Clinical physiology of the pulmonary system
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Lung volumes

Tidal volume is the volume of air that moves in and out of the lungs with each breath. In the normal dog and cat this ranges between 10 and 20 ml/kg. [1-8] An animal's ability to generate a normal tidal volume is diminished by airway narrowing and by increased lung or chest wall stiffness. The product of tidal volume and breathing rate is minute ventilation.

Inspiratory reserve volume 65 ml/kg dog; 45 ml/kg cat	Inspiratory capacity 80 ml/kg dog 63 ml/kg cat	Vital capacity 96 ml/kg dog 75 ml/kg cat	Total lung capacity 120 ml/kg dog 90 ml/kg cat
Tidal volume 10-20 ml/kg			
Expiratory reserve volume 18 ml/kg dog; 12 ml/kg cat	Functional residual capacity 25-50 ml/kg dog 25-30 ml/kg cat		
Residual volume 17 ml/kg dog; 15 ml/kg cat			

An animal can take a deeper breath than normal (inspiratory reserve volume). Inspiratory reserve volume can be diminished by neuromusclar weakness; pleural space filling disorders; abdominal distention diseases or tight abdominal wraps which cause anterior displacement of the diaphragm; chest wall abnormalities such as congenital malformations, flail chest, open pneumothorax, or thoracic wraps; and interstitial lung disease which decrease pulmonary compliance. The volume of air remaining in the lung at the end of a normal breath (the end-expiratory lung volume) is the functional residual capacity (FRC). [9] FRC is composed of the expiratory reserve volume and the residual capacity. FRC has been reported to be in the range of 25 to 50 ml/kg in normal dogs [4;5;7;8;10-16] and 25-30

ml/kg in cats. [16] FRC decreases in supine and lateral recumbency compared to prone, but the changes were not statistically significant.[9] Expiratory reserve volume is diminished by small airway disease or intra-thoracic tracheal collapse, both of which are associated with premature airway collapse, especially during a forced exhalation.   Residual volume is decreased by an increase in airway fluids which causes small airway and alveolar collapse. To the extent that these alveolar units are not recruited in the next tidal breath, atelectasis and alveolar filling also diminishes inspiratory reserve volume.

Vital capacity is the total amount of air that can be moved into and out of the lung with a peak inspiratory and expiratory effort, and represents the maximum tidal volume that an animal can attain. In humans, the maximum breathing capacity is the maximal minute ventilation that a person can sustain for 15 seconds.[17]

Total lung capacity is vital capacity plus residual volume and has been reported to be between about 115 and 120 ml/kg [10] for the normal dog, and 88   10 ml/kg for the cat. [9]

Age was reported to increase residual volume, residual volume/total lung capacity, and FRC/TLC, and to decrease inspiratory and expiratory reserve capacity, and total lung capacity.[18]

The distribution of pleural pressure and transpulmonary pressure

 The lungs are held to the thoracic wall by the surface tension of a thin layer of fluid lining the pleural space. Elastic fibers within the lung and the surface tension forces of the alveolar lining fluid represent a constant retracting force. These forces cause the lungs to collapse when the chest wall is opened, breaking the pleural surface tension forces

and allowing air to enter the pleural space. In a closed-chest, these inward forces cause the

average pleural pressure to be slightly subatmospheric (-3 to - 4 cm H_2O in the dog[19;20]).

Pleural pressure is not consistent throughout the pleural space.[19;20] The pleural

pressure in the non-dependent pleural space is more negative than the average because of

the weight of the lung "hanging" from the top of the thoracic cavity. The pleural pressure

in the dependent pleural space is more positive than the average because the weight of the

lung "sitting" on the bottom of the thoracic cavity. Pleural pressure gradients from the

non-dependent to the dependent pleural surfaces of the lung are proportional to lung height

(Table 1).   The overall vertical gradient averages about 0.2 to 0.4 cm H2O per centimeter

of lung height,[19;20] but this can be highly variable depending upon the position of the

animal, lung volume (increasing volume increases pleural surface pressure gradients),[19]

and external influences such as the weight of the mediastinal structures (which, in lateral

recumbency, pull away from the non-dependent lung and press upon the dependent lung)

and abdominal contents (which, in head-up positioning would pull away from the lung, and

in lateral or supine positioning would press upon the underlying lung), and abnormal

pleural fluid accumulations.

Approx values for pleural and transpulmonary pressure in the dog at FRC. [19;46]

Position of animal	Pleural surface of interest	Lung height (centimeters)	Pleural press (cm H_2O)	Transpulmonary pressure (cm H_2O)
Lateral	non-dependent	8.8	- 6	6
	dependent	---	0	0
Supine	non-dependent	11.7	- 4	4
	dependent	---	0	0
Prone	non-dependent	9.2	- 3	3
	dependent	---	0	0

Transpulmonary pressure is the pressure gradient from the alveoli to the pleural space. It is expressed as if one were standing on the inside of an alveolus, looking out (alveolar pressure minus pleural pressure). At FRC, with an open glottis, alveolar pressure is zero (equal to atmospheric). The average transpulmonary pressure, therefore, is approximately 4 cm H_2O (0 - [-4 cm H_2O]). The transpulmonary pressure in the non-dependent regions of the lung is more positive than the average while the transpulmonary pressure in the dependent regions of the lung is less positive than the average (Table 1). Since alveolar pressure is equal to atmospheric at FRC, the transpulmonary pressure gradients depend on the pleural pressure gradients, which are highly influenced by the weight of the lung and are proportional to the height of the lung.

The relative size of alveoli at FRC

At FRC, the alveoli in the non-dependent regions of the lung are larger than those in the dependent regions of the lung.[21;22] This is because the structure of the lung is distorted by its own weight [23;24]. The alveoli in the non-dependent regions are stretched and expanded by the weight of all of the inter-connected underlying

lung. Alveoli in the dependent regions are squashed and compressed by the weight of the overlying lung. While this difference in relative alveolar size is commonly attributed to the differences in transpulmonary pressure, it is actually due to the effects of gravity. The transpulmonary pressure gradient is a passive event set up by the effect of gravity on the weight of the lung; the same force that distorts the structure of the lung.

In the laterally recumbent or supine animal, the dependent alveoli are also compressed by the weight of the mediastinal structures (including the heart) and by the weight of the abdominal organs.

Alveolar stability

The lungs collapse to a minimal volume when the thorax is opened. The forces responsible for this collapse are the surface tension forces of the alveolar lining fluid and the elastic fibers within the lung parenchyma. In the closed chest, global collapse is prevented by the thin layer of pleural fluid which holds the lungs to the surface of the chest wall.

The trachea and bronchi are held open by cartilaginous rings or plaques, respectively, but these are absent in the lower airways. Small airways and alveoli depend upon other mechanisms to minimize collapse. Individual small airways and lung units are tethered to one another by collagenous and elastic fibers in such a way that they tend to hold each other open. The elastic fibers that contribute to global collapse when the chest wall is opened, minimize internal collapse of adjacent lung units, when the chest is closed.

Surfactant is a phospholipid, bipolar molecule (hydrophilic and hydrophobic ends), produced by the type II pneumocytes, which is distributed on the surface of the airway and

alveolar surface fluid. Surfactant reduces the surface tension of the lining fluid to about 28% of that of a water-air interface.[17;25] Surfactant reduces the tendency for the airways and alveoli to collapse. Since surface tension is also an impedance to lung inflation, surfactant also decreases the work of breathing. A decrease in the amount of surfactant either by decreased production or by dilution by transudates or exudates, increases the tendency for small airway and alveolar collapse, and the work of breathing.

The other important characteristic of surfactant is that of varying the surface tension of the lining fluid depending on the radius of the alveolus. The surface tension of a water-air interface is inversely proportional to the radius of the sphere; the pressure inside a sphere is directly proportional to surface tension and inversely proportional to radius (Laplace's equation: pressure   surface tension/radius). Smaller alveoli would have a higher internal pressure and would tend to empty their contents into the larger alveoli. Surfactant varies the surface tension of the surfactant-air interface in direct proportion to the radius of the alveolus. Larger alveoli have greater surface tension than do smaller alveoli.   The larger alveoli therefore tend to empty their contents into smaller alveoli and this helps keep the smaller alveoli open.

Nitrogen is poorly soluble in plasma and there is only a small alveolar to plasma partial pressure gradient since animals are equilibrated to atmospheric nitrogen concentrations. Nitrogen is not readily absorbed from the alveolar space and therefore provides a kind of gaseous skeleton for the small airways and alveoli. This is especially important when there is collapse of an airway conduit; the trapped gas pocket distal to the collapsed airway tends to stay open because the nitrogen therein is poorly absorbed. Enriched oxygen breathing replaces the nitrogen and promotes an absorption atelectasis,

especially when there is small airway collapse, because oxygen, in contrast to nitrogen, is readily absorbed.

In spite of these protective mechanisms, small airway and alveolar collapse still occurs in the normal animal. Atelectasis is especially prominent in the dependent lung regions when an animal is recumbent and unable to move around. In some types of lung disease, the accumulation of airway fluids dilutes surfactant and increases the surface tension of the alveolar lining fluid. This, in turn, increases the tendency for small airways and alveoli to collapse, and therefore increases the work of breathing. In the normal individual, frequent position changes and intermittent deep breaths (sighs) re-inflate these lung units and thereby minimize small airway and alveolar collapse. In the critically ill, recumbent patient, particularly those with pulmonary parenchymal disease, frequent position changes (every four hours) and intermittent sighs are important in minimizing small airway and alveolar collapse.

The small airways and alveoli are either open or they are collapsed (as an "all-or-none" phenomenon). Alveoli do not fill up like a glass of water; they are never partially-full of fluid. Whether they are open or closed depends upon the balance between the collapsing forces of surface tension and the expanding forces of transpulmonary pressure. When the surface tension forces exceed the transpulmonary forces, the small airway or alveolus collapses. The transition point at which this sudden collapse occurs is termed the critical closing pressure (when referring to transpulmonary pressure) or critical closing volume (when referring to lung volume or functional residual capacity). Positive pressure ventilation and positive end-expiratory pressure increase transpulmonary pressure and help maintain these small airways and alveoli above their critical closing pressure/volume.

Small airway and alveolar collapse is disadvantageous for several reasons. First, the collapsed lung unit can no longer participate in gas exchange and so lung function is impaired. Second, it requires more pressure to re-open these collapsed areas at the beginning of the next breath (because of surface tension) so the work of breathing is increased. Third, the breaking of this surface tension seal during the re-opening process imposes large perpendicular forces on the apposed epithelial cells, which eventually damages them.
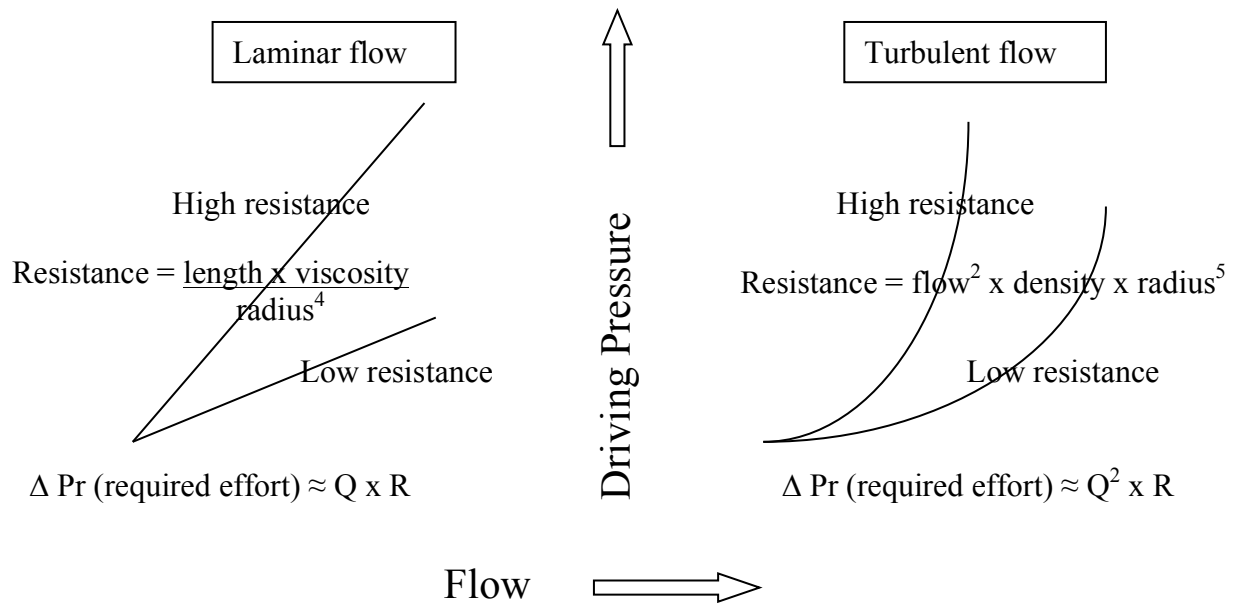
Resistance of air flow through tubes

Gas flow is directly proportional to the pressure difference between the two ends of the tube and is inversely proportional to resistance.

$$Flow = P_{upstream} - P_{downstream} / Resistance$$

The difference between upstream pressure and downstream pressure is termed driving pressure. Resistance to airflow depends a great deal upon whether the flow is laminar or turbulent. Resistance to laminar flow is directly related to the length of the tube and the viscosity of the fluid and is inversely related to tube radius[4]. Laminar flow is linearly proportional to the driving pressure difference. Turbulent flow occurs when there is a disruption in the orderly (laminar) flow of gas. This occurs at airway bifurcations and branches, and with partial airway obstructions. After a branching, flow becomes laminar again if there is a long enough run before the next branching. Resistance to turbulent flow is directly related to the density of the fluid and is inversely related to tube radius[5]. Turbulent flow is proportional to driving pressure[2]. Turbulent flow is undesirable because it causes a much greater resistance to flow than does laminar flow.

Laminar flow		Turbulent flow

High resistance

$$\text{Resistance} = \frac{\text{length} \times \text{viscosity}}{\text{radius}^4}$$

Low resistance

Δ Pr (required effort) $\approx$ Q x R

Driving Pressure

High resistance

$$\text{Resistance} = \text{flow}^2 \times \text{density} \times \text{radius}^5$$

Low resistance

Δ Pr (required effort) $\approx$ Q^2 x R

Flow $\Longrightarrow$

The likelihood that laminar flow will become turbulent is directly proportional to gas flow velocity, tube diameter, and gas density and inversely proportional to gas viscosity.[17] When the product of this equation (Reynolds number) is less than 2000, gas flow is predominantly laminar;

when it is greater than 4000, flow is predominantly turbulent.[17] Oxygen and nitrogen have a similar density and viscosity, and so breathing an enriched oxygen mixture does not increase the likelihood of turbulent flow or airway resistance. Nitrous oxide however has a very high density compared to nitrogen and increases the tendency for turbulent flow. Helium has a very low density compared to nitrogen and decreases the tendency for turbulent flow.

Normally the point of greatest air flow resistance is in the upper airway. The total cross-sectional diameter of the lower airways is large (they are small in diameter, but there

are many of them) and so the resistance to air flow is low.[26] Air flow in the upper airways

tends to be turbulent while in the lower airways tends to be laminar[17;27].

Pulmonary disease is often associated with reduced airway diameter which: 1)

increases the resistance to gas flow; 2) increases the driving pressure necessary to generate

the breath; 3) increases the likelihood of turbulence; and 4) increases the work of

breathing. Exaggerated breathing efforts associated with respiratory distress may be

associated with high gas flows, which also increase the likelihood of turbulent flow and

the work of breathing.

The dynamics of air flow physiology has been studied and values have been

reported for normal dogs [28] and cats[6;29], and for dogs with upper airway obstruction [28;30]

and cats with chronic bronchitis[6]

Lung expansion & pressure-volume relationship

Lung expansion follows chest wall

expansion during a spontaneous inspiration

because the lungs are held to the pleural surface by

the surface tension of the pleural fluid. The lungs

may also be expanded by the application of

positive pressure. In both situations there is an

increase in transpulmonary pressure. The

pulmonary pressure-volume curve is not linear.

There may be a horizontal bottom portion

associated with lung unit derecruitment (collapse) at the end of a breath and recruitment

Hysteresis = inspiratory and expiratory
pressure volume curves are not the same

Expiration

Average

Inspiration
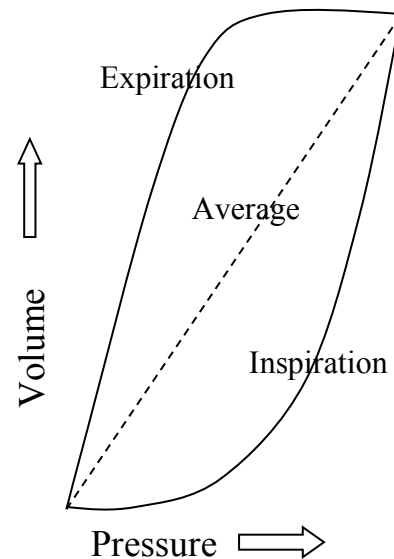
Volume

Pressure

(re-opening) at the beginning of the next breath. Pressure-volume studies in normal dogs often do not exhibit this portion of the curve unless transpulmonary pressure is decreased to below zero.[10;11;18] We commonly observe this horizontal portion of the curve during positive pressure ventilation of patients with diffuse lung disease.

TLC

Upper inflection point

Change in volume

Lower inflection point

FRC
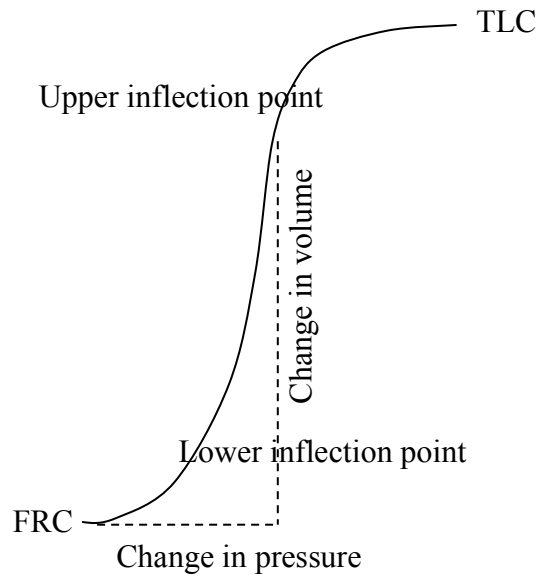
Change in pressure

There is always a steep vertical middle portion to the pressure-volume curve where most of the volume change occurs. This portion of the curve is shifted downward and to the right of normal in diffuse pulmonary parenchymal disease (the lung accepts less volume for a given change in pressure).[4;12;31]

There may be a horizontal top portion to the pressure-volume curve if the lungs are almost filled to capacity.

If the lung were a more perfectly elastic structure, it would undergo an immediate change in volume when a step change in pressure is applied. When the pressure is released, the decrease in

Diseased lungs exhibit lower compliance than normal

Volume

Normal lung

Diseased lung

Pressure
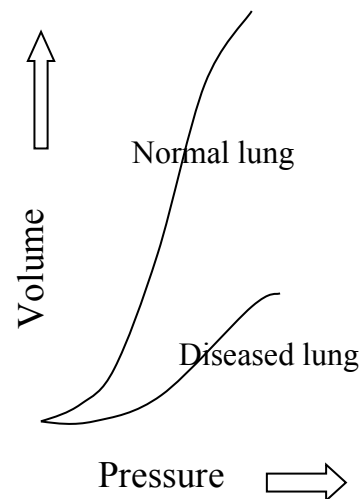
volume would retrace the course of the expansion.   The lung, however, is far from a

perfectly elastic structure. The lungs behave like an old rubber band in which the elasticity

of the rubber has degenerated and the rubber band seems to maintain a memory of its "just-

prior" state. The lung is reluctant and slow to expand when an increase in transpulmonary

pressure is applied to it and is reluctant and slow to collapse when the pressure is removed.

So the inspiratory pressure-volume curve of the lung is displaced to the right, and the

expiratory pressure-volume curve is displaced slightly to the left of a perfect elastic

structure. This is termed elastic hysteresis.   The clinical importance of elastic hysteresis is

two-fold. Expansion of the lung is somewhat time dependent; if there were an

instantaneous change in transpulmonary pressure, it would take a finite period of time for

the lungs to fully respond. Secondly, it takes more pressure to inflate a lung than it does to

keep it open thereafter. Pressure-volume measurements made during inflation will

generate different values than pressure-volume measurements made during deflation. This

is also an important premise upon which most lung recruitment ventilator strategies are

based: very high pressures initially to open as many lung units as possible and then a lower

positive-end expiratory pressure to keep them open thereafter.

It is the aim of most ventilator strategies to operate within the steep part of the

pressure-volume curve. Positive end-expiratory pressure is used to keep FRC above the

lower inflection point (above the critical closing pressure/volume) so as to minimize small

airway and alveolar collapse. An upper airway pressure is selected which does not exceed

the upper inflection point so as to minimize over-expansion trauma to alveoli.

The pressure-volume curve maintains its basic shape in diffuse pulmonary

parenchymal lung disease except that the vertical steep portion of the curve is shifted

downward and to the right and becomes much abbreviated.   The lower inflection point moves in this direction because of the increased tendency for small airway and alveolar collapse (a decreased residual volume, expiratory reserve capacity, and FRC). The upper inflection point moves in this direction due to congested small airways and alveoli which are not recruitable (a decreased inspiratory reserve volume and total lung capacity). Lung-protective ventilator strategies still aim to be within the steep part of the curve, for the same reasons mentioned above. Tidal volumes are correspondingly very small.

There are four phases of a breathing cycle: 1) the inspiratory flow phase where air is flowing into the lungs, 2) the inspiratory pause phase where no air is either entering or leaving the lung (it would be the equivalent of clamping the endotracheal tube at the end of the inspiratory flow phase), 3) the expiratory flow phase where gases are flowing out of the lung, and 4) the expiratory pause phase where no air is either entering or leaving the lung (fig. 8). During normal spontaneous breathing and for many ventilated patients, there is no inspiratory pause phase; the inspiratory flow phase cycles immediately to the expiratory flow phase.

Pressure-time wave form of a breathing cycle
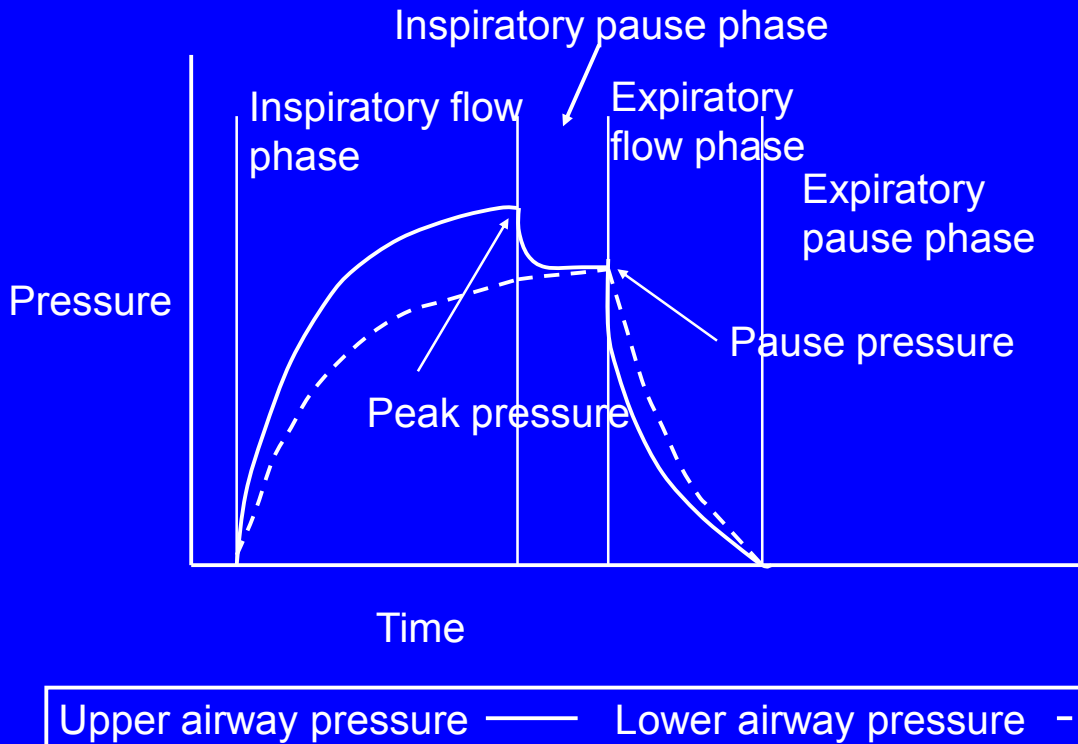
In order for there to be gas flow in any direction, the pressure must be higher at one end of the tube than the other. During the course of a normal breath (either spontaneous or mechanical), upper airway pressure is higher than lower airway pressure. The magnitude of the difference between upper and lower airway pressure is directly proportional to flow rate and airway resistance. If there is an inspiratory pause phase, air will continue to redistribute from the upper airways to the lower lung units. If the inspiratory pause phase is sufficiently long (a few

seconds) the two pressures will equilibrate and flow will cease.

Airway pressure is only measured at the level of the upper airway (usually inside the

ventilator). As a consequence of the continued distribution of volume from the upper airways to the lower lung units, the upper airway pressure will decrease during the inspiratory pause phase (fig. 8). The peak pressure is the highest upper airway pressure measured during the inspiratory flow phase. The pause pressure is the measured upper airway pressure at the end of the inspiratory pause phase, after the internal redistribution has taken place.

If there is no inspiratory pause, lower airway pressure does not have time to equilibrate with that of the upper airway before the beginning of exhalation. At the end of the inspiratory flow phase, upper airway pressure drops to atmospheric. The lower airway pressure, no matter what it has risen to during the inspiratory flow phase, exceeds upper airway pressure and the expiratory flow phase begins. Exhalation proceeds until the lower airway pressure equilibrates with upper airway pressure (expiratory pause phase).

An increase in transpulmonary pressure will expand the lungs and chest wall because of their elastic nature. There is, however, a delay in the expansion of the lungs and chest wall. The most important cause for the delay is airway resistance to air flow. A further delay is due to elastic hysteresis and tissue inertia. The elastic resistance to expansion ("elasticity"; "expandability"; "elastance" or "compliance" [which is the inverse of elastance]) of the lung is an important measure of lung mechanics. Compliance is calculated as the change in lung volume divided by the change in pressure required to obtain the change in volume (mls/cm H_2O). The number is usually indexed to body weight.

Compliance = tidal volume / change in pressure / body weight

When the change in transthoracic pressure (airway pressure minus atmospheric pressure) is used in the calculation, total thoracic compliance (lung and chest wall) is calculated. When transpulmonary pressure (airway pressure minus pleural pressure) is used in the calculation, lung compliance is calculated. The difference between total thoracic compliance and lung compliance is chest wall compliance.

$$1/\text{compliance}_{\text{chest wall}} = 1/\text{compliance}_{\text{thoracic}} - 1/\text{compliance}_{\text{lung}}$$

During spontaneous breathing, lung compliance can be calculated but total thoracic compliance cannot be calculated because there is no difference between airway and atmospheric (transthoracic) pressure at the end of the inspiratory pause phase. During positive pressure ventilation, both total thoracic and lung compliance can be calculated. Lung compliance can only be calculated when pleural pressure is measured. Pleural pressure is commonly measured via a balloon-tipped catheter which has been placed in the lower third of the esophagus.[32]

Dynamic compliance describes compliance calculations using the tidal volumes and the peak upper airway pressures measured during normal, continuous, tidal breathing. Static compliance describes compliance calculations using values obtained after an inspiratory pause of a few seconds, after upper and lower airway pressures have equilibrated. With normal tidal breathing, without an inspiratory pause, upper and lower airway pressures do not have a chance to equilibrate (due to air flow resistance) and neither has the lung volume had time to reach a plateau value (due to the time dependence of lung and chest wall elastic hysteresis and inertia). Dynamic compliance calculations generate lower values, compared to static compliance calculations when measurements are made under identical conditions because the upper airway pressure is higher than ity would be after equilibration (a higher denominator value in the compliance equation) and the lung

Dynamic and static compliance (ml/cm H_2O/kg) in dogs.

Dynamic	
Total thoracic	2.4 0.2[47]
Lung	4.1 0.3[47] 5.3 1.3[10] 5.3 1.4[7] 5.2 1.3[2] 4.6 1.4[48] 3.8 1.2[49]
Chest wall	7.3 0.6[47]
Static	
Total thoracic	3.0 0.6[10]
Lung	5.9 1.4[10] expired = 4.39(kg$^{1.05}$) = approximately 4.8 to 5.2 ml/cm H_2O/kg[11] inspired = 3.59(kg$^{1.04}$) = approximately 3.8 to 4.2 ml/cm H_2O/kg[11]
Chest wall	6.7 2.9[10]

[2,7,48]Dynamic measurements in awake dogs
[47,49]Dynamic measurements in anesthetized, paralyzed dogs
[10]Static measurements in awake, trained dogs
[11]Static measurements in anesthetized dogs

volume is lower than it would be after equilibration (a lower numerator value in the compliance equation). Dynamic compliance calculations includes a component of airway resistance, which in disease, can be substantial. Dynamic lung compliance in the cat has been reported to be 16.8   0.72 ml/cm H_2O.[29]

A true static compliance, where a step-wise, prolonged inspiratory hold is performed to allow complete equilibration between upper airways and lower lung units, is difficult to achieve in clinical patients. A short end-inspiratory pause (less than 0.5 seconds) can be used to allow equilibration between upper and lower airway pressures (pause pressure) which eliminates most of the air flow resistance component and gives the alveoli most of the time that they need to achieve full expansion. The difference between peak pressure and pause pressure is predominantly attributed to airway resistance. Some ventilators provide graphic displays which can be used to assess whether or not the inspiratory pause time is sufficiently long to allow complete equilibration. The pressure-time display in the volume control mode allows direct visualization of the airway pressure during the inspiratory pause phase; when the airway pressure ceases to decrease during the inspiratory pause phase, equilibration has been reached . The flow-time display in the pressure control mode allows visualization of flow during the inspiratory pause phase; if flow returns to zero prior the beginning of the expiratory flow phase, equilibration has been reached. A low inspiratory flow rate (a long inspiratory time) also allows near equilibration between the upper airways and lower lung units, and eliminates much of the air flow resistance component. Either technique is an attempt to simulate static, equilibrated conditions for the purpose of calculating a static compliance value in clinical patients.

The calculated compliance will be lower when generated with values which include either the lower or upper horizontal portions of the pressure-volume curve, where relatively little volume change occurs with changes in pressure. Compliance will be highest when generated with values obtained from completely within the steep part of the pressure-volume curve, where the change in volume per change in pressure is greatest. Compliance measurements are also higher when calculated with values obtained during lung deflation (4.8 to 5.2 ml/cm H_2O/kg) compared to calculations made during lung inflation (3.8 to 4.2 ml/cm H_2O/kg). [11]

Compliance calculations are often made during mechanical ventilation. The tidal volume actually received by the patient is somewhat less than the apparent tidal volume delivered by the ventilator because during the application of the positive pressure, gases are compressed within the patient breathing circuit and the flexible patient circuit tubing expands. This volume of gas compression and tubing expansion must be subtracted from the apparent tidal volume delivered by the ventilator or measured by the expiratory volumeter to more accurately determine the tidal volume received by the patient. This volume of gas compression and tubing expansion varies from circuit to circuit and with the utilization of different airway pressures, and can represent a large proportion of the apparent tidal volume if the patient is relatively small or if the breathing circuit is relatively large. The volume of gas compression and tubing expansion can be measured by disconnecting the patient from the ventilator (hand ventilate the patient during this procedure), plugging the patient port, and measuring the "tidal volume" of gas compression and tubing expansion. This volume should then be subtracted from the apparent tidal volume delivered by the ventilator for the purposes of compliance

calculations. Some newer ventilators calculate this volume during the self-calibration process and automatically subtract it from displayed volume measurements and compliance calculations.

The pulmonary pressure-volume curve represents the big picture of what is happening for millions of individual alveoli. Individual alveoli start at different positions on their pressure-volume curve and expand to different volumes, notwithstanding maximal filling of all alveoli. Individual lung units also expand at different rates; there are fast and slow alveoli. Fast alveoli are those that have reduced compliance but normal airway conduits; slow alveoli are those that have narrowed airway conduits but normal compliance. During the inspiratory pause phase, gases will redistribute from the fast alveoli (those that filled completely by the end of the inspiratory flow phase) to the slow alveoli (those that had not filled completely by the end of the inspiratory flow phase). Diffuse lung disease generally impairs lung function by either increasing airway resistance (which prolongs alveolar filling time) or by decreasing lung unit compliance (which shortens filling time), or both. There are two important consequences to the enhanced heterogeneity of alveolar filling which occurs in lung disease. First, it will take more time for slow alveoli to plateau (inspiratory pause time may need to be increased for the purpose of estimating static lung compliance). Second, the enhanced differential expansion rates of two adjacent alveoli will increase the shear forces on the delicate septal tissues of their common wall.

The clinical importance of compliance is that it is invariably decreased in disease. A decrease in surfactant activity, caused by the dilution of surfactant secondary to the accumulation of airway fluids, or by decreased production of surfactant by the type II

pneumocytes, decreases lung compliance. Lung compliance is also decreased by the accumulation of interstitial fluids or infiltrate. Chest wall compliance is decreased by pleural or peritoneal filling disorders or chest wall restrictive disorders. The measurement of compliance can provide an index of the severity of the disease process. The monitoring of it can provide guidelines with regard to optimal ventilatory settings and can provide an index of the progression of the disease process. Mechanical ventilation in the face of decreased compliance requires higher airway pressure settings.

Work of breathing

During inspiration, energy is expended to overcome the frictional resistance to gas flow through the airways, and elastic recoil of the lungs and chest wall. In the normal lung, at rest, all of the work of breathing is performed by the inspiratory muscles. The potential energy stored in the expanded elastic tissues of the lung and chest wall normally provide for exhalation. The work performed by the respiratory muscles is small in the healthy, resting animal. Respiratory muscle oxygen consumption is less than 2% of the total metabolic rate, [17] but this can increase dramatically in lung disease. Airway narrowing increases the work of breathing necessary to overcome airway resistance. The lungs are usually less compliant in diffuse pulmonary parenchymal disease which increases the amount of work necessary to overcome elastic recoil.

Animals tend to adopt a ventilation strategy that minimizes the work of breathing[17] When airway resistance is high, animals prefer not to fight air flow resistance with high gas flow velocity and will tend to breath slow but deep. Compliance is normal so the animal can accommodate an increased tidal volume with minimal increase in work. When

lung compliance is low, animals prefer not to fight the high elastic recoil with large tidal

volumes, and will breath shallow but rapidly. Airway resistance is normal and so the

animal can accommodate an increased gas flow velocity with minimal increase in work.

Animals with reduced lung compliance and increased airway resistance have no way to

compensate and must suffer an increased work of breathing.

A person's maximal breathing capacity (MBC)(the maximum amount of air that

can be moved in and out of the lungs for a 15 second period of time) is about 15-20 times

the resting minute ventilation[17]. Sustained breathing efforts can only be comfortably

maintained at about 30% of the MBC, afterwhich, the feeling of breathlessness occurs.   As

MBC decreases in respiratory disease, the animal's limit for a comfortable breathing effort

also decreases.   In compensation, the animal reduces its activity. Eventually, as the

disease progresses, the animal is dyspneic even at rest.

The minute ventilation/respiratory muscle oxygen consumption relationship is not

linear. High minute ventilation is associated with a disproportionately higher rate of

oxygen consumption. Eventually more oxygen is consumed by the respiratory muscles

than is provided by the increased breathing effort. Respiratory muscle fatigue occurs when

oxygen delivery cannot keep up with oxygen consumption and the energy necessary to

maintain the breathing effort is no longer available.

Dead space

When a breath is taken, the alveoli fill, but some of the alveoli are not being

perfused. This represents alveolar dead space ventilation. Very little alveolar dead space

exists in the   normal lung (Table 3). This is also evidenced by the small end-tidal to

arterial PCO_2 gradient

and effective alveolar ventilation.in normal animals. End-tidal carbon dioxide decreases

with an increase in alveolar dead space ventilation (the end-tidal to arterial PCO2 gradient

would increase). Alveolar dead space is also increased in hypovolemia due to the

diminished distribution of blood flow to the non-dependent regions of the lung; and with

pulmonary thrombo-embolism

Dead space in dogs

	Tidal vol (ml/kg)		Physiologic	Anatomic	Alveolar	Ref
Small mask	16.1 → 6.5 11.3 → 3.3 15.5 → 5.3 14 → 1	Relative (%)	47 → 6 59 → 19 52 63 → 3	42 → 8 57 → 18 46	4 → 5 6 → 3	3 2 5 50
	16.1 → 6.5 11.3 → 3.3	Absolute (mL/kg)	7.6 → 3.1 5.6 → 1.4	6.5 → 2.0	1.2 → 2.2	3 2
Large mask	20.4 → 14.2	Relative (%)	54 → 5	50 → 7	6 → 5	3
	20.4 → 14.2	Absolute (mL/kg)	11.0 → 7.9	9.8 → 5.7	1.1 → 1.4	3
Intubated	18.3 → 13.0	Relative (%)	41 → 7 41 → 5 42 & 45 →8	33 → 9	9 → 5	3 49 42
	18.3 → 13.0	Absolute (mL/kg)	7.7 → 5.5	5.3 → 1.9	2.4 → 3.9	3
Tracheostomy	20.4 → 14.6	Relative (%)	35 → 11	25 → 7	10 → 5	3
	20.4 → 14.6	Absolute (mL/kg)	7.4 → 5.5	4.4 → 1.7	3.0 → 4.0	3

The portion of the inspired tidal volume which fills the airways (nares to terminal bronchioles), where no gas exchange occurs, represents anatomic dead space. Anatomic dead space can be measured post-mortem by making a latex cast of the airways and measuring its volume by water displacement. The functional, in vivo, anatomical dead space volume is, however, less than the physical size of the conducting airways because of the parabolic flow profile of the inspired column of air. The molecules in the center of a laminar air stream travel faster than those at wall of the airway. By this mechanism, fresh gases are able to reach the alveoli prior to displacement of all of the physical dead space volume of the conducting airways. The functional, in vivo, anatomic dead space in the normal dog, breathing a normal tidal volume ranges between 35 and 55% of the tidal volume.

The anatomic dead space is not a fixed volume when expressed either as an absolute volume (ml/kg) or as a proportion of tidal volume (%). Large tidal volumes are associated with an increase in the physical size of the large conducting airways; they are distended by the increased transpulmonary pressure.   The increase in alveolar volume, however, is so much greater than that of the conducting airways, that anatomic dead space, expressed as a percent of tidal volume, decreases.[33] The opposite is true for small tidal volumes.

Alveolar plus anatomic dead space is physiologic dead space. Physiologic dead space may also be expressed as an absolute volume (ml/kg) or as a percentage of tidal volume. The functional physiologic dead space can be calculated by the Bohr equation:

$$V_D/V_T = (PaCO_2 - P_ECO_2)/(PaCO_2 - P_ICO_2)$$

where $PaCO_2$ = arterial PCO_2, P_ECO_2 = mixed-expired PCO_2, and P_ICO_2 = inspired PCO_2. With large tidal volumes, absolute physiologic dead space (ml/kg) increases, but relative physiologic dead space (% of tidal volume) decreases[33] The opposite is true for small tidal volumes. An increased physiologic dead space is likely present if the total minute ventilation is high but the PaCO2 is not low or if the end-tidal PCO_2/ $PaCO_2$ gradient is increased.

Whenever an animal is attached to a mechanical apparatus, an additional dead space (mechanical or apparatus dead space) is added to the physiological dead space of the breathing system. A large face mask, for instance, increased the physiologic dead space from 47% (with a small face mask) to 54%[3] Endotracheal intubation bypasses nasal cavity dead space and decreases the physiologic dead space from 47 % (with a small face mask) to 41%. A tracheostomy further decreased the physiologic dead space to 35%.[3]

Apparatus dead space is associated with the rebreathing of unaltered alveolar gases which filled the dead space volume at the end of the last breath. These gases contain lower concentrations of oxygen and higher concentrations of carbon dioxide compared with fresh inspired gases. The rebreathed gas mixture will proportionately change the composition of the inspired gases. Apparatus dead space always engenders rebreathing and it should always be minimized. This is especially important if the patient is small or has marginal ventilatory capacity.

Effective alveolar ventilation equals total minute ventilation minus physiologic dead space (including apparatus dead space). Alveolar minute ventilation is usually

defined by the partial pressure of carbon dioxide in arterial blood (PaCO$_2$). Physiologic

dead space normally ranges from 40 to 60% of the tidal volume, but can be lower with

reductions in anatomic dead space and with large tidal volumes. Physiologic dead space

(%) can also be quite high in panting and in animals with diffuse parenchymal lung

disease.

Heat and evaporative water loss associated with breathing

Air is usually inspired at a temperature and water content which is below that of the

body. The air is warmed to body temperature and is 100% humidified as it passes down

the airway. During exhalation, some of the heat is returned to the upper airway surfaces

from the relatively warmer air stream from the lower airways. As the air cools, the excess

water vapor condenses on the surfaces of the upper airways. The upper airways act as a

counter-current condenser-humidifier.

Artificial airways such as endotracheal tubes function in a similar manner,

although they are not nearly as effective. Commercial condenser-humidifiers ("artificial

noses") can be attached to an endotracheal or tracheostomy tube to enhance the

humidification of the inspired air for animals that are intubated for an extended period of

time. These devices are economical, light-weight and disposable. There are different sizes

and they should be matched to the size of the patient. These devices accumulate water and

mucous, and will obstruct air flow if they are not replaced with a new unit (approximately

daily). Obstruction is especially a problem with undersized devices and in patients with

excessive airway secretions.

Air is inspired at widely varied temperatures and humidity. The temperature of

exhaled air in the nasal-breathing dog at rest varies with the inspired air temperature (Table 4) [34] [35] The humidity of the expired air is 100%.

Approximate exhaled air temperature at various inspired air temperatures[34]

Inspired air temperature (^{o}C)	Expired air temperature (^{o}C)
0	15
10	20
20	25
30	30
40	40

The water lost by breathing is the difference between the water content of the inspired air and that of the expired air. If, for instance, air is inspired at 20°C and 50% humidified (contains 8.7 mg of water/L) and is exhaled at 25°C, 100% humidified (23.1 mg of water/L), the net water loss is 14.4 mg of water per liter of air breathed. If a 10 kg dog breaths a minute ventilation of 200 ml/kg/minute, the calculated water loss would be 29 mg of water per minute; 1.7 gm per hour; or 42 gm (or mls) per day (4.2 ml/kg/day). This would increase to 6.2 ml/kg/day if the inspired air was only 10% humidified and would decrease to 1.7 ml/kg/day if the inspired air was 100% humidified. Daily respiratory water losses in the normal-breathing animal are small and are usually ignored in most fluid therapy plans.   This is a different matter, however, in an animal that is panting (see below).

Heat loss via the respiratory tract occurs via two mechanisms. First, expired air is warmer than the inspired air. This mechanism is quantitatively minor because the specific

heat of air is very low. A 10 kg dog inhaling air at 20°C and exhaling air at 25°C at a
minute ventilation of 200 ml/kg/hour would only lose about 4.5 kcal of heat per hour by
this mechanism[36].

Water content and vapor pressure of 100% saturated air at various temperatures [51]

Temperature		Water content	Vapor pressure		Temperature		Water content	Vapor pressure
(C)	(F)	content	pressure		(C)	(F)	content	pressure
		(mg/L)	(mm Hg)				(mg/L)	(mm Hg)
0	32	4.8	4.6		25	77	23.1	23.8
2	35.6	5.6	5.3		26	78.8	24.4	25.2
4	39.2	6.4	6.1		27	80.6	25.6	26.7
6	42.8	7.3	7		28	82.4	27.2	28.3
8	46.4	8.3	8		29	84.2	28.8	30
10	50	9.4	9.2		30	86	30.4	31.8
12	53.6	10.7	10.5		31	87.8	32.1	33.7
14	57.2	12.1	12		32	89.6	33.8	35.7
15	59	12.8	12.8		33	91.4	35.7	37.8
16	60.8	13.6	13.6		34	93.2	37.6	39.9
17	62.6	14.8	14.5		35	95	39.6	42.2
18	64.4	15.4	15.5		36	96.8	41.8	44.6
19	66.2	16.2	16.5		37	98.6	44	47
20	68	17.3	17.5		38	100.4	46.3	49.7
21	69.8	18.3	18.7		39	102.2	48.7	52.4
22	71.6	19.4	19.8		40	104	51.2	55.3
23	73.4	20.6	21.1		41	105.8	54.4	58.3
24	75.2	21.8	22.4		42	107.6	57.6	61.5

The major portion of the heat lost during breathing is due to the energy that it takes to
convert liquid water to water vapor (the latent heat of the evaporative process) (0.58
kcal/ml of water). A 10 kg dog inhaling air at 20°C, 50% humidified and exhaling air at
25°C, 100% humidified, would lose about 24.1 kcal of heat per day by this mechanism[36].
Respiratory heat loss would increase if the inspired air was colder than 20°C or the
humidity was lower than 50%[35] The total respiratory heat loss in this example (2.86

Kcal/kg/24 hours) could theoretically account for a 3.4 ^{o}C decrease in temperature in a 10 kg dog if it were to happen instantaneously.[37] Actual measured heat loss in 4 experimental dogs (weight approximately 25 kg) with a minute ventilation of 200 ml/kg/min was 5.5 Kcal/kg/24 hours[35] which exceeds the theoretical value calculated above. The respiratory heat loss in the normal-breathing patient is greatly overshadowed by daily heat production and is usually ignored. Heat loss varies directly with minute ventilation which varies markedly between individual dogs at rest. [33;35] Actual measured heat loss in 2 experimental dogs (weight approximately 25 kg) with a minute ventilation of 600 ml/kg/min was 16.4 Kcal/kg/24 hours [35].

Panting

When a dog pants, air may be inhaled through the nose and exhaled through the mouth and nose or air may be inhaled through the mouth and the nose and exhaled through the mouth and nose.[34;38] There is an accompanied increase in blood flow to the tongue and the nasal and tracheobronchial epithelium.[38] There is also an increase in salivation.[34]

A panting dog's minute ventilation may be as high as 1000 to 1500 ml/kg/min.[33;39] If a panting dog breathes air at 20°C, 50% humidified and exhales air at 25°C, 100% humidified, it would lose at least 21 to 31 mls of water/kg/day and 144 to 214 Kcal of heat. An theoretical instantaneous loss of 144 to 214 Kcal would decrease body temperature by 17 and 26°C, respectively.

Distribution of tidal volume

At FRC, the alveoli in the non-dependent regions of the lung are relatively larger

than are the alveoli in the dependent regions. The non-dependent alveoli are therefore

higher on their respective pressure/volume curve (and closer to the upper inflection point).

Since these alveolar units are closer to capacity at the beginning of the breath, they can

only accommodate a small change in volume to fill them to capacity. Alveoli in the

dependent regions of the lung are relatively smaller at FRC. They are lower on their

respective pressure/volume curve; closer to their lower inflection point. They can accept

more volume for a given change in pressure because they start at the beginning of the steep

portion of their pressure-volume curve. Since the inherent mechanical properties of the

lung are considered to be the same throughout the lung, the change in volume associated

with a given change in pressure, for each alveolus, depends upon the relative starting

position of the alveolus on its pressure-volume curve.[22] Alveoli in the dependent regions

of the lung consequently receive a larger share of each tidal volume and are better

ventilated than are alveoli in the non-dependent regions in the normal animal. [40] This may

not be true for very shallow breaths or very fast breathing rates and gas flow rates [40] such

as in panting or high frequency jet ventilation. Abnormal pleural pressure caused by

pleural space or abdominal space filling disorders, changes in breathing pattern

(diaphragmatic or intercostal), and positive pressure ventilation when the chest wall is

open, will also affect the distribution of the inspired tidal volume.

Alveoli in the dependent regions of the lung, irrespective of the position of the

animal, notwithstanding atelectasis or thoracotomy, and on a per alveolus basis, are better

ventilated. Many studies, however, use methodology that reports ventilation on the basis

of a horizontal slice of lung rather than on a per alveolus basis. This has important

implications with regard to the distribution of ventilation and perfusion as measured by

global imaging techniques especially when different body positions are compared. The lung somewhat resembles a pyramid with its broad-base toward the diaphragm and toward the spine. In cross-section, there is greater lung mass and therefore a larger number of alveoli at the "base end" of the lung than at the "apex end". From a horizontal perspective, slices of lung toward the "base end" of the lung receive a proportionately larger share of each tidal volume, irrespective of the position of the animal.

At FRC, the alveoli in the dependent regions of the lung are at a lower position on their pressure-volume curve and they are therefore closer to their respective critical closing pressure or volume. In addition, in lateral or dorsal recumbency, the weight of the heart and other mediastinal structures, and the abdominal contents, rest upon the underlying lung. The dependent lung regions, in any position, are the first to exhibit small airway and alveolar collapse. This is especially important in the recumbent, immobile patient. Frequent position changes are an important aspect of the intensive management of these patients to help minimize dependent small airway and alveolar collapse.

The regional pattern of small airway and alveolar collapse in diffuse lung disease is however much more heterogenous than just in the dependent lung regions. Histologically there are hyper-inflated alveoli from gas-trapping due to premature airway collapse; normally ventilated alveoli; poorly ventilated alveoli; and collapsed, non-ventilated alveoli, immediately adjacent to one another. There are marked local differences in inflation time constants and much opportunity for differential expansion of adjacent lung units. This differential expansion is thought to perpetuate the shear stress and damage to the delicate septal tissues (alveolar epithelium and capillary endothelium), which, in turn, perpetuates the parenchymal lung damage.

Distribution of perfusion

The pulmonary vasculature is a low resistance system which normally exerts little control over the distribution of the pulmonary blood flow. Gravity, however, has a big effect. Blood is heavy (1 gm/ml) and vascular pressure increases toward the dependent regions of the lung, and decreases toward the non-dependent regions, compared to the pressure at the level of the pulmonary artery. Increasing transvascular hydrostatic pressure in the dependent regions distends the pulmonary vessels, which, in turn, decreases resistance to blood flow through them. Consequently a greater proportion of the cardiac output flows through the dependent regions of the lung.

In all cases, flow through a tube is directly proportional to the difference between an upstream and a downstream pressure. This difference in pressure is often assumed to be arterial inflow pressure (P_{art}) and venous outflow pressure (P_{ven}). This is only appropriate when the "intra-organ" pressure is less than P_{ven}, which is often not the case. Cerebral perfusion pressure, for instance, is not calculated as arterial - central venous pressure (CVP), but as arterial - intracranial pressure (ICP) because ICP is higher than CVP. There is an analogous situation in the lungs. The pulmonary capillaries and veins are thin-walled vessels which are susceptible to compression by perivascular pressure. As previously discussed, transpulmonary pressure is greatest in the non-dependent regions of the lung and lowest in the dependent regions. As discussed above, there is also an increase in blood pressures from the non-dependent to the dependent regions of the lung.

There are three theoretical zones of the lung which are defined by the relationship between transpulmonary pressure (perivascular; P_{alv}), capillary inflow pressure (P_{art}), and

capillary outflow pressure (P_{ven})[17;41]   It is conventional to use the term "alveolar pressure",

even though the pressure at issue is transpulmonary pressure. In zone I, in the non-

dependent regions of the lung, there is no flow because P_{alv} exceeds P_{art}. There is very

little to no zone I in the lung of the normal dog. In zone III, in the dependent regions of the

lung, flow is proportional to the difference between P_{art} and P_{ven} pressure. P_{alv} is not a

factor since it is lower than venous outflow pressure. Zone II, in the middle of the lung,

driving pressure is the difference between P_{art} and P_{alv} rather than the difference between

P_{art} and P_{ven}.

Pr art $\bigcirc$ ⬭ Capillary ⟩——⟨ Pr ven

Pr alv

Zone II of the lung is a Starling resistor: Capillary pressure gradually decreases
from the arterial end of the capillary to the venous end. When transpulmonary
(Palv) exceeds venous pressure at the end of the capillary, it collapses. Part is,
however, greater than P alv and blood continues to flow into the capillary until the
luminal pressure at the end of the capillary exceeds Palv, at which time the
collapsed segment springs open. The rapid run-off of blood from the end of the
capillary causes the intra-luminal pressure to fall below that of Palv and the
terminal capillary collapses. The process cycles continuously.

Zones of the lung

Region	Zone	Relative pressures	Flow situation
Nondependent	I	$P_{alv} > P_{art} > P_{ven}$	No flow ($P_{alv} > P_{art}$)
Middle	II	$P_{art} > P_{alv} > P_{ven}$	Intermittent flow ($P_{alv} > P_{ven}$)
Dependent	III	$P_{art} > P_{ven} > P_{alv}$	Free flow ($P_{art} > P_{ven}$)
Very dependent	IV	$P_{tis} > P_{art} > P_{ven} > P_{alv}$	No flow ($P_{tis} > P_{art}$)

P_{alv} = regional alveolar (transpulmonary) pressure
P_{art} = capillary inflow pressure
P_{ven} = capillary outflow pressure
P_{tis} = pericapillary pressure.

Zone II represents a Starling resistor. When the pressure surrounding the capillary (P_{alv}; transpulmonary pressure) is greater than the venous-end outflow pressure, the terminal capillary segment collapses and there is no flow out of the capillary. But since P_{art} is greater than P_{alv}, flow continues into the capillary, which increases the end-capillary pressure at the outflow end. When the end-capillary pressure exceeds perivascular pressure, the collapsed end-capillary segment "pops" open. As blood flows out of the capillary, the end-capillary pressure once again drops below that of perivascular pressure, and the capillary segment collapses and flow ceases. The process repeats itself very rapidly, such that flow appears to be continuous, but in reality is quite intermittent. The clinical significance of zone II is that P_{alv} (transpulmonary pressure), particularly as it relates to positive pressure ventilation, can have an important impact on the resistance to blood flow through the lung. The zone concept is used to explain the general idea about the forces which regulate driving pressure in the capillaries of the lung. The lung, however, is much too heterogenous to suggest that there are actually identifiable horizontal lines which separate two distinctly different lung zones, even in the normal lung, much less the diseased lung.

The accumulation of interstitial fluids in the dependent regions of the lung or fibrosis, increases tissue pressure and may cause narrowing and collapse of regional capillaries. When pericapillary pressure exceeds arterial pressure (zone IV), there is no capillary blood flow. There is very little, if any, zone IV in the lung of the normal dog, but this can increase substantially in disease.

Ventilation/perfusion relationships

The matching of ventilation and perfusion is obviously important to proper lung function. It does no good to ventilate an alveolus that is not being perfused (alveolar dead space) and it does no good to perfuse an alveolus that is not being ventilated (atelectasis). In the normal lung, ventilation and perfusion are not uniformly matched and this disparity increases in lung disease.

Both ventilation and perfusion increase toward the dependent regions of the lung. Since blood is heavier than lung parenchyma, perfusion increases at a greater rate than does ventilation. The non-dependent regions of the lung have a higher-than-average ventilation/perfusion (V/Q) ratio while the dependent regions of the lung have a lower-than-average V/Q ratio (Table 7). The blood gases of the end-capillary blood in the non-dependent regions of the lung reflect their relative hyperventilation (higher-than-average oxygen and lower-than-average carbon dioxide), while those of the dependent regions represent their relative hypoventilation. (lower-than-average oxygen and higher-than-

The blood gas effect of regional ventilation-perfusion mismatching[17]

	Ventilaton (% of tidal volume)	Perfusion (% of cardiac output)	V/Q	PcO_2* (mm Hg)	$PcCO_2$* (mm Hg)
Nondependent	20	10	2.00	120	30
Middle	35	30	1.17	105	40
Dependent	45	60	0.75	95	42

*PcO_2 and $PcCO_2$ = end-capillary PO_2 and PCO_2, respectively

average carbon dioxide).

Since a greater proportion of the pulmonary blood flow traverses the dependent portion of the lung, the dependent lung regions have a greater influence on the net blood

gases of arterial blood. When atelectasis or edema fluid develops, the problem often predominates in the dependent regions of the lung,. This is unfortunate since the greater dependent blood flow will now be exposed to an even worse V/Q mismatch.

Critically ill patients, in general, oxygenate better in the prone position than in the supine position. [42] This is attributed to the fact that in the supine position, when atelectasis develops, it develops in the regions of the lung which have the greater number of alveoli (in the horizontal plane). The net effect of atelectasis is minimized in the prone position because there is less horizontal lung mass in lung regions toward the sternum. Some patients with lung disease have a "preferred" position where oxygenation is the best, while some patients have a "non-preferred" position where oxygenation is unacceptable and such positions should be avoided.

The pulmonary vasculature is not, however, without any active neural or mediator control over vascular tone. Endothelial and muscle cells have numerous receptors which mediate vasodilation (alpha$_2$ agonists, beta$_2$ agonists, acetylcholine, histamine, ATP-P$_{2y}$, adenosine-A$_2$, prostacyclin, substance P, atrial natriuretic hormone, bradykinin, endothelin-ET$_B$, vasopressin) or vasoconstriction (alpha$_1$ agonists, ATP-P$_{2x}$, adenosine-A$_1$, thromboxane, angiotensin, endothelin-ET$_A$,).[17] Pulmonary hypoxic vasoconstriction, in response to low mixed-venous or alveolar PO$_2$, improves V/Q matching and lung performance. Inappropriate vasodilation or constriction caused by disease or drugs, enhances V/Q mismatching and causes hypoxemia.

Alveolar gas composition

Atmospheric air at sea level primarily contains nitrogen and oxygen, small amounts of water and carbon dioxide, and very small amounts of other gases and pollutants.

Normal atmospheric and alveolar gas concentrations at sea level

	Air (%) [mm Hg]	Alveolus (%) [mm Hg]
Oxygen	(21) [160]	(14) [105]
Carbon dioxide	(0.03) [0.3]	(5) [40]
Nitrogen	(78) [593]	(74) [565]
Water vapor	(1) [8]	(7) [50]

The partial pressure of oxygen is calculated as barometric pressure (760 at sea level) x 21% = 160 mm Hg. Inspired air becomes fully humidified when it is breathed into the alveoli. The vapor pressure of water in fully saturated air at 38 ^{o}C is 50 mm Hg (Table 20-5). The net partial pressure of the inspired oxygen is then calculated as barometric pressure (760 mm Hg at sea level) minus water vapor (50 mm Hg at 38°C) x 21% = 150 mm Hg. Venous blood is continuously delivers carbon dioxide to the alveoli and removes oxygen from the alveoli as it traverses the capillary bed. The carbon dioxide and oxygen diffuse down a partial pressure gradient until the partial pressure between the alveolus and the capillary blood is equilibrated. Alveolar gas composition, compared to atmospheric, has a higher water vapor and carbon dioxide, and a lower oxygen, partial pressure and concentration (Table 8). Alveolar PO$_2$ (P$_A$O$_2$) can be calculated by the alveolar air equation:

$$P_AO_2 = ([P_b - P_{H2O}] \times \% \text{ oxygen}) - PaCO_2 (1/RQ)$$

where P$_b$ = barometric pressure; P$_{H2O}$ = partial pressure of water of saturated air at body temperature; and RQ is respiratory quotient, the ratio of carbon dioxide production to

oxygen consumption. ($[P_b - P_{H2O}]$ x % oxygen) calculates the partial pressure of inspired

oxygen (P_IO_2). The P_AO_2 can be calculated for any altitude by inserting the appropriate

barometric pressure for that altitude into the formula for P_IO_2. The P_AO_2 can be calculated

for any inspired oxygen concentration by substituting the appropriate oxygen concentration

into the P_IO_2 formula. The P_IO_2 at sea level and 21% oxygen, is invariably about 150 mm

Hg. If an average RQ in a critically ill patient is about 0.9, 1/RQ = 1.1. The alveolar PO_2

equation can therefore be shortened to:

$$P_AO_2 = 150 - (PaCO_2 \text{ x } 1.1)$$

At sea level and 21% oxygen, P_AO_2 is calculated to be about 106 mm Hg.

The effect of altitude on barometric pressure and inspired oxygen[17]

Altitude (ft)	Altitude (M)	Barometric pressure (mmHg)	Inspired PO2 (mmHg)	% O_2 required for sea level P_IO_2
0	0	760	149	20.9
2000	610	707	138	22.6
4000	1220	659	127	24.5
6000	1830	609	118	26.5
8000	2440	564	108	28.8
10,000	3050	523	100	31.3
15,000	4575	429	80	42.8
20,000	6100	349	63	49.3
30,000	9150	226	37	83.2

Assessing blood oxygenation

Blood oxygen can be expressed in three different ways: the partial pressure of

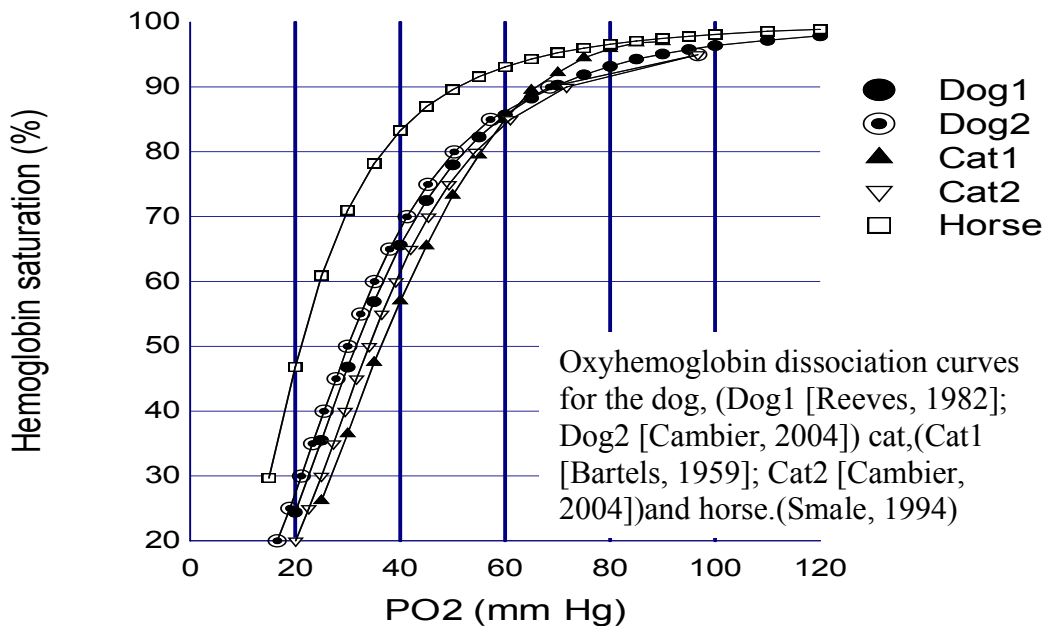oxygen dissolved in the plasma (PO_2; units = mm Hg), the percent saturation of the

hemoglobin (SO_2; units $=$ %), and the whole blood oxygen content (ContentO$_2$; units $=$ mls of oxygen per 100 mls whole blood).

The Partial Pressure of Oxygen (PO_2)

The PO_2 is the partial pressure (the vapor pressure) of oxygen dissolved in solution in the plasma and is measured with a blood gas machine with a silver anode/platinum cathode system in an electrolyte solution (polarography) separated from the unknown solution (the blood) by a semipermeable (to oxygen) membrane.   The arterial PO_2 (PaO$_2$) is a measure of the ability of the lungs to efficiently move oxygen from the atmosphere to the lungs. The normal PaO$_2$ at sea level ranges between 80 and 110 mm Hg. Hypoxemia is usually defined as a PaO$_2$ < 80 mm Hg. A PaO$_2$ of less than 60 mm Hg marks severe hypoxemia and treatment should be implemented. There are only two treatments: 1) increase the inspired oxygen concentration; 2) mechanical ventilation; or some combination of the two.

Venous PO_2 reflects tissue PO_2 and bears no correlation to arterial PO_2. Mixed or central venous PO_2 ranges between 40 and 50 mm Hg. Values below 30 mm Hg may be caused by anything that decreases the delivery of oxygen to the tissues (hypoxemia, low cardiac output, vasoconstriction); values above 60 mm Hg (while breathing room air) suggest reduced tissue uptake of oxygen (shunting, septic shock, metabolic poisons). Venous blood for such evaluations must be from a central vein such as the jugular, anterior vena cava, or pulmonary artery. Continuous mixed-venous oxygen-hemoglobin saturation can be measured via a pulmonary artery catheter containing a fiberoptic infrared light source. The reflected light beam is proportional to the degree of hemoglobin oxygenation.

Hemoglobin saturation (%)

100
90
80
70
60
50
40
30
20

● Dog1
◉ Dog2
▲ Cat1
▽ Cat2
□ Horse

Oxyhemoglobin dissociation curves for the dog, (Dog1 [Reeves, 1982]; Dog2 [Cambier, 2004]) cat,(Cat1 [Bartels, 1959]; Cat2 [Cambier, 2004])and horse.(Smale, 1994)

0   20   40   60   80   100   120

PO2 (mm Hg)

Oxyhemoglobin saturation

Hemoglobin saturation measures the percent saturation of the hemoglobin and is related to the PaO_2 by a sigmoid curve. The clinical information derived from the measurement of hemoglobin saturation (SaO_2) is similar to that obtained from a PaO_2 measurement in that they are both a measure of the ability of the lung to deliver oxygen to the blood stream. The "numbers of concern" are, however, different:

Correlation between PaO_2 and SaO_2.

PaO_2	SaO_2	Importance
> 80	> 95	Normal
< 60	< 90	Serious hypoxemia
< 40	< 75	Very serious hypoxemia

The percent hemoglobin saturation can be measured with a bench top oximeter or a pulse oximeter, or it can be extrapolated from the measured PO_2 via a standard oxyhemoglobin dissociation curve. Oximetry is based upon the pattern of red to infra-red

light absorption of hemoglobin: oxyhemoglobin, reduced hemoglobin, methemoglobin, and carboxyhemoglobin each absorb light differently. At least one wave length of light, preferably one that maximizes the difference between the hemoglobin species of interest and the others, is required to identify each species of hemoglobin. Pulse oximeters use only two wave lengths (660 and 940 nm) and are designed to measure oxygenated and unoxygenated hemoglobin. If methemoglobin or carboxyhemoglobin are present in high concentrations, they will absorb light and will impact the measurement made by the pulse oximeter. Due to the biphasic absorption of methemoglobin at both the 660 and 940 nm wavelengths, abnormal accumulations of this hemoglobin species tends to push the pulse oximeter reading toward 85% (underestimating measurements when SaO_2 is above 85% and overestimating it when below 85%). Carboxyhemoglobin absorbs light like oxyhemoglobin at 660 nm but hardly at all at 940 nm and this would increase the apparent oxyhemoglobin value. Fetal hemoglobin produces very little effect on measured hemoglobin saturation. Indocyanine green dye and methylene blue dye absorb light and will generate falsely low saturation measurements

Tissue, venous and capillary blood, non-pulsatile arterial blood, and skin pigment also absorb infrared light. Pulse oximeters have different ways of separating this background absorption from the change in light absorbance associated with pulsatile arterial blood. There is a fairly narrow spectrum of wavelengths that both pass through skin and yet are absorbed by hemoglobin. Differences in tissue absorption or scatter of light, different thicknesses of tissue, smaller pulsatile flow patterns and small signal to noise ratios, and incompletely compensated light emitting diodes may account some of the inaccuracies associated with pulse oximeters. Inaccuracies may also generate from

baseline read errors (motion), differences in sensor location, and electrical or optical interference. The accuracy of a pulse oximeter is greatest within the range of 80 and 95%, and is determined by the accuracy of the empirical formula that is programmed into the instrument. For most clinical purposes, most pulse oximeters are sufficiently accurate *approximations* of hemoglobin saturation, but their accuracy should be verified by an in vitro standard. There are substantial bias and precision variations and response times between products at different levels of saturation.

Pulse oximeters attach to a patient externally (tongue, lips, tail, toenail). A pulse oximeter is an automatic, continuous, audible monitor of mechanical cardiopulmonary function. It specifically measures pulse rate and hemoglobin saturation, and requires reasonable pulmonary and cardiovascular function in order to achieve a measurement. One of the common reasons for poor instrument performance has been peripheral vasoconstriction; the instrument will not be able to pick up a pulse. Its value as an ongoing monitor in detecting hypoxemia has been established. Accuracy should be verified from time to time with an arterial blood gas measurement.

SaO_2 may not be too discriminating when a animal is breathing an enriched oxygen
mixture since such measurements would be positioned on the upper plateau of the dissociation curve. The difference between a PaO_2 of 500 and 100 mm Hg in an animal breathing 100% oxygen is very important; the corresponding decrease in SaO_2, from 99 to 98%, would hardly be noticed.

Whole blood oxygen content and oxygen delivery

Oxygen content is dependent upon both hemoglobin concentration and PO_2. Oxygen content is calculated by the formula: $(1.34 \times Hb \times SaO_2) + (0.003 \times PO_2)$ or may be measured with a galvanic cell quantitative analyzer. The relationship between oxygen content and PO_2 is also defined by a sigmoid curve. Hemoglobin concentration is quantitatively the most important contributor to oxygen content (anemia is a far more potent cause of decreased oxygen content than is hypoxemia). The partial pressure of oxygen is important because it provides the driving pressure for the flow of oxygen molecules from the plasma to the mitochondria. Content is important as a reservoir of oxygen to buffer the decrease in PO_2 that would occur when oxygen molecules diffuse out of the plasma. Oxygen delivery is the product of oxygen content and cardiac output.

The PaO_2 at which human hemoglobin is 50% saturated (P_{50}) is about 27 mm Hg.

P_{50} is a common way to define the position of the curve; whether it is shifted to the left (a

lower P_{50} value due to higher hemoglobin affinity for oxygen) or to the right (a higher P_{50}

value due to lower hemoglobin affinity for oxygen). The P_{50} for canine hemoglobin is

about 29 mm Hg. The P_{50} for feline hemoglobin, however, is about 36 mm Hg. This

represents a rightward shift of the oxyhemoglobin dissociation curve for the cat compared

to the dog. Like hemoglobin saturation, oxygen content does not increase much when the

PO_2 is raised above 100 mm Hg; the hemoglobin is mostly full and further increases in

Effect of anemia, hypoxemia, and oxygen breathing on PO_2, SO_2, and ContentO_2

Condition	F_IO_2	PO_2 (mm Hg)	SO_2 (%)	Hemoglobin (gm/dl)	ContentO_2 (ml/dl)
Normal	0.21	100	98	15	19.9
Anemia	0.21	100	98	5	6.9
Hypoxemia	0.21	50	85	15	17.3
Hyperoxemia	1.0	500	99.9	15	21.6
Anemia & hyperoxemia	1.0	500	99.9	5	8.2
Anemia & hypoxemia	0.21	50	85	5	5.8

content are attributed mostly to an increase in dissolved oxygen in the plasma.

The treatment for excessive anemia is an infusion of a hemoglobin-containing

solution. However, in the interim, between recognition of severe anemia and

implementation of the transfusion, does an enriched inspired oxygen concentration benefit

the patient? Clearly, even 100% inspired oxygen does not increase the oxygen content

very much in the anemic patient and not nearly enough to provide all of the oxygen

requirements of the patient. Anemia causes problems for the patient when the blood

oxygen content becomes insufficient to meet the metabolic requirements of oxygen consumption. It is no necessary to meet the entire oxygen consumption requirements of the animal with the oxygen therapy. It is only necessary to increase the oxygen content enough to move the animal from a little below the "death line" to a little above it. Sometimes a little bit of help can make a lot of difference to a patient and oxygen therapy is recommended in the anemic patient.

Oxygen delivery is the product of oxygen content and cardiac output. Animals can tolerate a decrease in oxygen content if they can increase their cardiac output to compensate. Animals tolerate anemia and poor cardiac output poorly. Oxygen delivery needs to be sufficient to meet the consumption requirements of the patient. Normally oxygen delivery far exceeds oxygen consumption. Oxygen extraction normally ranges between 20 and 25% of the oxygen delivery. Mixed venous oxygen represents the balance between whole body oxygen delivery and oxygen consumption.   Mixed or central venous PO_2 ranges between 40 and 50 mm Hg in normal dogs.   When oxygen delivery is decreased (low cardiac output, anemia, hypoxemia,, vasoconstriction), the tissues continue to "draw" their normal amount of oxygen and so oxygen extraction increases and venous oxygen decreases. Venous PO_2 values below 30 mm Hg are usually attributed to excessively low oxygen delivery, but could be caused by high oxygen consumption. Values below 20 mm Hg should be considered life-threatening. When oxygen delivery finally becomes too low to support oxidative phosphorylation, lactic acidosis ensues. Venous PO_2 values above 60 mm Hg (while breathing room air) are primarily suggestive of reduced tissue uptake of oxygen (shunting, septic shock, metabolic poisons, hypothermia), but could also be attributed to high oxygen delivery .

Oxygen delivery (DO_2) (ml/min/M^2) resulting from various combinations of packed cell volume (PCV) and cardiac output (Q) (assuming normal lung function and a PaO_2 of 100 mm Hg)(normal range for Q is 3.5 to 5.5).*

	Q = 6.5	5.5	4.5	3.5	2.5
PCV = 40	1155	977	799	621	444
30	873	739	604	470	336
25	731	618	506	394	281
20	588	498	407	317	226
15	446	378	309	240	172
10	304	257	210	164	117

*It has been recommended to maintain DO_2 above 550-600 ml/min/M^2. Anemic patients can maintain oxygen delivery if they can increase cardiac output to compensate. Anemia and low cardiac output combine to produce very low values for oxygen delivery.

Mechanisms of hypoxemia

Hypoxemia may be caused by a low inspired oxygen concentration, hypoventilation, or venous admixture. A low inspired oxygen must be considered any time an animal is attached to mechanical apparatus such as a face mask, Bain's circuit, anesthetic machine, ventilator, or in an enclosed environment such as oxygen cage or anesthetic induction chamber. Hypoventilation is defined by an elevated $PaCO_2$. Venous admixture represents a reduced efficiency of lung oxygenating ability. Venous admixture is all of the ways in which venous blood can get from the right side of the circulation to the left side of the circulation without being properly oxygenated; this less-than-optimal oxygenated blood then admixes with optimally-arterialized blood flowing from the more normal lung units and dilutes its oxygen content. There are 4 causes of venous admixture:

low ventilation/perfusion regions; small airway and alveolar collapse; diffusion defect; anatomic right-to-left shunts. A fifth cause of venous admixture is low venous oxygen content secondary to low cardiac output and increased tissue oxygen extraction.

Low ventilation/perfusion regions occurs secondary to airway narrowing from bronchospasm (reflex or disease induced), fluid accumulation along the walls of the lower airways, or epithelial edema. The effect is hypoventilation of the involved lung units relative to their blood flow and suboptimal arterialization of the blood flowing through the area. This is a common mechanism of hypoxemia in mild to moderate pulmonary disease. This mechanism of hypoxemia is very responsive to oxygen therapy because even though the lung unit is being hypoventilated, the high alveolar oxygen concentrations normalize the oxygenation of the blood flowing through the area (PaO_2 values may reach expected values (500 mmHg) when breathing 100%). A low V/Q disturbance could also be attributed to an increase in blood flow to the area. This may be part of the explanation for hypoxemia in pulmonary thrombo-emolism.

Small airway and alveolar collapse (a no ventilation but still-perfusion scenario) is caused by spontaneous collapse of small airways and alveoli caused by either positional stasis or by an increase in airway fluids which increases surface tension and collapsing tendency. The effect is that the blood flowing through the area will not be arterialized at all (it will remain venous blood when it exits the gas exchange area). This is a common mechanism of hypoxemia in moderate to severe pulmonary disease. This mechanism is not responsive to oxygen therapy - oxygen cannot get down to the gas exchange area. These small airways and alveoli must be opened by positive pressure ventilation if they are to become functional gas exchange units.

Diffusion impairment, due to a thickened respiratory membrane, is an uncommon cause of hypoxemia. I, however, the type 1 pneumocytes are damaged by inhalation inflammatory injury, they are replacement by the thick, cuboidal type 2 pneumocytes (which will eventually become type 1 pneumocytes). This mechanism of hypoxemia is partially responsive to oxygen therapy.

Anatomical shunts are right-to-left extra- or intrapulmonary shunts where the blood flows from the right side of the circulation to the left side without ever coming into contact with a functional gas exchange unit. This is not a common mechanism of disease in clinical medicine. It is responsive to neither oxygen therapy nor positive pressure ventilation, and requires surgical correction.

In pulmonary parenchymal disease, lungs often perform poorly for the purposes of oxygenation and yet are well able to eliminate carbon dioxide (hypocapnic hypoxemia). This is due to the fact that alveolar-capillary units that are working relatively well can compensate for those that are working relatively poorly with respect to carbon dioxide elimination, but not for oxygen intake. The reason for this is that at the normal alveolar/arterial blood PCO_2 values are positioned on the steep, linear portion of the PCO_2/CO_2 content curve and an increase in alveolar ventilation causes a proportional decrease in CO_2 content. In contrast, normal alveolar/arterial blood PO_2 values are positioned on the upper, flat portion of the oxyhemoglobin dissociation curve and an increase in alveolar ventilation causes very little increase in O2 content.

Estimating the magnitude of venous admixture

1) The alveolar - arterial PO_2 gradient (A-a PO_2) is the difference between the calculated alveolar partial pressure of oxygen (P_AO_2) and the measured arterial partial pressure of oxygen (PaO_2). Alveolar PO2 is calculated as inspired PO_2 (P_IO_2) – $PaCO_2$ (1.1). The 1.1 is 1/RQ, assuming RQ = 0.9, which is a reasonable average for critically ill patients. Inspired PO_2 is not the oxygen concentration of air that is breathed in; it is the concentration of oxygen in the air entering the alveoli after it has been fully humidified. It is calculated as barometric pressure – 50) x F_IO_2 (which is the concentration of oxygen [expressed as a fraction] in the air that is breathed in). The 50 is the vapor pressure of water when the air is 100% saturated at body temperature. At sea level, breathing 21% oxygen, P_IO_2 is invariably about 150 mm Hg. The A-a PO_2 is normally about 10 mm Hg when breathing 21% oxygen at sea level and is about 100 mm Hg when breathing 100% oxygen. If the calculated A-a PO_2 is greater than 15 mm Hg when the animal is breathing room air or greater that 150 mm Hg when the animal is breathing 100% oxygen, the animal has venous admixture. The greater the A-a PO_2 , the greater the venous admixture. The expected A-a PO_2 at intermediate inspired oxygen concentrations has not been established and must be extrapolated.

2) There are only four gases of note in the alveoli (nitrogen, water vapor, oxygen, and carbon dioxide). Barometric pressure and the partial pressures of nitrogen and water vapor do not change. Blood flowing through the lungs adds carbon dioxide to and removes oxygen from the alveoli at a rate that is comparable to metabolic production and consumption of these two gases. Alveolar PCO_2 and PO_2 are, therefore, approximately reciprocally related in the normal lung. A change in $PaCO_2$ should be associated with an

opposite and approximately equal (1.0 to 1.2 x) change in the PaO_2. The $PaO_2 + PaCO_2$ added value for arterial blood should be about 140 ± 20 mm Hg, when the animal is breathing 21% oxygen at sea level. A discrepancy develops with progressive venous admixture such that the added PaO_2 and $PaCO_2$ values drop progressively below 120 mm Hg; the greater the discrepancy between the added value and 120 mm Hg, the greater is the venous admixture.

3) When breathing 21% oxygen, changes in $PaCO_2$ have an important impact on PaO_2 and must be taken into account when calculating the expected PaO_2. With progressively higher inspired oxygen concentrations, changes in $PaCO_2$ have a progressively less important effect on PaO_2 and, for clinical purposes, can legitimately be ignored at inspired oxygen concentrations over about 40%. A common rule-of-thumb is that the anticipated PaO_2 should be at least 5 times the inspired oxygen concentration (50% x 5 = an anticipated $PaO_2 > 250$ mm Hg). If the PaO_2 is only 3 to 5 x the inspired oxygen concentration, a mild oxygenating inefficiency exists; between 2 and 3 x = moderate lung inefficiency; while < 2 = severe venous admixture.

The PaO_2/F_IO_2 ratio is frequently used in the medical literature and represents this same idea except F_IO_2 is expressed as a fraction instead of a whole number (0.50 instead of 50%). This represents only a decimal point change in the dividend. In normal lungs the PaO_2/FiO_2 ratio is > 500 mm Hg; values between 300 and 500 represent mild oxygenating inefficiency; values between 200 and 300 represent moderate lung inefficiency; and values below 200 represent severe venous admixture.

4) If mixed venous blood can be obtained, the venous admixture can be calculated:

$Q_S/Q_T = (CcO_2 - CvO_2) / (CcO_2 - CaO_2)$. Q_S/Q_T = venous admixture expressed as a percent of cardiac output that would have to traverse the lung venous blood, assuming the rest is optimally arterialized. CcO_2 = oxygen content of end-capillary blood; CvO_2 = oxygen content of mixed venous blood; and CaO_2 = oxygen content of arterial blood. Oxygen content (ml/dl) is calculated as: $(1.34 \times Hb \times SO_2) + (0.003 \times PO_2)$ where SO_2 is percent hemoglobin saturation with oxygen. Venous admixture is normally less than 5% of the cardiac output; values over 10% are considered to be increased. Venous admixture may increase to over 50% in diffuse lung disease.

Appendix I.

Formulas for calculating heat loss by inspired air warming and humidification.

1. Heat loss due to warming of the inspired air per hour = [(0.24)(inspired - expired air temperature)(1.3)(minute ventilation)(60)]/1000; where 0.24 = specific heat of inspired air (cal/gm/^{o}C,) and 1.3 = density of air (gm/L).[44]

2. Heat loss due to the latent heat of vaporization of the humidification process per hour = [(0.58)(inspired - expired air water content [mg/L])(minute ventilation)(60)]/1000; where 0.58 = latent heat of vaporization of water (Kcal/gm).[45]

Appendix II.

Heat content of the body

The average specific heat of the body is 0.83 Kcal/kg/^{o}C.[44] The heat content of a 10 kg dog at 38 ^{o}C is calculated to be 315.4 Kcal. A theoretical instantaneous loss of 28.6 Kcal (normal daily respiratory heat loss) would decrease body temperature to 34.6 ^{o}C if no heat were produced by metabolic processes (315.4 - 28.6 = 286.8; 286.8 Kcal/(10 x 0.83) = 34.6 ^{o}C). A theoretical instantaneous loss of 144 to 214 Kcal in the panting dog would decrease body temperature to 21 and 12 ^{o}C, respectively if no heat were produced by metabolic processes.

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