Lung Function Fundamentals

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Introduction

Understanding lung function is vital for both intensivists and anaesthetists. Normal lung physiology is unfortunately extremely complex, and this complexity is further enhanced in sick lungs! Lacking smart and well-programmed supercomputers to simulate normal lung physiology, we tend to rely on gross over-simplification. The relationship between our current understanding of how lungs function, and what *actually happens* is perhaps similar to the relationship between counting on one's fingers and advanced matrix algebra! Unfortunately, many of the fruitful *analogies* that we use have been turned into dogma!

In most textbooks, you will encounter a vast array of "laws", which examination candidates in particular are encouraged to regurgitate, often with minimal understanding. For the record, here are some of them:-

A List of Laws

Note that this mildly formidable table is mainly for reference purposes.
The wise reader will skip over it, and come back from time to time.
All equations are discussed in a friendly fashion in the body of the text!
Those we are on "first name" terms with (Henry, Charles & Graham) will be used less extensively!

Name	Equation	Meaning
Boyle's Law	P.V = K	In a container filled with gas, if you decrease the volume, the pressure will correspondingly increase, and vice versa.
Dalton's Law		In a mixture of gases, each gas behaves as if it were on its own: it exerts a *partial pressure* that is independent of that exerted by other gases in the mixture.
Hooke's Law	$\Delta L \propto \Delta T$	The change in length of a spring is proportional to the tension exerted on the spring.
Laplace's Law	$\Delta P = 2.T/r$	The pressure inside a bubble exceeds the pressure outside the bubble by twice the surface tension, divided by the radius. In other words, the smaller a bubble, the more the pressure

		inside it exceeds the pressure on the outside.
Poiseuille's Law	$R = 8.L.eta/(pi.r^4)$	Where laminar flow occurs, the resistance to flow decreases with the *fourth power* of the radius - if you double the radius, the resistance decreases sixteen times! Resistance also depends on the eta, (the viscosity of the gas or fluid), as well as the length of the tube being assessed (L). Note that with turbulent flow, things are completely different - we can't even talk about "resistance" as the drop in pressure is not directly related to flow, but to flow squared!
The Fanning Equation	$\Delta P \propto 1 / r^5$	With turbulent flow, for any particular flow rate, pressure drop depends on the fifth power of the radius of the tube.
Fick's Law	$Vgas \propto A * \Delta P / L$	Gas transfer through a membrane is proportional to membrane surface area (A) and partial pressure gradient across the membrane(ΔP), and inversely proportional to thickness (L).
Graham's Law	$D \propto sol / MW^{0.5}$	Diffusion of molecules is inversely proportional to the square root of their molecular weight, and directly proportional to their solubility.
Henry's Law		The number of molecules of gas dissolved in solution is proportional to the partial pressure of the gas.
Charles' Law	V = K'. T	As the temperature of an amount of gas increases, so does its volume (maintaining a constant pressure). We can combine this with Boyle's law to get: PV = nRT Where n is the number of moles of gas, and R is a constant, the **universal gas constant**. At standard temperature and pressure, a mole of gas occupies 22.4 litres. The actual value for CO_2 and N_2O is about 22.2 litres.
Reynold's number	linear gas velocity * diameter * density / viscosity	Reynold's number is dimensionless. Turbulence occurs if Reynold's number is over 1000, and flow is entirely turbulent if it exceeds 1500.

Basic Ideas

Atmospheric oxygen arose as a toxic by-product of the very first photosynthetic organisms, which were possibly quite similar to today's blue-green algae. Smarter organisms rapidly learned to use this oxygen, and minimise its toxic effects. When they possibly unwisely decided to abandon their individual identities and co-operate to form multicellular organisms, and moved onto land, then their problems really began! They needed:

1. Ways of acquiring atmospheric oxygen in large quantities;
2. A method to transport this O_2 to distant, oxygen- starved cells;
3. Processes for removal of carbon dioxide, the principal metabolic waste product.

All of these are more-or-less adequately fulfilled by the tightly entwined cardiovascular and respiratory systems. The respiratory system is a marvellous, efficient pump for passing air over the capillary bed of the lung, where oxygen moves into the blood and CO_2 is removed from the blood. The inefficient and failure-prone cardiovascular system then takes over, finally distributing oxygen to oxygen-hungry cells throughout the body. The inefficiency with which this occurs can be seen if we look at the **oxygen cascade**, which documents the changes in partial pressure of oxygen from inspired air down to the mitochondrion where the oxygen is actually used. Oxygen moves down a gradient, from a partial pressure of about 160mmHg in the atmosphere, down to about 4-20mmHg in the mitochondrion! The steps are:

Inspired oxygen	160 mmHg
Alveolar oxygen	~ 120 mmHg
Oxygen in the blood	~ 100 mmHg
Oxygen at tissue level	~ 4-20 mmHg

Considering these in more detail we find:

1. Atmospheric pressure at sea level is about 760mmHg, and the concentration of oxygen is 20.95%. Using Dalton's Law we calculate that in dry, inspired air, the partial pressure of oxygen is 159mmHg. Unfortunately, air within the lungs is 100% saturated with water. We need to re-think! If we know that the partial pressure of water vapour at 37 degrees Celsius is 47mmHg, we can work out that the partial pressure of the remaining gases is (760 - 47)mmHg. We'll call this barometric pressure that excludes water vapour pressure the 'dry barometric pressure', or P_{Bdry}. Applying Dalton's law yet again, we determine that the inspired PO_2 is therefore actually 149mmHg, once the air has become fully hydrated in the nose. Let's abbreviate the inspired PO_2 to **PiO_2**. But wait a bit..

2. Oxygen is taken up in the lung! This will decrease the amount of oxygen in the alveolar air. The decrease will be directly related to the amount of oxygen taken up, and inversely related to the alveolar ventilation. In other words, the greater the alveolar ventilation, the less the effect of this oxygen uptake on the fraction of oxygen in the alveolar air. This is an expression of the "universal alveolar air equation". We say:

   alveolar PO2 ~ P_{Bdry} * (FiO2 - fractional O2 uptake)

   Where the fractional O2 uptake is equal to: **O2 uptake / alveolar ventilation**

   We may abbreviate alveolar PO2 to **P_AO2**. Thus:

   P_AO2 ~ P_{Bdry} * (FiO2 - O2 uptake / alveolar ventilation)

   Note that this is only approximate - differences between inspired and expired volumes will affect the estimate. In addition, if you guessed that P_AO2 fluctuated with each breath, you would be correct, but this variation is normally only about 3mmHg.

(There are more convenient ways of estimating P_AO2, although many of these are fairly inaccurate!) Plugging values into the above, we might get something like:

$P_AO2 = (760 - 47) * (0.2095 - 250/5000)$

Where the true barometric pressure is 760mmHg - the partial pressure of water vapour at 37 degrees is 47mmHg, the inspired oxygen concentration is 20.95%, the oxygen consumption is say 250 ml/minute, and the alveolar ventilation is 5 litres/minute. This gives us a P_AO2 of about 114 mmHg. We rush on, inexorably down the oxygen cascade!

3. In a healthy young adult breathing air, the gradient from alveolus to capillary is minimal - under 15mmHg. In the 'normal' elderly person, this may rise to 37mmHg! (One convenient estimate of this gradient is simply 4 + age/4 mmHg)! In the critically ill, this *alveolar/arterial oxygen difference* may be hundreds of millimetres of mercury. Nevertheless, even in the normal young individual we still take a small step down, to an arterial partial pressure of oxygen (**P_aO2**) of about 100mmHg.

   Another useful estimate for PaO2 at sea level (in healthy subjects breathing air) is given as:

   PaO2 = 102 - 0.33 * (age in years)

   This is expressed in mmHg, and we stress that the confidence limits for this estimate are fairly wide: +- 10mmHg.

4. The big drop comes at the tissue level, where the PO2 within the mitochondrion has been estimated to be as low as 4-20mmHg! In some normally functioning cells this PO2 may even drop to 1mm Hg!

   Perhaps this is the PO2 that our ancient unicellular ancestors first found that they could effectively use, and there has been no (heh) pressure to subsequently change, or perhaps this low PO2 is a trade-off related to the number of capillaries needed to support the tissues, but we know one thing, and that is that we could sure use a bigger tolerance margin in critically ill patients!

In the following sections, we will look at the way some of the above steps have been "fine-tuned" to achieve near-optimal function. Our first consideration is the actual mechanics of the lung.

The lung as a low-pressure air pump

- Introduction
- More Mechanical Properties

1. Resistance
2. Lung elasticity
3. Chest wall elasticity

- Lung Volumes

The wonderfully intricate architecture of the lung is a consequence of one thing: the need for surface area. In the adult human, a lung volume of say four litres is exposed to an alveolar area of between fifty and one hundred square metres - a sphere of the same volume would have an area of only $0.1m^2$!

Introduction to the lung: basic anatomy & mechanics

The respiratory tract may be seen as a branching tree-like structure, with about seventeen levels of branching between the trachea and the respiratory bronchioles. As on average the number of branches doubles at each level, we end up with about 2^{17} respiratory bronchioles, or about 130 000 of them. Some authorities have introduced the concept of the "primary lobule", which is the zone supplied by one of these first order respiratory bronchioles. Each primary lobule contains about two thousand alveoli, and is about 3.5mm in diameter. Branches within the primary lobule give rise to alveolar ducts, which in turn give off alveoli. All in all, there are about twenty three intricate levels of branching within the respiratory tree!

A primary lobule at FRC has a volume of about 23 microlitres, and alveoli have on average a diameter of about 200 microns. We are interested in how air gets into and *out of* these primary lobules.

The diameter of an alveolus was, remarkably, estimated with astonishing accuracy by the Rev Stephen Hales in 1731.

We will not here discuss the anatomy and physiology of the upper airway, which deserves a whole page of its own! First we note that the respiratory system is remarkably effective in achieving movement of air - a normal inspiratory breath of say 500ml in an adult requires a distending pressure of under 3cm H_20, and this distension occurs remarkably rapidly, with flow rates of a litre per second or more! How does this occur?

The lungs move in response to external forces - during normal inspiration these forces are the movement of the diaphragm, and movement of the chest wall by the intercostal muscles. Gentle resistances oppose this movement. These resistances are:

1. Frictional resistance to gas flow
2. Elastic resistance of the tissues themselves.

The work required to overcome the frictional resistance is lost, but the work done in overcoming the elastic resistance of the tissues is largely stored in those tissues, and this is why so little effort is needed to breathe out - a substantial part of the work we did in moving air into the lungs is regained when we breathe out, and normal expiration is thus largely passive.

A useful analogy is to consider the lung as a spring - if we put energy in (stretch the spring) then the volume increases, and when we release the tension, the volume decreases again (the spring shortens). In an analogy to Hooke's law, we say that:

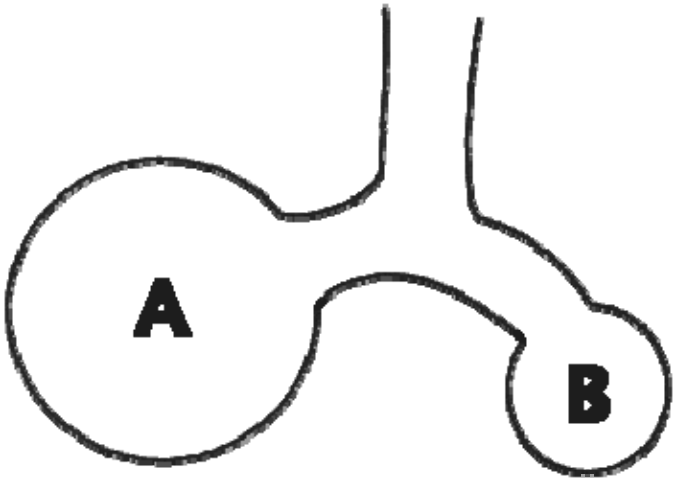
$$\Delta V \propto \Delta P$$

where V is volume and P is pressure. The **compliance** of the lung is the more or less constant value relating the volume and pressure changes i.e.

$$C = \Delta V / \Delta P$$

We can see that if a normal lung has a volume change of 500 ml for say 2cm H_20 pressure change, its compliance is 250ml/cmH_20.

We still have not explained why it is so easy to inflate the normal lung. Instead of explaining immediately, we will note a further problem. Consider the following diagram of two connected alveoli:



Note that the surface tension within an alveolus is about 20mN/m. If we apply Laplace's law to each of the fluid-lined alveoli in turn, then we find a remarkable discrepancy in the pressure gradients across the walls of the two alveoli, alveolus A and alveolus B. This surely means that air will move from the small to the big alveolus, as the pressure in the smaller alveolus is higher! The small alveolus will get smaller, the large one will get larger, and so on until the small alveolus collapses completely! Why does this not happen in real life?

And a third problem! The surface tension of water is about 72mN/m, yet in alveoli we have remarkably low values of about 20mN/m, as noted above.

Fortunately, the answer to all our questions is at least partially contained in one word: **surfactant**! Surfactant, composed of mainly dipalmitoyl phosphatidyl choline, with a touch of

phosphatidyl glycerol thrown in, not only lowers the surface tension of the alveolar fluid, but it *lowers the surface tension more as the alveolar radius decreases*! Also note that because the surface tension is lowered, the negative pressure in the fluid lining the alveolus is correspondingly decreased, and thus there may be a decrease in the pressure driving fluid from the vasculature into the alveolus!

It appears that even the above is a considerable over-simplification. In the above diagram, we considered just two alveoli, but remember that a 'primary lobule' has about two thousand adjacent alveoli. What will be the effect of partial collapse of one alveolus on surrounding alveoli? Surely a traction will be exerted on them? It is thought that the presence of surrounding alveoli is also important in preventing collapse of any particular alveolus.

Further mechanical properties

We know that air flow is impeded by airway resistance, and also because of the elastic properties of the lung and chest wall. Let's examine these in more detail:

1. **Resistance to Airflow**

   Resistance to airflow is a major contributor to work of breathing. In any system, flow may be laminar or turbulent. Analysis of laminar flow is far simpler than that of turbulent flow. Unfortunately for us, we encounter both within the respiratory system. Turbulent flow is seen with:

   - high flow rates
   - changes in diameter
   - angles
   - branching tubes

   all of which are common in the respiratory system. Turbulence is importantly also dependent on Reynold's number.

   Laminar flow is governed by Poiseuille's law. Importantly, halving the radius of a tube will increase the resistance by *sixteen* times. Note that with laminar flow, the drop in pressure is related to the flow rate, and so we can talk about the "resistance" of a tube, independent of flow. That is:

   $$\text{Pressure drop} \propto \text{Flow}$$

   With turbulent flow, the pressure drop depends on the **square** of the flow rate, and thus "resistance" will vary with flow. At any particular flow, the pressure change is also related to the *fifth* power of the radius (the Fanning equation).

   With a mixture of turbulent and laminar flow, pressure drop is defined by:

$$\Delta P = k1 * flow + k2 * flow^2$$

In man we have a convenient approximation:

$$\Delta P = 2.4\ (flow)^{1.3}\ cmH_2O.$$

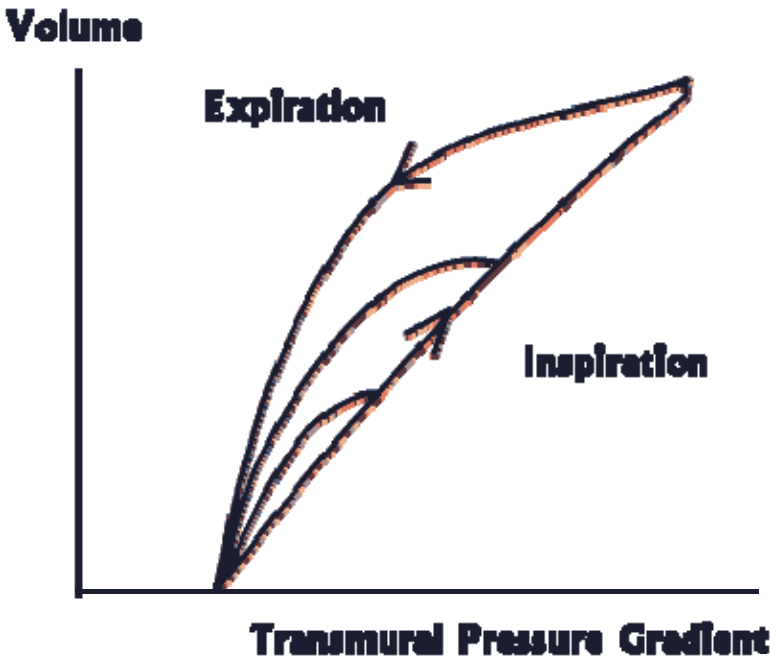
(If you are working in kPa, then the constant multiplier is about 0.24 and not 2.4).

Ancillary notes

E. *Relationship between airway resistance and lung volume* Because airway resistance varies inversely with lung volume, various maneuvers have been used to standardise resistance. One way is to firstly use "conductance" (the reciprocal of resistance), and secondly divide the conductance by lung volume, to compensate for the influence of lung volume. This adjusted conductance is termed the "specific conductance", abbreviated sG_{aw}.
F. *Flow-related collapse (dynamic airway compression)* Expiration is normally a passive action - energy transferred to elastic components of the lung is used to help expiration. With forced expiration (for example in emphysema, where destruction of lung tissue decreases the effectiveness of the elastic components in achieving expiration), increasing effort is not rewarded by increasing flow rates. This is particularly marked towards the end of expiration, where flow rates tend to converge on the same curve, regardless of effort. The reason for this convergence is that expiratory flow is limited by "flow-related collapse". A pressure gradient exists from distal alveoli (high pressure) to proximal airways (lower pressures). As we move into the larger airways, the pressure drops to a point where the luminal pressure is exactly equal to the high intra-thoracic pressure (the **equal pressure point**). Beyond this point, the only factor that keeps the airways open is their intrinsic elasticity, which will be overcome at high enough pressures, causing airway narrowing.

Elastic Properties of the Lung

Above we said that the behaviour of the lung is analogous to that of a spring - change in pressure is accompanied by a proportional change in volume. We might expect that if we push air into the lung and then plot volume change versus pressure change that we would get a straight line. This is indeed more or less what happens on inspiration, but what happens on expiration? Consider the following plot that shows pressure changes that occur when varying volumes of air are very slowly pushed into a lung:



The expiratory limb of the curve does NOT follow the inspiratory limb! Also note that as the tidal volume increases, the loop widens! What is happening? For any particular volume, the pressure on the expiratory curve is less than that on the inspiratory one. This is because the elastic recoil on expiration is always less than the distending transmural pressure gradient required to inflate the lung. This is a manifestation of loss of energy, and is a property that is common to all bodies that obey Hooke's law.

We call the above property *hysteresis*. If we slowly inflate a lung, and then simply leave it inflated, the pressure in that lung will drop exponentially to a value about 70 to 80% of the initial value. Most of this change is complete after about a minute. We term the compliance calculated from this "final" pressure the **static compliance**. The corresponding compliance calculated using the initial, higher pressure value is the **dynamic compliance**, and it will always be lower than the static compliance.

Quite apart from the elastic hysteresis described above, the lung possesses other time-dependent behaviour. The lung appears to have a "memory" of its recent history, in that low-volume ventilation for a period of time tends to cause a reduction in compliance. This reduction may be reversed by taking subsequent deep breaths (even a single deep breath). This was the motivation for introducing a "sigh" mode to certain mechanical ventilator designs, a concept that has fallen into disfavour, although some are making spirited attempts to re-introduce such practices!

Causes for time-dependent lung elasticity.
There are many candidates, including:

- "Stress relaxation". This is commonly seen in certain materials when stretched, and is postulated to be important in the mechanism of hysteresis in the lung.
- Redistribution of air between different alveolar units (those with different "time constants").
- Changes in surfactant activity with changes in volume!
- Changes in pulmonary blood volume! (Rather theoretical).

Elastic Properties of the Chest Wall

It is vital to distinguish between the elastic properties of the lung and those of the surrounding chest wall. All too often, clinicians (especially those in ICU) confuse total thoracic compliance with lung compliance. When we come to discuss acute lung injury, we will see that it is the pressure distending the alveolus that is critical in determining whether we injure the lung with our ventilation. If we were to take a rabbit (for example), encase its chest wall in plaster of Paris, and then ventilate it using high transthoracic pressures, we would not necessarily be inflicting high trans*pulmonary* pressures on the unfortunate animal. We know from the few studies that have looked at this, in the critically ill, that total thoracic compliance often bears little relationship to pulmonary compliance!

How do we separate pulmonary and chest wall compliance?
In order to do this, we need some measure of intrapleural pressure, that is, the pressure within the "potential" space between the pleura. Unfortunately, this is not easy to obtain, and the pressure also varies with the site of the transducer and the posture of the subject. The easiest method of obtaining a measure of this pressure is to use an intra-oesophageal balloon catheter, as a correctly positioned oesophageal balloon reflects intra-pleural pressure with 'reasonable' fidelity. Air-filled balloon catheters are commonly used for this purpose.

A noteworthy point is that if the thoracic cage is opened, the lungs tend to collapse, but the thoracic cage will tend to expand to a volume about one litre greater than FRC (in an adult). Interestingly, the diaphragm too contributes to this complex relationship, as even when relaxed it has a residual tone that enhances the functional residual capacity of the lung by about 400ml. (This tone is abolished during anaesthesia)!

Note the relationship between total thoracic compliance, lung compliance, and chest-wall compliance:

$$1 / C_{total} = 1 / C_{lung} + 1 / C_{thoracic\ cage}$$

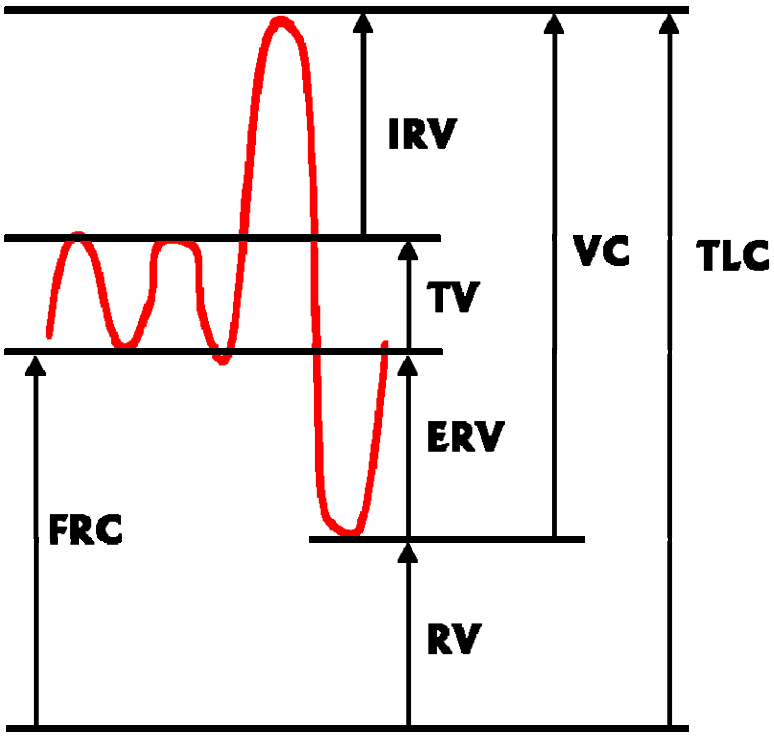
Some people use the idea of **elastance** where the elastance is the reciprocal of the compliance. We can then add elastances, rather than adding the reciprocals of compliances. It seems terribly wanton to introduce new terms, for the inability to take a reciprocal!

Regional Variation in Lung Ventilation

Ventilation within the lungs is greatest near the bases, in the upright position. This is probably mainly due to variation in intra-pleural pressure as we move from apex to base - pressure is more negative near the apex. Effectively, this probably causes more expansion of the apices at FRC. As the person inhales, it is easier to expand the bases, as these are less distended than the apices! Note that at lower lung volumes, the situation may be reversed, with poor ventilation of the bases.

Lung Volumes

Clinicians especially, lay great emphasis on lung volume, its subdivisions, and divergence of volumes from normal. This is peculiar, as there is relatively little evidence that changes in volume, even quite gross derangements, are consistent predictors of clinical outcome in the individual patient, especially post-operatively. Physiologists (who are often "splitters" at heart) have labelled a variety of components of the total lung capacity. The following diagram shows the changes in volume (on the vertical axis) against time (on the horizontal axis) as an individual breathes, initially tidal volumes, and then inspires and expires maximally. are:



- FRC = Functional Residual Capacity
- TV = Tidal Volume
- VC = Vital Capacity

- RV = Residual Volume
- TLC = Total Lung Capacity
- ERV = Expiratory Reserve Volume
- IRV = Inspiratory Reserve Volume

Note that simple spirometry obviously cannot provide any of the volumes that include RV, the residual volume left in the lung after maximal expiration. We need other methods to find TLC and FRC.

Perhaps the volume that has received most attention is the Functional Residual Capacity (FRC), the volume of gas in the lung after a normal expiration. The FRC is determined by the balance between the inward elastic recoil of the lungs, and the outward recoil of the thoracic cage, mentioned above. As already noted, the FRC decreases with paralysis and anaesthesia. Other factors influencing the FRC include:

- Body size (increase of about 32-51 ml/cm of height)
- Gender (10% less in women of the same height)
- Posture (Supine posture decreases FRC by 0.5 to 1 litre in an adult)
- Lung pathology.

Note that there is **no** substantial effect of age on FRC!

Measuring FRC
There are Three main approaches to measuring FRC:

11. *Nitrogen washout*
    The subject breathes 100% O_2, after breathing air. If we collect all the expired gas, and measure the final concentration of nitrogen in the pooled expired gas we can calculate the volume present in the lung at the start of the washout. Knowing the concentration of N2 in air (78%) we can calculate FRC.

12. *Helium wash-in*
    The subject is connected to a spirometer of known volume, containing a known amount of helium. After equilibration, the new concentration of helium is noted, and used to determine total volume. We know the concentration of helium before (C1) and after (C2), we know the spirometer volume (V1) and can therefore determine the FRC using: **V2 = V1 * (C1 - C2)/C2.**

13. *Body plethysmography*
    The subject is placed in a "body box", which is gas-tight. (S)he breathes against an occluded airway, and pressure changes at the mouth and in the box are recorded. Application of Boyle's law then permits calculation of FRC:
    1. We find the change in box volume, ΔV by:

       P1.V1 = P2.V2 (by Boyle's law) and

V2 = V1-ΔV, thus
P1.V1 = P2. (V1 -ΔV)

2. Next we apply Boyle's law to the gas in the lung, where

   P3V3 = P4.(V3 + ΔV),
   and knowing P3, P4 and ΔV, we can therefore determine V3, the FRC.

Dead Space
Not all the air that passes into the respiratory tract reaches alveoli. Even in normal individuals, about one third of a tidal volume is wasted in the anatomical dead space! (This is a remarkably constant proportion for most animals, even giraffes!) We often talk about the V_D/V_T ratio, in other words, the ratio of dead space to tidal volume. Dead space may be:

- Apparatus dead space
- Anatomical dead space (related to the volume of the conducting passages)
- Alveolar dead space (related to alveoli that are well ventilated but poorly perfused, so they effectively contribute to the dead space).

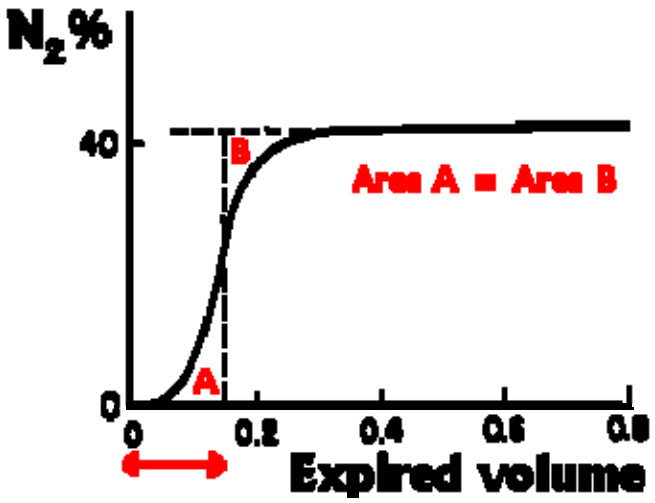
The physiological dead space is the sum of the anatomical and alveolar dead spaces, and represents all components of the tidal volume that do not take part in gas exchange.

Physiological dead space can be calculated using Bohr's method. This uses the equation:

$$[CO2]_A * (V_T - V_D) = [CO2]_{expired} V_T$$

In other words, the product of alveolar CO2 concentration and the amount of inspired air reaching the alveoli equals the expired CO2 concentration times the tidal volume. It is easy to measure the tidal volume and the expired concentration of CO2, so all we need to determine physiological dead space is the alveolar CO2 concentration. In most cases, we can simply substitute in the arterial PCO2, as the two are generally very similar.

The Anatomical dead space can be determined by watching the change in N2 concentration (using a rapid N2 analyser) following a single breath of 100% oxygen. N2 concentration is measured as the subject breathes out, increasing from zero (at the start of inspiration) to a plateau (where almost pure alveolar gas is being expired). Fowler showed that if a vertical line is drawn such that areas A and B are equal in the following diagram (after West), then the anatomical dead space is the volume expired up to the vertical line, indicated by the (red) arrow in the diagram.



The blood:air interface

Movement of molecules across the interface

Gas molecules move with remarkable ease between alveolar air and blood, traversing the 0.5 micron barrier by passive diffusion. This means that we can apply all those eponymous little rules which make pulmonary medicine so irritating - Fick's law, which tells us that more diffusion will occur if we increase the surface area, decrease the thickness of the alveolo-capillary membrane, or increase the partial pressure gradient across the membrane, and also Grahams law (from which we learn that bigger, or less soluble molecules move more slowly).

The consequences of these laws are:

- Different gases will have different behaviour: for example, as nitrous oxide (N_2O) diffuses across the alveolar wall into blood, the partial pressure of (N_2O) rises rapidly, so the main factor determining transport of this gas across the wall is the flow of blood through the capillaries. In contrast carbon monoxide is so rapidly and avidly bound by haemoglobin that the partial pressure across the alveolar wall is always large. This means that transport of CO is limited by the properties of the wall, and NOT by capillary flow.

- The main gas we are concerned with is of course oxygen. The behaviour of O_2 lies somewhere in between that of CO and (N_2O). In resting man, the average erythrocyte spends about 0.75 seconds within the alveolar capillaries, and is fully oxygenated in about a third of this time. Exercise is different - here, the erythrocyte may zip through the capillary in 0.25 seconds, so it is easy to see that if there is any disturbance in the alveolar wall, oxygen saturation may drop with

exercise. This is the basis for assessing some people with lung disease (especially restrictive lung disease) by checking arterial PO2 before and after exercise.

- The behaviour of CO2 is interesting. CO2 diffusion through tissues is rapid, about twenty times as fast as that of O2, but it is just conceivable that in severe disease of the alveolar wall CO2 removal might be limited by diffusion abnormalities.

Things become more complex, for two reasons:

17. Oxygen diffusion is also affected by the further distance that gas molecules have to move before they encounter a haemoglobin molecule to react with;
18. The rate of reaction of O2 with haemoglobin is finite, and this delays uptake of O2 by the red cell.

In other words, diffusion is also affected by capillary volume within the lung. Decreases in diffusion with various diseases may therefore also be due to structural changes in lung capillaries, and not only "thickening of the alveolo-capillary interface".

(As an aside, normal individuals at high altitude may also show diffusion-limited O2 transfer across their alveolar walls, but otherwise this limitation *is* a manifestation of pulmonary disease.)

Based on the above, we define the **Diffusing capacity of the lung** as

$$D_{L_{gas}} = \Delta V_{gas} / \Delta P_{gas}$$

For example, the diffusing capacity of the lung for carbon monoxide, D_{Lco} is the volume of CO transferred divided by the difference between alveolar and blood partial pressures of CO. Experimental determination of D_{Lco} is thus rather easy, as owing to the rapid uptake of CO by haemoglobin, the PaCO is always negligibly small provided we get the subject to inhale a low concentration of CO. D_{Lco} then becomes:

$$D_{Lco} = \Delta V_{CO} / P_{Aco}$$

Because of the effect of pulmonary capillary volume on diffusion, and other factors, many physiologists (especially Europeans) don't like to talk about "diffusing capacity" of the lung for CO, and prefer to call this the "Transfer factor".

Practically, we determine D_{Lco} using the **single breath method** where a single breath of CO is taken, and the rate of disappearance of CO is calculated after the subject has held their breath for ten seconds. (Derived from initial and final CO concentrations in the inspired & expired air). Note that this can be combined with inspiration of helium for V_A determination, killing two birds with one stone!

An unfortunate metaphor, as the procedure is safe, its main limitation being the ability of subjects to hold their breath for ten seconds!

An alternative method of determining D_{Lco} is the **steady state method**, where a tiny concentration of CO is inhaled until a steady state concentration is reached, and the rate of disappearance is then measured for a further short period, along with the alveolar concentration. This compensates for the inconstant aveolar CO concentration that we encounter in the single breath method.

Flow of blood through the Lung

The pulmonary circulation is not merely a pint-sized version of the systemic circulation. Important contrasts between systemic and pulmonary circulations exist. These are highlighted by considering:

- Pressure differences
- The tissue surrounding the capillaries
- Sites of resistance within the circulation
- Capacitance vessels
- Distribution of flow within the lungs.

Pressure differences

The pulmonary circulation is a remarkably low-pressure system, arterial pressures running at a mean of about 15mmHg. In keeping with this, pulmonary vascular resistance is extremely low, and the pulmonary arteries are thin-walled. The reason why this is so is thought to be one of efficiency - systemic arteries must carry blood to distant organs and there is considerable variation in and regulation of flow to those organs. The lung merely accepts the whole blood volume, whatever!

The tissue surrounding the capillaries

There is very little of this - really just the extremely thin alveolo- capillary membrane, comprising attenuated pneumocytes and endothelial cells separated by a minute basement membrane. The capillaries can therefore easily collapse, especially if intra-alveolar pressure is raised. The peri-capillary tissue is thought to be under tension from the surrounding elastic lung parenchyma - it is easy to see how the transcapillary Starling forces might easily change to favour passage of fluid into the pulmonary interstitium!

Sites of resistance within the circulation

Pulmonary vascular resistance (PVR) is a convenient fiction, described by the ratio of pressure change to flow within the circulation. As the pressure drop within this circulation is normally so small, the PVR is about one tenth of the systemic vascular resistance. (To confuse things various units of resistance have been proposed, such as mmHg/l/min, and dynes.sec.cm^{-5}. Normal values are about 1.8mmHg/l/min, or 140 dynes.sec.cm^{-5}, or perhaps 0.24 kPa l^{-1}min).

This convenient simplification masks vast differences. In the systemic circulation, the site of resistance is mainly arterial, while in the pulmonary circulation, there is a substantial

contribution from the capillaries and even from the venous side of the circulation!! This may have profound implications for assessing the diseased pulmonary circulation.

Furthermore, as venous *or* arterial pressure rise, so the pulmonary vascular resistance *falls*! This is thought to be mainly due to recruitment of under-perfused vessels, but may also be related to distension of capillaries, especially at higher pressures. Pulmonary volume (that is, amount of air in the lung) also affects PVR in a complex fashion, PVR being increased at both extremely low and very high lung volumes!

Capacitance vessels
In the systemic circulation, veins are the main capacitance vessels. Not so in the lungs, where capillaries distend markedly with pressure and are important for their capacitive effects.

Distribution of flow within the lungs.
There are remarkable inequalities in blood flow through various regions of the lung. These variations in flow are mainly related to height above the heart, which is not too remarkable when one considers the low pressures present in the pulmonary circulation - hydrostatic pressure alone will result in a pressure difference of approximately 30cm H_20 from the base of the lung to the apex. This led West to propose his "Three Zones" of the lung [West et al. J Appl Physiol 1964 19 p713] - in the topmost Zone 1, there is no flow because the pressure is not sufficient, in the lowest Zone 3 flow is continuous because intravascular pressure always exceeds alveolar pressure, while in the middle zone 2, flow depends remarkably on the difference between arterial and alveolar pressures - venous pressure is irrelevant as it is lower than alveolar pressure. Note that in the normal lung, there should be NO zone 1, as the pressure is just sufficient to perfuse the apices! Some have subsequenly proposed a "zone 4" which might occur in the bases where poorly expanded lung might actually result in narrowing of extra-alveolar vessels with reduced flow.

Of great importance in the lung, especially in disease states, is *hypoxic vasoconstriction*. Here, hypoxia in an alveolus causes marked contraction of that little smooth muscle present in the walls of nearby arterioles, markedly diminishing flow to the affected region. This can be seen as an 'attempt' by the lung to normalise ventilation/perfusion ratios (see below). This vasoconstriction tends to occur dramatically below a PO2 of about 70mmHg, and may therefore become important at altitude too.

Ventilation versus Perfusion!

It is clear that adequate lung ventilation and good perfusion are not enough to ensure that blood passing through the lung is well oxygenated, and that CO2 is removed. For this gas exchange to take place, there must be a matching of ventilation and perfusion. Bearing this in mind, let's take a practical look at causes of hypoxaemia. If the oxygen content of

the blood is diminished despite having normal haemoglobin levels we have several possible explanations. We therefore take..

A PRACTICAL LOOK AT HYPOXAEMIA

Consider the following possible causes:

1. Alveolar hypoventilation
2. Shunting of deoxygenated blood past the lung
3. Mismatch between ventilation and perfusion: well perfused
4. Lowered FiO2
5. Diffusion abnormality (in grossly abnormal lungs) areas may be poorly oxygenated, and vice versa.

We can for practical purposes ignore diffusion in most individuals, so we are left with four main causes of hypoxaemia. We will here consider the three most problematical causes: hypoventilation, shunt, and finally ventilation/perfusion mismatch, often abbreviated to "V/Q mismatch".

24. Alveolar hypoventilation

The alveolar gas equation in one of its incarnations (already discussed above) allows us to see the impact of hypoventilation on oxygenation. It can be seen that at an FiO2 of 21%, hypoventilation will have a substantial effect on oxygenation. This is however easily compensated for by increasing the FiO2. At high FiO2, even minuscule ventilation can maintain alveolar PO2 for ages.

Note that there may be a lag of several minutes between an alteration in ventilation and equilibration of PaO2 (and especially, PaCO2). This is because of the buffering effect of reserves within the body (small in the case of oxygen, larger for CO2). During this transition period, values for respiratory quotient will be deranged.

25. Shunt

If deoxygenated blood is shunted past the alveoli and not oxygenated, this will proportionally decrease the oxygen content of the arterial blood. In normal people, the amount of shunt is tiny (perhaps 1%, reflecting venous blood from the bronchi entering the pulmonary veins, as well as coronary venous blood entering the left ventricle via the Thebesian veins!). Generally, if we cannot determine the amount of oxygen in the "shunted" blood, we *assume* that this is the same as that of mixed venous blood, and make our calculations accordingly.

To calculate shunt, we must know the total amount of blood moving through the system (QT), and the oxygen content of the arterial, capillary and mixed venous blood (We will abbreviate these last three to CaO2, CcO2, and CvO2, the 'standard' abbreviations being a bit more clumsy). Knowing these, we calculate as follows:

amount of O2 out = amount in

thus:

QT * CaO2 = Qs * CvO2 + (QT - Qs) * CcO2

Rearranging, we get:

Qs = (QT * CaO2 - QT * CcO2) / (CvO2 - CcO2)

A convenient way of expressing this is to talk of the shunt as a fraction of QT (We then don't need to know absolute QT). This is therefore given by rearranging the above to:

Qs/QT = (CcO2 - CaO2)/(CcO2 - CvO2)

It is relatively easy to test for a shunt - simply give the subject 100% oxygen to breathe, and see if the PaO2 increases. If there is a true shunt, there will be no response, as the shunted blood is still not being exposed to the increased FiO2, and so will still make its evil contribution to arterial hypoxaemia!

26. V/Q Mismatch

V/Q mismatch is more tricky than shunt. Theoretically, the ratio of ventilation to perfusion in any one alveolus can range from zero to infinity: in the normal individual with a cardiac output of say 5 l/minute and an alveolar ventilation of perhaps 4l/minute, the ideal ratio would be 0.8, but even in normal people, there is some variation from this ratio, most alveolar units falling in the range of 0.5 to 2.0. As one ages, so the scatter of ratios increases, to perhaps 0.3 to 5.0 ! This is well shown in Nunn p 167, Fig 8.5.

A convenient method of cheating!
Determining the scatter of V/Q ratios in small sections of the lung is technically demanding. It is far more convenient (if less accurate) to regard the lung "as if" it had three compartments comprising:

0. well-ventilated poorly perfused alveoli
1. well-perfused underventilated alveoli
2. optimally perfused AND ventilated alveoli. (The Riley model).

This is clearly sub-optimal, but we can then apply our equations for shunt and physiological dead space, getting some idea about what is going on. We must remember that this is only a very poor approximation, however!

Another convenience is to consider the relationship between PO2 and PCO2 within an alveolar unit as we alter the V/Q ratio. Think about it - if there is no blood flow, then PAO2 might be say 149mmHg (at sea level), while PCO2 will be zero. With no ventilation, the PCO2 will increase to that of venous blood (say 45mmHg) with a PO2 equal to the venous PO2, perhaps 40mmHg. We can therefore plot a curve of PO2 versus PCO2 that encompasses *all possible ratios* for alveoli within a particular individual.

Regional variation in V/Q ratios
There are substantial variations in these ratios in the upright lung. Ventilation increases gradually as we move from apex down to base of the lung, while perfusion is much more dramatically affected, being low at the apices and rich at the bases. Thus V/Q ratios decrease as we move from the apex downwards. This improves with exercise.

Transport

Gas transport to and from the peripery is very elegant. We consider it briefly:

Oxygen Transport

Most oxygen is carried in the blood as oxyyhaemoglobin. The small contribution that dissolved oxygen makes to transport is usually negligible. (It can be calculated using Henry's law - for each mmHg of PO2 there is 0.003ml O2 dissolved per 100ml of blood, absolutely minuscule).

Haemoglobin (Hb) is much more effective in transporting oxygen, carrying about 1.39 ml of O2 per gram of pure Hb. We are all aware of the shape of the Hb:O2 dissociation curve and its importance in tissue oxygen delivery, as well as how the curve is right-shifted by:

- lower pH
- higher PCO2 (Bohr effect)
- higher temperature
- higher concentrations of 2,3 diphosphoglycerate in the red cell, usually induced by chronic hypoxia.

The most convenient equation relating Hb saturation and PO2 is

$$SO2 = 100 * (PO2^3 + 2.667*PO2) / (PO2^3 + 2.667*PO2 + 55.47)$$

It is however only valid above a PO2 of about 4kPa (30mmHg; PO_2 values in the equation are in *kilopascals* --- 1kPa is about 7.5 mmHg).

Transport of Carbon Dioxide

This is carried in three forms:

31. dissolved
32. As bicarbonate
33. As carbamino compounds, especially carbaminohaemoglobin.

Because CO2 is twenty times more soluble in blood than is oxygen, about 10% of CO2 carriage is by this method, Bicarbonate is formed from carbonic acid, which in turn is made from H_2O and CO2, the latter reaction being speeded by carbonic anhydrase within the red blood cells. Bicarbonate floods out of the red cell, and chloride shifts in in a compensatory manner. Deoxygenation of blood increases its CO2-carrying ability (the Haldane effect) because the heightened affinity of deoxyhaemoglobin for hydrogen ions speeds the formation of bicarbonate, and also because reduced Hb forms carbamino-haemoglobin more readily! About 30% of CO2 is transported as carbaminoHb. The CO2 dissociation curve is far more linear than the Hb curve, and does not display the sigmoid allosteric shape of that curve.

The Tissue Level

As we have indicated, the biggest drop in the oxygen cascade is here at the level of the tissues. The standard textbooks on respiratory medicine hardly address this vital issue! I will update this section as I acquire more information - please feel free to contribute.

Control

Control of breathing in man is immensely complex. We will conveniently look at three levels in the control of breathing:

34. The anterior horn cell
35. The brainstem
36. Feedback Regulation

The anterior horn cell

The human respiratory system is interesting in its dual use of both the diaphragm and intercostal muscles for ventilation. Shneerson [Disorders of Ventilation Blackwell

Scientific 1988, ISBN 0 632 01668 X] describes the functional anatomy of the muscular components of the respiratory pump rather well. We will superficially consider the neuromuscular components.

Descending pathways to the anterior horn cells innervating the muscles of respiration are:

- bulbospinal fibres in the ventrolateral cord (mainly involuntary);
- more dorsal corticospinal fibres;
- a third fairly diffuse group (for cough, and other non-rhythmic events)

How does the respiratory system compensate for changes in load? This is very efficient, and compensation occurs within one breath! This is thought to occur because "instructions to shorten" go to both the muscle fibres and *intrafusal fibres in the muscle spindles*. Differential shortening (caused by a large load preventing shortening of normal fibres) will be picked up and a large feedback signal will result in further stimulation of the muscle. Note that this is more important in the intercostal muscles, as spindles are sparsely scattered in the diaphragm.

The brainstem

Formerly everyone except Ramon y Cajal thought that complicated pontine mechanisms controlled respiration. The neuroanatomist Cajal got it right in 1909, claiming that respiratory rhythms originate in the medulla! There are probably two important groups of neurones, a dorsal group near the tractus solitarius controlling timing of inspiration, and a more complex ventral group. The ventral group includes the (expiratory) nucleus retroambigualis, nucleus ambiguus, nucleus para-ambigualis (inspiratory), and Bötzinger complex. There are thought to be at least six types of specific neurones in the medulla that control respiration.

Pontine regulatory mechanisms do exist, and are thought to "fine-tune" the above. Various other centres influence breathing, especially in relation to sneezing, swallowing and coughing. There is a wide variety of other reflexes that affect breathing including:

- Baroreceptor reflexes (carotid sinus, aortic receptors)
- Lung stretch reflexes (inflation reflex, deflation reflex, Head's paradoxical reflex)
- J-receptor responses (bronchial and pulmonary juxta-capillary receptors)
- Upper respiratory tract reflexes
- Musculoskeletal afferents (during exercise)

Feedback Regulation

Two sets of chemoreceptors regulate breathing:

45. **Central Chemoreceptors**
    These are usually by far the most important. They respond mainly to changes in cerebrospinal fluid pH. As arterial PCO2 rises, so CSF pCO2 will increase, this

causing a drop in pH. Breathing is stimulated, reducing PaCO2, and so on. With prolonged respiratory acidosis or alkalosis, the response becomes dulled, possibly related to compensatory normalisation of the CSF pH by movement of $HCO3^-$ ions. Severe hypoxia may depress central chemoreceptors.

46. **Peripheral chemoreceptors**
    Less important in normal man than the central chemoreceptors, the carotid bodies become stimulated with:
    - **hypoxaemia**
    - low arterial pH (whether due to PCO2 or not)
    - hypoperfusion
    - fever
    - certain drugs (Acetyl choline, nicotine..)

    These bodies, the metabolically most active tissue in the body, contain glomus cells which synapse with nerve endings of the glossopharyngeal nerve, and their stimulation results in stimulation of respiration. The peripheral response to PCO2 is about one fifth of the central one.

There is a complex interaction between the peripheral and central responses to hypercapnia and hypoxia. The response to PCO2 is slower than that to PO2, linear, and varies widely from person to person. A typical slope for the CO2 response curve would be about 2 litres/minute/mmHgPCO2. The curve becomes steeper at lower PaO2's.

If the PCO2 is sufficiently lowered, apnoea may result, despite a low PaO2. This is termed the "apnoeic threshold", but may not be present in some individuals. Metabolic acidosis does not change the slope of the CO2 response curve, but shifts it left.

The relationship between PaO2 and minute ventilation at constant PCO2 is complex and non-linear, but if we plot *saturation* against minute ventilation, we obtain a convenient almost linear curve down to a saturation of about 70% !The response to hypoxia is enhanced by hypercarbia, acidosis and exercise. With gross hypoxia of rapid onset hypocapnia depresses respiration, but compensation occurs over about six days. After years of chronic hypoxia, hypoxic drive becomes markedly attenuated.

References

The readily available textbooks are adequate as an introduction to the physiology and testing of the lung. Consider using:

- West JB **Respiratory Physiology - the essentials** 4 ed. Williams & Wilkins, 1990. ISBN 0-683-08942-0.
  A good basic textbook, which has the merit of being short and explicit.

- Nunn JF **Nunn's Applied Respiratory Physiology** 4 ed. Butterworth-Heinemann 1993. ISBN 0 7506 1336 X.
  A superb book, if you have the time. Go get it!