



# Novel gas exchange analysis in COVID-19 lung disease

Mike Hughes

National Heart and Lung Institute, Imperial College School of Medicine, Hammersmith Hospital, London, UK.

Corresponding author: Mike Hughes ([mike.hughes@imperial.ac.uk](mailto:mike.hughes@imperial.ac.uk))



Shareable abstract (@ERSpublications)

A new method of measuring mean alveolar  $P_{O_2}$  and  $P_{CO_2}$  (as opposed to the classical ideal alveolar air analysis) with arterial  $P_{O_2}$  and  $P_{CO_2}$ , is applied to patients with COVID-19 lung disease, acutely and after recovery <https://bit.ly/3Tuaffb>

Cite this article as: Hughes M. Novel gas exchange analysis in COVID-19 lung disease. *Eur Respir J* 2023; 61: 2201962 [DOI: 10.1183/13993003.01962-2022].

Copyright ©The authors 2023.

This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact [permissions@ersnet.org](mailto:permissions@ersnet.org)

Received: 9 Oct 2022  
Accepted: 11 Oct 2022

## Intrapulmonary shunt and alveolar dead space in COVID-19 pneumonitis

The study by HARBUT *et al.* [1] reported in this issue of the *European Respiratory Journal* analyses gas exchange in patients with acute coronavirus disease 2019 (COVID-19) lung disease; arterial oxygen and carbon dioxide tension ( $P_{O_2}$  and  $P_{CO_2}$ ) and the mean (or mixed) value for alveolar ( $\bar{A}$ )  $P_{O_2}$  and  $P_{CO_2}$  (not an “ideal” [2] but the actual value) were measured, when patients (and healthy controls) were breathing air. From the mean alveolar to arterial  $P_{O_2}$  and arterial to mean alveolar  $P_{CO_2}$  gradients ( $\bar{A}aP_{O_2}$  and  $a\bar{A}P_{CO_2}$ ), the authors computed intrapulmonary shunt and alveolar dead space using the classical three compartment model of RILEY and COURNAND [2] (but, with important differences: see later). HARBUT *et al.* [1] argued that intrapulmonary shunt should be a marker for alveolar consolidation, as in lobar pneumonia, but at a more microscopic level; alveolar dead space, on the other hand, should be a surrogate for pulmonary microvascular obstruction and thrombosis, *e.g.* following severe endothelial injury.

30 patients were studied, initially 3–15 days from the start of COVID-19 symptoms, and subsequently during recovery [1]. They had mild to moderate hypoxaemia ( $P_{aO_2}$  mean 68.3 mmHg, range 52–106 mmHg); 18 (60%) received supplemental oxygen. 24 out of 30 became in-patients, but only one was admitted to intensive care (and recovered). 18 of 30 patients had elevated shunt plus elevated dead space (*versus* healthy controls); five had a raised shunt only, and three had just a raised dead space. At recovery, only two patients had continuing (but minimally elevated) shunt (down from 23), but eight still had high alveolar dead space (down from 21). The authors [1] claim that their method, which is applicable at the bedside, can distinguish intravascular pathology (most likely at a microvascular level) from alveolar and epithelial injury leading to airspace flooding/consolidation and intrapulmonary shunt.

These results represent a significant step forward in the analysis of gas exchange in a clinical setting. The methodology (see below) gives a more accurate assessment of intrapulmonary shunt and alveolar dead space from arterial and mean alveolar measurements of  $O_2$  and  $CO_2$  than the well-established analysis of  $\dot{V}_A/\dot{Q}$  mismatch using the ideal alveolar air approach [2]. This method, and its validation, recently published [3], will be the focus of the remainder of this editorial.

## A new analysis of $O_2$ and $CO_2$ exchange

The paper of WAGNER *et al.* [3] “Using pulmonary gas exchange to estimate shunt and deadspace in lung disease...” has two sections: theory and practice. Theoretically, gas exchange across the blood–gas barrier is governed by two factors: solubility ( $\lambda$ ) in blood for  $gas_x$ , and the ratio of ventilation to perfusion ( $\dot{V}_A/\dot{Q}$ ); the latter may vary from unit to unit of gas exchange such that in any one unit:

$$P_A/P_{\bar{v}} \sim P_c/P_{\bar{v}} = \lambda/(\lambda + \dot{V}_A/\dot{Q}) \quad (1)$$

where A and c are the mixed alveolar gas and mixed capillary blood components of any unit of gas exchange (instantaneous partial pressure equilibration between them is assumed),  $\bar{v}$  is the mixed venous

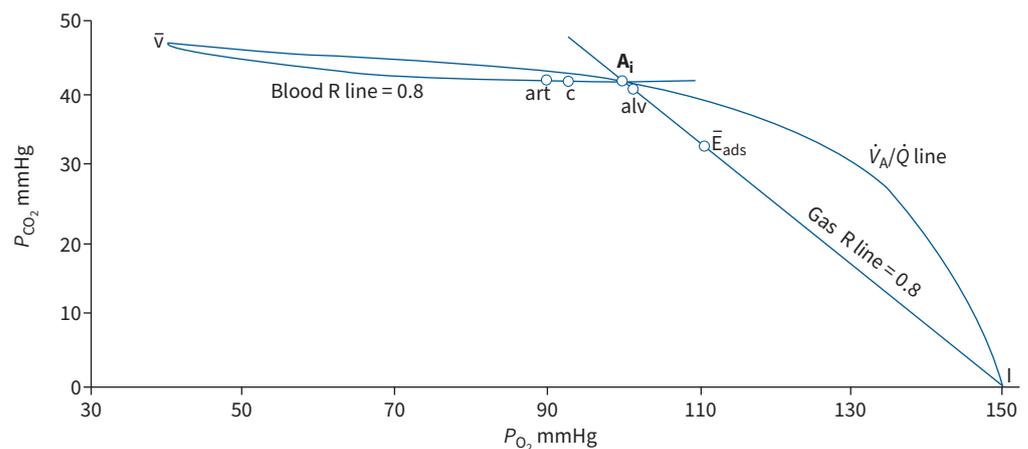


blood (common to all units), and  $\lambda$  is the blood solubility of gas<sub>x</sub> (essentially, for O<sub>2</sub> and CO<sub>2</sub>,  $\lambda$  is the tangent to the blood dissociation curve  $\Delta C/\Delta P$ , where C is O<sub>2</sub> or CO<sub>2</sub> content (mL·mL<sup>-1</sup>) and P is partial pressure at a particular instantaneous point on the curve). WAGNER *et al.* [4] used this relationship (equation 1) in their multiple inert gas elimination technique (MIGET) in which six inert gases of different solubilities ( $\lambda$  range of 10<sup>4</sup>-fold) were infused until a steady state was achieved; from their individual retention ( $P_A/P_v$ ) and excretion ( $P_E/P_v$ ), where  $\bar{E}$  is mixed expired gas,  $\dot{V}_A$  or  $\dot{Q}$  could be plotted against  $\dot{V}_A/\dot{Q}$  for a lung of 50 notional compartments.

In the more recent paper, WAGNER *et al.* [3] had a two compartment model, either 1) 50% of blood flow ( $\dot{Q}$ ) shunted (zero  $\dot{V}_A/\dot{Q}$ ), and 50% with normal ventilation and  $\dot{V}_A/\dot{Q}$ ; or 2) 50% of ventilation ( $\dot{V}_A$ ) unperfused with  $\dot{V}_A/\dot{Q}$  of infinity, and 50% with normal blood flow and  $\dot{V}_A/\dot{Q}$ . The authors showed (in their figure 2) that the relative  $\bar{A}-a$  or  $a-\bar{A}$  partial pressure gradient was about  $\times 3$  greater for O<sub>2</sub> versus CO<sub>2</sub> in the shunt model, and  $\times 1.7$  greater for CO<sub>2</sub> versus O<sub>2</sub> in the dead space model, *i.e.* shunt is more dominated by  $\bar{A}aP_{O_2}$  and alveolar dead space by  $a\bar{A}P_{CO_2}$ . They attributed this to the approximately 10-fold greater solubility ( $\lambda$ ) of CO<sub>2</sub> in blood versus O<sub>2</sub> over the physiological range of partial pressures. Nevertheless, in their figure 3, where they had models with a mixture of shunt and dead space (in essence, three compartments), the value of  $AaP_{O_2}$  was influenced by the value of  $aAP_{CO_2}$  and *vice versa*. Thus, it becomes essential to measure the gradient for CO<sub>2</sub> as well as O<sub>2</sub> to apportion shunt and dead space correctly when both are present. This is where the analysis of WAGNER *et al.* [3] differs from that of RILEY and COURNAND [2].

**The ideal alveolar air analysis of RILEY and COURNAND [2]**

Rapid response O<sub>2</sub> and CO<sub>2</sub> gas analysers were not available in 1949, and there were doubts about the accuracy of end-expired samples for defining mean alveolar  $P_{O_2}$  and  $P_{CO_2}$ . RILEY and COURNAND [2] found an ingenious solution, using the  $P_{O_2}-P_{CO_2}$  diagram of FENN *et al.* [5], and proposed that in the steady state the ratio of oxygen uptake to CO<sub>2</sub> production (the respiratory quotient (RQ) or respiratory exchange ratio (R)), normally around 0.8, must be the same for the lung as for the body as a whole (figure 1). Thus, mean  $P_{AO_2}$  and  $P_{ACO_2}$  must lie along a line, in a plot of  $P_{CO_2}$  (y-axis) against  $P_{O_2}$  (x-axis), with a slope ( $P_{CO_2}/P_{O_2}$ ) of 0.8, starting from the inspired point ( $P_{O_2} \sim 150$  and  $P_{CO_2}$  0 mmHg). Similarly, mean capillary (c)  $P_{O_2}$  and  $P_{CO_2}$ , in partial pressure equilibrium with mean alveolar gas tensions, must lie along a line starting from the mixed venous point ( $\bar{v}$ ), with a slope (which, in terms of concentrations, is linear) for the blood content ratios  $(C_{vCO_2} - C_{cCO_2})/(C_{CO_2} - C_{vO_2})$  also equalling 0.8. When the slope of blood content ratio line of 0.8 is re-expressed in terms of  $P_{O_2}$  and  $P_{CO_2}$  (the blood R line in figure 1), the intersection of



**FIGURE 1** Graphical analysis of the calculation of ideal alveolar air ( $A_i$ ; ideal point) modified from RILEY and COURNAND [2]. Blood or gas carbon dioxide tension ( $P_{CO_2}$ ) is plotted against oxygen tension ( $P_{O_2}$ ) (in mmHg) with the gas inspired (I; air) set at  $P_{O_2}$  150 and  $P_{CO_2}$  0 mmHg (see text). Curved line joining point I to point  $\bar{v}$  (the  $P_{CO_2}-P_{O_2}$  of mixed venous blood) is the  $\dot{V}_A/\dot{Q}$  line, reflecting all possible alveolar  $P_{CO_2}$  and  $P_{O_2}$  values for  $\dot{V}_A/\dot{Q}$  ratios from zero (at  $\bar{v}$ ) to infinity (at I) at a lung and body respiratory quotient (RQ or R) of 0.8. Gas and blood R lines, constructed for  $R=0.8$ , intersect at the “ideal” point. “art” is the  $P_{CO_2}-P_{O_2}$  of mixed arterial blood in a healthy subject, “c” is the composition of mixed blood leaving alveolar capillaries (arterial minus anatomic shunt), alv of mixed alveolar gas, and  $\bar{E}_{ads}$  of mixed expired air corrected for apparatus dead space.

blood and gas R lines defines the alveolar  $P_{O_2}$  and  $P_{CO_2}$  for an ideal lung with a single  $\dot{V}_A/\dot{Q}$  ratio ( $\sim 0.86$ ) appropriate for an RQ (or R) of 0.8. The ideal alveolar air concept is more easily understood graphically, as portrayed in figure 1.

**Defining the “ideal” point in practice, and dead space to tidal volume ratio ( $V_D/V_T$ )**

The blood RQ line (figure 1) becomes flat as it approaches the gas R line. Therefore, RILEY and COUNNAND [2] proposed, reasonably, that the arterial  $P_{CO_2}$ , which is positioned on the flat part of the curve, could define the intersection of the gas and blood R lines and, thus, the ideal alveolar  $P_{O_2}$  and  $P_{CO_2}$ . The ideal alveolar  $P_{O_2}$  could be calculated (approximately) as inspired  $P_{O_2}$  minus  $P_{aCO_2}$  divided by the gas R slope (0.8). This way of calculating the Aa $P_{O_2}$  gradient has been used in respiratory physiology and medicine for the past 72 years!

Dead space as a fraction of tidal volume ( $V_D/V_T$ ) is calculated from the gas R line (figure 1) as the ratio  $(A_i - \bar{E}_{ads})/(A_i - 1)$ , or in terms of  $P_{CO_2}$  as  $(P_{aCO_2} - P_{ECO_2})/(P_{aCO_2} - P_{ICO_2})$ ; since  $P_{ICO_2}$  is zero, this simplifies to  $(P_{aCO_2} - P_{ECO_2})/P_{aCO_2}$ . In the analysis of WAGNER *et al.* [3], alveolar dead space equals  $(P_{aCO_2} - P_{ACO_2})/P_{aCO_2}$ , where  $\bar{A}$  equals alv in figure 1.

**Why the “ideal” point and  $V_D/V_T$  are not the optimal solutions**

In lung disease,  $P_{aCO_2}$  cannot be relied on to predict mixed or mean  $P_{AO_2}$ . In intrapulmonary shunt,  $P_{aCO_2}$  will be greater than  $P_{AO_2}$ , by 2.3 mmHg for a 30% shunt alone and by 9.0 mmHg for 30% alveolar dead space alone (table 1); thus, the ideal alveolar air analysis [2] will underestimate the true mixed or mean alveolar to arterial ( $\bar{A}aP_{O_2}$ ) gradient. Although 2.3 mmHg a $\bar{A}P_{CO_2}$  gradient (A in table 1) is not a big difference (and the effect on the shunt calculation would be small), the error would be much greater if there was a combination of increased shunt and increased dead space (table 1). Figure 4 in WAGNER *et al.* [3] shows a complex interaction between the  $\bar{A}aP_{O_2}$  and the a $\bar{A}P_{CO_2}$  gradients, which means that both need to be defined for intrapulmonary shunt and dead space fractions to be measured accurately.

The  $V_D/V_T$  of RILEY and COUNNAND [2] includes the anatomic dead space ( $\sim 33\%$  of total in a resting healthy subject); this significantly reduces its sensitivity.

The  $\bar{A}aP_{O_2}$  and a $\bar{A}P_{CO_2}$  gradients in table 1 show that shunt and dead space affect  $O_2$  and  $CO_2$  exchange independently, differing from the RILEY and COUNNAND [2] analysis portrayed in figure 1. For example, in A there is a small a $\bar{A}P_{CO_2}$  gradient even when there is no alveolar dead space, and in B an  $\bar{A}aP_{O_2}$  gradient exists in the presence of zero shunt. In C and D, the  $\bar{A}aP_{O_2}$  gradients are the same despite a 14% difference in shunt, but there is a 20% difference in dead space. There are similar a $\bar{A}P_{CO_2}$  gradients in D and E, despite different alveolar dead spaces, because of a 39% difference in shunt. In E, a substantial  $\bar{A}aP_{O_2}$  exists (26 mmHg) with a small shunt (5%) because there is a significant dead space (23%). In other words,  $\bar{A}aP_{O_2}$  is not an accurate reflection of intrapulmonary shunt (formerly called “venous admixture”) and a $\bar{A}P_{CO_2}$  is not a true representation of alveolar dead space.

**The analysis of WAGNER *et al.* [3]: practical matters**

**Computerisation**

The older, graphical approach cannot be expected to cope with the complexity of the blood dissociation curves for  $O_2$  and  $CO_2$ , and their interaction. Body temperature, hydrogen ion concentration, haemoglobin and  $P_{50}$  all need to be taken into account. With the advent of digital computers, and expert programming,

**TABLE 1** Mean (or mixed) alveolar to arterial gradients for oxygen ( $\bar{A}aP_{O_2}$ ) and arterial to mean alveolar gradients for  $CO_2$  (a $\bar{A}P_{CO_2}$ ) in mmHg, intrapulmonary shunt (as % of total pulmonary blood flow) and alveolar dead space (as % of total alveolar ventilation) for different combinations of shunt and alveolar dead space

	$\bar{A}aP_{O_2}$ mmHg	a $\bar{A}P_{CO_2}$ mmHg	Shunt % total blood flow	Dead space % total ventilation
A Shunt only	48	2.3	30	0
B Dead space only	13	9.2	0	30
C Mixed: shunt = dead space	63	11.3	30	30
D Mixed: shunt >> dead space	63	7.5	44	10
E Mixed: dead space >> shunt	26	7.5	5	23

Calculated from figure 3b in WAGNER *et al.* [3].

these complexities became manageable. The pioneers in this field, in the late 1960s, were KELMAN [6] and WEST [7].

### Expired gas analysis

Measurements of inspired and expired  $P_{O_2}$  and  $P_{CO_2}$  and tidal volume need to be made, in a controlled way over 3–5 min, using a noseclip and mouthpiece. This type of monitoring is now routine in cardiopulmonary exercise testing. A steady state, as judged by a stable end-tidal  $P_{CO_2}$ , a constant respiratory rate and adequate tidal volume are needed for the calculation of inspired and expired ventilation, and oxygen consumption (from which cardiac output and  $P_{vO_2}$  are computed). During this monitoring period, radial artery blood is sampled over several breaths. Details can be found in the article by HARBUT *et al.* [1]. The calculation (and its justification) of mean alveolar tensions from the expired  $P_{O_2}$  and  $P_{CO_2}$  profiles is described in detail in WAGNER *et al.* [3].

### Conclusion

WAGNER *et al.* [3] have shown, by their theoretical analysis and practical approach, that mean (or mixed) alveolar ( $\bar{A}$ )–arterial  $P_{O_2}$  and  $P_{CO_2}$  gradients (and intrapulmonary shunt and alveolar dead space) can be measured with greater accuracy than with the classical ideal alveolar air approach [2], particularly in disease when substantial shunt and dead space co-exist (as they usually will). This is a big step forward in gas exchange pathophysiology. HARBUT *et al.* [1] have used this method and analysis to show that shunt and alveolar dead space, representing different pathological processes, may be present together in patients with COVID-19 lung disease. The time has come to extend this analysis to other pulmonary conditions.

Conflict of interest: None declared.

### References

- 1 Harbut P, Prisk GK, Lindwall R, *et al.* Intrapulmonary shunt and alveolar dead space in a cohort of patients with acute COVID-19 pneumonitis and early recovery. *Eur Respir J* 2023; 61: 2201117.
- 2 Riley RL, Cournand A. Ideal alveolar air and the analysis of ventilation–perfusion relationships in the lungs. *J Appl Physiol* 1949; 1: 825–847.
- 3 Wagner PD, Malhotra A, Prisk GK. Using pulmonary gas exchange to estimate shunt and deadspace in lung disease: theoretical approach and practical basis. *J Appl Physiol (1985)* 2022; 132: 1104–1113.
- 4 Wagner PD, Saltzman HA, West JB. Measurement of continuous distributions of ventilation-perfusion ratios: theory. *J Appl Physiol* 1974; 36: 588–599.
- 5 Fenn WO, Rahn H, Otis AB. A theoretical study of the composition of the alveolar air at altitude. *Am J Physiol* 1946; 146: 637–653.
- 6 Kelman GR. Digital computer subroutine for the conversion of oxygen tension into saturation. *J Appl Physiol* 1966; 21: 1375–1376.
- 7 West JB. Ventilation–perfusion inequality and overall gas exchange in computer models of the lung. *Respir Physiol* 1969; 7: 88–110.