.
- W = ΔP × ΔV, if we want to expand the lung (so the lung can take 500ml, the **tidal volume**). Higher volume, higher pressure and higher work of breathing!
  Which means more ATP utilisation.

Remember the four Take home messages

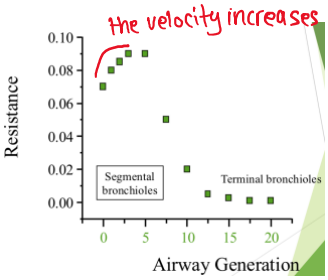
1) Normally: R is small and negligible
2) Normally: R resides in large airways not in the small ones
3) Small airways participate in the increase in R disease/pathological conditions.
4) R, when increased is Manifested mainly during expiration rather than during inspiration.

- We will discuss every point now :)

1. Normally, R is small and negligible: We know that very small forcing pressure is needed to overcome that resistance (1mmHg is enough!). In other words, the statement reflects a situation where the resistance to flow is so small that the driving pressure difference (ΔP) required to sustain flow is minimal.

2. Normally, R resides in large airways not in the small ones: Under normal physiological conditions (in a person without increased airway resistance), the airways resistance resides in the large airways not small airways. We have said that R=1, 40-45% comes from trachea and above (large airways), 40% from 7th or 4th generation (medium sized airways), which means from generation 15 and beyond (small airways), the airway resistance is zero! **How can we know that?**

- From the velocity! When air moves faster (**high velocity**), it creates more **resistance**, remember that Velocity (V) is related to flow (Q) and area (A):
  V=Q/A
  This means that for a constant flow, as the total cross sectional area increases (like in the smaller airways), the velocity decreases, reducing resistance.
- Unlike in the cvs, where the cross-sectional area looks like ( ) and the velocity looks like ( ), here it doesn't look like this, the velocity increases up to 5 generations.



- The **cross-sectional area** plays a key role. In **larger airways**, the total cross-sectional area is smaller, so velocity increases and resistance is higher. However, in **smaller airways** (like the bronchioles), the cross-sectional area is **larger** overall, which reduces the velocity and resistance.

- The **velocity** increases in the first few generations, where the cross-sectional area is smaller (hence, higher resistance).
- In **smaller airways** (like generation 15 and beyond), the total cross-sectional area is much larger, so the velocity decreases and resistance is lower.

- **Large Airways vs Small Airways:**
- **Large Airways (Trachea, Main Bronchi):**
  - **Cartilage present**: Keeps the airways **non-collapsible**.
  - **Large diameter**: Even with mucus, the large diameter prevents blockage.
- **Small Airways (Bronchioles):**
  - **Small diameter**: Makes them more susceptible to obstruction.
  - **No cartilage**: They are more flexible and can collapse.
  - **Smooth muscles**: Can contract when irritated, leading to **bronchoconstriction**.
  - **Mucus secretion**: In conditions like asthma, **leukotrienes** can trigger excessive mucus production from **goblet cells**. This mucus is initially **water and protein**, but the water is reabsorbed, leaving a **protein plug.**
  - **An extra table to compare small and large Airways:**

Feature	**Small Airways**	**Large Airways**
Diameter	Small (e.g., bronchiole)	Large (e.g., trachea)
Cartilage	No cartilage	Have cartilage that prevents collapse
Smooth Muscle	Present, can contract (bronchoconstriction)	Absent or minimal smooth muscle
Cross-Sectional Area	Very large cross-sectional area (beyond generation 15)	Smaller cross-sectional area
Airway Resistance	Minimal under normal conditions, but increases in pathological conditions	Major contributor to resistance under normal conditions (40-45%)
Mucus Secretion	Excessive mucus secretion can occur in conditions like asthma	Mucus presence can occur but doesn't cause significant blockage due to larger diameter

3. Small airways participate in the increase in R disease Conditions (Pathological Conditions):

- In conditions like inhaling irritants or in internal conditions like **asthma**, **Leukotrienes** can be produced which can lead to excessive mucus secretions and

bronchoconstriction, the small airways contribute to **increased resistance in pathological conditions** due to:

- **Small diameter** (more easily obstructed).
- **No cartilage** (lack of structural support).
- **Smooth muscle contraction** (leading to bronchoconstriction).
- **Excessive mucus secretion** from goblet cells, this mucus consists of water and protein, the water will be reabsorbed back to the epithelium and the left solid protein plug

- **Consequences**:
  - **Bronchoconstriction** and **inflammatory changes** (including **swelling/edema**) increase airway resistance.

Treatment for Increased Resistance:

- **Mucolytic drugs**: To break down and lyse the mucus plug.
- **Anti-inflammatory drugs** (e.g., **glucocorticoids/steroids**): To reduce inflammation.
- **Antibiotics**: If mucus becomes a breeding ground for bacterial growth.
- **Bronchodilators**:
  - **Beta-2 agonists** (e.g., **Salbutamol, Albuterol**) to relax smooth muscles in the bronchioles, widening the airways. These drugs have no effect on the heart as B1, they specifically target **Beta-2 receptors** on the bronchioles.

4- R, when increased is Manifested mainly during expiration rather than during inspiration: when R increases, the patient faces difficulty in exhaling (to get the air out) because the airways get narrower, making it difficult for air to leave the lungs.
During **inhalation**, the airways open up, so it's easier to breathe in. But during **exhalation**, the airways can collapse, trapping air inside.

We are done with discussing the 4 important sentences

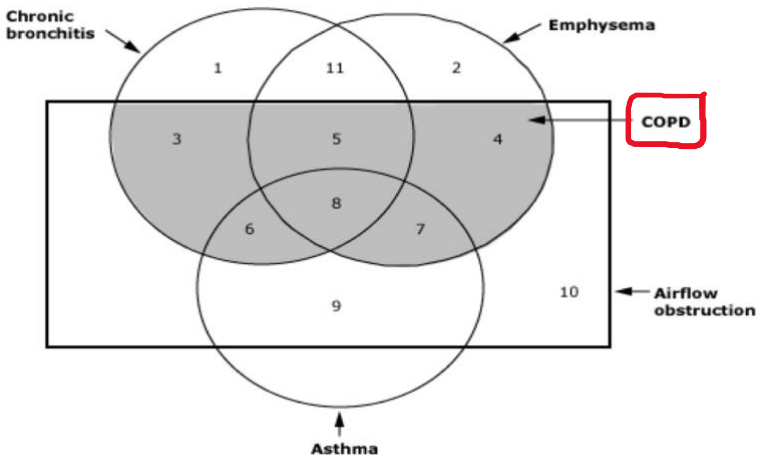
When we talk about Poiseuille's Law which says that: **$R = 8 \cdot \eta \cdot L / \pi \cdot r^4$**, the length and the viscosity are constants, won't change. However, the only thing which can change is the radius (what really matters!)

FACTOR	AFFECTED BY	MEDIATED BY
Length of the system	Constant; not a factor	
Viscosity of air	Usually constant; humidity and altitude may alter slightly	
Diameter of airways		
Upper airways	Physical obstruction	Mucus and other factors
Bronchioles	Bronchoconstriction	Parasympathetic neurons (muscarinic receptors), histamine, leukotrienes
	Bronchodilation	Carbon dioxide, epinephrine (β_2-receptors)

As the drugs we mentioned above

Now we will talk about COPDs

- **COPDs** = chronic obstructive pulmonary diseases, we can categorise it in three groups:
    - Emphysema انتفاخ الرئة (too much air in the lung)
    - Chronic bronchitis التهاب القصبات المزمن
    - Asthma (when it is **chronic**), there is acute asthma mainly in children, 90-95% resolves automatically at puberty, approximately 5% will be chronic.
- **Note**: when someone has emphysema, he could have some sort of chronic bronchitis (mainly emphysema but not pure!) and the chronic bronchitis patient could have some sort of emphysema. Also, Asthma can be overlapped, in number 8 in the diagram for example, the patient may have the three diseases! The grey area represents the COPD, don't worry, you will not be asked to know all the types and what each number represents, but you have to know that an overlap may occur, and we can explain every disease alone.



- Emphysema has three types, and it is diagnosed in a pathological manner (meaning that confirmation typically requires examining lung tissue under a microscope to identify structural changes), while the chronic bronchitis is diagnosed clinically, as when we have a patient who has cough with sputum , for three months in two consecutive years = this patient is having chronic bronchitis for sure ! But if a patient has that cough a year then the next year he hasn't, he doesn't have chronic bronchitis. There is some tests to tell which is which.

Let's dive into emphysema:)

Emphysema

- Is a chronic progressive condition, the alveolar tissue is destroyed leading to decrease surface area available for diffusion

- As we remember, Oxygen diffusion requires adequate surface area.
- In emphysema:
  - **Surface area decreases significantly.**
  - **Infiltration occurs** and **the thickness increases**, further reducing oxygen levels.
  - **Destruction of capillaries** impairs oxygen exchange. Normally, capillaries are connected in a **parallel configuration**, which minimizes total resistance (the total resistance is less than the smallest one), 1/Rt=1/R1+1/R2+… **So Destruction of capillaries** reduces the number of branches, causing: **Increased vascular resistance** which will affect the pulmonary artery pressure, How?

=>The answer is in **Pulmonary Artery Pressure and Right Ventricular Afterload:**

- Initial pulmonary artery pressure: **14 mmHg** (calculated as 2/3 of 8 + 1/3 of 25, the pulmonary arterial pressure is mean pressure of systolic (25mmHg) and diastolic (8mmHg). Since the heart spends more time in diastole, the formula to calculate the mean pressure is 1/3 *systolic pressure + 2/3 * diastolic pressure).
- This pressure was adequate for the normal, low resistance system.
- With increased resistance:
  - **Higher pressures (for example 24, 34, or 40 mmHg)** are required to overcome the resistance.
- The **right ventricle bears the burden** of generating these higher pressures, leading to:
  - **Increased afterload** (load imposed on the right ventricle after-contraction).
  - Right ventricle works harder, potentially resulting in **right ventricular failure**.
  - All that will lead to: **Cor pulmonale**, which is Right ventricular failure caused by increased pulmonary resistance due to chronic lung disease like emphysema.

-Any lung disease (obstructive or restrictive) leads to **decreased PO_2** (partial pressure of oxygen) will have different effects on systemic circulation and pulmonary circulation.

- ***Systemic Effects:*** In skeletal muscles, low O_2 acts as a **strong vasodilator** (the strongest among the 10 local vasodilators).
- ***Pulmonary Circulation Response:*** In the lungs, the logic is different:
  - **Hypoxia/hypoxemia** (low oxygen levels) **causes vasoconstriction** instead of vasodilation.
  - The reason: If an area of the lung lacks oxygen, it does not make sense to supply it with blood!
  - **Result:** Vasoconstriction in hypoxic regions of the lung.
  - **Impact on Pulmonary Arterial Pressure:**
  - Vasoconstriction increases **pulmonary arterial pressure**:
    - Normal pulmonary pressure: <20 mmHg.

        - Pulmonary hypertension: >20 mmHg.
            - **Consequences for the Heart:**
    - Increased pulmonary arterial pressure leads to:
        - **Increased right ventricular afterload** (load the ventricle must overcome after contraction).
        - **Then Right ventricular dilatation** and, potentially, **right ventricular failure**.
- Again, that's what is called **Cor Pulmonale:** Right heart failure caused by lung disease and pulmonary hypertension.
    - Common causes:
        - Chronic obstructive pulmonary diseases (e.g., emphysema, chronic bronchitis).
        - Pulmonary fibrosis or other restrictive lung diseases.
    - Typical patient profile: A smoker with chronic hypoxia caused by conditions like emphysema or chronic bronchitis.

- Alveolar tissue is destroyed leading to decrease surface area available for diffusion

- Cigarette smoking stimulates macrophages and leukocytes to secrete protein digesting enzymes that destroy tissue.

- Decreases ability of bronchioles to remain open during expiration...bez of destruction of elastic fibers which keep small airways open, therefore, obstruction comes from outside. Unlike in chronic bronchitis, obstruction comes from inside.

=> Normally, bronchioles are **surrounded by elastic fibers** to keep the bronchioles open. In smoking, "Nicotine" will destroy the anti-proteases, such as anti-trypsin.
=>This will lead to make the proteases free and able to digest the proteins like elastin.
=>This will lead to shrinkage of bronchioles.

- In **emphysema**, the obstruction is coming from outside, which is smoking. Destruction of elastic fibers means no resistance. While in **Chronic bronchitis**, mucous starts to build up among the years Increasing the thickness. So, this is an insidious cause of obstruction.

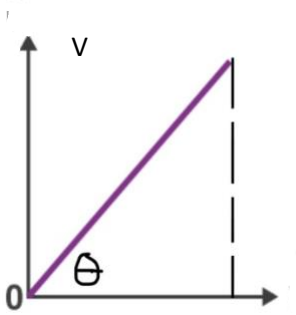
Elastic fibers absence impact:

- Compliance is How easy we can distend the structure, how much volume we can change per pressure unit Δv/Δp

  - Recall from previous lectures, we can inflate the lung by making the surrounding pressure more negative, this will lead to expansion of the lung

  Also, we talked about **Boyle's law** "P x V = C in closed chamber" and the story of tube with a balloon at its end in a box where we change the volume. So, if we increase the volume, pressure will decrease (becomes more negative). The more pressure decreases mean more filling of the balloon.

Just a note before discussing the curve, always the independent variable will be on X-axis, while the dependent variable will be on Y-axis



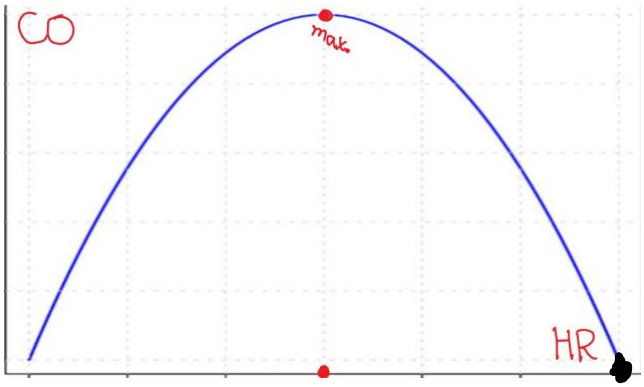
Tan θ= opposite/adjacent
= Δy/Δx
= Δv/Δp

= compliance

Notice that the increase in the slope means more compliance.

- in emphysema, compliance of the lung increases but since there is no elastic fibers, no return of the bronchioles to normal.

Let's see these curves (هنا نقول الفضيلة تقع بين رذيلتين):

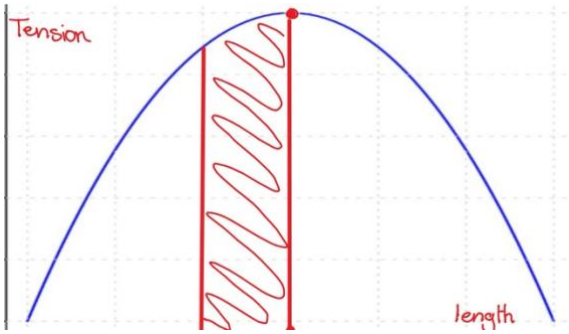


At the red point, the HR value that gives us the best CO value

As CO= HR x SV, so once HR increases, SV will decrease. At the black point where the curve interacts with the X-axis for example if HR value was 400 and the SV is 0 --> CO=0

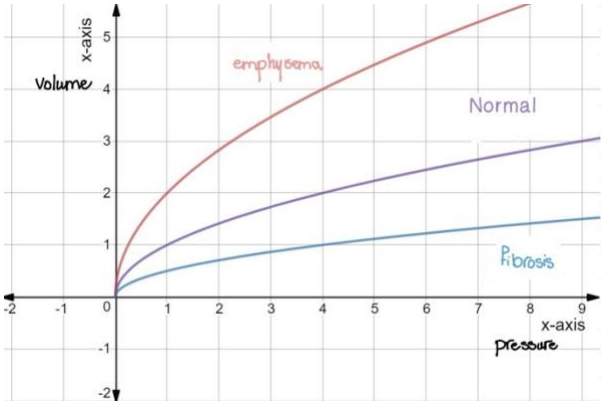
Another example, Frank – starling. The red area represents the normal range in human

Length here is the length of sarcomere. As in plants, it is good to irrigate them but to an extent where after it it's as bad as not irrigating them .



So, what you need to understand from all mentioned earlier is that if compliance increases more than normal is bad, we have expiration, and we need to empty the bronchiole which will not happen if there are no elastic fibers.

In contrast to emphysema, pulmonary fibrosis decreases compliance due to inability to expand the bronchioles which is also bad.



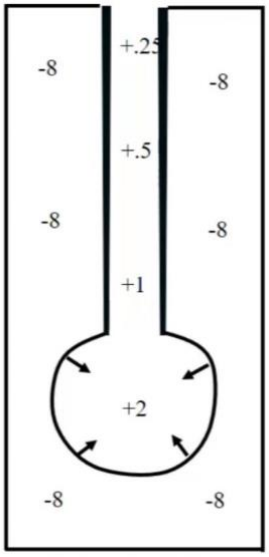
Now let’s dive into the common pathology in obstructive diseases

Notice that alveolar pressure= 2, then it starts to decrease from the beginnig of the airways until the mouth.

Air always move from high to low pressure. as you can see pressure difference between alveoli and surrounding is 10 .

Why 8 ? to overcome the elastic forces we've mentioned earlier.

keep in mind during, where air flow exist, means there is another force we should include it in the calculations, the Non-elastic forces (30%), this make things a little harder.



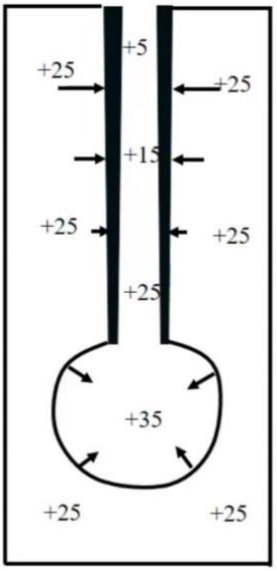
Passive Expiration

Notice here where there's obstruction. here +2 is no more useful, we need +35 which is a huge number.

In surrounding, pressure is 25 to keep expantion so bronchioles stay opened. Also it is important to act on alveoli increaseing ΔP, But the problem is that this intrapleural pressure also acts on airways closing them (remember that pleural cavity forms the vicinity of the small airways)

so these patients may face problem during expiration due to complete obstruction.

they may overcome this problem by closing their lips (purse lips gently), so backward pressure increases, this is only when they're awake.



Forced Expiration

Extra notes about the image above: The muscles raise intrapleural pressure to +25, which will act on alveoli. This increases alveolar pressure to +35 and creates a strong ΔP (pressure gradient) to push air out of the lungs. But this same high intrapleural pressure (+25) can push inward on the airways (since intrapleural pressure surrounds the airways externally). In smaller airways, this inward pressure can narrow or collapse the airway, especially at points where airway pressure falls below intrapleural pressure (e.g., at +15 in the image above).

Control of Bronchiolar Diameter

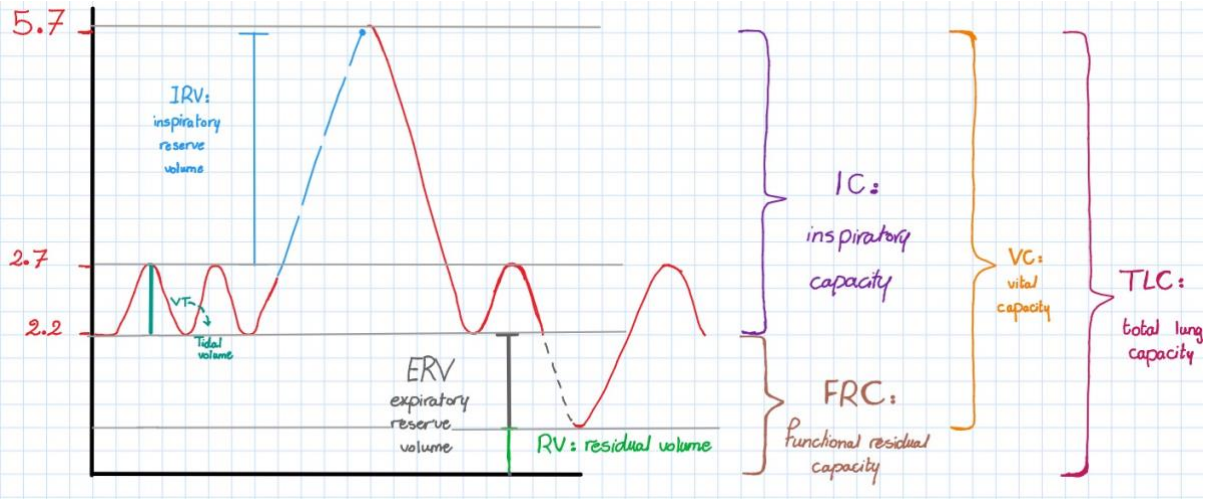
- Nervous
  - Sympathetic
    - B, receptors dilate (salbutamol, dobutamine, albuterol, fenoterol, terbutaline).
  - Parasympathetic
    - Acetylcholine constricts bronchioles
  - Humoral
    - Histamine, acetylcholine >> Constrict
    - Adrenergic (ß2 agonists) > Relax

COPD

1. Emphysema 2. Chronic bronchitis +3. Bronchial asthma...only when asthma becomes chronic.

Now let’s discuss some important concepts,

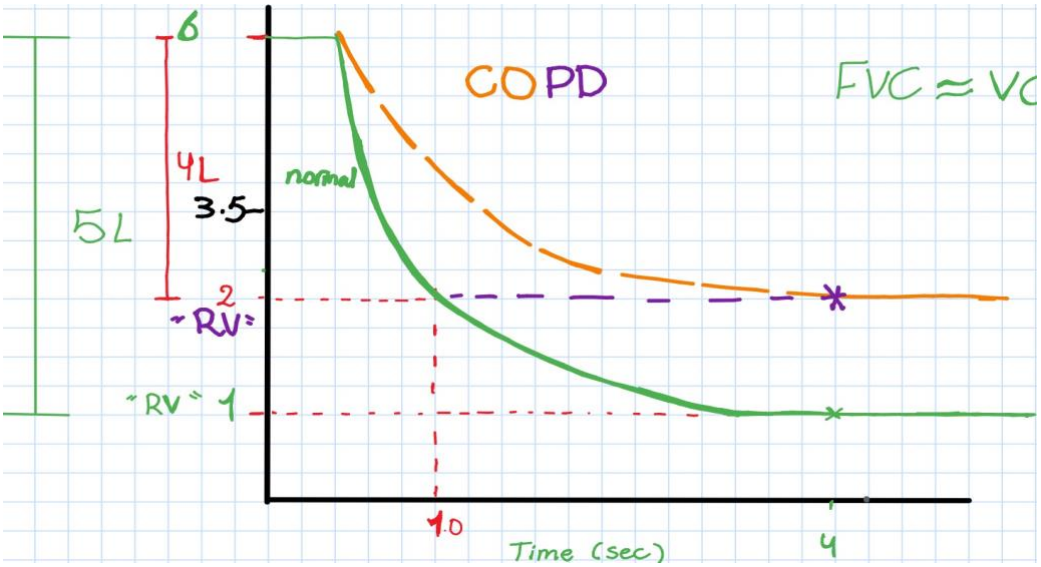
!! we don’t inhale into a totally collapsed lung, it is like ESV in CVS, there is remnant, so lung content is not 0 at any point in normal situations.



- During inspiration, the volume will increase from 2.2 to 2.7 --> this is tidal volume (VT).
- We can use all our inspiratory muscles (diaphragm, external intercostal, accessory. and neck muscles) to reach 5.7 (3L increase) --> this is inspiratory reserve volume (IRV) احتياطي ما بنستخدمه
- Before inhaling again (at 2.2L), we can exhale like half (1.1L) --> this is Expiratory reserve volume (ERV).
- Even if you tried your best to empty your lung, there will be a remnant air inside it --> this is residual volume (RV) , it is the volume that stays in the lung following forced expiration (using all muscles).
- If you added 2 volumes together you get capacity.
- IRV + VT = IC (inspiratory capacity).
- ERV + RV = FRC (functional residual capacity) --> volume of air present in the lungs before taking VT.
- IRV + VT + ERV = VC (vital capacity) --> if you filled your lungs to the maximum. then completely empty them --> volume of air which can be exhaled forcefully.
- IRV + VT + ERV + RV =TLC (total lung capacity) --> the maximum volume of air both lungs can take.

Pulmonary function tests

- COPD patients have problems with exhalation.
- Look here in the following curve:



- We ask a healthy man to inhale to maximum e.g. 6L
- Then we ask him to empty his lungs as fast as possible and we check the needed time e.g. 4 sec to empty the lung reaching RV eg.1L
- The 5L represents VC, but we will call it FVC (forced vital capacity) why? Because all forces were used
- So, we assume that FVC ≈ VC But they are not equal, VC is greater than FVC
- At 1st second, 4L were emptied from the healthy lung we call it FEV_1 (forced expiratory volume)
- While in COPD patient, RV is higher=2L so he emptied 4 instead of 5L & FEV_1 =2.5L

Let's give an example:

We have a Man who is 20 yrs old, his weight is 70kg and his height is 170cm

		Predicted	Observed	Observed / predicted
	FEV_1	4 L	4L	100%
	FEV_1	4L	3L	75%
	FEV_1	4L	4.5L	110%

- We use FEV_1 to diagnose obstruction and for staging.
- You must know that FEV_1 value decrease with COPD & it indicate the severity of it.

Version 2:
- Adding a picture on page3
- Removing R units (was mmHg) and adding (delta p of 1mmHg is enough to overcome it) on p3
- Adding: (too much air in the lung) on p6
- RV instead of VT on page13
- Intrapleural and pleural instead of perituniem p 12