The Physiology of Ventilation

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Introduction

The diffusion of gases brings the partial pressures of O_2 and CO_2 in blood and alveolar gas to an equilibrium at the pulmonary blood-gas barrier. Alveolar P_{CO_2} (P_{ACO_2}) depends on the balance between the amount of CO_2 being added by pulmonary blood and the amount being eliminated by alveolar ventilation ($\dot{V}_A$). In steady-state conditions, CO_2 output equals CO_2 elimination, but during non-steady-state conditions, phase issues and impaired tissue CO_2 clearance make CO_2 output less predictable. Lung heterogeneity creates regional differences in CO_2 concentration, and sequential emptying raises the alveolar plateau and steepens the expired CO_2 slope in expiratory capno-

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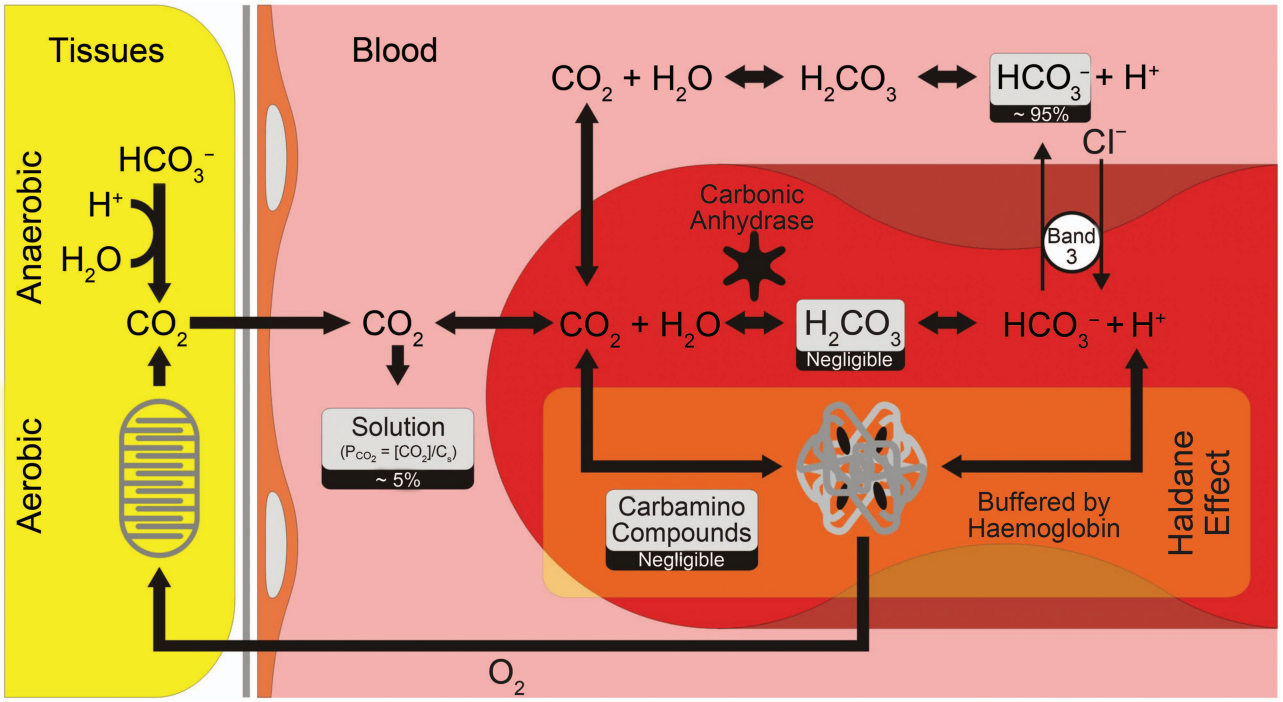

Fig. 1. Carbon dioxide transport in blood. CO_2 produced during cell metabolism reaches the blood by simple diffusion driven by a partial pressure gradient (higher in tissue, lower in blood). To allow CO_2 to be cleared from tissues, this gradient must remain high. A series of reactions keeps CO_2 in solution low. Once in plasma, CO_2 diffuses into red cells, where carbon anhydrase catalyzes the reaction with water to produce carbonic acid (H_2CO_3), which subsequently dissociates into hydrogen (H^+) and bicarbonate (HCO_3^-). Once again, the accumulation of either H^+ or HCO_3^- would stop those reactions. However, protons are buffered by hemoglobin, and bicarbonate is exchanged for extracellular chloride (Cl^-) by AE1 (Band 3). For more details, see text.

grams. Lung areas that are ventilated but not perfused form part of the dead space. Alveolar dead space is potentially large in pulmonary embolism, COPD, and all forms of ARDS. When PEEP recruits collapsed lung units, resulting in improved oxygenation, alveolar dead space may decrease; however, when PEEP induces overdistention, alveolar dead space tends to increase. Measuring physiologic dead space and alveolar ejection volume at admission or examining the trend during mechanical ventilation might provide useful information on outcomes of critically ill patients with ARDS.

Physiology of Carbon Dioxide

In normal conditions, CO_2 is produced at the tissue level during pyruvate oxidation as a result of aerobic metabolism. The respiratory quotient shows the relationship between oxygen consumption ($\dot{V}_{O_2}$) and CO_2 production ($\dot{V}_{CO_2}$): respiratory quotient = $\dot{V}_{CO_2}/\dot{V}_{O_2}$. In aerobic metabolism, the respiratory quotient varies from 0.7 to 1 as a function of the substrate being burned to produce energy. Tissue P_{CO_2} can also increase as a consequence of bicarbonate (HCO_3^-) buffering of non-volatile acids (eg, lactate) during tissue dysoxia,[1,2] which can result in a respiratory quotient of > 1[3]; lipogenesis can also produce a respiratory quotient of > 1 under aerobic conditions.[4] Regardless of its origin, CO_2 has to leave the tissues, be transported in blood, and be eliminated in the lungs, or respiratory acidosis will develop.

CO_2 transport in blood is complex. Tissue CO_2 enters capillary blood by simple diffusion resulting from a pressure gradient. Thus, CO_2 capillary pressure must remain low for diffusion to continue. The 2 main mechanisms that keep CO_2 capillary pressure low are continuous capillary flow and the low proportion of CO_2 in solution. Blood flow is the main determinant of tissue CO_2 clearance, and low flow increases the tissue P_{CO_2}-venous P_{CO_2} difference.[5,6] Various mechanisms maintain the proportion of CO_2 at low levels in solution in plasma (~5%). Figure 1 shows the ways CO_2 is transported. Once in blood, CO_2 easily diffuses into red cells, where carbonic anhydrase catalyzes the reaction with water to form carbonic acid, which rapidly dissociates into HCO_3^- and H^+. Although no carbonic anhydrases are present in plasma, it seems that their presence in endothelial cells in pulmonary capillaries enables some activity in plasma.[7] Even though carbonic acid is almost completely dissociated within red cells, the accumulation of HCO_3^- and H^+ would limit the amount

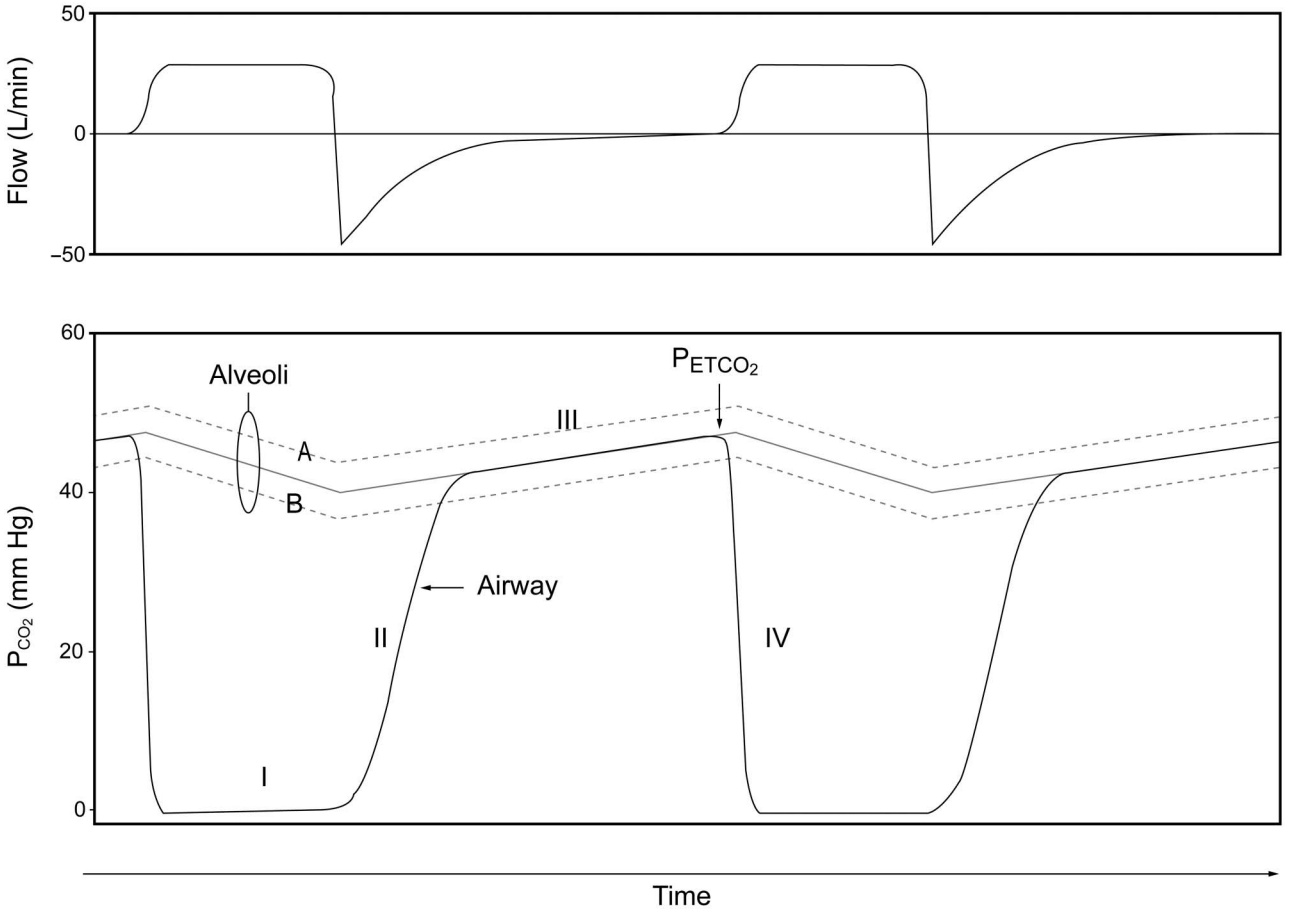

Fig. 2. Alveolar and airway CO_2 during the ventilatory cycle: flow (upper graph) and mean alveolar and airway CO_2 pressure scalars (lower graph). Alveolar P_{CO_2} (P_{ACO_2}) is lower at end inspiration (as far as fresh air dilutes alveolar gas) and higher at end expiration (because blood keeps releasing CO_2 into the alveolus). P_{ACO_2} varies between alveoli: it is higher (A) in units with lower $\dot{V}_A/\dot{Q}$ ratios (closer to mixed venous P_{CO_2}) and lower (B) in units with higher $\dot{V}_A/\dot{Q}$ ratios (closer to inspired P_{CO_2}). Airway CO_2 is zero during inspiration (provided there is no rebreathing, phase I of the capnogram). At the very beginning of expiration, CO_2 remains zero as long as the gas comes purely from airway dead space; it then increases progressively (phase II) when units start to empty (low time constant units first, high time constant units later). Phase III is considered to represent alveolar gas, and the end of phase III (end-tidal P_{CO_2} [P_{ETCO_2}]) is used as a reference of mean alveolar gas composition. Phase IV of the capnogram shows the sudden fall in P_{CO_2} at the start of inspiration.

of CO_2 that blood can transport. However, H^+ is buffered by hemoglobin, and HCO_3^- is exchanged for Cl^- by Band 3 (anion exchanger 1 [AE1]), a membrane transport protein.[8] As a consequence, bicarbonate is the main form of CO_2 transport, accounting for ≈95% of the total (mainly in plasma).

In normal conditions, a negligible amount of CO_2 is transported as carbamino compounds, but this mechanism can be markedly increased by inhibition of carbonic anhydrase (eg, by acetazolamide). CO_2 binds mainly to α-amino groups at the ends of both α- and β-chains of hemoglobin. Reduced hemoglobin is 3.5 times more effective than oxyhemoglobin as a CO_2 carrier, so the release of oxygen at the tissue level increases the amount of CO_2 that hemoglobin can carry. This is the major component of the Haldane effect. The other component is related to H^+ buffering: as hemoglobin releases oxygen, it becomes more basic, and its buffering capacity increases (see Fig. 1).[9]

P_{ACO_2}

P_{ACO_2} depends on the balance between the amount of CO_2 being added by pulmonary blood and the amount eliminated by $\dot{V}_A$. As the former is nearly continuous and the latter is not, P_{ACO_2} varies during the ventilatory cycle (Fig. 2). P_{ACO_2} can be calculated (when inspired gas is free from CO_2) as CO_2 output/$\dot{V}_A$. $\dot{V}_A$ is the difference between tidal volume (V_T) and dead-space volume (V_D).

In steady-state conditions, CO_2 output equals $\dot{V}_{CO_2}$; during non-steady-state conditions, phase issues and impaired tissue CO_2 clearance make CO_2 output less predictable.[10] So, the equation can be re-written as: $P_{ACO_2} = \dot{V}_{CO_2}/\dot{V}_A$. However, the magnitude of these variables varies in dif-

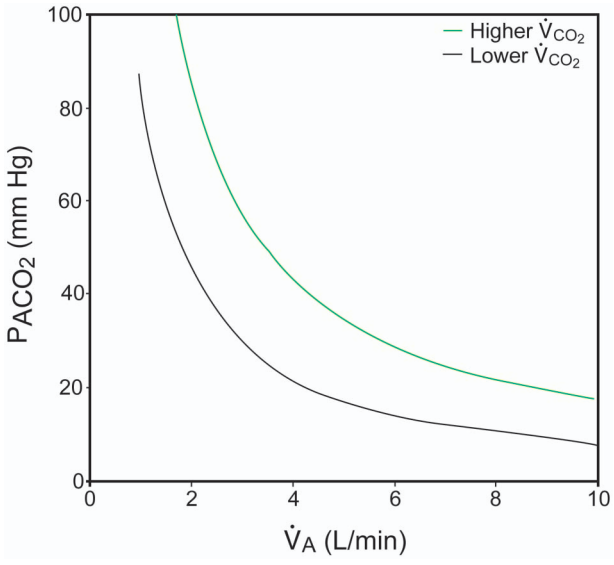

Fig. 3. Nonlinear relationship between alveolar ventilation ($\dot{V}_A$) and alveolar P_{CO_2} (P_{ACO_2}). The effects of changes in $\dot{V}_A$ on P_{ACO_2} are far more evident when basal $\dot{V}_A$ is lower. Higher CO_2 production ($\dot{V}_{CO_2}$) = 200 mL/min, and lower $\dot{V}_{CO_2}$ = 100 mL/min.

ferent conditions, so corrections have to be made. $\dot{V}_A$ measurements are expressed in body temperature and pressure saturated with vapor (BTPS); $\dot{V}_{CO_2}$ is expressed in standard temperature and pressure dry (STPD) conditions; and P_{ACO_2} measurements are expressed in body temperature and pressure dry (BTPD) conditions. So the above equation must be used in the form: P_{ACO_2} (BTPD) = 0.863 $\times$ $\dot{V}_{CO_2}$ (STPD)/$\dot{V}_A$ (BTPS), where 0.863 is a constant that summarizes the corrections when $\dot{V}_{CO_2}$ and $\dot{V}_A$ measurements are not provided in the same units.

Figure 3 (constructed from the adjusted equation) shows the relationship between P_{ACO_2} and $\dot{V}_A$ for 2 different $\dot{V}_{CO_2}$ values. This relationship is not linear: as P_{ACO_2} decreases, the increase in alveolar ventilation necessary to reduce P_{ACO_2} increases.

P_{aCO_2}

When venous blood arrives at pulmonary capillaries, the events illustrated in Figure 1 occur in the opposite order. The fall in plasma P_{CO_2} resulting from CO_2 diffusion to the alveolus results in CO_2 being released from red cells, so carbonic acid is converted to CO_2 and H_2O (carbonic anhydrase facilitates the reaction in both directions). The drop in carbonic acid concentration leads to new formation of H_2CO_3 from bicarbonate (from the cytoplasm and plasma through Band 3) and protons (free and from hemoglobin). CO_2 is also free from carbamates. As the environment becomes more basic, hemoglobin's affinity for O_2 increases (Bohr effect).

P_{CO_2} depends on CO_2 concentration and the solubility coefficient in blood (SC_B): $P_{CO_2} = CO_2 \times SC_B$. SC_B varies with temperature; at 37°C, it is 0.0308 mmol/L/mm Hg.[11]

At the pulmonary blood-gas barrier, the diffusion of gases brings the P_{O_2} and P_{CO_2} of blood and alveolar gas to an equilibrium, and when blood leaves the pulmonary capillaries, it has the same P_{O_2} and P_{CO_2} as alveolar gas. However, the blood that arrives at the left atrium has lower P_{O_2} and higher P_{CO_2} because venous admixture and shunt (both physiologic and large) contaminates it with venous blood. Likewise, exhaled gas has higher P_{O_2} and lower P_{CO_2} than alveolar air because dead space pollutes it with fresh air (Fig. 4).

The Concept of Dead Space

The concept of dead space accounts for those lung areas that are ventilated but not perfused. The V_D is the sum of 2 separate components of lung volume. One is the nose, pharynx, and conduction airways, which do not contribute to gas exchange and are often referred to as anatomic or airway V_D. The mean volume of the airway V_D in adults is 2.2 mL/kg,[12] but the measured amount varies with body[13] and neck/jaw[12] position. The second component consists of well-ventilated alveoli that receive minimum blood flow, which is referred to as alveolar V_D. In mechanical ventilation, the ventilator's endotracheal tube, humidification devices, and connectors add mechanical dead space, which is considered part of the airway V_D. Physiologic V_D consists of airway V_D (mechanical and anatomic) and alveolar V_D; in mechanical ventilation, physiologic V_D is usually reported as the fraction of V_T that does not participate in gas exchange.[14-16] Alveolar V_D can result from an increase in ventilation or a decrease in perfusion.[10] The gas from the alveolar V_D behaves in parallel with the gas from perfused alveoli, exiting the lungs at the same time as the gas that effectively participates in gas exchange and diluting it; this is evident as the difference between P_{aCO_2} and end-tidal P_{CO_2} (P_{ETCO_2}).[15,16] Beyond that, if the amount of gas that reaches the exchange areas surpasses the areas' capacity for perfusion (high $\dot{V}_A/\dot{Q}$ ratio), the excess gas supplied by ventilation behaves like alveolar V_D (functional concept) (Fig. 5).

Measurement of Dead Space

In critical patients, correct measurement and calculation of dead space provides valuable information about ventilatory support and can also be a valuable diagnostic tool. Nuckton et al[17] demonstrated that a high physiologic V_D/V_T was independently associated with an increased risk of death in subjects diagnosed with ARDS. Changes in the shape of the capnographic curve often indicate ventilatory maldistribution, and several indices have been developed

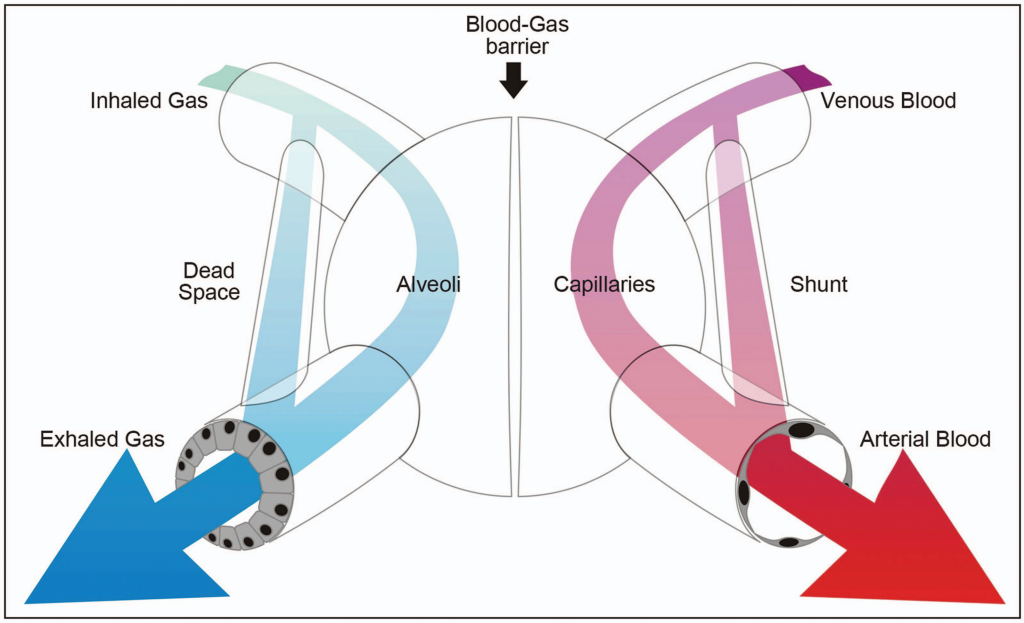

Fig. 4. Model of relationship between ventilation and perfusion. Even when the gases at the blood-gas barrier are in complete equilibrium, the composition of effluent (expiratory) gas differs from that of alveolar gas because effluent gas also contains gas from the alveolar dead space (whose composition is that of the inspired gas). Similarly, the composition of arterial blood differs from that of capillary blood to the extent that it is mixed with shunt blood (whose composition is that of mixed venous blood). This concept (the calculation of the difference between expected composition and actual composition of the effluent media) is the basis for calculating both alveolar dead space and shunt.

to quantify maldistribution based on the geometrical analysis of the volumetric capnographic curve.[18,19]

Bohr

Bohr's dead-space fraction (V_D/V_T) is calculated as $(P_{ETCO_2} - P_{\bar{E}CO_2})/P_{ETCO_2}$,[15] where $P_{\bar{E}CO_2}$ is the mean expired P_{CO_2} per breath, calculated as $\dot{V}_{CO_2}/V_T \times (P_b - P_{H_2}O)$, where P_b is barometric pressure and $P_{H_2}O$ is water-vapor pressure. It is simple but cumbersome to collect $P_{\bar{E}CO_2}$ using a Douglas bag.

In certain situations, the Bohr equation's use of P_{ETCO_2} can be problematic. In exercise, in acute hyperventilation, or in presence of different alveolar time constants, P_{ACO_2} rises, often steeply, during expiration of alveolar gas, so P_{ETCO_2} will depend on the duration of expiration. The dead space so derived will not necessarily correspond to any of the compartments of the dead space (instrumental, anatomic, and alveolar).[15,16,20]

Enghoff

In 1931, Enghoff first demonstrated that the physiologic dead space remained a fairly constant fraction of V_T over a wide range of V_T. Physiologic V_D/V_T calculated from the Enghoff modification of the Bohr equation[15] uses P_{aCO_2} with the assumption that P_{aCO_2} is similar to P_{ACO_2}: physiologic $V_D/V_T = (P_{aCO_2} - P_{\bar{E}CO_2})/P_{aCO_2}$.

Langley

Langley et al[21] plotted the volume of CO_2 elimination per breath ($\dot{V}_{eCO_2}$) against the total expired volume to contrive an alternative method of calculating airway dead space. This curvilinear graph is shown in Figure 6. A straight best-fit line is extrapolated from the linear portion of the graph, and the intercept of this line on the volume axis (X axis) represents the dead space. This method correlates with Fowler's method for calculating airway V_D (Fig. 7) but has the added advantage that it does not rely on visual interpretation to determine equal areas. Although several factors can influence airway V_D, in the critical care setting, this volume remains relatively unchanged. Any changes in measured physiologic V_D/V_T, without added equipment dead space, are mostly a result of changes in alveolar V_D. It is clearly alveolar V_D and its inherent interaction with physiologic V_D that are most important clinically.

Alveolar Ejection Volume

The advanced technology combination of airway flow monitoring and mainstream capnography allows noninva-

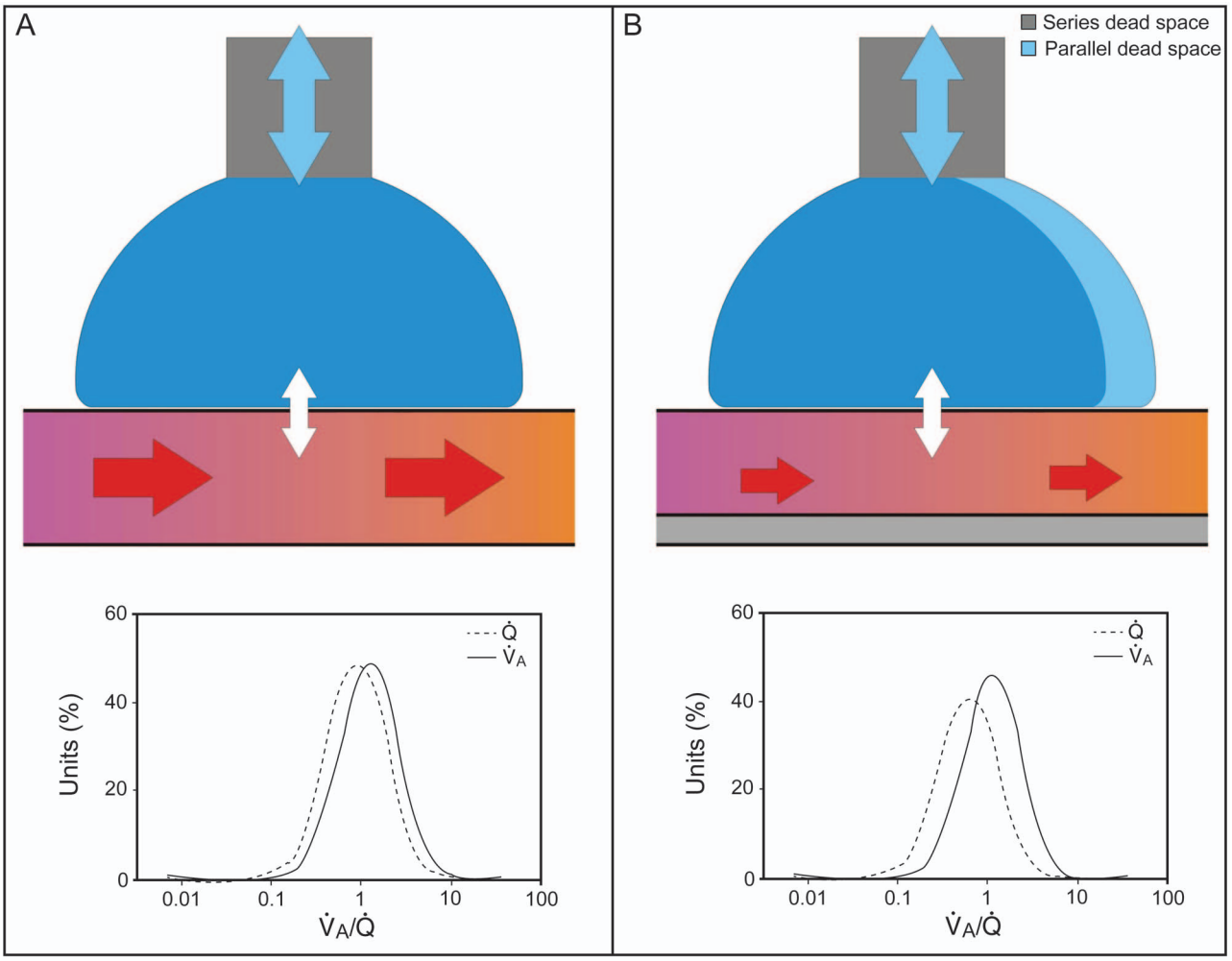

Fig. 5. Alveolar dead space. A: An ideal unit (top) receives nearly equal amounts of ventilation and perfusion. B: When perfusion drops (and ventilation is kept constant) (top), a fraction of the ventilation the unit is receiving (gray area) does not adequately participate in gas exchange and behaves like parallel dead space (it leaves the lungs at the same time as alveolar ventilation [$\dot{V}_A$]). Bottom: histograms for ventilation and perfusion for each situation. For clarity, only units with $\dot{V}_A/\dot{Q} > 0$ and lower than infinite are plotted (neither shunt nor serial dead space is shown).

sive breath-by-breath bedside calculation of $\dot{V}_{eCO_2}$ and the ratio between alveolar ejection volume (V_{AE}) and V_T independent of ventilatory settings.[22,23] V_{AE} can be defined as the fraction of V_T with minimum V_D contamination, which may be inferred from the asymptote of the $\dot{V}_{eCO_2}/V_T$ curve at end of expiration, whereby V_D is equal to zero. V_{AE} is defined as the volume that characterizes this relationship, up to a 5% variation.[23]

Using the $\dot{V}_{eCO_2}/V_T$ curve, the fraction of volume flow corresponding to alveolar gas exhalation can be calculated. After a given volume has been exhaled, $\dot{V}_{eCO_2}$ progressively increases to reach a total amount of $\dot{V}_{eCO_2}$ elimination in a single expiration. The increase in $\dot{V}_{eCO_2}$ is slightly nonlinear because of alveolar inhomogeneity, in other words, because of the presence of a certain amount of alveolar gas contaminated by parallel V_D. At the very end of expiration, the gas exhaled comes only from the alveoli, so it is pure alveolar gas. From this curve, the last 50 points of every cycle are back-extrapolated by least-squares linear regression analysis. Assuming a fixed amount of V_D contamination (dead-space allowance), a point on the $\dot{V}_{eCO_2}/V_T$ curve representing the beginning of the V_{AE} is obtained. The V_{AE} is then obtained as the value of the volume at the intersection between the $\dot{V}_{eCO_2}/V_T$ curve and a straight line having the maximum value at end of expiration and a slope equal to 0.95 (1 − dead-space allowance) times the calculated slope (Fig. 8). V_{AE} is expressed as a fraction of expired V_T (V_{AE}/V_T).[24]

The V_{AE}/V_T ratio, an index of alveolar inhomogeneity, correlates with the severity of lung injury and is not in-

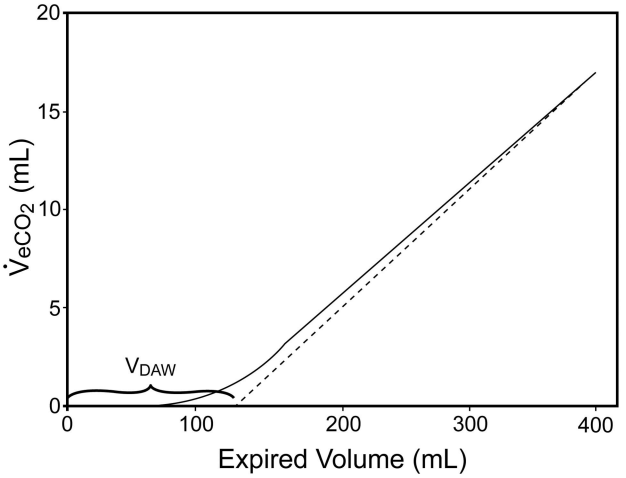

Fig. 6. Langley's method for calculating airway dead-space volume (V_{DAW}). Single-breath expiratory carbon dioxide volume ($\dot{V}_{eCO_2}$) is plotted versus expired volume. Airway V_D can be calculated from the value obtained on the volume axis by back-extrapolation from the first linear part of the $\dot{V}_{eCO_2}$ versus volume curve (solid line).

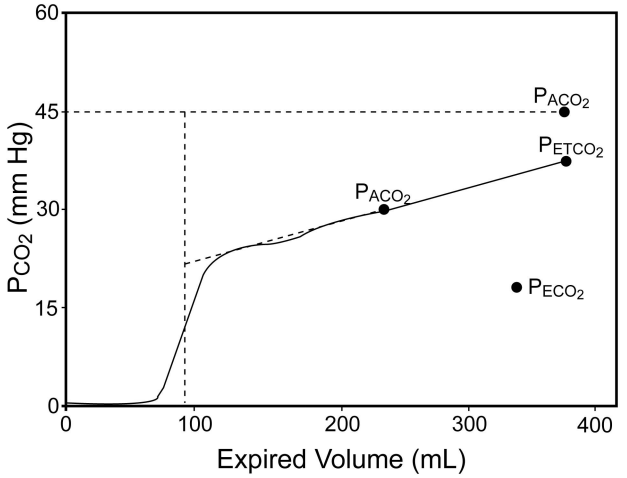

Fig. 7. Single-breath expiratory volumetric capnogram recorded in a mechanically ventilated subject with COPD. P_{ETCO_2} = end-tidal P_{CO_2}; $P_{\bar{E}CO_2}$ = mixed exhaled P_{CO_2}; P_{ACO_2} = mean alveolar P_{CO_2}. The solid lines indicate Fowler's geometric method of equivalent areas to calculate airway dead space. Airway dead space is measured from the beginning of expiration to the point where the vertical line crosses the volume axis.

fluenced by the set ventilatory pattern in acute lung injury (ALI) or ARDS patients receiving mechanical ventilation.[23] It follows that V_{AE}/V_T might have clinical applications in lung disorders characterized by marked alveolar inhomogeneity, and indeed, measurement of V_{AE}/V_T at ICU admission and after 48 h of mechanical ventilation, together with P_{aO_2}/F_{IO_2}, provided useful information on outcome in critically ill patients with ALI or ARDS.[25]

Causes of Elevated Dead Space in Mechanically Ventilated Patients

In patients with lung disease, V_D can be large. Patients with unevenly distributed ventilation and perfusion have lung units in which the amount of ventilation is high relative to the amount of blood flow. The P_{CO_2} in gas coming from these units is lower than P_{aCO_2}. During expiration, this gas mixes with gas coming from other lung areas in which ventilation and perfusion are more closely matched, diluting it so that expired P_{CO_2}, including P_{ETCO_2}, can be greatly different from P_{aCO_2}. In addition, the P_{CO_2} of expired gas in patients with obstructive airway disease may increase steeply during expiration because lung units that empty late are poorly ventilated and contain gas with higher CO_2 concentrations. The effect of these late-emptying lung units on expired P_{CO_2} leads to a difference between P_{aCO_2} and P_{ETCO_2} (Fig. 9).[26]

Pulmonary Embolism

Pulmonary embolism is most commonly due to blood clots that travel through the venous system and lodge in the pulmonary arterial tree. Spatial differences in blood flow between respiratory units in the lung cause inefficient gas exchange that is reflected as increased alveolar V_D. Occlusion of the pulmonary vasculature by an embolism will result in a lack of CO_2 flux to the alveoli in the affected vascular distribution. The mechanical properties may not be greatly affected, so these alveoli empty in parallel with other respiratory units with similar time constants. Because ventilation to the affected alveoli continues unabated, P_{CO_2} in these alveoli decreases.[27]

In patients with sudden pulmonary vascular occlusion due to pulmonary embolism, the resultant high $\dot{V}/\dot{Q}$ mismatch produces an increase in alveolar V_D. This effect enables volumetric capnography to be used as a diagnostic tool at the bedside: in the context of a normal D-dimer assay, a normal alveolar V_D is highly reliable to rule out pulmonary embolism.[28] In patients with clinical suspicion of pulmonary embolism and elevated D-dimer levels, calculations derived from volumetric capnography such as late dead-space fraction had a statistically better diagnostic performance in suspected pulmonary embolism than the traditional measurement of the $P_{(a\text{-}ET)CO_2}$ difference.[28] Moreover, a normal physiologic V_D/V_T ratio makes pulmonary embolism unlikely. Finally, volumetric capnography is an excellent tool for monitoring thrombolytic efficacy in patients with major pulmonary embolism.[29]

COPD

Mismatch of the distribution of ventilation and perfusion within any single acinus results from spatial differ-

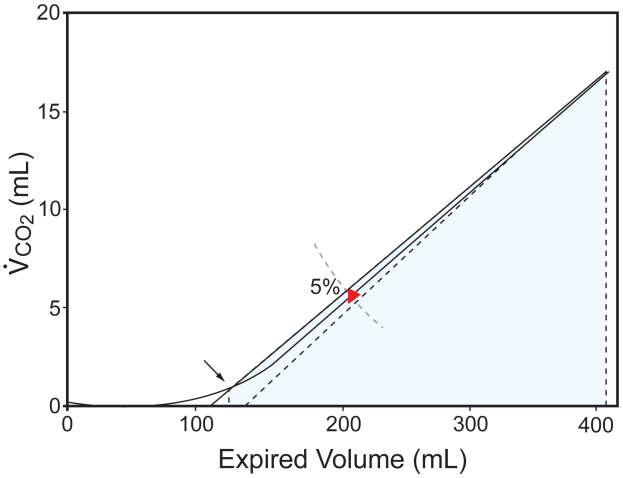

Fig. 8. Determination of alveolar ejection volume (V_{AE}) in a healthy subject. CO_2 production ($\dot{V}_{CO_2}$) is plotted as a function of expired volume. From this curve, the last 50 points of every cycle are back-extrapolated to represent the ideal lung behavior (straight dashed line). Assuming a fixed amount of dead-space contamination of 5% (red arrow), a straight line is plotted. Alveolar ejection begins at the intersection between the sampled curve and the straight line (black arrow). The volume between this point and end of expiration is the V_{AE} (shaded area).

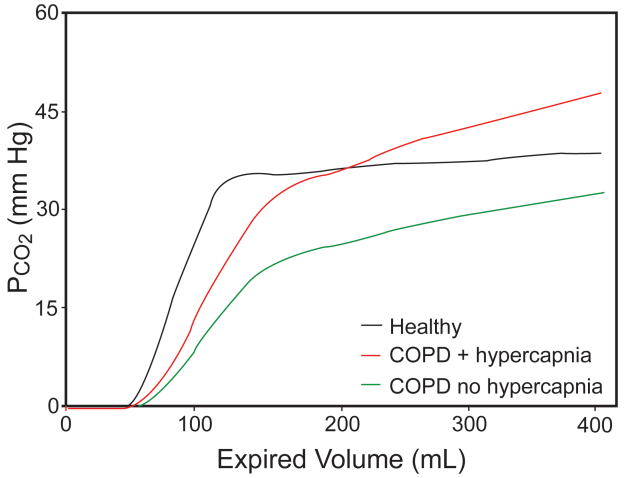

Fig. 9. Three single-breath volumetric capnograms during mechanical ventilation in different scenarios: a subject with normal lungs and 2 subjects with COPD with and without hypercapnia.

ences in gas-flow distribution due to the differences in the time constants of the respiratory units. P_{ACO_2} will vary between respiratory units. In this situation, individual respiratory units will empty sequentially at differing rates and times dependent upon mechanical properties.

Pulmonary heterogeneity is, together with airway obstruction, a cardinal feature in the functional impairment of COPD. Heterogeneity, mostly dependent on peripheral involvement, increases with the severity of the disease; therefore, volumetric capnography, a technique that basically explores regional distribution, can be a good tool to determine the degree of functional involvement in patients with COPD (see Fig. 9).[30,31]

Ventilation to regions with little or no blood flow (low P_{ACO_2}) affects pulmonary dead space. In patients with airflow obstruction, inhomogeneities in ventilation are responsible for the increase in V_D. Shunt increases physiologic V_D/V_T as the mixed venous P_{CO_2} from shunted blood elevates the P_{aCO_2}, increasing physiologic V_D/V_T by the fraction that P_{aCO_2} exceeds the non-shunted pulmonary capillary P_{CO_2}. The accuracy of physiologic V_D/V_T measurement can be improved with a forced maximum exhalation, which reduces the $P_{(a\text{-}ET)CO_2}$ difference and physiologic V_D/V_T because of more complete emptying of the lungs, including peripheral alveoli that have a higher P_{CO_2} level. Furthermore, maximum exhalation is generally preceded by maximum inhalation, resulting in a more even distribution of gases within the alveoli.[32,33]

ARDS

Even mild forms of ARDS can severely alter respiratory system mechanics.[34,35] Most of these changes affect peripheral structures beyond the conducting airways: the interstitium, alveolar spaces, and small airways. The main consequence of peripheral lung injury is the development of heterogeneities that affect the efficacy of respiratory gas exchange and ventilatory distribution.[34,35]

Patients with ARDS have lung regions with low $\dot{V}/\dot{Q}$ (and high P_{ACO_2}) that usually coexist with others having high $\dot{V}/\dot{Q}$ (and low P_{ACO_2}). The combination of these 2 conditions secondary to severe alveolar and vascular damage results in increased pulmonary dead space. Moreover, pulmonary dead space is increased by shock states, systemic and pulmonary hypotension, and obstruction of pulmonary vessels (massive pulmonary embolus and microthrombosis). Dead space accounts for most of the increase in the minute ventilation requirement and CO_2 retention that occur in severe ARDS,[34] and the extent of lung inhomogeneities increased with the severity of ARDS and correlated with physiologic V_D/V_T.[36] Mechanical ventilation can substantially affect dead-space measurements, making the variations in dead space more complex.[37]

Effects of Mechanical Ventilation on Dead Space

Mechanical ventilation makes it more difficult to understand variations in dead space at the bedside. On the one hand, PEEP levels that recruit collapsed lung can reduce dead space, primarily by reducing intrapulmonary shunt. On the other hand, overdistention promotes the development of high $\dot{V}/\dot{Q}$ regions with increased dead space.[38] Therefore, a number of pulmonary and non-pulmonary

factors might affect interpretation of dead-space variations at the bedside.

Several studies in subjects with ARDS have shown that hypoxemia is due to intrapulmonary shunt and regions with very low $\dot{V}/\dot{Q}$.[39] The multiple inert gas elimination technique has also shown that patients with ARDS have a large percentage of ventilation distributed to unperfused or poorly perfused regions.[39] Coffey et al[38] found that oleic acid-induced ARDS in dogs resulted in high V_D/V_T by increasing shunt, inert gas dead space, and mid-range $\dot{V}/\dot{Q}$ heterogeneity. Capnographic findings in patients with ALI and ARDS are consistent with a high degree of ventilatory maldistribution and poor ventilatory efficiency. Blanch and co-workers[25] reported that indices obtained from volumetric capnography (Bohr's V_D/V_T, phase 3 slope, and V_{AE}/V_T) were markedly different in subjects with ALI and ARDS than in control subjects. Bohr's dead space and phase 3 slope were higher in subjects with ALI than in control subjects and higher in subjects with ARDS than in both control and ALI subjects. Moreover, V_{AE}/V_T was lower in subjects with ALI than in control subjects and lower in subjects with ARDS than in both control and ALI subjects.

Effect of V_T

In recumbent, anesthetized, normal subjects, increasing V_T increases ventilatory efficiency. Studies in normal subjects[40] have shown that the convection-dependent non-homogeneity of ventilation increases with relatively small increases in V_T, whereas non-homogeneity due to interaction of convection and diffusion in the lung periphery decreases. In an earlier study, Romero et al[23] found that V_{AE}/V_T changed significantly with volume in normal subjects but not in subjects with ARDS. Even earlier, Paiva et al[41] showed that phase 3 slope decreases with increased V_T in normal subjects. It might seem reasonable to expect that the increase in V_T in subjects with ARDS would recruit some alveolar units and thus improve the degree of alveolar homogeneity to some extent.[42] In fact, however, recruited units would contribute to improvement in ventilatory and mechanical efficiency only if they were strictly normal and homogeneous. We can reasonably suppose that the reason that V_{AE}/V_T does not increase with V_T in patients with ARDS is that recruited alveoli are mostly diseased or that increased V_T does not effectively recruit new lung areas. Nowadays, V_T is no longer used to increase oxygenation because it causes injuries to lungs and distant organs and poor outcome.[34,35,43] Currently, the use of a lung-protective ventilation strategy has also been extended to intermediate-risk and high-risk patients undergoing major surgical procedures because it was associated with improved clinical outcomes and reduced health-care utilization.[44] This brings us to the current hypotheses that elevated physiologic V_D/V_T and decreased V_{AE}/V_T are signs of poor prognosis in ARDS, and their evolution during treatment has an impact on final outcome.[17,25,45,46]

Effect of PEEP

Alveolar V_D is significantly increased in ARDS and does not vary with PEEP. However, when PEEP is administered to recruit collapsed lung units (resulting in improved oxygenation), alveolar V_D decreases unless overdistention impairs alveolar perfusion. Breen and Mazumdar[47] found that the application of PEEP at 11 cm H_2O to anesthetized, mechanically ventilated, open-chested dogs increased physiologic V_D, reduced $\dot{V}_{eCO_2}$, and resulted in a poorly defined alveolar plateau. These changes were mainly produced by a significant decrease in cardiac output due to PEEP. In dogs with oleic acid-induced ARDS, Coffey et al[38] found that low PEEP reduced physiologic V_D/V_T and intrapulmonary shunt. Conversely, in the same animals, high PEEP increased the fraction of ventilation delivered to areas with high $\dot{V}/\dot{Q}$, resulting in increased physiologic V_D/V_T. When Tusman et al[48] tested the usefulness of alveolar V_D for determining open-lung PEEP in eight lung-lavaged pigs, they observed 2 interesting physiologic effects. First, alveolar V_D showed a good correlation with P_{aO_2} and with normally aerated and non-aerated areas on computed tomography in all animals, yielding a sensitivity of 0.89 and a specificity of 0.90 for detecting lung collapse. However, PEEP also induced airway dilation and increased airway V_D, thus affecting the global effect of both on physiologic V_D/V_T. Finally, variations in dead space with the application of PEEP largely depend on the type, degree, and stage of lung injury. Experimental ARDS induced by lung lavage potentially allows for much greater recruitment at increasing increments of PEEP[49-51] than experimental ARDS models induced by oleic acid injury or pneumonia, and comparisons with human ARDS remains speculative.

Blanch et al[37] studied the relationship between the effects of PEEP on volumetric capnography and respiratory system mechanics in subjects with normal lungs, with moderate ALI, and with severe ARDS. Compared with control subjects, subjects with ARDS had markedly decreased respiratory system compliance (C_{RS}) and increased total respiratory system resistance. Increasing PEEP improved respiratory mechanics in normal subjects and worsened lung tissue resistance in subjects with respiratory failure; however, it did not affect volumetric capnography indices. Other authors have corroborated these findings. Smith and Fletcher[52] found that PEEP did not modify CO_2 elimination in subjects immediately after heart surgery. Beydon et al[53] studied the effect of PEEP on dead space in subjects with ALI. They found a large physiologic V_D/V_T that remained unchanged after PEEP was raised from 0 to

15 cm H_2O. In healthy anesthetized subjects, Maisch et al[54] found that physiologic V_D/V_T and maximum C_{RS} during a decremental PEEP trial were lowest after a recruitment maneuver. However, at the highest PEEP level during the incremental PEEP trial when P_{aO_2} and the increase in lung volume induced by PEEP peaked, physiologic V_D/V_T deteriorated. Therefore, physiologic V_D/V_T and C_{RS} are more sensitive than P_{aO_2} measurements for detecting lung overdistention.[19,40,54] Seminal studies on the effect of PEEP in $P_{(a\text{-}ET)CO_2}$ difference showed similar results.[55] Finally, Fengmei et al[56] evaluated the effect of PEEP titration following lung recruitment in subjects with ARDS on physiologic V_D/V_T, arterial oxygenation, and C_{RS}. Interestingly, they found that optimal PEEP in these subjects was 12 cm H_2O because, at this pressure, the highest C_{RS} in conjunction with the lowest physiologic V_D/V_T indicated a maximum number of effectively expanded alveoli.

Variations in dead space and its partitions resulting from PEEP largely depend on the type, degree, and stage of lung injury. When PEEP results in global lung recruitment, physiologic V_D and alveolar V_D decrease; when PEEP results in lung overdistention, physiologic V_D and alveolar V_D increase. Therefore, volumetric capnography may be helpful to identify overdistention or better alveolar gas diffusion in patients with ARDS.

Effect of Inspiratory Flow Waveforms and End-Inspiratory Pause

Patients receiving pressure controlled inverse-ratio ventilation had lower P_{aCO_2} than those receiving the normal inspiratory/expiratory ratio.[57] Several studies have reported that an exponentially decreasing inspiratory flow pattern results in modest improvements in P_{aCO_2} and dead space. These phenomena are explained by an increased mean distribution time for gas mixing, during which fresh gas from the V_T is present in the respiratory zone and is available for distribution in the lung periphery. The mean distribution time of inspired gas is the mean time during which fractions of fresh gas are present in the respiratory zone.[19,58,59] It was recently proposed that setting the ventilator to a pattern that enhances CO_2 exchange can reduce dead space and significantly increase CO_2 elimination or alternatively reduce V_T. This option is especially interesting when lung-protective ventilation results in hypercapnia. In particular, doubling the proportion of the inspiratory cycle from 20 to 40% (without creating auto-PEEP),[59] increasing end-inspiratory pause up to 30% of the inspiratory cycle,[58] or both[60] markedly reduced P_{aCO_2} and physiologic V_D/V_T, allowing the use of protective ventilation with low V_T and enhancing lung protection.

Prone Position, P_{aCO_2}, and Dead Space

In patients with severe ARDS, prone positioning improves survival.[61] In the prone position, recruitment in dorsal areas usually prevails over ventral derecruitment because of the need for the lung and its confining chest wall to conform to the same volume, with more homogeneous overall dorsal-to-ventral lung inflation and more homogeneously distributed stress and strain than in the supine position.[62] Because the distribution of perfusion remains nearly constant in both postures, prone positioning usually improves oxygenation and may be associated with a decrease in P_{aCO_2}, an indirect reflection of the reduction in alveolar V_D.[63] Gattinoni et al[64] also reported improved prognosis in subjects in whom P_{aCO_2} declined after an initial prone position session. Charron et al[65] showed that prone positioning induced a decrease in plateau pressure, P_{aCO_2}, and alveolar V_D/V_T ratio and an increase in P_{aO_2}/F_{IO_2} and C_{RS}; these changes peaked after 6–9 h. In fact, the respiratory response to prone positioning appeared more relevant when P_{aCO_2} rather than P_{aO_2}/F_{IO_2} was used. Protti et al[66] investigated the gas exchange response to prone positioning as a function of lung recruitability, measured by computed tomography in a supine position. Interestingly, changes in P_{aCO_2}, but not in oxygenation, were associated with lung recruitability, which was in turn associated with the severity of lung injury.

Prognostic Value of Dead-Space Measurement

Alterations in the pulmonary microcirculation due to epithelial and endothelial lung cell injuries are characteristic of most forms of ARDS. Consequently, pulmonary ventilation and pulmonary and bronchial circulation are compromised, and pulmonary artery pressure and dead space increase. A high physiologic V_D/V_T fraction represents an impaired ability to excrete CO_2 due to any kind of $\dot{V}/\dot{Q}$.[38] Traditionally, pulmonary hypertension in the course of ARDS was considered a predictor of poor outcome.[67] However, in the era of lung-protective ventilation using low V_T, elevated systolic pulmonary artery pressure early in the course of ARDS is not necessarily predictive of poor outcome, although a persistently large dead space in early ARDS remains associated with increased mortality and fewer ventilator-free days.[68]

Several studies have demonstrated this association. Nuckton et al[17] demonstrated that a high physiologic V_D/V_T was independently associated with an increased risk of death in subjects with ARDS. The mean physiologic V_D/V_T was 0.58 early in the course of ARDS and was higher in subjects who died than in those who survived. The dead space was an independent risk factor for death (for every 0.05 increase in physiologic V_D/V_T, the odds of death increased by 45%). Raurich et al[45] studied mortality and

dead-space fraction in 80 subjects with early-stage ARDS and 49 subjects with intermediate-stage ARDS. In both stages, the dead-space fraction was higher in subjects who died than in those who survived and was independently associated with a greater risk of death. Similar results were reported by Lucangelo et al[25] regarding measuring the V_{AE}/V_T fraction at admission and after 48 h of mechanical ventilation in subjects with ALI or ARDS and by Siddiki et al[69] regarding estimating physiologic V_D/V_T from the calculation of $\dot{V}_{CO_2}$ using the Harris-Benedict equation. Finally, Kallet et al[70] tested the association between the V_D/V_T fraction and mortality in subjects with ARDS diagnosed using the Berlin Definition[34] who were enrolled in a clinical trial incorporating lung-protective ventilation and found that markedly elevated physiologic V_D/V_T (> 0.60) in early ARDS was associated with higher mortality. In the clinical arena, measuring or estimating physiologic V_D/V_T at bedside is an easy method to predict outcome in ARDS and should be routinely incorporated to monitor respiratory function in patients receiving mechanical ventilation.[71]

Conclusions

Understanding the physiology of ventilation and measuring the dead-space fraction at bedside in patients receiving mechanical ventilation may provide important physiologic, clinical, and prognostic information. Further studies are warranted to assess whether the continuous measurement of different derived capnographic indices is useful for risk identification and stratification and for tracking the effects of therapeutic interventions and mechanical ventilation modes and settings in critically ill patients.

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