This short review will cover two elements of gas exchange. First, some fundamental principles will be reviewed. Second, details of pulmonary gas exchange disturbances in common lung diseases will be illustrated.

THE FUNDAMENTAL PRINCIPLES OF GAS EXCHANGE

Diffusion
The lung exists for gas exchange – uptake of O₂ and elimination of CO₂. While ventilation (bringing fresh air to the alveoli and returning alveolar gas to the environment) and blood flow (bringing blood to the alveoli) are both active, energy-requiring processes, gas exchange itself is passive, occurring by simple diffusion. O₂ diffuses from alveolar gas into the pulmonary capillary blood and binds to Hb while CO₂ diffuses from pulmonary capillary blood into the alveolar gas. This diffusive process is very fast, requiring only about 0.25 seconds for a given red cell to fully take up O₂ (Wagner, 1977). CO₂ diffusion is even faster, and with the 0.75 second red cell transit time usually available in the normal lung at rest, the diffusive process is fully capable of supporting both O₂ and CO₂ exchange.

The diffusive process is so rapid because of two design elements: First, the alveolar wall (capillary endothelium, interstitial matrix and alveolar epithelium) is no more than about 1/3 to 1/2 of a micron in thickness. Second, the alveolar surface area is enormous despite a modest 3-4 liters of lung volume because the lung is divided into about 300 million alveoli. A single large alveolus of this volume would have a surface area much less than 1 m², but 300 million small alveoli with the same total volume have a total combined surface area of about
80 m². The rate of diffusion is proportional to surface area and inversely proportional to thickness of the alveolar wall (West, 2008).

Diffusion may however not proceed to completion under some well-defined circumstances – a) in health when the red cell transit time is reduced (heavy exercise), especially at altitude when the air to blood PO₂ gradient (that drives net diffusion of O₂ into the blood) is reduced (Torre-Bueno et al., 1985; Wagner et al., 1987), and b) in disease, when the structure of the lungs is abnormal so that the alveolar wall becomes thick and the alveolar surface area becomes reduced. This is the hallmark of interstitial pulmonary fibrosis, and during exercise, such patients commonly desaturate because of limited diffusing capacity (Agustí et al., 1991).

**Ventilation/perfusion matching and inequality**

Subdividing the lung into so many tiny alveoli (average diameter about 300 microns) imposes substantial challenges to gas exchange. Perhaps the most important is that statistically it is simply impossible to equally distribute either ventilation or blood flow equally to all alveoli. This implies that some alveoli will have excess ventilation compared to average while other will have excess blood flow compared to average. Since the distribution of ventilation and blood flow are not perfectly matched, some alveoli will end up with a ratio of their ventilation (Vₐ) to their blood flow (Q) less than average and others will have a ventilation/perfusion (Vₐ/Q) ratio greater than average.

Thus, compared to a hypothetically perfect lung in which every alveolus has the same Vₐ/Q ratio (which must equal the ratio of total alveolar ventilation to total pulmonary blood flow), real lungs, even in health, display a distribution of Vₐ/Q
ratios. This variance has two principal sources: First, gravity (West, 1977). In an upright normal person, the apex receives less ventilation and far less blood flow than does the base. Thus, the \( \dot{V}A/\dot{Q} \) ratio at the apex is above average while that at the base is below average. Between these extremes, the \( \dot{V}A/\dot{Q} \) ratio falls smoothly from apex to base. The second source of variance is random and/or structurally based. Here, at any given horizontal level between apex and base, there is substantial variation in local ventilation and also in local blood flow related to geometry (airway/blood vessel diameter and length and branching angle variation). It has been found that the variation in \( \dot{V}A/\dot{Q} \) ratios from apex to base caused by gravity is sufficient to explain the minor interference to overall gas exchange that is typical of normal subjects. This implies that the second cause of variation must somehow end up with local ventilation and local blood flow being fairly well matched to each other- or else, substantial arterial hypoxemia would ensue. Figure 1 shows the distribution of \( \dot{V}A/\dot{Q} \) ratios in normal young healthy subjects (Wagner et al., 1974a). As can be seen, the \( \dot{V}A/\dot{Q} \) ratio is normally distributed (on a logarithmic scale) and ranges from about 0.3 to about 3.0, or across one decade of \( \dot{V}A/\dot{Q} \) ratios. This is a minor degree of inequality, and causes no more than a 5-10 mm Hg drop in arterial \( \text{PO}_2 \), negligibly affecting arterial \( \text{O}_2 \) saturation and tissue \( \text{O}_2 \) availability.

It is critical to appreciate that any distribution of the \( \dot{V}A/\dot{Q} \) ratio - where some alveoli have a high \( \dot{V}A/\dot{Q} \) ratio, others have a normal ratio and still others a subnormal ratio - interferes with pulmonary gas exchange, and in particular that alveoli with high \( \dot{V}A/\dot{Q} \) ratio cannot compensate for those with low \( \dot{V}A/\dot{Q} \) ratio. The greater the degree of \( \dot{V}A/\dot{Q} \) dispersion (also called inequality), the greater will be the interference to gas exchange. In most pulmonary diseases, \( \dot{V}A/\dot{Q} \) inequality is the most important cause of arterial hypoxemia, and it can become severe.
enough to be fatal. Figure 2 shows how arterial PO$_2$ would fall and arterial PCO$_2$ would rise as V/A:Q inequality increases. To show the pure effects of inequality, these calculations (based on algorithms published by West in 1969) (West, 1969b) explicitly assume no compensatory changes in either total ventilation or cardiac output, which would normally increase and mitigate the gas exchange disturbances to some extent.

As Figure 2 shows, V/A:Q inequality will become evident not just as arterial hypoxemia, but also as arterial hypercapnia, although for most patients, the hypercapnia is able to be reversed by increasing total ventilation. However, even when hypercapnia can be reversed by hyperventilation, the hypoxemia usually is not corrected. This commonly seen differential response of the two gases is fully explained by their differently shaped dissociation curves – linear for CO$_2$, non-linear for O$_2$; steeper for CO$_2$ than for O$_2$. It is important to realize that the difference in responses does NOT mean that O$_2$ and CO$_2$ exchange follow different rules – both are affected negatively by V/A:Q inequality, as is true for all gases, including the gaseous anesthetics (West, 1969a; West et al., 1974).

**Shunting and deadspace**

The extremes of the V/A:Q ratio are: a) zero (where V is zero but Q continues), and b) infinitely high (where Q is zero but V continues). The former is termed shunt and the latter deadspace. The common causes of a shunt are alveolar consolidation (as in pneumonia), alveolar edema (as in left heart failure), and alveolar collapse (as in complete airway obstruction or in pneumothorax). From the standpoint of gas exchange, the key common denominator in these conditions is the complete lack of alveolar ventilation in the affected region with continuing blood flow (even when the latter is reduced by hypoxic
vasoconstriction, it is not abolished). The common cause of deadspace is pulmonary thromboembolism. Shunting affects O\textsubscript{2} more than CO\textsubscript{2}; deadspace affects CO\textsubscript{2} more than does O\textsubscript{2}. That said, when shunts exceed about 40% of the cardiac output, hypercapnia will develop unless there is compensatory hyperventilation.

It is often asked why is it important to know whether hypoxemia is due to V\textsubscript{A}/Q inequality with areas of very low (but non-zero) V\textsubscript{A}/Q ratio versus due to shunting. One answer is that the causes may be different, and thus the therapeutic approach may also need to be different. Another answer is the response to 100% inspired O\textsubscript{2}. V\textsubscript{A}/Q inequality without shunting allows the arterial PO\textsubscript{2} to rise to that of normal subjects, while shunting does not, as shown in Figure 3.

**Total ventilation and pulmonary blood flow**

While diffusion, V\textsubscript{A}/Q inequality and its extremes (shunting and deadspace) are the major factors within the lung itself affecting arterial PO\textsubscript{2} and PCO\textsubscript{2}, the levels of total ventilation and pulmonary blood flow also play important roles in affecting arterial PO\textsubscript{2} and PCO\textsubscript{2}. A reduction in total ventilation, even in the complete absence of V\textsubscript{A}/Q inequality, is well known to cause hypoxemia and hypercapnia. In fact, the fall in PO\textsubscript{2} can be predicted from the rise in PCO\textsubscript{2} using the well-known alveolar gas equation.

When pulmonary blood flow falls, there is essentially no effect on arterial PO\textsubscript{2} and PCO\textsubscript{2} in a normal lung. The effect is seen on pulmonary arterial (mixed venous) PO\textsubscript{2}, which falls in accordance with the Fick principle of mass conservation. However, when pulmonary blood flow falls in a patient with V\textsubscript{A}/Q inequality, shunting, or diffusion limitation, the effects are different and arterial PO\textsubscript{2} will fall
as well, with little effect on arterial PCO₂ (Figure 4). This can be especially
dramatic during pure O₂ breathing when a shunt is present as Figure 5 shows. A
constant 20% shunt can result in an arterial PO₂ as low as 100 mm Hg or as high
as 400 mm Hg, depending on the value of pulmonary blood flow.

Conversely, when cardiac output is elevated, this will buffer the fall in PO₂ from
VA/Q inequality or shunting, and thus suggest less gas exchange disturbance
that is actually present.

**PULMONARY GAS EXCHANGE IN COMMON LUNG DISEASES**
Short summary descriptions of patterns of VA/Q inequality and their effects on
O₂/CO₂ exchange now follow. These are presented featuring their VA/Q
distribution pattern as determined by the multiple inert gas elimination technique
(Wagner et al., 1974d; Wagner et al., 1974c; Evans and Wagner, 1977).

**Asthma**
Many patients with asthma, especially when well-controlled, have little VA/Q
inequality and thus normal gas exchange. An asthma attack almost always
causes VA/Q inequality usually characterized by a collection of alveoli having
VA/Q ratios much lower than normal (Figure 6) – a bimodal pattern of VA/Q
inequality (Wagner et al., 1978). These alveoli may not be spatially located
together however, since asthma is a disease with widespread regional variation
in that different airways in the same lung are affected differently. This bimodal
pattern may be the result of severe blockage in some airways (from edema,
mucus and bronchoconstriction), with sparing of others. Even if some airways are
completely obstructed, shunting is rarely seen, possibly because of persisting
collateral ventilation from neighboring, less affected, alveoli.
Often hypoxemia is mild despite moderately severe inequality. This can be explained by the higher than normal cardiac output frequently seen in asthmatics, caused by anxiety plus the use of beta-adrenergic agonists. A high cardiac output will lead to a high PO₂ in the mixed venous blood, which in turn raises the arterial PO₂ and buffers the hypoxemia that otherwise would be more severe. Sometimes, patients without acute symptoms will have considerable V/Qt inequality, and this is considered due to peripheral airways partially obstructed with mucus, since when a bronchodilator is given, overall airways resistance falls but V/Qt inequality persists. Arterial PCO₂ is usually slightly reduced due to hyperventilation, unless respiratory muscle fatigue is present.

**Chronic Obstructive Pulmonary Disease (COPD)**

V/Qt inequality is the gas exchange hallmark of COPD and explains gas exchange in most patients (Wagner et al., 1977) (Figure 7). Patients with emphysema as the major component exhibit areas of high V/Qt ratio, thought due to ventilation continuing (even if reduced) in areas with extensive alveolar wall destruction and thus little blood flow. Patients with chronic bronchitis often exhibit areas of low V/Qt ratio, presumably explained by airway obstruction by mucus and edema reducing local alveolar ventilation. The latter patient group may have an additional component of overall hypoventilation, aggravating CO₂ retention. COPD patients do not show diffusion limitation, even on exercise, and generally do not have shunting (unless during an exacerbation they develop alveolar consolidation).

**Interstitial Pulmonary Fibrosis (IPF)**
VA/Q inequality is also a major consequence of pulmonary fibrosis (Agustí et al., 1991). Areas of low VA/Q ratio are commonly found (Figure 8). These are thought due to locally reduced compliance from thick collagen deposits reducing local ventilation. Shunting is also seen, and may be the result of continuing perfusion of alveoli whose few remaining capillaries are buried within thick alveolar walls so deeply that effectively no O₂ reaches them. DLCO is always reduced in IPF, but diffusion limitation severe enough to contribute to resting arterial hypoxemia is seen only when DLCO falls to below about 50% of normal. However, during exercise, arterial PO₂ plummets in most IPF patients, and this is caused by diffusion limitation now becoming a substantial problem, even when resting DLCO is above 50%. Normal subjects employ capillary recruitment and distention to buffer the red cell transit time and increase alveolar surface area available for gas exchange. Red cell transit time could otherwise fall dramatically as cardiac output rises during exercise. Patients with IPF have extensive capillary destruction, and likely have no ability to recruit or distend capillaries, so that even with relatively small increases in cardiac output, transit time falls in the face of a reduced DLCO.

**Pulmonary Thrombo-Embolism (PTE)**

PTE causes a very different pattern of VA/Q inequality, but just as above, VA/Q inequality is the major explanation of altered arterial blood gases. Vascular obstruction by PTE leads to areas of high VA/Q ratio (poorly perfused but still ventilated alveoli), and/or deadspace (completely unperfused but ventilated alveoli) (Dantzker et al., 1978; Kapitan et al., 1989). The picture looks very much like that of emphysema (Figure 7A). Basically, the affected areas themselves carry out little or no gas exchange as they have essentially no blood flow. But they remain ventilated, depriving the rest of the normally perfused and ventilated
lung of an often substantial fraction of total ventilation. This is therefore tantamount to hypoventilation of the normal, perfused regions of the lung, and the result will be a rise in arterial $\text{PCO}_2$ and fall in $\text{PO}_2$ that can both be (mostly) reversed by hyperventilation. In this way, arterial hypoxemia can be prevented.

Sometimes, a shunt is also seen, even when the chest Xray is clear. Most feel that this represents one of two phenomena – either opening of arterio-venous channels (that do not exchange gas) due to high pulmonary vascular pressures, or microatelectasis from abnormal surfactant metabolism. Diffusion limitation is not seen in PTE (Wagner et al., 1977).

**Acute Respiratory Distress Syndrome (ARDS)**

ARDS from acute lung injury has many causes and consequences, but pulmonary gas exchange abnormalities are common to them all (Wagner et al., 1974b). $\dot{V}_A/\dot{Q}$ inequality is usually severe, and areas of both low and high $\dot{V}_A/\dot{Q}$ ratio are seen. So too, shunting is very common and may be severe. Diffusion limitation on the other hand is not observed. How both total ventilation and cardiac output are maintained through assisted ventilation and drug and fluid management may have a major effect on gas exchange. This is a very complex area with many scenarios and factors at work, but Figure 9 shows common patterns of $\dot{V}_A/\dot{Q}$ inequality and shunting. Summarized succinctly, shunting occurs when alveoli become filled with fluid or cellular debris, both common in ARDS. Areas of low $\dot{V}_A/\dot{Q}$ result when regions are underventilated due to airways becoming obstructed with secretions and/or to reductions in compliance from alveolar fluid accumulation. With treatment, as completely unventilated alveoli start to improve and their alveolar cellular and fluid debris starts to clear, shunts become converted to areas of low $\dot{V}_A/\dot{Q}$ ratio as ventilation begins to be restored.
Areas of high $\dot{V}A/\dot{Q}$ develop when ventilatory inflation pressures are high, because this distends alveoli and compresses alveolar wall capillaries, reducing their blood flow. This happens especially in the gravitationally non-dependent regions of the lung (Hedenstierna et al., 1979). High $\dot{V}A/\dot{Q}$ regions will also develop if the ARDS causes microscopic or macroscopic pulmonary thromboembolism. These abnormalities in $\dot{V}A/\dot{Q}$ distribution combined with alterations in total ventilation, cardiac output and inspired O$_2$ concentration combine to cause complex changes in gas exchange that require considerable effort to unravel.

**SUMMARY**

This brief review reminds us that there are four principal causes of arterial hypoxemia: diffusion limitation, $\dot{V}A/\dot{Q}$ inequality, shunting and hypoventilation, with a fourth “cause” when cardiac output falls, because of the consequences for mixed venous PO$_2$. Diffusion limitation is common in normal subjects exercising at altitude, and in elite athletes exercising heavily at sea level, but in lung disease is found only in interstitial pulmonary fibrosis, and then usually only during exercise when its effects can be profound. $\dot{V}A/\dot{Q}$ inequality on the other hand is minimal in health, yet is the major cause of altered gas exchange in all common lung diseases. Patterns of $\dot{V}A/\dot{Q}$ inequality vary considerably across diseases, but always rationally depend on the pathology and associated predictable effects on blood flow and ventilation distribution. Shunting is common in acute lung diseases but uncommon in stable, chronic lung diseases. Hypoventilation is obvious in certain settings, such as chest wall trauma and ventilatory depression by drugs, but is not common in stable chronic diseases, chronic bronchitis being the notable exception. It may play a role when there is respiratory muscle fatigue.
in asthmatics, and when patients with CO$_2$ retention are given additional inspired O$_2$. 
Reference List

Note: These are purposefully references to the original work, thus explaining why they are mostly from the 1970-1990 period.


