Respiratory Physiology: Gas Exchange and Respiratory Mechanics

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Respiration provides oxygen (O\textsubscript{2}) and removes carbon dioxide (CO\textsubscript{2}) for the body. An extraordinary anatomic arrangement of functional units (the alveoli) delimited by extra-thin walls (epithelium and endothelium) creates the interface for gas exchange between air and blood. Repetitive expansion and collapse of the chest wall facilitates movement of gas in and out of the lungs. This review focuses on the mechanical events that regulate the exchange of O\textsubscript{2} and CO\textsubscript{2} between the body and the outside environment.

Gas exchange.

How much O\textsubscript{2} gets from the atmosphere to the arterial blood—the alveolar air equation. Oxygen constitutes approximately 21% of the air. At sea level, air exerts a pressure of 760 mmHg; once inside the airways, it is saturated by water vapor (47 mmHg) and the partial pressure of O\textsubscript{2} in the inspired air (PiO\textsubscript{2}) can be calculated:

\[
\text{PiO}_2 = (760 - 47) \text{ mmHg} \times 0.21 \approx 150 \text{ mmHg}
\]

In the alveoli, one volume of O\textsubscript{2} is exchanged for 1.2 volumes of CO\textsubscript{2} (at a normal respiratory quotient [RQ] of 0.8). Hence, with a normal PaCO\textsubscript{2} of 40 mmHg, the alveolar PO\textsubscript{2} (PAO\textsubscript{2}) will be:

\[
\text{PAO}_2 = \text{PiO}_2 - \text{PaCO}_2 \times 1.2 \approx 100 \text{ mmHg}
\]

Past the pulmonary capillaries, the arterial blood receives a small amount of non-oxygenated blood (e.g., from the bronchial circulation), and the PaO\textsubscript{2} decreases slightly below 100 mmHg.

Causes of hypoxemia. Understanding how oxygen moves from the air to the arterial blood (Figure 1) provides a convenient framework to classify the various causes of hypoxemia. From ‘top to bottom’ these include:

Low PiO\textsubscript{2}. The most common cause of a low PiO\textsubscript{2} is breathing at high altitude. As a reference, breathing air at 5,300 feet in Denver lowers the PiO\textsubscript{2} from 150 to approximately 120 mmHg, and breathing air at 30,000 feet on the summit of Mount Everest lowers the PiO\textsubscript{2} to 40 mmHg. Although rare, causes of low PiO\textsubscript{2} at sea level are generally related to the accidental administration of a hypoxic mixture.

Low PAO\textsubscript{2}—hypoventilation. The alveolar air equation explains how hypventilation, in addition to hypercarbia, can cause hypoxemia. While a normal PaCO\textsubscript{2} and RQ will result in a PACO\textsubscript{2} of 48 mmHg and a PAO\textsubscript{2} of 100 mmHg, an increased PaCO\textsubscript{2}, e.g., 80 mmHg, will decrease the PAO\textsubscript{2} to 150 - 80 x 1.2 = 54 mm Hg. This scenario underlies the importance of immediately administering O\textsubscript{2} to the patient that seems to be hypoventilating, as supplemental O\textsubscript{2} will rapidly increase PiO\textsubscript{2} and offset the effects of a high PaCO\textsubscript{2} in the alveolus. Common causes of hypventilation include: a) a decrease of the central drive to breathe, as it occurs with the administration of hypnotics and opiates; b) respiratory muscle weakness, in syndromes such as Guillain-Barre’ and polineuropathy of critical illness; and c) high resistive or elastic ventilatory loads (see below), as it occurs in severe asthma and abdominal distention.

Impaired diffusion across the alveolo-capillary membrane is rare. Although this seems to contradict the observation that the diffusing capacity of carbon monoxide for the lung (DLCO) is a sensitive test to quantify impairment of lung function, the DLCO is primarily affected by abnormality in ventilation / perfusion ratio rather than of gas diffusion per se.

Low PaO\textsubscript{2}. Under normal circumstances, the PaO\textsubscript{2} is slightly lower than the PAO\textsubscript{2} (see above). Additional increase in this gradient occurs in physiological conditions such as aging, the sitting and supine positions, and with the induction of general anesthesia. The decrease of PaO\textsubscript{2} under these circumstances is due to the absence or decrease in the following:

- Decrease in alveolar ventilation (VA).
- Decrease in the diffusion surface area (DS).
- Increase in the blood flow (Q).
of ventilation to variable areas of the lung, which results in shunt and low ventilation / perfusion (V/Q) ratio respectively. These two phenomena are part of the same physiological continuum, but may have different clinical implications.

1. **Shunt** occurs when there is no ventilation at all to alveoli that receive blood flow. Under these circumstances, the PaO\textsubscript{2} is equal to the PvO\textsubscript{2}. The fraction of total pulmonary blood flow (Qt) that is shunted away from unventilated alveoli (Qs) can be calculated from the difference in content of O\textsubscript{2} between the pulmonary capillary (CcO\textsubscript{2}) and the arterial (CaO\textsubscript{2}) and venous (CvO\textsubscript{2}) blood, as:

\[
\frac{Qs}{Qt} = \frac{(CcO_2 - CaO_2)}{(CcO_2 - CvO_2)}
\]

where the CcO\textsubscript{2} is calculated using the PAO\textsubscript{2} as a surrogate for the PO\textsubscript{2} in the capillary blood. Clinically, true shunt occurs in the presence of intracardiac right- to- left flow, and in diverse pulmonary pathology such as atelectasis, pneumonia, and acute lung injury / acute respiratory distress syndrome (ALI/ARDS). An important feature that differentiates shunt from a low V/Q ratio is that with shunt, increasing the PiO\textsubscript{2} through the administration of supplemental O\textsubscript{2} will not correct the hypoxemia. The appropriate intervention to increase PaO\textsubscript{2} under these circumstances is to recruit the collapsed alveoli through, e.g., the application of positive end-expiratory pressure (PEEP).

2. **Low V/Q**. A low PaO\textsubscript{2} is due more commonly to combinations of low and high V/Q than to shunt (see below). As V/Q decreases, the arterial blood gas tensions will approach those of the mixed venous gas (Figure 1). Two corollaries are important. *First*, although the PaCO\textsubscript{2} should also increase towards its venous value, the extent of it is unpredictable in the spontaneously breathing patient, as a higher PaCO\textsubscript{2} will rapidly stimulate alveolar ventilation and restores normocarbia. *Second*, coexisting and opposite V/Q abnormalities do not average out but result in hypoxemia. Figure 2 illustrates this phenomenon. While the O\textsubscript{2} content leaving the alveolus with a low V/Q approximates the content of venous blood (16 and 14 ml O\textsubscript{2}/100 ml respectively in this example), the O\textsubscript{2} content leaving the alveolus with a high V/Q is barely higher than in the normal alveolus (20 and 19 ml O\textsubscript{2}/100 ml of blood respectively). This is due to the shape of the hemoglobin- O\textsubscript{2} dissociation curve: once the hemoglobin is fully saturated, further increase in PaO\textsubscript{2} will dissolve in plasma, adding very little to the total content of O\textsubscript{2}.

**Low PvO\textsubscript{2}**. A decreased PO\textsubscript{2} in the mixed venous blood (PvO\textsubscript{2}) will feed venous blood with a lower PO\textsubscript{2} through areas of low V/Q and shunt, further decreasing the PaO\textsubscript{2}. The extent of the resulting hypoxemia is difficult to predict, because it is affected by the magnitude of the underlying V / Q abnormality and because a low PvO\textsubscript{2} elicits local vasoconstriction that counteracts the low V / Q to a certain extent. However, it is important to think of this as a cause of hypoxemia in at least two common circumstances in anesthesia and critical care. *First*, during shivering the PvO\textsubscript{2} may decrease significantly and cause hypoxemia, which is corrected by the administration of supplemental oxygen. *Second*, a low PvO\textsubscript{2} may result from a low cardiac output and consequent increase in O\textsubscript{2} extraction by the periphery; hence, hypotension from low blood flow can cause hypoxemia!

**The PaCO\textsubscript{2}**. Carbon dioxide and water are the end- products of aerobic metabolism. Carbon dioxide is stored in tissues, and transported in blood as carbamino compounds, bicarbonate, and dissolved CO\textsubscript{2}. The latter determines the PCO\textsubscript{2}, and is eliminated as a gas from the lungs. At steady state, the PaCO\textsubscript{2} results from the equilibrium between production of CO\textsubscript{2} by cellular metabolism (VCO\textsubscript{2}) and its elimination by the lungs through alveolar ventilation (VA):
\( \text{PaCO}_2 = \frac{\text{VCO}_2}{\text{VA}} \)

It is also important to note that the VA is linearly correlated with the PaCO\(_2\). In other words, if the PaCO\(_2\) rises (see below) the VA increases nearly instantly and steeply. Albeit with some variability, an increase of the PaCO\(_2\) of 1 mm Hg results in an average increase of VA of 1 - 2 l/min. Of course, we know that many of the drugs that we use in anesthesia (chiefly hypnotic and opiates) blunt this response.

**Causes of hypercarbia.**

High CO\(_2\) production occurs with fever, shivering, excessive caloric / carbohydrate intake, and, to its maximum extent, in malignant hyperthermia (MH) and neuroleptic malignant syndrome (NMS). However, except for MH and NMS, the increase of VCO\(_2\) is generally transient, and may or may not cause hypercarbia depending upon the ability of the respiratory system to increase the VA in response to the hypercarbia. Such response may be limited in the anesthesia practice by the administration of anesthetics, hypnotics and opiates.

Low CO\(_2\) elimination is the most common cause of hypercarbia in anesthesia and critical care practice, and it includes two main causes: hypoventilation and dead space ventilation.

1. **Hypoventilation** increases PaCO\(_2\) by hindering the elimination of the CO\(_2\) produced metabolically. As discussed earlier, hypoventilation may also causes hypoxemia. Immediate treatment of hypoventilation includes supplemental O\(_2\) and ventilatory support.

2. **High V/Q and dead space.** Similarly to low V/Q and shunt, high V/Q and dead space are a continuum of the same phenomenon. As perfusion to an alveolus decreases, the gases dissolved in the venous blood fail to reach the alveolus; less CO\(_2\) is eliminated, the exhaled PCO\(_2\) decreases and, at a constant VCO\(_2\), the PaCO\(_2\) will rise. These phenomena are at the basis of the measurement of the physiological dead space fraction, which is the fraction of unperfused (or ‘dead’) ventilatory space (Vd) over the tidal volume (Vt):

\[
\text{Vd/Vt phys} = \frac{\text{PaCO}_2 - \text{PECO}_2}{\text{PaCO}_2}
\]

This definition of physiological dead space (Vd/Vt phys) includes the anatomical (proximal airways) and the alveolar dead space (Vd/Vt alv). The Vd/Vt phys is calculated using the mean exhaled CO\(_2\) (PECO\(_2\)), which is measured as the exhaled PCO\(_2\) averaged over several breathes. While the anatomical dead space is for the most part fixed (approximately 25% of the total ventilation) the Vd/Vt alv is the most useful of these parameters, because it is close to 0 in normal lungs, and it increases with the inefficiency of ventilation due to disease. The Vd/Vt alv can be calculated:

\[
\text{Vd/Vt alv} = \frac{\text{PaCO}_2 - \text{PetCO}_2}{\text{PaCO}_2}
\]

where PetCO\(_2\) is the PCO\(_2\) at end- expiration, or ‘end- tidal’. When the expiratory flow reaches a plateau, the PetCO\(_2\) is highly representative of the PACO\(_2\). A normal PECO\(_2\) is approximately 30 mmHg, and a normal PetCO\(_2\) is 38 - 40 mmHg (nearly the same as PaCO\(_2\)).

**Respiratory mechanics.**

Moving air in and out of the lungs- the law of motion of the respiratory system. When we breathe, we generate a negative pressure with the respiratory muscles (Pmus) that that causes a flow (V) of gas in the airways and an increase of volume of the lungs (Vt). Exhalation occurs by passive elastic recoil. This rhythmic movement is opposed by the impedance of lung and chest wall (the ‘respiratory system’) composed by the resistance to flow through the airways (Raw) and the elastance (E) or ‘stiffness’ of the respiratory system. When a patient is mechanically ventilated, the pressure to generate flow is applied from the exterior, generally a positive pressure from a ventilator (Pvent); when a patient is partially ventilated (e.g., on pressure support ventilation) the pressure will be a combination of negative (Pmus) and positive (Pvent) pressure. These phenomena describe the law of motion of the respiratory system:

\[\text{Paw} = \text{Pmus} + \text{Pvent} = \text{V} \times \text{Raw} = \text{Vt} \times \text{E}\]

where Paw is the pressure at the airway. This relationship has important corollaries:

1. Ventilation works the same whether spontaneous, mechanical, or a combination of the two.
2. The mechanical characteristics of the respiratory system, i.e., resistance and compliance (C, the reciprocal value of elastance), are important determinants of the effects of ventilation.
3. If we set a variable on a ventilator (e.g., \( V_t \)) and measure another (e.g., \( P_{aw} \)) we can then calculate the third one, \( R_{aw} \) or \( C \).

**Bedside measurement of respiratory mechanics.** Modern ventilators (including anesthesia ventilators) have the capability to measure with acceptable precision pressure, flow and volume. A practical way to assess respiratory mechanics during anesthesia and intensive care includes:

1. Setting the ventilator on volume-limited, constant (‘square-wave’) flow.
2. Verifying that the patient is adequately relaxed and is not taking spontaneous breaths.
3. Performing an end-inspiratory pause (‘inspiratory hold’), which separates the dynamic component of the \( P_{aw} \) (peak inspiratory pressure [PiP]) from the static component or plateau pressure (Pplat) and allows to calculate Raw and C.
4. Performing an end-expiratory maneuver (rarely available in anesthesia ventilators) to measure the intrinsic positive end-expiratory pressure (PEEPi).

**Figure 3** shows an airway pressure trace obtained as described, with the respective measurements of mechanics-compliance and resistance:

\[
C = \frac{V_t}{P_{plat} - \text{PEEP}}
\]

\[
R_{aw} = \frac{(\text{PiP} - \text{Pplat})}{V}
\]

The volume-limited mode provides the value of \( V_t \); the end-inspiratory pause creates a semi-static condition (Pplat) that takes away the pressure component due to airway resistance (PiP - Pplat). Normal values of C of the respiratory system (Cr\(s\), sum of C of the lung [Cl] and of the chest wall [Ccw]) is 80 - 100 mls / cm H\(_2\)O.

The volume-limited mode also provides a convenient way to calculate Raw by setting the inspiratory flow rate at 60 l/min (1 l/sec), which will allow to divide the PiP - Pplat difference by 1. Normal Raw is 1 - 3 cmH\(_2\)O/l/sec.

Finally, it is important to understand the concept of intrinsic PEEP (PEEPi), or ‘auto-PEEP’. During normal ventilation (spontaneous and mechanical), at end-expiration the lung returns to functional residual capacity (FRC), and the alveolar pressure (estimated by the Paw) equals atmospheric pressure (‘zero’). When there is expiratory flow limitation, as in asthma, emphysema, and upper airway obstruction, the lung volume may not reach FRC before the next breath. In these conditions, the lung volume at end-expiration is larger than FRC, and the alveolar pressure higher than 0. PEEPi has similar effects of externally applied PEEP: it can increase PaO\(_2\) and decrease cardiac output.

However, differently from applied PEEP, the PEEPi has to be overcome by the patient’s effort in order to start each breath. This wasted effort (wasted because it does not generate any volume) can be taxing on subjects with borderline respiratory function and contribute to failure. Additional complexities of respiratory mechanics relevant to our practice include the effect of lung volume and the effect of the chest wall.

**Compliance over a range of lung volumes (Figure 4).** The bedside measurement of compliance described above is carried out at the \( V_t \) set on the ventilator. Although an acceptable approximation in normal circumstances, in conditions that decrease (ALI/ARDS) or increase (emphysema) lung volume, the relationship between alveolar volume and pressure is no longer linear additional measurements at various lung volumes may be of value. A more comprehensive measurement of compliance includes constructing a semi-static pressure / volume curve by delivering a series of lung volumes, possibly from FRC to total lung capacity (TLC), with respective measurements of Pplat. The compliance is the slope of the pressure / volume line. Under normal circumstances, this relationship is...
almost linear, flattening as it nears TLC (25 - 30 cmH$_2$O). In situations characterized by a low lung compliance, such as ALI/ARDS, the shape of this relationship changes. Here, the curve is not only moved to the right (lower compliance) but also assumes a sigmoid shape, indicating that at the two extremes of lung volume (near FRC and near TLC), compliance is much lower. This finding has potential clinical implications:

1. Breathing over the steep part of the line is most efficient, because it causes the least increase in pressure for a given volume.
2. Recruiting collapsed alveoli will increase FRC and reduce the initial flat segment of the curve. This may be accomplished by a level of PEEP at or above the flat segment.
3. Setting end-inspiratory pressure below the value of the high flat segment may avoid lung overdistention.

In clinical practice, this kind of measurement is cumbersome and requires a high degree of expertise. Nevertheless, the physiological principles behind it are useful to select the level of PEEP and of Ppl to set on a ventilator.

The lung, the chest wall, and the transpulmonary pressure. While we generally use the term ‘compliance’ referring to the compliance of the lungs, what we are actually measuring with the method described above is the overall compliance of the respiratory system (Crs), which includes in equal parts the compliance of the lung (Cl) and of the chest wall (Ccw).

In many cases, changes of Crs are a reasonable estimate of changes of Cl. However, in certain situations, our measurements of Pplat may not accurately estimate pressures exerted by the lung, and our use of Crs as a surrogate of Cl may lead to incorrect decisions. To better understand these phenomena, we need to review the concept of transpulmonary pressure (Ptp):

$$P_{tp} = P_{plat} - P_{pl}$$

Where Pplat is the surrogate for alveolar pressure, and Ppl is the intrapleural pressure.

Since normal Cl and Ccw in humans are equal, if we apply 10 cmH$_2$O PEEP to the airway of a normal subject, half of this pressure will be transmitted across the lung, resulting in a Ppl of 5 cmH$_2$O and a Ptp of 5 cmH$_2$O (Table 1). If the subject has stiff lungs (e.g., ALI/ARDS) less PEEP is transmitted, and the Ptp will be higher; if the subject has a stiff chest wall (e.g., laparoscopic surgery) more PEEP will be transmitted and the Ptp will be lower.

Consider the circumstance of an acutely injured lung (e.g., ALI/ARDS) that can be damaged by high ventilating pressures (‘ventilator-induced lung injury’), the Pplat. However, the pressure that hurts the lung is not the Pplat but the Ptp. Hence, in the ALI/ARDS lung we have to be concerned when we reach a high Pplat (e.g., 30 cmH$_2$O) because with a stiff lung the Pplat is a good estimate of the

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<th>$V_t$ = 800 ml</th>
<th>Pplat</th>
<th>Ppl</th>
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<tbody>
<tr>
<td>Normal</td>
<td>10</td>
<td>5</td>
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<tr>
<td>Low $C_L$</td>
<td>20</td>
<td>5</td>
<td>15</td>
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<tr>
<td>Low $C_{cw}$</td>
<td>20</td>
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Table 1: Effects of changes in compliance of lung and chest wall on transpulmonary pressure.
Ptp. On the contrary, during laparoscopic surgery or during ALI/ARDS with abdominal distention, a high Pplat is due also to a low Ccw and thus overestimates the Ptp. Reducing the VT out of concern of a high Pplat under these circumstances may lead to alveolar derecruitment and hypoventilation. The most common way to measure Ppl is via an esophageal balloon (esophageal pressure). Unfortunately, measuring Ppl is imprecise and somewhat cumbersome, requiring specialized equipment and significant expertise.

Another situation where the pressure measured at the airway may not correctly estimate the pressure in the alveoli occurs when a patient is adding *spontaneous breathing efforts* to a set level of mechanical support, typically during pressure support ventilation. Here, the VT results from the combination of the pressure applied by the ventilator and the pressure generated by the patient. Unfortunately, the latter cannot be measured by the ventilator, and the displayed Paw is not a reliable surrogate of the Ptp. For example, a patient generating a VT of 700 mls on 10 cmH₂O of pressure support may give the impression to have an excellent Cl (C_RS = 700 mls/10 cmH₂O = 70 ml/cmH₂O). However, we do not know how much additional pressure the patient is generating to get to that 700 mls VT. An example of this situation is shown in Figure 5, where the proper calculation of the distending pressure (through the use of an esophageal balloon) shows that the patient’s compliance was significantly lower than one would have estimated just by looking at the set Paw during pressure support ventilation.
Suggested reading

11. Hess DR. Ventilator waveforms and the physiology of pressure support ventilation. Respir Care 2005;50:166.