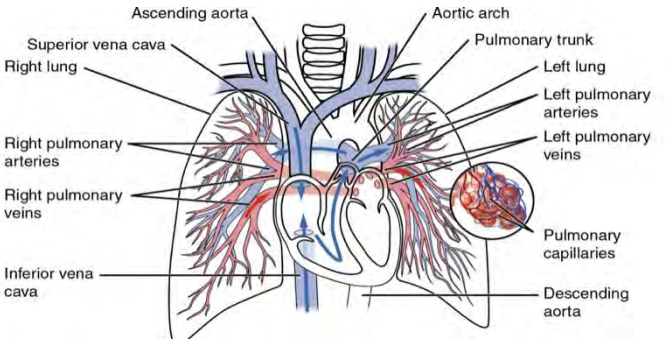
1. Introduction to the Module

Lecture Content:
Functions of the Respiratory System
Anatomy - structure and function relationships
Gas Movement in the cardiorespiratory system
Tidal breathing relationship to gas exchange.

Functions of the Respiratory System all relates to it's anatomy. All cardiac output flows through the pulmonary circulation. There is a large surface area for diffusion. All the CO is going through the blood vessels towards the lungs, this makes the lungs it a useful site.



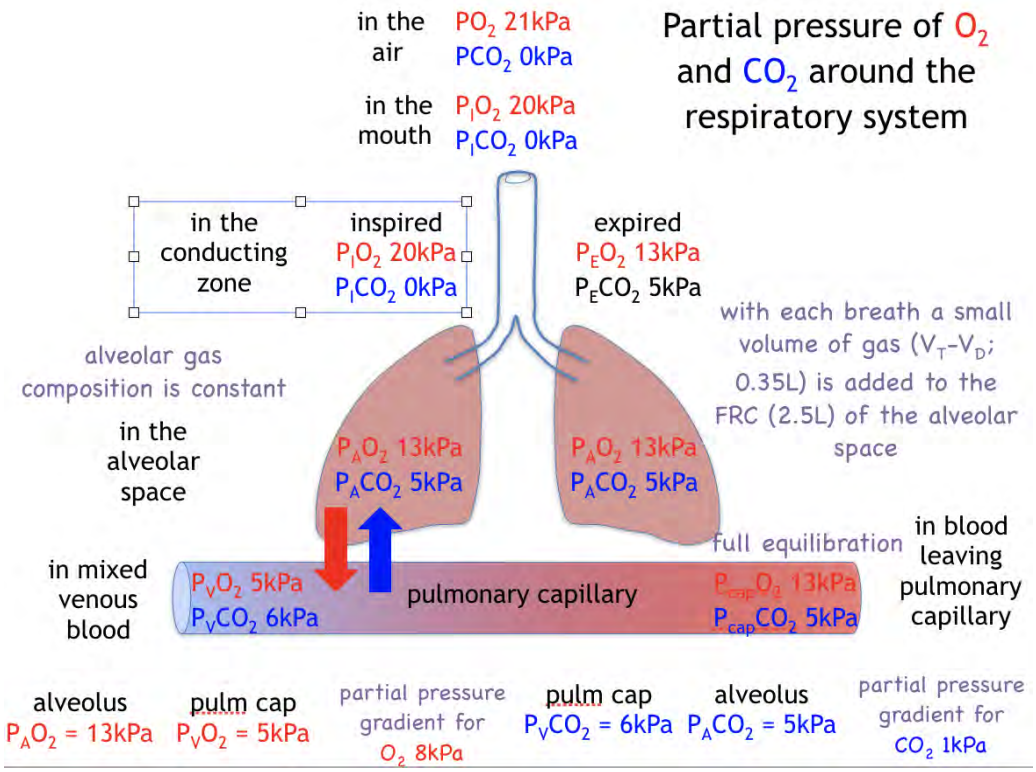
Functions:

- Gas Exchange - Large SA and close proximity. This is very efficient.
- Blood pH control - Henderson Hassel-Bach equations.
- Remove blood clots from the circulation
- Defence against microbes - it is good for immune function. There will a lot of WBC that live in the lungs.
- Heat and Water loss through ventilation - there is heat exchange with the air but this is controlled. We do not want to lose much water through this.
- Blood reservoir (Pulmonary vessels)
- Metabolic functions - active and inactive stuff e.g Ang II, BL, PGs, 5HT, Hist, Adr/Nadr, Sub P.

Functions of the upper airways:
Filtering - articulate matter gets stick on the lining of the mucus.
Warming - There is a good blood supply to the nose, this acts as a heat exchanger
Humidifying - we also add eater water to the heat air. There is fluid lining the membrane to the alveoli to stop them form drying out.
Distribution.
Trachea has a C-shaped hyaline cartilage ring. This gives structure. As we move down into the bronchus and bronchiole, we have more smooth muscle.

We have nerves, sensory and motor nerves. They give use control of the smooth muscle.

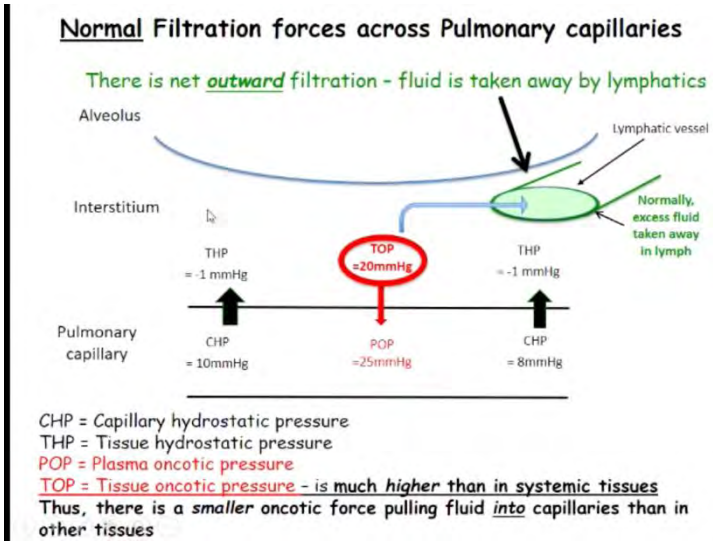
Capillaries are embedded in the wall, and so there is a short diffusion distance.
Clara cells produce mucus and the cilia cells push the mucus out.
Type 2 cell, they are missing in babies. This produces respiratory stress making it hard from them to breath.



In the atmosphere - 21kPa of oxygen. CO2 is 0kPa. As soon as we breath in, we humidify the air, adding H20 vapour, which is another gas, so there is less room for oxygen and so the partial pressure of inspired oxygen goes down to 20kPa. At sea level, there is not much impact but the amount of water vapour we use to humidify it is constant, so up a mountain we would push less oxygen into the lungs because the partial pressure of atmospheric oxygen is lower.
Tidal breath in is about 500 ml, about 150 ml stays in the respiratory, it doesn't reach the alveoli where gas exchange occurs exchange (They stay in the dead space). Their partial pressure stays the same as inspired partial pressure. The 350 ml that goes into the alveolar space, the oxygen falls to 13 kPa to oxygen. We can see a massive impact on CO2 (there is 5kPa increase).

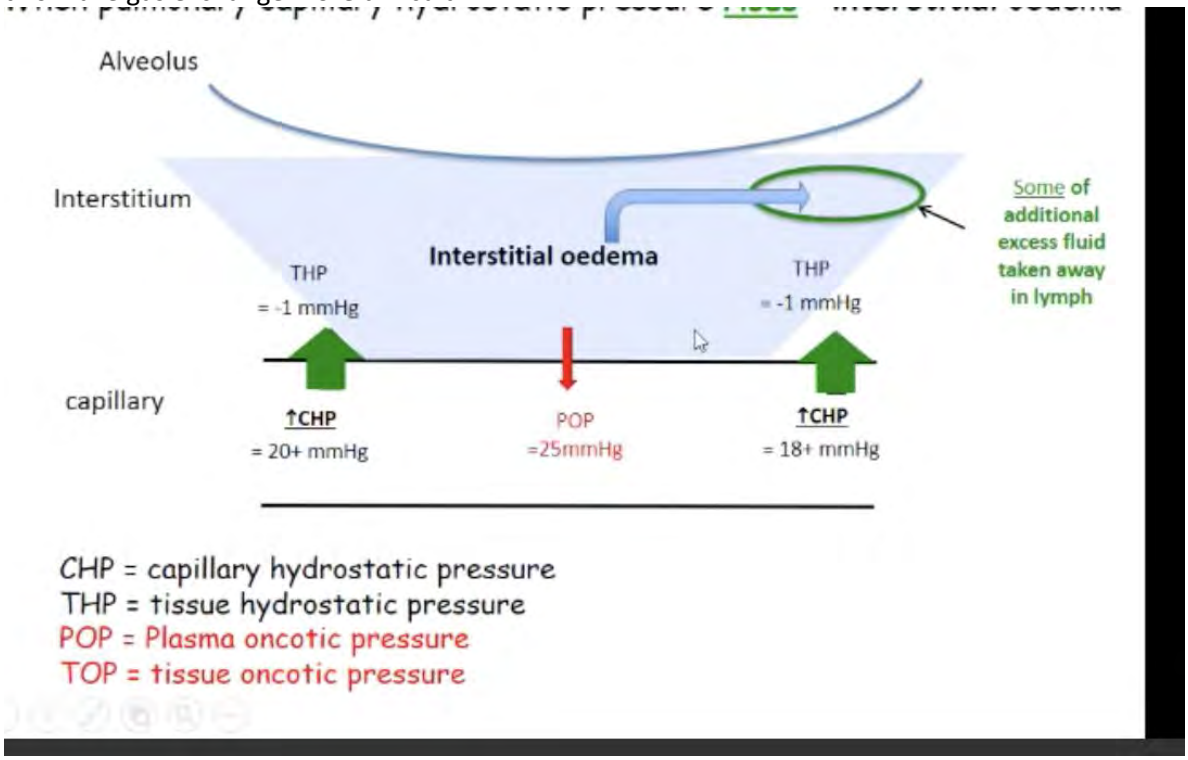
Exchange surface:
We want to maintain the alveolar composition is constant. If this changes every time we breath in and out, every time we breath, then every time that we breath out, the blood in the capillaries would not be getting oxygenated well and we would have an hypoxic and hypercapnic gas mixture around the body. If there is high levels of CO2, the blood would have a lower pH. High pH if there is high levels O2.
We each breath, we add a small volume (~.35L) to the alveolar space which already has the FRC. We are adding 350 mL to the 2.5 L of FRC. As we do this, we take some of the gas away in the blood.

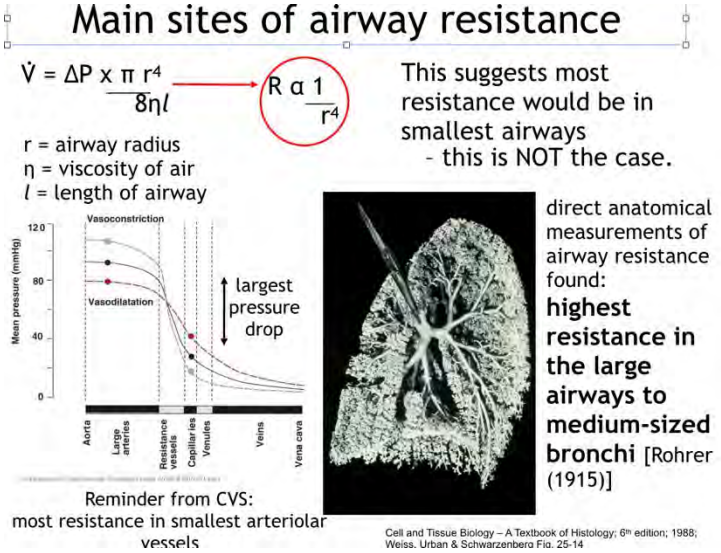
The mixed venous blood in the pulmonary capillary, has 5 kPa of oxygen and 6kPa (increased) CO2. We have a partial pressure gradient between the lungs and the venous end capillary. There is a 8 kPa gradient for the partial pressure of the oxygen. This is to drive the diffusion of oxygen into the de-oxygenated blood. This happens between 0.35 seconds, there is full equilibration. For CO2, we have a 1 kPa difference but because it is very diffusible, this is sufficient so this can occur and this gives full equilibration of the blood. The capillary will have the same composition (partial pressure) that iis the alveolar space.
Left side of the heart - CO2 stays the same but some deoxygenated O2 enters (without taking part in gas exchange). this is from some of the coronary vessels and bronchiole circulation, which



This shows normal pressures
CHP is 10mmHg in the PC and drops to 8mmHg in the venous end.
POP is about 25mmHg
THP is 1 mmHg (it is always)
TOP in the PC is 20mmHg compared to the negligible amount in the PC. This is because there are proteins in the interstitium. This reduces the gradient to pull water in through osmosis. Thus, there is a smaller oncotic force pulling fluid into capillaries than in other tissues.
This doesn't really matter since the interstitium has a dense lymphatics system and normally excess fluid is taken away in the lymph so this is the net outward filtration. The alveolar are kept dry.

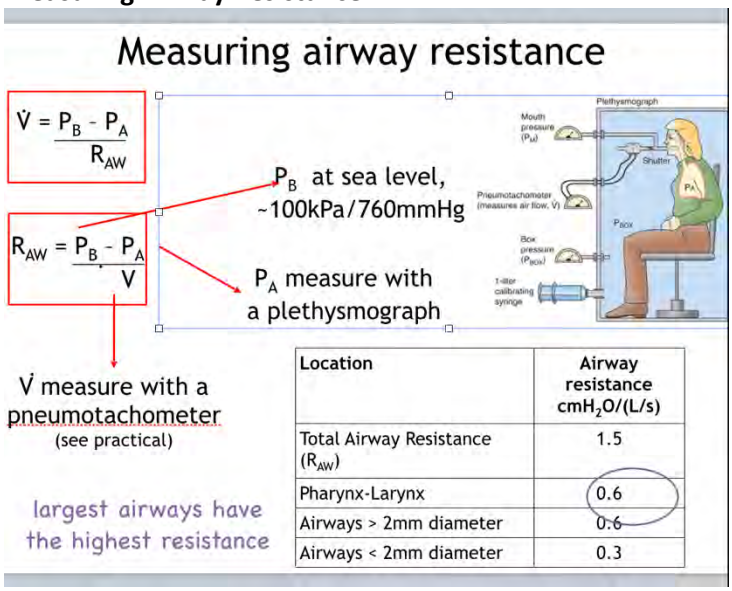
Increased Filtration out of Pulmonary Capillaries - Interstitial Oedema
When pulmonary capillaries hydrostatic pressure rises- this results in interstitial oedema. Some of the additional excess fluid is taken away by the lymphatics but this is not sufficient enough. This tends to widen the gap between the capillary and the alveoli. Diffusion pathway has increased and this make gas exchange more difficult.





The main determinant of airway resistance is the radius. The smaller the smaller the airway the greater the resistance - this is the case in the CVS, but not in the RS.
In the RS - the highest resistance (largest pressure drop) is in the large airways to medium-sized bronchi (within the first 10 generations - the trachea, bronchi etc.)

Measuring Airway Resistance



Location	Airway resistance $cmH_2O/(L/s)$
Total Airway Resistance (R_{AW})	1.5
Pharynx-Larynx	0.6
Airways > 2mm diameter	0.6
Airways < 2mm diameter	0.3

We can measure airflow very easily.
We know what the barometric pressure is, at sea level it is ~100 kPa/760 mmHg. We can measure the ventilation with a pneumotachometer and we can also alveolar pressure using a whole body plethymospgraph.
Put someone in a sealed box, and when they breathe, the pressure changes that occurs in their respiratory system causes pressure changes in the box. We can use a pressure transducers to measure the changes and that gives us a measure of alveolar pressure. We can see if airway flow changes with disease.
We can see in a healthy person, total airway resistance is very low ~1.5 cmH20/L/second
Most of the airway resistance, 1.2cmH20/L/s is in the airways that are greater than 2mm in diameter. Half of that is in the pharynx-larynx itself. There is little airways resistance in the smaller airways.
So airways resistance is greater in the largest airways.

Dorsal Respiratory Group - Dorsal side of the medulla

It is where respiratory rhythm is generated. There are chemical receptors in those vicinities. There is an overlap/ close proximities between the neurons that cause you to breath and the neurons that sense the chemical conditions in the brains.

There are rostral, intermediate and caudal chemoreceptors.

The brain is protected by the blood-brain barrier. It prevents certain substances form crossing into the CNS. The BBB is a capillary network that feed blood into the brain. It has a capillary like structure where filtration/reabsorption can occur.
In a normal capillary there are fenestrations that enable the filtration and reabsorption. In the BBB there are astrocytes and pericytes and no fenestrations but instead tight junctions. So substances do not cross the BB easily. One of the substances that do not cross are charged molecules.

The central chemoreceptors gen qerate 80% of total ventilatory response to CO2.
They are inhibited by hypoxia.
The ISF - can sense CO2 and the CO2 can react with H20 to give HCO3- and H+. The H+ are formed in the brain because they cannot cross the BBB. H+ increase is detected by the central chemoreceptors, this stimulates the medullary respiratory neurones and adjustment of ventilation.

Slow Response:

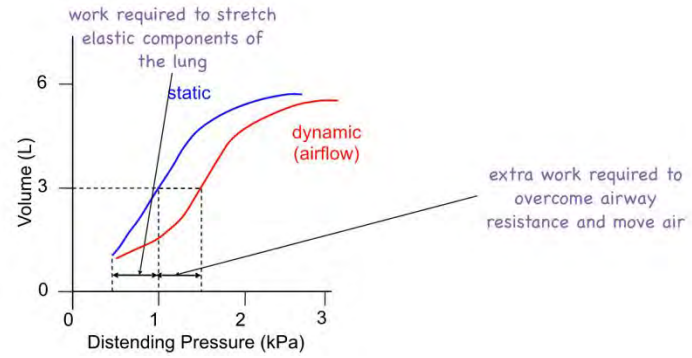
- 10-30s onset
- Minutes of equilibrium
- Little or no protein buffering
- Not responsive to metabolic acidosis/alkalosis.

There have been numerous sites identified of chemosensitive cells within the brain stem.

1. Ventral Chemoreceptor Sites
- Retrotrapezoid nucleus (RTN)
- Nucleus paragigantocellularis
- Parapyramidal region of raphe nuclei
- Ventral respiratory column.
2. Dorsal Chemoreceptor Sites
- Solitary Tract nucleus (NTS)
- Area postrema
- Locus coeruleus.
3. Midline Sites
- Midline raphe nuclei
4. Glial Cells?

RTN is in the ventral medulla. The NTS links to it, so does the KF (site of respiratory rhythm).
If you make RTN acid by putting acid on it, you will see an animal will breathe harder. There is an increase in ventilation and tidal volume. The phrenic nerve fires harder in this condition.

RTN in the CNS are not recording hypoxia but are recoding H+ so the hypothesis is that there is a pH sensitive ion channels, TASK channels/GPR4, Ca2+ channels and ATP channels
TASK (type of K+ leak channel)- if they are inhibited then this causes depolarisation and neurotransmission.
It is due to the H+



Static - no air flowing into the lung
If we see what distending pressure we need to get a certain volume of a lung, that is the energy we need to stretch the elastic components of the lung.
Dynamic - air movement
To get to the same volume, we require a greater distending pressure. This is the extra work we require to overcome airway resistance and move air
Both require us to use energy.
Any of the elastic components of the airway resistance changes, that changes the amount of energy we need.
We get changes in the elastic recoil of the lung and chest wall or changes in how the airways changes normally - we require more energy to breathe, eventually we will not have enough energy to breath and we get changes in alveolar gases

Diseases of the respiratory system increase the work of breathing by changing:

1. Compliance of the lungs, chest wall or total respiratory system, and/or
2. Airway resistance.

Overview:

- Asthma: increased airway resistance, obstructive disease.
- Chronic obstructive pulmonary disease (COPD): emphysema (breakdown of the structure of the alveoli) changes lung compliance (increase) and also affects airway resistance, obstructive disease - loose the integrity of the parenchyma. Elastic structure of the lung is essential to help keep the airways open.
- Fibrosis: decreased lung compliance, restrictive disease.

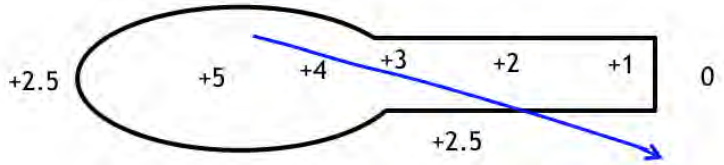
How do these diseases affect the normal functioning of the respiratory system?

Airway Resistance:
Prevalence:

- 300 million sufferers worldwide
- 7% UK adult population
- Prevalence increasing - due to increased population
- Complex aetiology - genetic and environmental factors.

Pathology and symptoms:

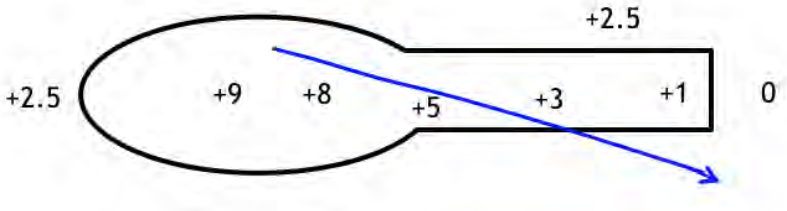
- Chronic airway inflammation - infiltration of immune cells into the airways that release inflammatory mediators causing swelling of the airways and that inflammation reduces the effective diameter of the airways and leads to:
- Increased airway responsiveness - more sensitive to allergens
- Bronchoconstriction during asthma attack
- Airway obstruction
- Wheeze, cough and dyspnoea symptoms



If you generate a positive interpleural pressure, then all the pressures will change. The pressure in the alveoli space is the pleural pressure and the elastic recoil. The 2.5 from the pleural pressure and the 2.5 from the elastic recoil will give 5 in the alveolar space.
Even though the pressure is greater, there still needs to be a gradient that goes down to allow air movement.
The alveolar pressure is greater than the interpleural space and then decreases until it is equal with the interpleural space - equal pressure point this is called a choke point, because after that the pressure outside is greater than inside forcing those airways to close - giving a flow limitation.

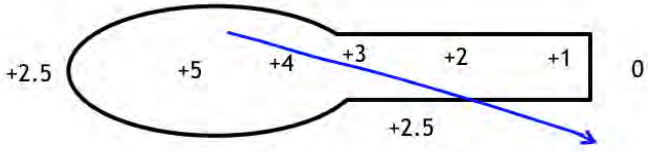
Location of the EPP will be determined by:
Generation of driving pressure – determined by P_{el}
Fall in pressure along the airway – determined by Reynolds & Bernoulli
If the equal pressure point occurs lower down or higher up that will tell us where we have the tendency for our airways to collapse. If it occurs higher up, we have cartilage in our airways and they are structures that help prevent collapsing of the airways, but we start to lose cartilage around generation 10-11. If the equal pressure point is down in the smaller airways, below generation 10-11, then there will be collapse.
When there is airway collapse, there is no airflow. Then when you try to blow out but there is no airflow, the pressure inside will start to rise until the pressure is enough to open the airways. There is then loss of pressure and airway collapse. This is a dynamic situation.

Forced Expiration from TLC



At TLC, there is the highest alveolar pressure from the high pleural pressure and maximized total lung recoil. If the alveolar pressure is 9, then we can see the equal pressure point is quite high in the airways.

Forced Expiration from below TLC



If there is a forced expiration and a lower lung volume, there cannot be generation of a greater alveolar pressure because there is no maximization of the elastic recoil, then the gradient starts from a lower number which means the equal pressure point has moved further down the airways and so there is a limitation on how fast there can be an exhale.

Intrapleural space- pressure inside is sub-atmospheric (99.5 kPa) - (it is not negative!, it is negative compared to the barometric pressure).
In the ICA - there is intrapleural fluids - so there are the two surfaces that are close together. There is a small lining of fluid. The fluid is going to be circulating. The movement so the fluid and the drainage. What factors affect it's movement. For anything to flow there needs to be a pressure gradient. Does supine and prone affect the movement of fluid.

Introduce a pneumothroax to avoid puncturing the lungs, and the distance between the parietal and visceral pleura will increase.

If we just look at the lung. Alveolar and plureal pressure is acting on the kung. The alveolar pressure is acting to hold the lungs. The intrapleural pressure - is making the air flow inside

Lung distending pressure = P(in) - P(out).
=. Alveolar pressure - pleural pressure
= 100 -99.5 = 0.5 0.5
This means that it is slightly distending because there is a positive distending pressure

If we just look at the chest wall. Internal pressure here is the intapleural pressure and the external pressure it is the barometric pressure. 99.5-100 kPa. So at FRC, the chest wall is less distended than it would like to be.

Hole in the chest wall. Air will go in and the intrapleural pressure and the atmospheric pressure will equilibrate. Lung distending pressure is 0 kPa, it will recoil on itself (call an pneumothorax).
The chest wall distending pressure would also be 0 kPa so the chest wall would expand.
Air can go into the intrapleural space.

Inspiration:
Phrenic nerve goes to the diaphragm, causes contraction. This is an ATP dependent process. It lowers the intrapleural pressure (to 99 kPa), lung distending pressure increases (100-99 = 1 1 kPa). We have increased it by reducing the internal pressure. This results in the increase of the lung volume so the alveolar pressure decreases. This creates a pressure gradient so the barometric pressure is now greater than the alveolar pressure so we can get airflow into the lungs.
What controls the change in the lung volume. Lung compliance controls this.

Change in volume is the given change in pressure.
X -axis is distending pressure. At FRC = 0.5 kPa.
Y-axis is lung volume. At FRC= 2.5 Litres.

During Quiet Inspiration - lung distending pressure increases to 1 kPa. Lung volume Is going to increase to 3L.

The more you distend the lung, it becomes less compliant.

Gradient of the line to calculate the compliance.

If you got 2 and 3 kPa, so it is the change in volume between the two.
N - 7.5
E - 2.5
F - 20
Fibrosis - the l