Novel gas exchange analysis in COVID-19 lung disease

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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

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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 (λ) 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 $unit_y$:

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

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 λ is the blood solubility of gas_x (essentially, for O_2 and CO_2, λ is the tangent to the blood dissociation curve ΔC/ΔP, where C is O_2 or CO_2 content ($mL \cdot mL^{-1}$) 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 (λ range of 10^4-fold) were infused until a steady state was achieved; from their individual retention ($P_A/P_{\bar{v}}$) and excretion ($P_{\bar{E}}/P_{\bar{v}}$), 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 ×3 greater for O_2 *versus* CO_2 in the shunt model, and ×1.7 greater for CO_2 *versus* O_2 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 (λ) of CO_2 in blood *versus* O_2 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_2 as well as O_2 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_2 and CO_2 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_2 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} ~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 $(C_{\bar{v}CO_2} - C_{cCO_2})/(C_{cO_2} - C_{\bar{v}O_2})$ 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

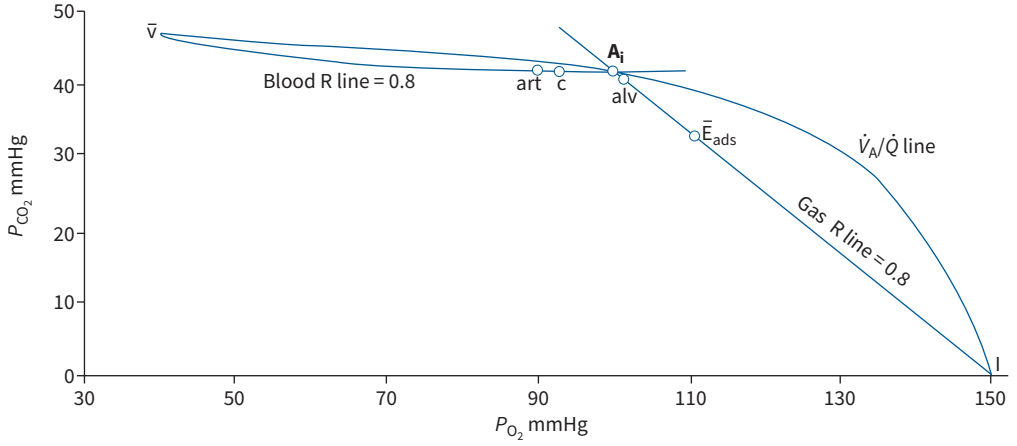

FIGURE 1 Graphical analysis of the calculation of ideal alveolar air (A_i; ideal point) modified from Riley and Cournand [2]. Blood or gas carbon dioxide tension (P_{CO_2}) is plotted against oxygen tension (P_{O_2}) (in mmHg) with the gas inspired (I; air) set at P_{O_2} 150 and P_{CO_2} 0 mmHg (see 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 (~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 Cournand [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 AaP_{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 $(A_i - \bar{E}_{ads})/(A_i - I)$, or in terms of P_{CO_2} as $(P_{aCO_2} - P_{\bar{E}CO_2})/(P_{aCO_2} - P_{ICO_2})$; since P_{ICO_2} is zero, this simplifies to $(P_{aCO_2} - P_{\bar{E}CO_2})/P_{aCO_2}$. In the analysis of Wagner *et al.* [3], alveolar dead space equals $(P_{aCO_2} - P_{\bar{A}CO_2})/P_{aCO_2}$, 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 Cournand [2] includes the anatomic dead space (~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 Cournand [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 P50 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 $P_{\bar{v}O_2}$ 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.

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